CLINICAL PROFILE AND THYROID FUNCTION OF PATIENTS ATTENDING NEW MULAGO HOSPITAL THYROID CLINIC

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THIS IS TO CERTIFY THAT THIS THESIS/DISSERTATION WAS ACCEPTED BY ENTRUSTE FOR AWARDS OR OTHER HIGHER DEGREES OF INTEGRATED MEDICINE

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DEDICATION

Dedicated to Costant, Angella-Merci: my parents and Isaac my beloved cousin.
DECLARATION

I declare that the work submitted in this dissertation is the result of my own original study except where otherwise acknowledged.

This work has not been submitted for any other degree award in any University.

________________________________________

DR. MUTAKIRWA JOHNBOISCO
(CANDIDATE)
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<tr>
<td>T₃</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>T₄</td>
<td>Thyroxine</td>
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<tr>
<td>TRab</td>
<td>Thyrotropin receptor antibodies</td>
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<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
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<tr>
<td>TSI</td>
<td>Thyroid Stimulating Immunoglobulins</td>
</tr>
<tr>
<td>FNAC</td>
<td>Fine needle aspiration for cytology</td>
</tr>
<tr>
<td>TFT's</td>
<td>Thyroid functional tests</td>
</tr>
<tr>
<td>TBII</td>
<td>Thyrotropin binding Inhibitory Immunoglobulins</td>
</tr>
<tr>
<td>TC</td>
<td>⁹⁹ᵐ⁻Technetium Pertechnatate</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>STN</td>
<td>Solitary Nodule</td>
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<tr>
<td>MNG</td>
<td>Multinodular Goitre</td>
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DEFINITIONS

Hyperthyroidism: Means an over active thyroid gland leading to elevated thyroid hormones causing thyrotoxcsis.

Hypothyroidism: This is a condition of decreased thyroid hormone function.

Thyroid disorders: This refers to a diversity of diseases due to abnormal function or structure of the thyroid gland.

Euthyroidism: This refers to a state of normal thyroid hormone function in the body.

Sub clinical hyperthyroidism: This refers to a condition of no clinical signs and symptoms of thyroid dysfunction with normal thyroid hormones but suppressed thyroid stimulating hormone TSH.

Subclinical hypothyroidism: This refers to a condition where there is elevated TSH, and normal thyroid hormones but the patient is clinically asymptomatic.

Normal serum sTSH and thyroid hormones
sTSH; 0.4-5.01 μ IU/ml
T4; 58-154.7 nmol/l
T3; 0.79-2.5 nmol/l
ACKNOWLEDGEMENT

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ABSTRACT

Introduction: Thyroid diseases are common endocrine diseases in the whole world. These diseases are also common in Uganda since its in an iodine deficiency region but the prevalence of different disorders and their related function are not known.

Objectives: To describe the clinical pattern of common thyroid disorders and related thyroid function among patients presenting in New Mulago Hospital thyroid clinic.

Design: This was a cross sectional study of patients with thyroid disease in New Mulago Hospital over a period of 3 months.

Methodology: Patients with signs and symptoms suggestive of thyroid disorders were recruited from the medical out patient thyroid clinic, and elsewhere within the hospital. These were evaluated for the clinical features, thyroid function status and the type of thyroid disease was determined. The patients' clinical profile and examination findings were documented using a questionnaire. The thyroid function status was determined using immunometric assays (IMA) and other relevant investigations which included thyroid ultrasound. Thoracic inlet x-ray, radioisotope uptake and fine needle aspirations for cytology were done where indicated in a small number of study patients.

Results:
A total of 62 patients were seen and evaluated. Twenty seven (44.7%) of the patient were hyperthyroid while 4 were hypothyroid. Twenty eight of sixty two were new patients and eight of them (28.6%) of them were hyperthyroid. Graves diseases contributed 66.7% of the hyperthyroid patient and was the commonest cause of hyperthyroidism. The third common group was of sub clinical hyperthyroism (14.5%).
A total of 56 goiters were seen of which 27 were diffuse, 27 multinodular and 2 were solitary. Nineteen of the 56 patients with Goiters were simple colloid goiters and 26 were hyperthyroid.

Conclusions:

1. The commonest cause of hyperthyroidism among hyperthyroid patients is grave disease with a prevalence of 66.6%.

2. Sensitive serum TSH assays can detect as many as 97% of all the patients with thyroid function disorders.
CHAPTER ONE:

INTRODUCTION AND RATIONALE OF THE STUDY.

1.1 Background

Thyroid diseases are among the most common endocrine disorders in the world. The patients with thyroid diseases were first described in Uganda in 1934\(^1\). These were patients with goitres along the Semliki river on Uganda's Western border. Twenty years later, while examining school children in 1954, Dean noted that nearly every pupil in a certain boarding school had an enlarged thyroid gland\(^2\). This showed that goitre as a symptom for thyroid disorders had a very high incidence in Uganda. This is not surprising since Uganda lies in the iodine deficiency areas like many other countries in Africa.

Thyroid hormones are important for growth and metabolism. The thyroid disorders mainly hypothyroidism and hyperthyroidism have significant adverse consequences on life at all ages. The disorders are common in developing countries\(^3\) though their prevalence in the population is not known. Endocrine diseases in general are responsible for 1-5% of the total mortality in the world\(^4\).

There are a number of studies on thyroid function done in Mulago hospital in the 1970's and thyroid disorders were described in the study population\(^12,13,14,15\). S.K Kajubi in 1977 showed that about 94% of the goitres seen were due to iodine deficiency and most of the nodules were cold on radiiodine uptake\(^12\).
In all the above studies, goitre was a common feature in all the patients with thyroid disorders and was attributed to iodine deficiency. Patients with thyroid autoimmune disorders such as Graves' disease were rare. There has been a lot of changes since then on the population's life-style such as the introduction of iodised table salt and this could have had an effect on the overall thyroid status of the population.

There was need therefore to study the prevalence, clinical features and thyroid function among patients presenting with thyroid disorders. This would give the current trend of the prevailing thyroid disorders and hence the need for this study.

1.2 Statement Of The Problem

Diseases of the thyroid are among the most common afflictions involving the endocrine system. The prevalence of these disorders is second to that of diabetes mellitus among the common endocrine disorders. In 1999, a total of 438 patients with thyroid disease were seen who were all females relative to 980 new patients seen with diabetes mellitus in Mulago Hospital.

There are a number of studies which were done in 1970s in Mulago hospital but they tended to concentrate on iodine deficiency goitres and their related function. It was noted in these studies that prevalence of thyrotoxicosis was low relative to other areas like Europe but there are suggestions from Zimbabwe and Democratic Republic of Congo that there is increased incidence of iodine induced hyperthyroidism due to uncontrolled salt iodisation. More so thyroid function assessment was done using different criteria leading to variable prevalences in the study populations.
1.3 Objectives of the study

1.3.1 General objective:
To describe the clinical pattern of common thyroid diseases in patients attending New Mulago Hospital Thyroid clinic.

1.3.2 Specific objectives
1. To describe the prevalence of specific thyroid disorders among patients attending Mulago Hospital.
2. To describe the prevalence of clinical features of specific thyroid disorders among patients attending Mulago hospital thyroid clinic.
3. To determine the thyroid status among patients presenting with thyroid disease in New Mulago Hospital Thyroid clinic.

1.4 Justification of the study

Thyroid diseases are common and more so among women in their middle ages causing morbidity in the productive fraction of the population.

The sensitivity of the clinical examination for diagnosis of thyroid disease is low even in the hands of trained clinicians. Christensen - SB et al in an examination of 49 patients for operation due to hyperparathyroidism could only detect 38% of the thyroid disorders. More so American Association guidelines recommend that thyroid status be evaluated primarily in- patients clinically suspected of abnormal thyroid function among many other indications.

Other than diagnosis, definitive management of thyroid disorders depends on correct physical assessment complemented by reliable biochemical assays of thyroid
hormones. The study will therefore aim at providing guidelines for proper assessment of patients and enable clinicians to manage and follow up patients properly. The information could also help in planning for the future of the clinic services.

The information gathered in this study will not only help in the management of individual patients, immediately but it will also help in planning for the future of these patients in terms of both diagnostic and therapeutic facilities.
CHAPTER TWO:
LITERATURE REVIEW

2.1 Prevalence of thyroid diseases

Although most physicians appreciate that thyroid disorders are relatively common in the general population the true prevalence is less certain\(^4\). This is more so in Africa where population studies are limited. The prevalence of hyperthyroidism and hypothyroidism in adults and adolescents is estimated at 1-4% in the whole world \(^5,7\).

In 1979, in Connecticut USA, during annual physical examination in a general practice of 1544 patients, Baldwin D.B et al found a 5.8% incidence of thyroid disease\(^5\). The disorders included nodular goitre, thyroiditis, Graves' disease, hyperthyroidism, simple goitre and iatrogenic hyperthyroidism. Reidwein, D et al did a prospective multi-centre study on 924 patients with untreated hyperthyroidism and found that 9.2% had autonomous adenomas and 59.6% had Graves’ disease, while 31.2% had unclassified thyroid disease\(^6\).

All the above studies were done in "selected patients" presenting at health institutions. The prevalence of thyroid disease in the whole community was done in Whickham England where hyperthyroidism was found to be relatively more common affecting 2% of women and 0.2% of men where as overt hypothyroidism was found in 1.4% of women and 0.4% of men\(^7\). In this same survey goitres were present in 4.5% of men and 12.1% of women. Similar results were obtained in Sweden on women picked at random by Christensen B et al which showed the prevalence of 2.3% and 0.8% for both hyperthyroidism and hypothyroidism respectively\(^8\). Even in areas of adequate iodine intake, such as Framingham the prevalence of goitres was 4% when a study...
was done in 1968. The difference in sex hormones i.e. oestrogens versus the androgens could explain the increased frequency of thyroid dysfunction in females. When age was considered in this population based study the prevalence of thyroid dysfunction was higher in the elderly where hypothyroidism was 3.5% in males and 17.5% in females. This implied that there is a tendency of decreased thyroid function in the elderly. Similar areas in Africa had higher prevalences of goitres with hardly any clinical hyperthyroidism or hypothyroidism. An example is the population based survey done in Chinamora, Zimbabwe where 29% of the population had endemic goitres with less than 4% having sub clinical hypothyroidism and less than 1% with subclinical hyperthyroidism.

In East Africa researchers have found markedly varying prevalences of hyperthyroidism and hypothyroidism in the populations studied. The prevalence of hyperthyroidism ranged from 0.5 - 11.5% depending on the study methods used. No specific aetiology of these thyroid disorders such as Graves disease, thyroiditis were described other than goitres due to iodine deficiency. A retrospective study by Kalk WJ et al in South Africa showed a different picture. He reviewed records of 688 black patients with thyrotoxicosis for a period of 5 years and noted that 88% of cases had Grave’s disease and the female to male ratio was 7.9:1. The study also revealed a bimodal age distribution with peaks at ages of 35-54 years and those elder than 64 years.

In 1993 in Mulago hospital Kobusingye C. reviewed retrospectively, 367 histopathological specimen results of goitres over a 5 year period and found only 0.55% having toxic goitres which is lower relative to an earlier review by S.K Kajubi
in 1977 where out of a total of 923 thyroid patients seen over 5 years 5% had thyrotoxicosis using radio iodine uptake\textsuperscript{12}. This was similar to a study by Kungu A. of 575 pathological specimens where a near similar incidence of thyrotoxicosis was found\textsuperscript{4}. Kobusingye’s patient were mainly surgical patients with goitres and the diagnosis was clinical. This could have left out significant fractions of patients with thyroid disorders with hyperthyroidism or hypothyroidism. Hence this could explain the low incidence of toxic goitres in the retrospective study. It should also be noted that different methods were being used to diagnose thyrotoxicosis.

Thyroid cancer is a fascinating tumour because of the tremendous variation in tumor aggressiveness. Even though about 4% of the total population have thyroid nodules the global incidence of cancer is estimated at 0.008% and this shows that most of the nodular lesion are benign \textsuperscript{16,67} The common histology forms of thyroid cancer are papillary, follicular, medullary and anaplastic. Other rare malignant thyroid tumors include lymphoma, squamous cell carcinoma, poorly differentiating thyroid carcinoma tall cell and columnar cell carcinoma, mixed follicular-parafollicular thyroid carcinoma and teratomas, plasmacytomas and metastases from lung, kidney, breast or melanoma. About 10,000 new case of thyroid cancer are diagnosed annually in the U.S and it was estimated that 1000 deaths are due to cancer.

The papillary thyroid carcinoma accounts for about 70% of thyroid cancers in United States whereas in endemic countries a greater proportion of thyroid cancers are follicular or anaplastic carcinomas. Out of 175 patients studied by Kobusingye O in 1993, 16 patients had thyroid cancer giving a prevalence of 9.5% among patients with goitres where 12.5% had papillary carcinoma and about 67% had follicular
carcinoma. This was comparable to the prevalence of 7.5% of thyroid cancers in 129 cases by Makoba.G, where aspiration for cytology was done and not open surgery as in Kobusingye's study. Probably the difference in prevalence of the thyroid cancer was due to the method used to obtain the biopsy.

Patients with thyroid cancers can be classified into low and high risk groups based upon the age of the patient, histological grade of the tumor and size of the tumor. Patients with papillary carcinoma have a better prognosis than those with follicular carcinoma. This may depend on the grade of the tumor because in a study at Mayo clinic only 3.6% of patients with undifferentiated thyroid cancer were alive at the end of five years despite the treatment with surgery, radiation and chemotherapy.

2.2 Pathophysiology of hyperthyroidism and hypothyroidism

Hyperthyroidism

Hyperthyroidism is defined as over-activity of the thyroid gland. It is commonly due to Graves' disease. Graves' disease is associated with TSH receptor antibodies (Trab) that stimulates the thyroid gland. This TSI is an immunoglobulin G that mimics the action of thyroid stimulating hormone via cyclic AMP production. TSH receptor antibodies are found in 80-90% of patients with Graves disease. In a study by Grant S.J, et al of 48 patients with Graves disease, these antibodies were detected in 95.6% of the patients. Whereas Smyth P.P.A, et al demonstrated these antibodies in all the 27 patients he studied. There are other antibodies that inhibit thyroid stimulating hormone receptors i.e thyroid receptor binding inhibitory immunoglobulins (TBII) but these are more common in hypothyroidism than hyperthyroidism.
There are several theories as to why the body produces antibodies against its own receptors. These include the presence of TSH receptor like antigens in pathogenic bacterial or parasites. In 1976 Shenkman L et al demonstrated high titres of Yersinia enterocolitica in patients with thyroid disorders particularly Graves disease than in those with other disorders\(^1\). This led to the discovery of TSH "receptors" in the membranes of mycoplasma and Yerstinia which initiate formation of antibodies against these sites \(^2\),\(^3\). These lead to stimulation of antibodies that cross-react with indogenous TSH receptors.

There is another hypothesis based on idiotypic network theory where the body produces antibodies against the idiotypic combining sites of primary antibody.

Hyperthyrodisism is also caused by toxic multinodular goitre called Plummer's disease, that is characterised by autonomously functioning multiple nodules in the thyroid gland. The aetiology of toxic multinodular goitre is not well defined but the role of autoimmunity has not been defined yet. Karailm Z. et al studied 48 patients with multinodular goitre and found that 11 patients had elevated TSI titres and the rest did not\(^4\). The same patients had elevated antithyroid antibody titres. Toxic multinodular goitre is preceded by non-toxic MNG and toxicity almost always results from exposure to increased quantities of iodine which enables autonomous foci to excrete excessive levels of hormones (Jod Basedow phenomenon). This is more likely an autonomously hyperfunctioning tissue but Savoie J.C et al demonstrated iodine-induced hyperthyroidism in 10 patients with apparently normal thyroid glands \(^5\). The mechanism underlying Jodbasedow phenomenon is related to rapid
iodination or proteolysis of previously iodine poor thyroglobulin or to the presence of a subpopulation of autonomous areas of functioning tissue.

Iodine deficiency most commonly manifests as a goitre, and is its primary cause. If the iodine deficiency is persistent, the goitre progresses from hyperplasia which is diffuse to multiple nodule formation which on iodine supplementation may lead to hyperthyroidism in these patients. The initial hyperplasia constitutes a colloid or simple goitre which is the commonest cause of euthyroid goitre in paediatrics.

More often than not, a solitary nodule rather than multiple thyroid nodules are found and may autonomously secrete thyroid hormones leading to thyrotoxicosis. These are usually benign hyperfunctioning neoplasms. In a study by Kalk W J et al in S. Africa nodular goitres were second to Graves disease as a cause of hyperthyroidism. Nodules more than 3 cm in diameter are associated with hyperthyroidism in 70% of cases whereas less than 2% of causes of hyperthyroidism are associated with smaller thyroid nodules.

**Thyroiditis as a cause of hyperthyroidism**

Acute suppurrative thyroiditis is an uncommon inflammatory disease of the thyroid probably due to the glands rich blood supply, lymphatic drainage and encapsulation that may minimise contiguous spread from local structures. It is caused by bacterial, fungal organisms, or parasitic infections. The most common organisms are streptococcus pyogens, staphylococal aureus and pneumococcus pneumoniae. In more than 50% of cases there is usually a pre existing thyroid disease. Even though transient elevations in serum thyroxine (T4) do occur due to discharge of
preformed hormone from an inflammed gland, hyperthyroidism per se does not occur\(^\text{30}\). The patients are hyperthyroid but are not thyrotoxic.

Subacute thyroiditis is divided into subacute granulomatous (painful) thyroiditis and subacute lymphocytic thyroiditis (painless)\(^\text{31}\). The former is due to viral infections and is responsible for about 5% of the visits to physicians due to thyroid abnormalities. It's associated with symptoms of hypermetabolism such as diaphoresis, tachycardia, palpitations and weight loss when there is co-existent hyperthyroidism\(^\text{32}\).

The painless thyroiditis occurs sporadically or is post partum and the former may contribute 5% to 20% of all the patients with thyrotoxicosis\(^\text{33}\). Post partum thyroiditis commonly presents as hypothyroidism and is described in the subsequent sub topic.

Patients with thyroid nodules are usually evaluated by radio iodine or technetium 99 m pertechnate scanning to determine whether the thyroid tumour was solitary or multiple and whether it was hyperfunctioning or hypofuctioning (hot or cold respectively). Patients with solitary cold thyroid nodules have a 20% chance of the nodule being malignant while hot nodules just hyperactive and benign.

### Hypothyroidism

Hypothyroidism is an appellation of thyroid hormone deficiency. This is not as common as hyperthyroidism. Primary hypothyroidism is the most common cause of thyroid failure in adults and it occurs more frequently in females than males. This is an autoimmune disease resulting in hypothyroidism which represents a spectrum ranging from Hashimotos thyroiditis (with goitre) to atrophic lymphocytic thyroiditis (no goitre or primary myxoedema)\(^\text{34}\). The latter is thought to be due to an antibody
that inhibits the growth of thyroid tissue by TSH\textsuperscript{35}. The degree of lymphocytic infiltration of the thyroid gland is correlated with the presence of antimicrosomal and antithyroglobulin antibodies in serum of affected patients\textsuperscript{36}.

Hypothyroidism may be a transient phenomenon after acute insult to the gland as in de Quervain's thyroiditis, post-partum thyroiditis, subtotal thyroidectomy or it may follow a few months of radioiodine therapy. Post ablative hypothyroidism commonly follows subtotal thyroidectomy and the incidence may be as high as 70\% after a long time\textsuperscript{37}. De Quervain's thyroiditis is also called subacute thyroiditis and the cause is a viral infection not autoimmune disease. Eylan E et al, in Israel demonstrated presence of mumps virus in ten patients out of the 11 patients with hypothyroidism during a mumps epidemic\textsuperscript{38}.

Green M. et al in 1964 followed 236 patients who had undergone partial thyroidectomy for thyrotoxicosis and observed that 6\% developed hypothyroidism after 10 years whereas 29\% of 918 patients who had radio iodine therapy developed hypothyroidism after the same period of time\textsuperscript{39}. Although the cause of this continuing progressive increase of hypothyroidism is uncertain there is a role of an autoimmune process because antithyroid antibodies do appear transiently during the course of the disease\textsuperscript{40}.

Post partum hypothyroidism commonly occurs four months after birth. It is a form of thyroiditis and is associated with autosomal antibodies in some patients. Hardy F.Y in a study of 901 pregnant women found that out of 243 women who developed hypothyroidism 117 had autosomal antibodies relative to 126 who did not have antibodies but developed hypothyroidism\textsuperscript{41}. Current knowledge suggests that pregnancy suppresses immunologic responsiveness and there is rebound effect
during the post-partum period. The thyroid injury observed may be due to increase natural killer cell activity. The role of natural killer cells activity and antibody dependent cell mediated cytotoxicity remain unclear.

Congenital hypothyroidism occurs once in every 4,000-5,000 births as a result of thyroid dysgenesis. Most cases exhibit primary hypothyroidism and are associated with thyroid ectopy, dysgenesis or agenesis and organification defects. In iodine deficient endemic goitre areas there is a 10% incidence of neonatal hypothyroidism and goitre. This is due to low iodine status because it's not seen in iodine sufficient areas. Congenital goitre due to chronic maternal iodine use is rare and has similar manifestations as in adults. Death from asphyxiation was reported in 8 out of 22 infants born with a goitre.

Excessive iodine intake can induce hypothyroidism. A prospective study of biochemically euthyroid patients with Hashimoto's thyroiditis who were treated with iodide revealed a high incidence of iodide related hypothyroidism that was reversible on cessation of iodides. This is due to failure of autoregulation of the thyroid gland or failure to escape from the Wolf-Chaikoff effect.

There are some substances reported in diet that induce hypothyroidism due to blockage of iodine uptake by thyroid gland and this may lead to goitre formation. These are called goitregens and include thiocyanate in millet, cassava, sorgum and potatoes. This has been studied by Eltom in rural and urban subjects in Western Sudan where he demonstrated higher incidences of thyroid dysfunction and goitres in rural populations than urban population due to different diets. Other than
thiocyanate in foods which cause hypothyroidism, thionamide substances have been described in certain vegetables such as cabbage, turnip, kola, and rape. Water is a frequent source of iodine but drugs like amiodarone, lithium, sulfonylureas do also cause hypothyroidism.

2.3 Diagnosis of common thyroid disorders

The diagnosis of thyroid disorders depends on the history, physical examination, determination of thyroid function status and histology studies if necessary. There are important aspects in the history such as presence of thyroid disease in the family, onset of the disease and associated symptoms that may define the function or the complications of the disease.

A familial history of goitre could be suggestive of Hashimotos thyroiditis, familial or endemic goitre or medullary thyroid cancer as found in multiple endocrine neoplasia type 2 (MEN 2a or 2b). The recent or rapid growth of solitary or dominant nodule raises the suspicion of neoplasia it's also important to illicit symptoms that may define the thyroid function status of the patient. The patient may be euthyroid, hypothyroid or hyperthyroid depending on the underlying function of the gland.

The physical examination is directed to features of particular interest in patients suspected of thyroid disorders. Thyroid diseases present with thyroid enlargement in 80-99% of the thyroid patients. This is the same in endemic and non endemic areas. The goitre may be nodular or diffuse, and the nodularity may be single or multinodular. Other than a goitre there are signs of thyroid disease that will help in defining the thyroid function such as myxoedema, tremors, atrial fibrillation and exophthalmos.
The determination of circulatory levels of thyroid hormones is essential for an accurate assessment of the functional status of thyroid patients. By means of modern day immuno radiometric assays (IRMAs) assays, small quantities of thyroid hormones can be detected to diagnose mild degrees of thyroid dysfunction.

a) Blood hormonal assays

Among many thyroid function tests in clinical practice, measurement of serum TSH comes closest to an ideal test because its synthesis and secretion in pituitary is under a positive control of thyrotropin releasing hormone and negative feed back by thyroid hormones. Earlier assays for serum TSH using radioimmunoassays and competitive protein binding lacked the sensitivity to be used as primary tests of thyroid function but the current sensitive TSH assays using immunometric assays can be used to distinguish euthyroid from hyperthyroid population. Primary hyperthyroidism is associated with high levels of thyroid hormones and depressed or undetectable levels of sTSH\(^5\). A minor rise or fall of thyroid hormones, particularly of FT\(_4\) ilicits an approximately ten times larger inverse change in pituitary TSH release. This makes TSH an extremely sensitive indicator of thyroid status\(^5\). The immunometric sensitive TSH assays (s TSH) detect low as well as high serum TSH levels, and have become the standard for detecting hyperthyroidism and hypothyroidism\(^6\) [normal sTSH = 0.4-5.01 μIU/m]

The second key test is the measurement of serum free T\(_4\) that is metabolically available and directly participates in the negative feedback to the pituitary and hypothalmus that is why it becomes important to assess its level. This is superior to measurement of total T\(_4\) which is not as reliable as patients have been found with hyperthyroxinemia or hypothyroxinemia yet they are clinically euthyroid making it an unreliable indicator of thyroid status. Normal values of total T\(_4\) are a range that
varies between 58-154.7 nmol/L. Total T₄ levels are altered by physiologic or pathologic changes in thyroid binding proteins. This necessitates the measurement of free thyroxine component (FT₄) or use of free thyroxine index (FTI) in order to assess a thyroid patient properly. This is more so in conditions which increase serum thyroid binding proteins such as pregnancy, oral contraceptive pills, or those that decrease TBG such as alcoholic liver diseases, nephrotic syndrome, steroid therapy or any major systemic illness.

Serum triiodothyronine (T₃), the most active thyroid hormone, varies in parallel with T₄ level. Normal ranges are between 0.79-2.5 nmol/L with higher levels in hyperthyroidism. Serum levels of serum T₃ are also affected by conditions which affect serum TBG level as listed above. Fransisco Bermundez et al studied 34 patients who were admitted for other illnesses and were clinically euthyroid and found that 24 patients had low levels of T₃ with associated low levels of TBG. It's a derivative of T₄ in the peripheral tissues with only a small quantity released directly by the thyroid. Even though serum T₄ is usually elevated in hyperthyroidism it misses 5% of cases that are due to triiodothyronine (T₃) toxicosis.
b) TSH receptor and thyroid antibodies.

It is recognised that several-functional types of antibodies may exist. Some antibodies stimulate thyroid gland function; thyroid receptor stimulating antibodies (TSI), while others inhibit the binding of TSH to its receptor; TSH receptor binding inhibitory immunoglobulins (TBI).

There are other antibodies such as thyroid antimicrosomal (TmAb) and antithyroglobulin (TgAb) which are measured to confirm or rule out autoimmune thyroid disease i.e Grave's disease or Hashimoto's thyroiditis\(^5\). Their presence suggest the possibility of Grave's disease or Hashimoto's disease especially if correlated with the clinical presentation. The prevalence of these antibodies is very variable depending on the selection of patients, type and quality of the assay plus laboratory techniques and these have limited their clinical application.

c) Radioisotopes scanning & uptake

Thyroid radionuclide imaging and uptake play an important role in management of thyroid disease when used in conjunction with blood tests, physical examination and other imaging procedures. Two iodine isotopes (iodine 123 & 131) and \(^{99m}\) technetium pertechnetate are commonly used but the latter is preferred and only used for imaging because of its short half life and absence of beta rays emission. The high count rates which result from the increased tracer amounts of \(^{99m}\) TC help to improve image quality however it does concentrate in thyroid tissue as well as iodine – 131 and body background activity is high.
The scintillation camera is used and is the standard imaging instrument in nuclear medicine. The imaging of palpable nodules allows normally functioning tissue to be distinguished from hypofunctioning (cold) or hyperfunctioning (hot) nodules. Patients with solitary cold thyroid nodules have a 20% chance of having a thyroid cancer while hot nodules are almost never malignant. Once a cold nodule is identified it is imperative that an aspiration for cytology be done to rule out malignancy.

Thyroid radiiodine uptake is no longer an important part of the work up for thyroid dysfunction because of availability of sensitive radio immunoassays techniques for serum levels of thyroid hormones and T.S.H. It remains important for calculating the therapeutic amount of radiiodine to be administered in thyroid cancer after total thyroectomy. This is because the uptake of $^{131}\text{I}$ in thyroid tissue is very high relative to background, and it allows detection of small and poorly functioning foci of metastatic differentiated carcinoma. Its also used in the perchlorate discharge tests to diagnose thyroid dishormogenesis. The normal uptake ranges from 10% to 35% in 24 hours.

d) Thyroid sonography & fine needle aspirations for cytology (FNAC)

The most important aim of sonography is to determine the nature of thyroid lesions that is to say solid or cystic. Other than ultrasound sonography computer tomography and magnetic resonance can be used to achieve the same purpose.

The ultrasound compliments information gained from history and physical examination. For nodules the scan will define the number of nodules; and the nature: solid or cystic. Most goitres due to iodine deficiency tend to be diffusely enlarged.
To differentiate malignant lesions from benign lesions it is necessary to do aspiration biopsy for cytology and all patients with thyroid nodules should have FNAC done on them.

With current high resolution equipment, nodules as small as 2 – 3 cm in diameter can be identified with frequency signal of 7.5 - 10 MHZ. About 75% of the nodules are of lower echogenicity and 15% are of higher echogenicity than thyroid tissue.

The function of confirming the malignancy is more specifically fulfilled with the use of fine needle aspiration for cytology (FNAC) during scanning. The accuracy in experienced hands is about 50%. A recent study by Makoba G. on the role of FNAC in patients with thyroid disorders found that 7.8% of 129 patients studied had malignancies and 13.2% were indeterminate.

f) Radiology

For large goitres the paratracheal extent of the thyroid gland can be assessed with thoracic x-ray. The postero-anterior view usually shows tracheal deviation. The thoracic inlet x-ray shows obliteration of the superior retrosternal space.

Occasional finding of calcifications are characteristic of malignancy but shell like cysts are typical of benign cysts. Finding of pulmonary infiltrations on chest x-ray is suggestive of thyroid cancer metastases though their absence does not rule out cancer metastases to lungs which are better detected by $^{131}$ I radioisotope scan.

Radiology is more useful in confirming presence of pressure on structures in the neck and retrosternal thyroid mass especially if the patient has pressure symptoms i.e dyspnoea, dysphagia and hoarseness. Posteroanterior and lateral views can show indentation and/or deviation of the trachea, and if taken with a barium swallow the
radiograph will show indentation and/or deviation of the oesophagus by the thyroid mass.

Conclusion: Modern immunometric assays, because of their sensitivity offer promise as first line thyroid screening tests. In unselected population, sTSH has a sensitivity of 89-95% and a specificity of 90-96% for overt thyroid dysfunction. This is in reference standards incorporating clinical history, examination, repeat measurements and/or additional testing including thyrotrophin releasing hormone tests. Therefore in this study clinical history examination and immunometric assays will be the basis of assessing the baseline thyroid function in the patients to be seen.
CHAPTER THREE:
METHODOLOGY

3.1 Study design

The study was a descriptive cross-sectional study of patients presenting with thyroid disease or symptoms suggestive of thyroid disease. They were clinically evaluated for features of thyroid disorders. Sampling was done by consecutive enrollment of all patients presenting in the thyroid clinic and elsewhere in the hospital who, during the period of study fulfilled the eligibility criteria.

3.2 Setting of the study

The study was based in New Mulago Hospital, especially in the Medical Thyroid out-patient clinic between the month of January and March 2001. New Mulago hospital is a national referral hospital but it also serves as a district hospital for Kampala District with a population of 1.78 million people.

3.3 Study population

The target population was all patients attending Mulago hospital with clinical signs and symptoms suggestive of thyroid disorders. The patients were with or without goitres.
3.4 Definition of cases

Inclusion criteria
All patients presenting with thyroid disorders to Mulago hospital (New and old patients).

All patients with symptoms suggestive of thyroid dysfunction e.g easy fatiguability, weight gain or loss, dry skin or hair, cold or heat intolerance, nervousness and palpitations.

Consent to the study was sought from the patients.

Exclusion criteria:
Patients with no signs and symptoms suggestive of thyroid disorder.

3.5 Data collection and management

3.5.1 Study Procedures
A structured questionnaire (Appendix I) was used to obtain basic information of identity and symptoms.

Each questionnaire was clearly labeled with a serial number and was administered in privacy. Additional information on previous clinical treatment and symptomatology to make a diagnosis was obtained from clinical records of the continuing (old) patients.

After recording the identification and symptoms, a physical examination to identify features of thyroid disease was done. A local examination of the thyroid gland was done to measure the size and grade the goitre (Appendix 111) using WHO criteria for grading goitres.
During the local examination of the thyroid the consistency, tenderness, mobility and retrosternal extension were also determined. The patients who were found to have a diagnosis such as pharyngitis, persistent fevers of unexplained origin, lymphadenopathy with no titre to explain the presenting symptoms were excluded from further work up (and patients with no thyroid disorders).

**Laboratory investigations:**

Blood was obtained after examination by performing venepunctures on dorsum of the hand or antecubital fossa using aseptic techniques.

Blood was collected in a bottle with a clot activator. It was centrifuged and serum was separated from the cells and kept in labelled cryovials at -20°C. The serum was thawed at a later time then hormonal assays and calibration were done by clinical chemistry department of Mulago hospital in batches of twenty two samples at a time to avoid interassay variation. Hormonal assays were done by immuno metric assays using microparticle enzyme immunometric assays (MEIMA) - from Abbot laboratories, Germany using an analyser [Abbot Automated Immundassay analyser model IMX]. The procedure of measuring hormone levels is summarised in appendix IV for sTSH. The others follow a similar procedure.

**Ultrasound scanning and thoracic inlet x-ray:** All the study patients with or without goitre clinically had ultrasound scan of the thyroid for the purpose of qualitative measurement of the thyroid gland size. FNAC was done on all the patients with solid or dominant nodules or adjacent lymph node infiltration. The slides were read by the pathologist to determine the nature of the goitre.
Fine Needle Aspiration And Radioisotope Uptake

Aspiration was done on patients with thyroid nodules (solitary and multinodular) and those with non toxic diffuse goitre that were suspicious of malignancy. Patients were made to lie supine and their necks were supported by a pillow, then aspirates were taken with a 22-25 gauge needles.

To reduce sampling error, a minimum of three aspirates from nodules were done. These were air dried for 20 minutes, fixed in alcohol and transported to pathology laboratory. In the lab they were stained with haematoxylin and eosin. Senior pathologist read the slides to determine the histological nature of the goitre.

Patients underwent technicium-99m thyroid imaging with the use of Tc-99m pertechnetate which was administered intravenously. Twenty minutes after, using a gamma camera, with a patient in a supine position while the neck and chin extended, pictures were taken in a left anterior and oblique views. Pictures were taken after 200,000-250,000 counts per view. Usually marker sources were placed lateral to the thyroid to calibrate the size.
3.5.2 Flow chart of study patients.

3.5.3 Measurements
The following information was collected in the questionnaire.
Clinical profile:

- Identification: Study number, age, address, marital status etc.
- Symptoms of the presenting complaints
- Physical signs on examination

Investigations:

- Total T4, T3 FT4 and TSH
- U/S scan results
- Radioisotope scan
- Thoracic inlet x-ray
- FNAC Results

3.6 Data analysis and presentation

The results were analysed using a computerised statistical package Epi info. 6.04.

Proportions, frequency distribution tables and graphic presentations were used to summarize the distribution of disorders and clinical features among the patients.

This was done according to the following:

a) The proportion of patients who had:
   i) Hyperthyroidism
   ii) Hypothyroidism
   iii) Euthyroidism
   iv) Subclinically hyperthyroidism or hypothyroidism.
   v) Congenital hypothyroidism

b) Prevalence of common clinical features among patients with different thyroid disorders (abnormal thyroid function)
Proportion of patients with other thyroid diseases such as Graves' disease, multinodular thyrotoxicosis, simple goitres and others.

The relationship or associations between hyperthyroidism and the clinical features were then analysed. This was done by using cross tabulations and chi-square tables of the variables above.

3.7 Quality control

i) A pretest using the questionnaire was done on about 5 patients to evaluate its suitability for the data collected by the principal investigator himself.

ii) The subjects interview and physical examination were done by the principal investigator to ensure consistency

3.8 Sample size

The sample size \((n)\) for a cross-sectional descriptive study is calculated using the Keish and Leslie formula below:

\[
 n = \frac{K}{1 + K/N}
\]

Where \(K = \frac{Z^2 P(1-P)}{d^2}\)

\(N = \) Annual total study population of 103 patients

\(Z = \) A point in the normal distribution curve corresponding to a confidence limit - in our case we took a 95% confidence limit which is 1.96.

\(P = \) Is the expected prevalence of thyroid dysfunction that is
approximately 7.8% from a study by Kobusingye C where serum TSH levels were done in 103 patients\textsuperscript{11}.

\begin{align*}
    D &= \text{Is the required precision of the estimate that is 5\% in this study.}
\end{align*}

Therefore for an average annual turn up of 107 patients in thyroid clinic. The calculated sample size using the above formula

\begin{align*}
    n &= 54 \text{ patients}
\end{align*}
CHAPTER FOUR:

RESULTS
A total of 95 patients were evaluated in the thyroid clinic and medical wards for thyroid disease between 8th January and 31st March 2001. Of the 95 patients screened, 62 patients consented and were recruited for the study while the rest were found not to have thyroid disease on evaluation or refused to consent to take part in the study. Out of 62 patients 28 patients were new in the clinic while 34 patients were old patients in the clinic and had been on treatment or were just being monitored. The new patients were not on any treatment for thyroid disease at the time of the study.

4.1 Socio-demographic characteristics
Fifty six patients were female (90.3%) while 6(9.7%) were males giving a female to male ratio of 9.3:1 for the patients studied.

Figure 1 showing sex of study patients
Figure 2 shows the distribution of patients by age and sex. The age range of the patients studied was 1-76 years with a mean age of 37.7 years and the standard deviation of 15.72 years. Thirty nine patients (62.9%) were aged between 20 years and 50 years and two patients (3.2%) were below 15 years of age. Most of the male patients were young where the average age was 24.8 years and none of them was above 50 years of age. On the other hand, female patients were older with average age of 39.8 years and 14 (22.2%) were aged about 50 years.
Region of residence

Table 1: Region of Residence

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kampala</td>
<td>26</td>
<td>41.9%</td>
</tr>
<tr>
<td>Others*</td>
<td>16</td>
<td>25.6%</td>
</tr>
<tr>
<td>Eastern**</td>
<td>9</td>
<td>14.5%</td>
</tr>
<tr>
<td>Western***</td>
<td>6</td>
<td>9.7%</td>
</tr>
<tr>
<td>Northern****</td>
<td>5</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

* Represents districts of Masaka, Luwero, Kiboga and Mubende.

** Represents districts of Mbale, Soroti, Jinja and Tororo

*** Mbarara and Bushenyi

**** Arua, Gulu, Lira, Nebbi

As shown in table 1 the majority of patients 42 (67.7%) resided in central Uganda and most of them were from Kampala (41.9%) and Mpi District (20.6%). Only a few of the patients (32.3%) resided in the other 4 regions of Uganda.
Table 2 Clinical symptoms of thyroid disease and their association with thyroid function

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Hyperthyroid</th>
<th>Hypothyroid</th>
<th>Euthyroid</th>
<th>Sub clinical hyperthyroid</th>
<th>Sub clinical hypothyroid</th>
<th>Total n =62 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goitre</td>
<td>27</td>
<td>1</td>
<td>18</td>
<td>8</td>
<td>1</td>
<td>55 (88.7)</td>
</tr>
<tr>
<td>Painful goitre</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>13 (21.0)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>8 (12.8)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>11 (17.7)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>10 (16.1)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>24 a</td>
<td>0</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>40 (64.5)</td>
</tr>
<tr>
<td>Weigh loss</td>
<td>19 b</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>28 (45.8)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>11 (17.8)</td>
</tr>
<tr>
<td>Sweating</td>
<td>22 c</td>
<td>1</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>36 (58.8)</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>20</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>31 (50.0)</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>10 (16.1)</td>
</tr>
</tbody>
</table>

ap < 0.01
bp < 0.01
cp = 0.01

4.2 Clinical characteristics

Fifty five patients (88.7%) presented with goitre of which 27 had overt hyperthyroidism, 18 were euthyroid, 8 had subclinical hyperthyroidism, 1 had hypothyroidism and 1 had subclinical hypothyroidism. Pain in goitres was a rare finding in all the patients with goitres. It was found in 21% of the patients and most of them were euthyroid. Dysphagia, hoarseness and dyspnoea were not common. Among all patients seen, dysphagia and hoarseness were present in 17.7% and 16.1% respectively while only 17.8% had dyspnoea.
Palpitations were a frequent symptom among hyperthyroid patients and the association was statistically significant (P-value < 0.01). Palpitations were also found in 57.1% of euthyroid and 44.4% of subclinically hyperthyroid patients. Weight loss was much more common among patients with hyperthyroidism (40.7%) than weight gain (14.8%). On the other hand, three out of four patients with hypothyroidism presented with weight gain.

Sweating which was present in half of all the patients seen was more associated with hyperthyroidism (81.5%) than euthyroidism (38.1%). Sweating seems to be related to heat intolerance which had a near similar distribution. Half of the patients with hypothyroidism (n=2) had cold intolerance and the rest were distributed between euthyroid and hyperthyroid patients (n=4).
Table 3: Clinical signs of thyroid disease and their association with thyroid function

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Hyper-thyroid</th>
<th>Hypothyroid</th>
<th>Euthyroid</th>
<th>Sub clinical hyperthyroid</th>
<th>Sub clinical hypothyroid</th>
<th>Total N=62 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goitre</td>
<td>17</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>29 (46.7)</td>
</tr>
<tr>
<td>Nodular</td>
<td>8</td>
<td>2</td>
<td>9</td>
<td>6</td>
<td>1</td>
<td>26 (41.9)</td>
</tr>
<tr>
<td>Diffuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onycholysis</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>7 (11.3)</td>
</tr>
<tr>
<td>Eye findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lid lag</td>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>10 (16.1)</td>
</tr>
<tr>
<td>Lid retraction</td>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>12 (19.4)</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>16 (25.8)</td>
</tr>
<tr>
<td>Cardiovascular findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse (&gt;100 bpm)</td>
<td>14</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>19 (30.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>6 (9.7)</td>
</tr>
<tr>
<td>Murmurs</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle wasting</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>Proximal muscle</td>
<td>13</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15 (24.2)</td>
</tr>
<tr>
<td>weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>p < 0.01

<sup>b</sup>p = 0.002

<sup>c</sup>p = 0.016 *fisher's exact test comparing hyperthyroidism and patients with thyroid disease.
Clinical signs of thyroid disease

Table 3 shows the frequency of major signs found on clinical examination among patients studied. Of all the 62 patients who had clinical examination 55 were found with goitres. Nodular goitre (n=17) were closely associated with hyperthyroidism than diffuse goitre whereas among the euthyroid patients, the two were equally presented.

Of the 7 patients who had onycholysis, 6 of them had hyperthyroidism (p < 0.01). No patient with pretibial myxoedema or finger clubbing was identified in these study group. Eye signs were associated with hyperthyroidism with exophthalmos being the commonest (P < 0.01). Among the euthyroid patients all of the three eye signs were found in one patient. This also applied to subclinical hyperthyroidism except exophthalmos where 2 patients were identified. There were 6 patients with hypertension (BP > 140/90) where four were euthyroid, one hypothyroid, one with subclinical hypothyroidism, and none was hyperthyroidic.

In musculo skeletal findings proximal muscle weakness was found in 13 patients out of 15 patients with hyperthyroidism. It also occurred in 2 patients with hypothyroidism but was not a feature in other patients. Muscle wasting was also a feature of hyperthyroidism (7 patients) and was either less common or absent in other patients.
Table 4: Clinical staging of the goitre

<table>
<thead>
<tr>
<th>Stage of goitre</th>
<th>Hyper-thyroid</th>
<th>Hypo-thyroid</th>
<th>Euthyroid</th>
<th>Sub clinical hyperthyroid</th>
<th>Sub clinical hypothyroid</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Ia</td>
<td>11</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Ib</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>4</td>
<td>21</td>
<td>1</td>
<td>9</td>
<td>62</td>
</tr>
</tbody>
</table>

The WHO criteria for staging goitres in iodine deficiency areas is shown in appendix IV. Based on this criteria of all the 62 patients studied, 5 (8.1%) had no goitres (stage 0) on examination while 57 (91.9%) had goitres. Two of the 5 patients with no goitres were children with congenital hyperthyroidism.

The majority of patients (71%) were distributed between Stage Ia (33.9%) and Ib (37.1%). Five hyperthyroid patients had Stage II goitre disease and only one had Stage III goitre. Sixteen of the patients who were euthyroid had Stage I (a + b) goitre disease. A similar trend was found among patients with subclinical hypothyroidism where six of the 9 patients had Stage I disease (Ia + Ib).

4.3 Thyroid function and serum hormonal assay

Table 5: Thyroid hormone concentration in blood of all 62 patients

<table>
<thead>
<tr>
<th>Serum hormonal assay</th>
<th>Range</th>
<th>Mean (Standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STSH [μ Ι. U/ml]</td>
<td>0.01 – 50.00</td>
<td>3.19 (10.0)</td>
</tr>
<tr>
<td>Thyroxine (T4) [nmol/l]</td>
<td>1.78 – 390.40</td>
<td>152.03 (81.2)</td>
</tr>
<tr>
<td>Triiodothyronine (T3) [nmol/l]</td>
<td>0.03 – 111.40</td>
<td>4.43 (14.0)</td>
</tr>
</tbody>
</table>
Serum levels of thyroid hormones sTSH, T\textsubscript{4}, T\textsubscript{3} were determined in all the sixty two two patients and the results are shown in table 5. The mean sTSH, T3, T4, were 3.19 lU/ml, (SD=10.0), 152.3nmol/L (S.D 81.2), 4.43nmol/L (SD=14.0) respectively. Normal ranges were determined as per the immunometric assay kits that were used. Of all the 27 patients with hyperthyroidism, twenty five had low sTSH and this also applied to the patients with subclinical hyperthyroidism (n=9).

Table 6: A table comparing serum hormonal assays and different classes of thyroid functions.

<table>
<thead>
<tr>
<th>Hormonal assays</th>
<th>Thyroid functional classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTSH T\textsubscript{4} T\textsubscript{3}</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>N N N</td>
<td>1</td>
</tr>
<tr>
<td>L H H</td>
<td>7</td>
</tr>
<tr>
<td>L N N</td>
<td>8</td>
</tr>
<tr>
<td>L N H</td>
<td>10</td>
</tr>
<tr>
<td>N N H</td>
<td>1</td>
</tr>
<tr>
<td>H N L</td>
<td>0</td>
</tr>
<tr>
<td>H N N</td>
<td>0</td>
</tr>
<tr>
<td>H L L</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27</strong></td>
</tr>
</tbody>
</table>

N: Normal serum hormonal range T\textsubscript{3}, T\textsubscript{4} and sTSH are sTSH; 0.4-5.01 \textmu{}U/ml, T\textsubscript{3}; 58-154.7 n mol/L and T3; 0.79-2.5n mol/L respectively.

L: Serum hormonal levels of T\textsubscript{3}, T\textsubscript{4} and sTSH below the stated normal range which are T\textsubscript{3} < 0.7nmol/L, T\textsubscript{4} < 58.7nmol/L and sTSH < 0.47 \textmu{}U/ml.

H: Serum hormonal levels of T\textsubscript{3}, T\textsubscript{4} and sTSH above the stated normal range which are T\textsubscript{3} > 2.5nmol/L, T\textsubscript{4} > 58 nmol/L and sTSH > 5.01 \textmu{}U/ml.
All patients with hypothyroidism (4 with overt hypothyroidism and one with subclinical hypothyroidism) had high levels of TSH. Levels of T3 and T4 were non specific in all patients except 2 patients with congenital hypothyroidism where T3 and T4 were consistently low. Here the sTSH was higher than 30 μU/ml. It should be noted that all twelve euthyroid patients had normal serum hormonal levels, except one who had a high T4.

Table 7: Comparison of type of goitre with thyroid function (according to U/S)

<table>
<thead>
<tr>
<th>Thyroid Function</th>
<th>Types of goitre</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diffuse</td>
<td>MNG</td>
<td>Solitary</td>
<td>No goitre</td>
<td>Total</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>16</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>8</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>S. Hyperthyroid</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>S. Hypothyroid</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>27</td>
<td>2</td>
<td>6</td>
<td>62</td>
</tr>
</tbody>
</table>

Table 7 shows a comparison of type of goitre and thyroid functions. Sixteen of the twenty seven patient with hyperthyroidism had diffuse goitres while 9 had multinodular goitres. This was in contrast to the euthyroid group where 10 patients had multinodular goitres relative to the 8 who had diffuse goitres.

Most of the patients with subclinical thyroid dysfunction had multinodular goitres (70%) than diffuse goitre 20%.

Solitary nodules were only found in two patients where one was hyperthyroid and the other euthyroid.

4.4 Fine needle aspiration for cytology (FNAC) results and radioisotope uptake
The FNAC was performed on MNG, solitary nodules and on those suspected to have thyroid cancer. Only thirteen patients out of twenty nine patients had fine needle
aspiration performed. All the aspirates except two were benign showing normal follicle cells with or without colloid as shown in table 8. Of the two, one was suspicious for malignancy and the other was haemorrhagic making it difficult to draw conclusions from it.

Table 8: FNAC results in the thirteen patients aspirated

<table>
<thead>
<tr>
<th>Histology</th>
<th>MNG</th>
<th>STN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal follicular cells</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>2</td>
</tr>
</tbody>
</table>

The patient whose results were suspicious for malignancy with a solitary nodule had had a thyroidectomy 10 years before and had re-growth of solitary nodules.

**Thyroid radioisotope uptake**

Radio isotope uptake was done in a total of 10 patients six of whom had multinodular goitre and four had diffused goitres. Two were uniformly hot, two were cold and two were mixed. Two of the four diffuse goitres were found to be uniformly hot (increased uptake) and two were uniformly cold (poor uptake) as shown in table 9.

Table 9: Comparison of thyroid uptake and types of goitre

<table>
<thead>
<tr>
<th>Thyroid uptake</th>
<th>Diffuse goitre</th>
<th>MNG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformly hot</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Uniformly cold</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Mixed uptake</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4</strong></td>
<td><strong>6</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>
4.5 Status of thyroid function of all study patients

Fifteen of the twenty eight patients who were new to the clinic were euthyroidic while eight were hyperthyroidic. About 48% of the new patients had a form of thyroid function disorder while the rest were euthyroidic. Of the 34 old patients 19 were hyperthyroidic while only 6 patients were euthyroidic (see table 10).

Table 10: Thyroid function of all study patients

<table>
<thead>
<tr>
<th>Status of Thyroid function</th>
<th>Frequencies</th>
<th>Total</th>
<th>%ge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New</td>
<td>Old</td>
<td></td>
</tr>
<tr>
<td>Euthyroidism</td>
<td>15</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>8</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>34</td>
<td>62</td>
</tr>
</tbody>
</table>

4.6 Aetiological diagnosis of thyroid disease

In all the 62 patients a probable aetiological diagnosis of thyroid function disorders and pain was only reached in 31 patients out of the sixty two patients. The rest were either classified as simple goitres or complicated goitres leading to thyroid disfunction as shown in table 11).

A diagnosis of Graves' disease was made in 18 patients of whom one had no goitre but had eye signs and elevated thyroid hormones. The rest of the hyperthyroid patients had multinodular goitres. The eighteen patients of Graves' disease formed 66.7% of all patients with hyperthyroidism. The two patients who had subacute thyroiditis were women and were euthyroidic. Simple goitres was a common diagnosis (30.6%) among all patients presenting in the clinic.
Table 11: Specific thyroid disorders among patients with thyroid disease

<table>
<thead>
<tr>
<th>Thyroid disorder</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves disease</td>
<td>18</td>
<td>29.0</td>
</tr>
<tr>
<td>Multinodular thyrotoxicosis</td>
<td>8</td>
<td>12.9</td>
</tr>
<tr>
<td>Congenital hypothyroidism</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Subacute thyroiditis</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Simple goitre</td>
<td>19</td>
<td>30.6</td>
</tr>
<tr>
<td>Others</td>
<td>13</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Twelve patients were classified to have other thyroid diseases and these were patients with or without goitre with abnormal thyroid hormones e.g. hypothyroid, thyrotoxic. They needed further evaluation to determine the cause of their thyroid dysfunction which was not possible in this study.
CHAPTER FIVE:
DISCUSSION

Epidemiology

This study was a descriptive study of patients with symptoms suggestive of thyroid disease who presented to Mulago Hospital thyroid clinic and medical wards of Mulago hospital. It documents the social demographic features, clinical profile, serum thyroid hormone assay and thyroid functions of the patients.

Before this study, there were studies done here that described iodine deficiency goitres and their function.\textsuperscript{11,12} None of these studies had combined use of clinical features and hormonal assays to assess thyroid function which is the reference method of assessing thyroid dysfunction.\textsuperscript{61}

The majority of the patients in this study were females (90.3%) with male to female ratio of 1:9.3. This is in sharp contrast to Kobusingye’s finding of male to female ratio of 1:21.6.\textsuperscript{11} The reason could be due to her patients being surgical patients who were more likely to present with goitres. The male to female ratio in this study is consistent with other studies of thyroid disease where a similar ratio of 1:10 were found among patients with hyperthyroidism or hypothyroidism.\textsuperscript{7,10} The difference in sex hormones i.e. oestrogen which modulate autoimmune diseases could explain the increased frequency of thyroid dysfunction in females than males.

Most patients (41.9%) were from around Kampala district. This is not unexpected as Mulago Hospital, the Uganda National referral hospital, is situated in the district and is a convenient source of free medical care for the local population.
More than 75% of the patients were in the age category of 20-50 years. This corresponds to the age commonly affected by autoimmune thyroid diseases. 40,50,62

Clinical features in patients with thyroid disease

Most patients (88.7%) presented with a complaint of neck swelling or goitre while 11.3% did not. Clinically, goitres varied from diffuse goitres (41.9%) to nodular goitres (46.7%) but on ultrasound examination, these were found to be equally distributed (46.7%) between the two types. The prevalence of goitre among the patients studied was consistent with similar findings in endemic and non-endemic areas. 39,47,48

There were less nodular goitres (n=27%) found on ultrasound examination than on clinical examination (n=29). This signifies the importance of conventional ultrasound in classifying goitres as diffuse or nodular thyroid disease; solid, cystic or mixed with an accuracy of 90%. This helps in therapeutic aspiration of cystic nodules and diagnostic aspiration for cytology of solid nodules to rule out malignancy. 54,64

There were 5 patients (8.1%) with abnormal thyroid function whose glands were of normal size (stage 0). This is a slight deviation from studies of thyroid diseases done in East Africa where all the patients studied had goitres. 11,12,13 However, the finding in this study was similar to those Nodyke et al where 10% of the studied patients had no goitres, although his patients were of middle age. 63 This suggests that local causes of abnormal thyroid function and goitres are not purely due to iodine deficiency as this would manifest with goitres.
Palpitations, sweating and weight loss occurred in 64.5%, 58.1% and 45.8% respectively of all the patients studied. Palpitations were present in 89% of patients with hyperthyroidism and there was a significant association between palpitations and hyperthyroidism ($p < 0.01$). Sweating and weight loss were also associated with hyperthyroidism ($p = 0.001$). The prevalence of these symptoms was comparable to that of 73.3% found among 30 thyrotoxic patients by Cardozo et al. 47

Cold intolerance was relatively a non specific and rare finding in hypothyroid patients. However, heat intolerance was a common feature among hyperthyroid patients (32.2%). The problem with cold intolerance could be due to a small number of hypothyroid studied (4) patients and two of them being less than 15 years of age making it difficult for objective assessment.

Among the common dermatological findings found, onycholysis in the finger nails occurred in 22.2% of hyperthyroid patients. This prevalence is high relative to an average range of dermatological disorders reported elsewhere of 0.5-4%. 64 Eye disease, specifically exophthalmos was common among hyperthyroid patients ($p < 0.01$). Exophthalmos was present in 48.6% of hyperthyroid patients which is similar to the same prevalence reported world-wide of over 50%. 66

Of the six patients with hypertension, none was hyperthyroidic yet hyperthyroidism is listed as one of the endocrinological causes of systolic hypertension. It is reported that elevation of the systolic pressure ($> 150$ mmHg) occurs in at least 50% of patients with thyrotoxicosis returning to age and sex normal values with treatment. 73
The absence of hypotension in this study patients could be due to small numbers of hyperthyroid patients.

Thyroid function status was determined on the basis of symptoms and signs of the study patients. Serum hormonal levels were done as additional evidence of thyroid status and based on sTSH alone. Twenty-five patients out of twenty-seven patients (92.5%) with overt hyperthyroidism and eight out of nine patients with subclinical hyperthyroidism had low serum TSH. Similarly, all the four patients with overt hypothyroidism and one with subclinical hypothyroidism had high serum TSH. It was therefore possible to determine as many as 97% (60/62) of all the patients with thyroid function disorders. This is in agreement with Roolwels findings in which he showed that sTSH was valuable in differentiating hyperthyroid and hypothyroid patients from euthyroid patients.65

It should be noted that ten patients with features of hyperthyroidism had normal serum T4 but elevated serum T3 levels. Six patients of the ten were new while four of were old patients and therefore on treatment. Their cause of hyperthyroidism can be falsely attributed to elevated levels of serum T3 (T3 thyrotoxicosis) which is known to contribute about 5% of all the patients with thyrotoxicosis71. But in the absence of measurement of free T4 which is the active fraction of the hormone and superior to the measurement of total T4 51 then the above assertion of T3 thyrotoxicosis can not be confirmed in this study.

Fine needle aspiration was done on 13 patients and only one patient's cytology was suspicious of malignancy. Makoba G. in a study of the role of ultrasound guided
FNAC of 129 patients found that 7.8% were malignant. The numbers of patients aspirated in this study were very small due to limited span of the study making it difficult to assess its role statistically.

Out of 10 patients who underwent radioisotope uptake studies, 6 had nodular thyroid disease of which 2 were uniformly hot, 2 were uniformly cold and 2 were of mixed uptake. In a review of 100 thyroid radio isotopes uptake studies by S.K. Kajubi in 1977, all the nodules were cold and this was attributed to lack of iodine affecting the thyroid. The presence of such hot nodules despite the small number suggests an increased autonomous function of these nodules causing hyperthyroidism. The radio isotopes uptake studies could not be completed on all the patients with nodules because of the shortage of the supply of radio isotopes by the hospital and faulty scintillating camera.

The presence of cold nodules is used to assign a probability of malignant disease on the basis of functional status of the thyroid gland. The risk of malignancy is estimated at 16% of the cold nodules, 10.5% of warm nodules and 5.5% of hot nodules.

In this study, Graves' disease was diagnosed on the basis of hyperthyroidism, diffuse goitre with ophthalmopathy or acropathy. Using this criteria, Graves' disease was diagnosed in 66.6% of all patients with hyperthyroidism. This is less than 88.1% found by Kalk et al in a ten year retrospective study of hyperthyroid patients. It was not possible to determine antithyroid antibodies which would have been more sensitive in determining patients with Graves' disease and those who were not. This
could explain why the prevalence of Graves' disease being much less than worldwide prevalence of 90% among hyperthyroid patients. Previous studies done locally had not assessed the contribution of Graves' disease as a cause of hyperthyroidism but instead had described all of it as toxic goitre. The contribution of dietary iodine supplement in recent years as a precipitant of hyperthyroidism is a possibility but was not assessed in this study. It is possible that this prevalence of Graves' disease is an underestimation because Graves' disease was found in patients with pre-existing nodules. This could be confirmed with new assays of TRab which have a high sensitivity of up to 99%.

The two patients with hypothyroidism were male and female. In both patients, the symptoms were very mild including sweaty cold palms, general malaise, grade 1a goitres and both had normal T3 and T4 but very high TSH. The normal levels of T3 and T4 are consistent with previous evidence that in iodine deficiency, preferential T3 synthesis can compensate for reduced iodine hence this could explain an unusual occurrence of hypothyroidism in iodine deficiency population.

Two of the sixty-six patients seen had congenital hyperthyroidism. This was of a myxoedematous type and they had no goitres. This shows that congenital hypothyroidism is not uncommon as in previous studies where in a retrospective study of 923 patients with thyroid disease over a period of 5 years, there was no patient seen with congenital hypothyroidism. The causes of congenital hypothyroidism were not ascertained even though dysgenesis is the commonest cause but iodine deficiency can also cause congenital hypothyroidism in iodine deficient areas.
Strength of the Study

1. In screening for thyroid disorders, a combination of clinical history examination, repeat measurements and additional testing including thyrotropin-releasing hormone test are a reference method for assessing thyroid dysfunction. This is close to what was used in assessing thyroid function of the study patients.

2. The Immunometric ("sensitive") TSH (sTSH) assays detect low as well as high TSH levels and have become the standard for detecting hyperthyroidism or hypothyroidism.

Limitations

1. Failure to do FNAC and radio isotopes studies on nodular goitres limited the scope of the diagnosis of thyroid disorders in this study.

2. Because of the limited study period, the new study patients were few compared to the old patients in the clinic. Since the analysis did not separate the two groups, old patients who were on treatment could have affected the frequency of signs and symptoms.

Conclusions

1. There is a prevalence of 48% of thyroid dysfunction disorders among new patients with thyroid disorders presenting to Mulago Hospital thyroid clinic.

2. The commonest cause of hyperthyroidism among hyperthyroid patients was Graves' disease with a prevalence of 56.6%.
3. Using sensitive serum TSH assays (sTSH) it was possible to detect as many as 97\% of all the patients with thyroid function disorders.

4. Congenital hypothyroidism was not uncommon among patients studied and its relationship with iodine deficiency should be looked for.

Recommendation

1. More studies are necessary to determine the amount of iodine intake and its role as a cause of hyperthyroidism.

2. With minimum resources serum sTSH assays alone can be used in addition to clinical history to screen patients for thyroid function disorders.
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APPENDIX I

QUESTIONNAIRE FOR CLINICAL PROFILE AND THYROID FUNCTION IN PATIENTS ATTENDING NEW MULAGO HOSPITAL THYROID CLINIC.

A IDENTIFICATION

Study No..........................
Thyroid clinic No...................
Age ....................................
Sex 1. Male 2. Female
Occupation.............................

B PRESENTING COMPLAINTS

2. Duration of goitre
3. Painful goitre 1= YES ( ) 2= NO
4. Dyspnoea 1=YES ( ) 2= NO
5. Dysphagia 1=YES ( ) 2= NO
6. Hoarseness 1= YES ( ) 2= NO
7. Palpitations 1. Present 2. Absent
8. Weight Loss 1. Present 2. Absent
9. Weight gain 1. Present 2. Absent
10. Sweating 1. Present 2. Absent
11. Temperature Intolerance 1. Present 2. Absent
3. Antithyroid drugs 4. Radioiodine
4. Radioiodine 5. Iodine 6. Others
15. Other diseases 1. YES 2. No

C CLINICAL FEATURES

1. Goitre size 1. Stage 0 2. Stage 1A 3. Stage 1B
4. Stage 11 5. Stage 111
3. Tenderness (1) Yes 2 No
4. Consistency (1) Soft 2 Hard (3) Firm
5. Nodules (1) None 2 Single (3) Multiple
6. Mobility (1) Yes (2) No
7. Bruit (1) Present (2) Absent
8. Skin texture (1) Normal (2) Coarse and dry (3) Warm and moist
9. Nail changes (1) soft 2 onycholysis (3) finger clubbing (4) Normal
10. Myxoedema (1) Present (2) Absent
11. Lid lag (1) Present (2) Absent
12. Lid retraction (1) Present (2) Absent
13. Exophthalmos (1) Present (2) Absent
14. Pulse bpm
15. B.P (1) Normal (2) Low for age (3) High for age
16. Murmurs (1)Systolic (2) Diastolic (3) Scratch 4 None
17. Pulse rythm (1) regular 2 irregular
18. Heart sounds 1 Normal 2 Loud 3 Distant
19. Muscle wasting 1 Present 2 Absent
20. Proximal muscle weakness 1 Present 2 Absent

**D THYROID HORMONAL ASSAYS**
1. Serum T₃
2. Serum T₄
3. TSH

**E THYROID ULTRASOUND**
3. Multiple cystic nodules 4 Multiple solid nodules
5. Diffuse goitre 6 No goitre

**F THORAX INLET X-RAY**
1. Normal 2. Tracheal compression
3. Tracheal deviation
G. FNAC RESULTS:
1. Benign  
2. Suspicious for malignancy  
3. Malignancy  
4. Inadequate

H. RADIOISOTOPE SCAN
1. Hot nodules  
2. Cold nodule  
3. Mixed nodules  
4. Diffuse increased uptake  
5. Diffuse poor uptake  
6. Solitary hot nodules  
7. Solitary/multiple cold nodule

I. DIAGNOSIS
1. Type of Goitre
   1. Diffuse toxic goitre  
   2. Diffuse non toxic goitre  
   3. Nodular non toxic goitre  
   4. Non toxic MNG  
   5. Toxic Nodular goitre  
   6. Carcinoma of thyroid

2. Thyroid function
   1. Hyperthyroid  
   2. Hypothyroid  
   3. Euthyroid  
   4. Subclinical hypothyroid  
   5. Subclinical hyperthroid

3. Others
   1. Painful thyroiditis  
   2. Painless thyroiditis
APPENDIX II

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Clinical profile and thyroid function of patients attending New Mulago Hospital thyroid clinic

A. Purpose & Background:
Dr. Mutakirwa Bosco of the Dept. of Medicine Mulago Hospital is doing a study to describe thyroid function & clinical features among patients with thyroid disorders. The description will help clinicians to know the prevalence of thyroid function disorders and common thyroid diseases. This may help in making a diagnosis contributing to better management of patients with thyroid diseases in future.

B. Procedures:
1. I will answer some questions about the state of my health.
2. A physical examination will be done on me.
3. Blood will be collected from me to perform TFT’s and will undergo ultrasound examination of my neck, fine needle aspiration of my neck and thoracic inlet x-ray irradiation

C. Risks and discomfort
The procedure of drawing blood will cause me some discomfort and may cause me localised infection or fainting.

1. The procedure is harmless and is usually done in hospital.
2. Participation in research may involve some loss of privacy. Records will be as confidential as possible. No individual identities will be used in any reports or publications resulting from this study.

D. Benefits: I will benefit from the study by having my disease reassessed and my laboratory examination done at no cost. This will help my doctors to treat my ailment accordingly.

Consent
Dr. Mutakirwa has explained this study to me. My participation is voluntary. No consequences whatsoever will result if I refuse to participate and I can withdraw from the study any time. I will not be denied medical care. I agree to participate in the study.

Date.............................................. Thumb print / Signature of participant(Name)

Date.............................................. Signature of person obtaining consent

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APPENDIX III:

WORLD HEALTH ORGANISATION GOITRE GRADING SYSTEM:

Stage 0: No goitre
Stage 1A: Goitre detectable only by palpation and not visible even when the neck is fully extended.
Stage 1B: Goitre palpable but visible only when the neck is fully extended.
Stage 11: Goitre visible with the neck in normal position. Palpation is not needed for diagnosis.
Stage 111: Very large goitre that can be recognised at a consideration.
Ultrasonic hTSH II test

The synthesis and secretion of hTSH is stimulated by thyrotropin releasing hormone (TRH), the hypothalamic tripeptide, in response to low levels of circulating thyroid hormones. Elevated levels of T4 and T3 suppress the production of hTSH via a classic negative feedback mechanism. Recent evidence also indicates that somatostatin and dopamine exert inhibitory control over hTSH release, suggesting that the hypothalamic-pituitary-thyroid axis will result in either under-production (hypothyroidism) or overproduction (hyperthyroidism) of T4 and T3.

In cases of primary hypothyroidism, T4 and T3 levels are low and hTSH levels are significantly elevated. In the case of primary dysfunction, either due to intrinsic hypothalamic or pituitary disease, central hypothyroidism, normal or marginally elevated basal TSH levels are often seen despite significant reduction in T4 and/or T3 levels. These inappropriate TSH values are due to a reduction in TSH bioactivity which is frequently observed in such cases. Routine TRH stimulation is advised to confirm the diagnosis in such cases. Secondary hypothyroidism typically results in an impaired hTSH response to TRH, while in tertiary hypothyroidism the hTSH response to TRH may be normal, prolonged or exaggerated. Anomalies do occur, however, which limit the use of TRH response as the sole means of differentiating secondary from tertiary hypothyroidism. Although elevated hTSH levels are nearly always indicative of primary hypothyroidism, some rare clinical situations arise which are the result of a hTSH-secreting pituitary tumor (secondary hypothyroidism). Such patients would display clinical signs of hyperthyroidism.

Primary hyperthyroidism (e.g., Grave's Disease, thyroid adenoma or nodular goiter) is characterized by high levels of thyroid hormones and depressed or undetectable levels of hTSH. The TRH stimulation test has been used to diagnose of hyperthyroidism. Hyperthyroid patients show a supramaximal response to the TRH test. In addition, large doses of glucocorticoids, somatostatin, dopamine and replacement doses of thyroid hormones reduce or totally blunt the hTSH response to TRH.

Earlier assays for serum TSH lacked the sensitivity to be used as a primary test of thyroid function. Sensitive TSH assays now available, with increased ability to clearly distinguish between euthyroid and hyperthyroid populations, are changing thyroid function testing. Analytical sensitivity, as a measure of detecting low concentration accuracy, is being replaced by functional sensitivity. The American Thyroid Association has formally recommended the use of functional sensitivity as the means to quantitate the sensitivity of TSH assays.

In the second generation TSH assays, which discriminate between the hyperthyroid and euthyroid patients exhibit a 20% CV at 0.1 mIU/mL. The sensitivity of the IMx Ultrasonic hTSH II assay meets these criteria see SPECIFIC PERFORMANCE CHARACTERISTICS section in this assay package insert. Other thyroid tests (FT3, FT4, T3 UPTAKE and T4), combined with the ability to accurately measure low levels of hTSH, improve the efficiency of thyroid diagnosis.

BIOLGICAL PRINCIPLES OF THE PROCEDURE

The IMx Ultrasonic hTSH II assay is based on the Microparticle Enzyme Immunoassay (MEIA) technology. The IMx Ultrasonic hTSH II reagents and sample are added to the reaction cell in the following sequence:

1. The probe/electrode assembly delivers the sample and Anti-hTSH Coupled Microparticles to the incubation well of the reaction cell.
2. The hTSH binds to the Anti-hTSH Coupled Microparticles forming an antibody-antigen complex.
3. An aliquot of the reaction mixture containing the antibody-antigen complex bound to the microparticles is transferred to the glass fiber matrix. The microparticles bind irreversibly to the glass fiber matrix.
4. The matrix is washed with Wash Buffer to remove unbound materials.
5. The Anti-hTSH: Alkaline Phosphatase Conjugate is dispensed onto the matrix and binds with the antibody-antigen complex.
6. The matrix is washed to remove unbound materials.
7. The substrate, 4-Methylumbelliferyl Phosphate, is added to the matrix and the fluorescent product is measured by the IMx optical assembly.

For further information, refer to your IMx System Operation Manual, Section 3.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Serum (including serum collected in separator tubes) and plasma (sodium heparin and triprolidine EDTA) specimens may be used with the IMx Ultrasonic hTSH II assay. Follow the manufacturer's processing instructions for serum or plasma collection tubes. Ensure that complete clot formation has taken place prior to centrifugation. Some patient specimens, especially those receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the specimen is centrifuged before a complete clot forms, fibrin may appear as particulate matter. For optimal results, a specimen should be free of particulate matter.

If the assay is performed within 24 hours after collection, the specimen should be stored at 2-8°C. If testing is delayed more than 24 hours, serum or plasma should be separated from the clot or red blood cells and stored frozen at -10°C or colder. Specimens stored frozen at -10°C or colder for 12 months did not show performance differences. Specimens must be mixed thoroughly after thawing, by LOW speed vortexing or by gently inverting, then centrifuged, to ensure consistency in the results. Avoid repeated freezing and thawing.

Specimens showing particulate matter, erythrocytes, or turbidity should be centrifuged before testing.

SAMPLE VOLUME

150 µL, approximately 4 drops from a disposable pipette of specimen is the minimum volume required to perform the assay.

NOTE: To obtain the recommended volume requirements for IMx Ultrasonic hTSH II Calibrators and Controls, hold the bottles vertically and dispense 3 drops into the sample well.

IMx Ultrasonic hTSH II PROCEDURE

The list of required materials and the procedure to perform a Calibration or MODE 1 Assay can be found in your IMx System Operation Manual, Section 3.

The IMx Ultrasonic hTSH II assay requires a minimum volume of 200 µL of MEA #2 Diluent Buffer in the buffer bottle in order to properly process an assay run. Before initiating an IMx Ultrasonic hTSH II assay, visually check that at least 200 µL of MEA #2 Diluent Buffer is present. Do not add diluent buffer to the buffer bottle or switch buffer bottles during an assay run.

DILUTION INFORMATION

Specimens with an hTSH value exceeding 100 mIU/mL (HIGH RANGE assay parameter 48.28) are flagged with the code ">100". To quantitate the concentration result, perform the Manual Dilution procedure.

Manual Dilution

A manual dilution can be performed by making a dilution of the specimen with the IMx Ultrasonic hTSH II Specimen Diluent (No. 48015-50) or the IMx Ultrasonic hTSH II Calibrator A (10 µL hTSH/mL, No. 48015-50) before pipetting the sample into the sample well. A 1:10 dilution (e.g., 100 µL sample and 900 µL Specimen Diluent or Calibrator A) is adequate for most samples. The dilution should be performed so that the diluted test results read greater than the analytical sensitivity of the assay (0.02 mIU/mL). To determine the concentration of hTSH in the specimen, multiply the concentration of the diluted sample by the dilution factor.
Ultrasensitive hTSH II test

<table>
<thead>
<tr>
<th>Bottle</th>
<th>hTSH Concentration (μIU/mL)</th>
<th>Range (μIU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>0.25</td>
<td>0.15 - 0.35</td>
</tr>
<tr>
<td>M</td>
<td>6</td>
<td>4.5 - 7.5</td>
</tr>
<tr>
<td>H</td>
<td>30</td>
<td>21 - 30</td>
</tr>
</tbody>
</table>

Preservative: Sodium Azide.

SPECIMEN DILUENT
IMx Ultra sensitive hTSH II Specimen Diluent (No. 4B01-50)
1 Bottle (10 mL) IMx Ultra sensitive hTSH II Specimen Diluent, TRIS buffer with protein stabilizers, Preservative: Sodium Azide.

WARNINGS AND PRECAUTIONS
For In Vivo Diagnostic Use Only.

The safety and handling precautions and limitations for the reagent pack, calibrators, controls and patient samples are described in your IMx System Operation Manual, Section 6.

The IMx Wash Buffer (Reagent Bottle #1) may cause mild skin or eye irritation. If this solution comes in contact with skin, eyes, or clothing, rinse immediately with water.

Some components of this product contain Sodium Azide. For a specific listing, refer to the REAGENTS section of this package insert. The components containing Sodium Azide are classified per applicable European Economic Community (EEC) Directives as: Harmful (Xn). The following are the appropriate Risk (R) and Safety (S) phrases.

R22 Harmful if swallowed.
R36 Keep away from food, drink and animal feedingstuffs.
S13 Keep out of the reach of children.
S36 Wear suitable protective clothing.
S46 If swallowed, seek medical advice immediately and show this container or label.

STORAGE INSTRUCTIONS
The storage condition for the IMx Ultra sensitive hTSH II Reagent Pack, Calibrators, MODE 1 Calibrator, Controls and Specimen Diluent is 2-8°C. The reagent pack, calibrators, mode 1 calibrator and controls can be used immediately after removing them from the refrigerator. Refrigerate calibrators, mode 1 calibrator, controls and specimen diluent immediately after use. Remove the reagent pack from the analyzer and refrigerate after completion of assay.

Reagents are stable until the expiration date when stored and handled as directed.

INSTRUMENT PROCEDURE
The following instrument software is required to perform the assay:
• IMx System Software Module Version 6.0 or higher.
• IMx Thyroid Assay Module Version 3.0 or higher.

IMx Ultra sensitive hTSH II ASSAY PARAMETERS
The following IMx Ultra sensitive hTSH II assay parameters have been factory set in the Thyroid Assay Module. These parameters can be printed, displayed and edited according to the procedure in your IMx System Operation Manual, Section 6. Ensure that the assay parameters for the IMx Ultra sensitive hTSH II assay in the Assay Module match these parameters or edit accordingly. The assay parameters that cannot be edited are noted with an asterisk (*).

QUALITY CONTROL PROCEDURES
CALIBRATION
Perform an assay calibration with each new lot of IMx Ultra sensitive hTSH II Reagent Pack.

For an IMx Ultra sensitive hTSH II assay Calibration, test all IMx assay-specific calibrator levels in duplicate in the first carousel positions followed by all levels of controls. Controls must be processed as a means of evaluating the calibration curve. The RESULTS section below provides an explanation of the type of curve fit used by the IMx Ultra sensitive hTSH II assay and the assay-specific checks that are used to evaluate the acceptability of the curve.

Once the assay calibration is accepted and stored, all subsequent runs are tested in MODE 1 with the MODE 1 Calibrator in position 1 of the carousel.

Refer to the IMx System Operation Manual, Section 5 for:
• Setting up an assay calibration run
• When recalibration may be necessary
• System and Operator Verification
• MEIA Calibration and MEIA MODE 1 Assay Test Results Tape Explanation

QUALITY CONTROL
The minimum control requirement for an IMx Ultra sensitive hTSH II MODE 1 Assay is one control on each carousel. All levels of controls should be processed at least one time during each 8 hour shift. If the quality control procedures in your laboratory require more frequent use of controls, follow those procedures.

When a new lot of the IMx Ultra sensitive hTSH II Reagent Pack is used, perform an assay calibration followed by all levels of controls. IMx Ultra sensitive hTSH II Control values must be within the range specified in the REAGENTS section of this package insert. If a control value is out of its specified range, the test results are invalid and assay recalibration may be indicated. See the IMx System Operation Manual, Section 10 for a description of troubleshooting procedures.

RESULTS
The IMx Ultra sensitive hTSH II assay utilizes a four parameter logistic curve (4PLC) data reduction method to generate a calibration curve. The following are assay-specific checks used to evaluate a calibration curve:

<table>
<thead>
<tr>
<th>Assay Parameters</th>
<th>Calibration Evaluation (AVGR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIN SPAN F-A</td>
<td>Calibrator F - Calibrator A</td>
</tr>
<tr>
<td>MAX SPAN F-A</td>
<td>Calibrator F - Calibrator A</td>
</tr>
<tr>
<td>MIN CHECK 1</td>
<td>Calibrator A/Calibrator B</td>
</tr>
<tr>
<td>MAX CHECK 1</td>
<td>Calibrator A/Calibrator B</td>
</tr>
<tr>
<td>MIN CHECK 5</td>
<td>Calibrator E/Calibrator F</td>
</tr>
<tr>
<td>MAX CHECK 5</td>
<td>Calibrator E/Calibrator F</td>
</tr>
</tbody>
</table>

The operator must confirm that the following parameters fall within the acceptable ranges:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>RERR (Rate Error)</td>
<td>±20</td>
</tr>
<tr>
<td>RMSE (Root Mean Square Error)</td>
<td>≤0.5</td>
</tr>
</tbody>
</table>

Test results reading less than the analytical sensitivity of the assay (0.02 μIU/mL) should be reported as <0.02 μIU/mL.

FLAGGED RESULTS
For a description of the flags that appear in the NOTE column on the test results tape, refer to your IMx System Operation Manual, Section 5.
ULTRASENSITIVE hTSH II TEST

Suspected hyperthyroidism based on low or undetectable hTSH levels should be confirmed with additional thyroid function testing along with other clinical information. Hypothetically, hTSH levels may appear elevated due to non-specific protein binding. For diagnostic purposes, the hTSH results should be used in conjunction with other data, e.g., symptoms, results of other thyroid tests (e.g., free T4, clinical impressions, etc.).

Performance of this assay has not been established with neonatal specimens.

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain known antibodies (HAMA). Such specimens may show elevated depressed values when tested with assay kits which employ mouse monoclonal antibodies. These specimens should not be used with the INVIA Ultrastar hTSH II assay.

Refer to the Specimen Collection and Preparation for Analysis section in this package insert.

EXPECTED VALUES

Samples from 512 apparently healthy individuals were evaluated with the INVIA Ultrastar hTSH II assay. The normal range calculated from these samples was 0.000 to 0.017 μIU/mL (mean 0.007). A frequency distribution plot of the data follows. It is recommended that each laboratory establish its own normal range based on data for its own population. Values depend upon age, sex, and environmental factors.

hTSH values between 5 and 15 μIU/mL may be associated with normal or minimally depressed serum T3 values. Confirmation of early (subclinical) hypothyroidism in these patients may be obtained either by observing an exaggerated TSH response to TRH or by observing that these hTSH values decline with exogenous thyroid hormone therapy. Values above 15 μIU/mL are usually associated with clinically evident hypothyroidism.

SPECIFIC PERFORMANCE CHARACTERISTICS

PRECISION

Precision was determined as described in the National Committee for Clinical Laboratory Standards (NCCLS) Protocol EP5-D. A freeze-dried, rat thyroid hormone (NIH-TRH) saturated buffer panel was assayed using a single lot of reagents and a single calibration curve, and 2 replicates of each concentration per day for 20 days. Data from this study are summarized in the following tables.