

## Research Article

# Presentation and Management Outcomes of Hyperthyroidism in a Sub-Saharan African Teaching Hospital

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## Abstract

**Background:** Hyperthyroidism is a common endocrine disorder in the sub-region and Graves' disease is the commonest cause. Previous epochs have alluded to a steady rise in its prevalence in the sub-region.

**Method:** This paper is a retrospective review of outcomes in the management of hyperthyroid patients with or without ophthalmic manifestations in a tertiary hospital in a resource-limited environment.

**Results:** A total of 228 hyperthyroid patients managed by the endocrinology, endocrine surgery, nuclear medicine and ophthalmology units over a 7 year period were reviewed. Four-fifth of the patients were females. Graves' disease was the commonest cause. The three standard modalities of care were available during the period of review, while the ophthalmology department was involved in the management of those with thyroid associated ophthalmopathy (TAO). Remission was achieved with Anti-Thyroid Medications (ATD) in two-thirds of patients. Patients subjected to surgical intervention (Total thyroidectomy) had no recurrence, while Radio-Active Iodine (RAI) treatment achieved remission in more than half of patients treated. All patients referred for ophthalmology care were managed successfully with conservative methods.

**Conclusion:** All current therapies have both advantages and disadvantages. The presence of all modalities of care will be most beneficial if a multidisciplinary approach is employed, where the best treatment option for each patient is jointly decided by relevant specialties, rather than the existing practice, where each specialty focuses on an 'ideal' treatment modality within their field. Total thyroidectomy remains a safe treatment modality in Low income countries.

**Keywords:** Hyperthyroidism, Grave's disease, Plummer's disease, radio-active iodine, Ibadan

## Background

Excess production of thyroid hormones results in an accelerated metabolic rate (hyperthyroidism) [1]. 60-80% of hyperthyroidism is attributed to Graves' disease [2] while toxic multinodular goiter (Plummer's disease), solitary toxic adenoma, thyroiditis and medication (Amiodarone) associated hyperthyroidism all account for other cases of hyperthyroidism [3]. The ideal treatment of hyperthyroidism should not only restore normal thyroid function, but should also prevent recurrence and forestall hypothyroidism with or without progression of ophthalmopathy [4]. Antithyroid Drugs (ATD), Radioactive Iodine (RAI) and surgical ablation (total thyroidectomy) are all established and viable options in the management of symptomatic hyperthyroidism. Although initial reports were disappointing; recent research on the autoimmune etiopathogenesis of Graves' disease suggest monoclonal antibody (anti CD 20) as another viable modality of care [4]. Thyroid Associated Ophthalmopathy (TAO) and the ophthalmic manifestations of hyperthyroidism are caused, most often, by an autoimmune related orbital inflammation, which causes deposition of Glycosaminoglycans (GAGs) in the soft tissues of the orbit and

ocular adnexa [5-7]. This may lead to lid lag and (or) lid retraction, chemosis, conjunctival injection and protrusion of the eyeballs (i.e. proptosis or exophthalmos). In extreme cases, connective tissue fibrosis and ocular restriction cause double vision [7,8] and sight loss may occur from optic nerve compression within the orbit [9].

Generally, all current therapies demonstrate variable advantages and disadvantages [10]. A multi-disciplinary approach, where treatment options for patient are decided by relevant specialties, would be the ideal way to treat patients rather than the existing practice, where each specialty focuses on an 'ideal' treatment modality within their field. Documented continental variations exist in High-Income Countries (HIC) as regards the preferred modality of care with a notable preference for I -131 in America while ATD and surgical treatment predominate in Europe and Asia respectively [11]. However, gaps exist in treatment protocols and modalities available in Sub Saharan Africa. This is largely due to the prevalence of uncoordinated healthcare system and poor funding.

This paper reviews the outcomes of management of hyperthyroid patients with or without ophthalmic manifestations in a tertiary hospital in a resource-limited environment while critically evaluating

**Table 1:** Patient characteristics and clinical diagnosis.

|   | Graves's Disease   | Toxic Multinodular Goitre | Solitary Thyroid Adenoma |
|---|--------------------|---------------------------|--------------------------|
| Gender M:F                                | 1:05               | 1:07                      | 1:06                     |
| AGE(year)                                 | 17 – 64 (38 ± 9.4) | 29 – 78 (45.7 ± 16)       | 21-63 (33 ± 11)          |
| (Mean ± SD)                               |                    |                           |                          |
| Ophthalmopathy                            | 43                 | 14                        | 1                        |
| Dermopathy                                | 3                  | -                         | -                        |
| WHO Goitre Size (Grade II and III)        | 83%                | 97%                       | 74%                      |
| <b>Symptoms and signs</b>                 |                    |                           |                          |
| a. Heat Intolerance                       |                    | 192(84%)                  |                          |
| b. Weight loss despite increased appetite |                    | 169 (74%)                 |                          |
| d. Insomnia                               |                    | 123(54%)                  |                          |
| d. Menstrual irregularity                 |                    | 93(41%)                   |                          |
| e. others                                 |                    |                           |                          |
| Eye signs (n=58)                          |                    |                           |                          |
| Lid lag                                   |                    | 22 (38%)                  |                          |
| Lid retraction                            |                    | 43(74.1%)                 |                          |
| Chemosis                                  |                    | 21 (36.2%)                |                          |
| Periorbital swelling                      |                    | 22 (37.9%)                |                          |
| Conjunctival Injection                    |                    | 28 (48.3%)                |                          |

potential for improvement in multidisciplinary care and treatment outcomes.

## Methods

This is a retrospective review of all patients treated for hyperthyroidism at the specialty clinics of the endocrinology, endocrine surgery, nuclear medicine and ophthalmology units at the University College Hospital (UCH), Ibadan, Nigeria from January 2009 to December 2015 (7 year period). All patients with diagnosis of hyperthyroidism using clinical (Wayne's Prognostic Index) and biochemical (serum thyroid function test) criteria, with completed treatment regimens were included. Those who dropped out without completing recommended treatment regimens and those with incomplete treatment records were excluded. Data was extracted from a specialty (thyroid) data base which was generated from patients' clinic folders, histopathology reports, and operative records. The analysed data include bio demographic details, clinical features, diagnosis, histology, post treatment outcomes and complications using SPSS version 17.0. The data was analysed using descriptive analysis for both categorical and continuous variables.

### Endocrine medicine protocol

Sequel to clinical and biochemical confirmation of hyperthyroidism, a full blood count, and liver function test is obtained before commencement of ATD's with counsel given on possible side effects of the ATD. Carbimazole is the preferred ATD except in patients who have drug reactions to carbimazole and in first trimester of pregnancy where propylthiouracil is used. Higher doses are used at initiation of therapy to achieve remission. The thyroid function is checked 4-6 weeks after commencement of therapy and then every 2- 3 months once the patient is euthyroid. As the clinical findings and thyroid function test approach or return to normal, the dose is tapered

to achieve a maintenance dose. In some patients with Graves' disease, after 18-24 months, an attempt at outright discontinuation may be attempted. Definitive treatment depends on etiology, prognosis and patient's preference after discussing all available options of treatment. Occasionally a beta blocker is used as adjunct to offer prompt relief of adrenergic symptoms whilst steroids are used in particular circumstances (e.g. thyroid storm or thyroiditis).

### Nuclear medicine protocol

After a detailed medical review; a full blood count, thyroid function test and thyroid ultrasound are the minimum investigations prior to Technetium-99 (Tc99m) - pertechnetate scintigraphy studies. Following intravenous injection of 3mCi Tc99m- Pertechnetate, planar images are acquired after 30 minutes using a Low Energy All-Purpose (LEAP) collimator. Activities of Iodine-131 for therapy are empirically determined based on thyroid scintigraphy findings. In the absence contraindications to I-131 therapy, the patients are advised on a low iodine diet and instructed to stop ATDs for at least 5 days prior to treatment. I-131 is administered orally as a capsule. Post treatment follow up is scheduled at 1, 3, and 6 months respectively. Treatment response was defined as biochemical euthyroidism or hypothyroidism at six months post RAI therapy. An assessment of treatment failure was made when patients remained biochemically hyperthyroid and symptomatic at 6 months after a single treatment of radioiodine. ATDs are commenced at the pre- treatment dose and the patients planned for a repeat RAI therapy. Once biochemically hypothyroid, thyroxine replacement was commenced and patients were followed up every 4<sup>th</sup> month until euthyroid or sent to the referring physician for follow up.

### Endocrine surgery protocol

Sequel to clinical and biochemical confirmation of euthyroidism.

**Table 2:** Specialty and clinical diagnosis.

| Specialty        | Graves's Disease | Toxic Multinodular Goitre | Solitary Thyroid Adenoma | Others          | N   |
|------------------|------------------|---------------------------|--------------------------|-----------------|-----|
| Medicine         | 66               | 23                        | 0                        | 1 (Thyroiditis) | 90  |
| Surgery          | 37               | 24                        | 9                        | 0               | 70  |
| Nuclear Medicine | 62               | 6                         | 0                        | 0               | 68  |
| Total            | 165              | 53                        | 9                        | 1               | 228 |

Pre-operative tests for surgically fit patients include chest and neck radiographs, serum calcium, and ultrasound guided FNAC (size, morphology and relationship to contiguous structures). Indirect laryngoscopy is requested and the patient is admitted and counseled for a total thyroidectomy as described by Delbridge et al. [12], which entails capsular dissection of both lobes of the thyroid gland and isthmus. The recurrent laryngeal nerves are identified by protocol only at the Berry's ligament area, whilst orthotopically placed parathyroid glands are also identified. Inadvertently removed or devascularised parathyroid glands are minced and re-implanted in the ipsilateral sternocleidomastoid muscle. Endotracheal extubation is immediately after surgery and serum calcium assay is done at 48hrs post operatively or if indicated clinically before then. Discharge is usually at 72hrs after surgery with L-Thyroxine at 1-2mcg per kg commenced at discharge. Outpatient care is scheduled for 2 and 6 weeks to ascertain if any perioperative complication has resolved or not. Complications persisting after six months are classified as permanent.

### Ophthalmology protocol

Ocular examination was performed according to the guidelines provided by the European Group for the study of Graves Ophthalmopathy (EUGOGO) [13] and as described in an earlier publication [14]. Patients presenting with lid retraction, lid lag and dry eye symptoms were offered ocular emollients and advised to wear protective spectacles, provided there was no corneal exposure. Severe proptosis associated with marked chemosis, lagophthalmos, exposure keratopathy or evidence of new onset optic neuropathy attributable to the increased intra-orbital pressure were predetermined as criteria for orbital decompression surgery or orbital radiation therapy. All patients received topical ocular emollients and were advised to wear protective glasses to manage symptoms of dry eye.

## Results

A total of 228 patients were managed by the 4 specialty units in the UCH, Ibadan during the 7 year period and were included in this review. Of these; 90 (39.5%), 68 (29.8%) and 70 (30.7%) patients were seen by Endocrinology, Nuclear medicine and Endocrine surgery respectively. There were 34 males and 198 females (M: F ratio=1: 5.8). The average age was 38±9.4 (range 17-74 years). The duration of symptoms at presentation was < 12 months in 137 (59.1%) and > 12 months in 113 (48.9%). All 58 (25%) evaluated by the ophthalmologist had some mild degree of Thyroid Associated Ophthalmopathy (TAO), and were managed conservatively with topical lubricant and spectacles or protective sunglasses. Lid retraction, lid lag and conjunctival injection were the commonest signs occurring in 23 patients (10%) of cases. Periorbital swelling was less common (4.8%) and chemosis was present in only 9 patients (4%). There was no recorded worsening of ocular symptoms post RAI. Large majority of our patients were non-smokers. Table 1 shows the patient characteristics and clinical

**Table 3:** Outcome of treatment.

| Nuclear Medicine (N=68)                                |                                    |
|--|------------------------------------|
| 1. Remission   | 36 (52.9%)                         |
| 2. Repeat of treatment                                 | 9 (13.2%)                          |
| 3. Failure of treatment                                | 14 (20.6%)                         |
| 4. Complications of treatment                          | -                                  |
| Medical Therapy (N=90)                                 |                                    |
| 1. Remission   | 61 (67.8%)                         |
| 2. Persistent Hyperthyroidism                          | 29 (32.2%)                         |
| 3. Complications of treatment                          | 10 (11.1%)                         |
| 4. Agranulocytosis                                     | 6 (2.6%)                           |
| Surgery (N=70)   |                                    |
| 1. Hypocalcaemia                                       | 3 (4.3%)                           |
| 2. Hematoma  |                                    |
| a. Compressive   | -                                  |
| b. Non-compressive                                     | 1 (1.4%)                           |
| 3. Seroma  | 4 (5.7%)                           |
| 4. Recurrent laryngeal nerve palsy                     |                                    |
| a. Temporary   | -                                  |
| b. Permanent   | -                                  |
| c. Bilateral   | -                                  |
| 5. Voice related issues (voice fatigue and hoarseness) | 9 (3.9%)                           |
| 6. Non suppurative Cellulitis                          | 2 (0.9%)                           |
| 7. Recurrence  |                                    |
| a. Hyperthyroidism                                     | -                                  |
| b. Goitre  | -                                  |
| Ophthalmology (N=58)                                   |                                    |
| 1. Corneal exposure                                    | -                                  |
| 2. Clinical improvement                                | All reported symptomatic           |
| 3. Optic neuropathy                                    | -                                  |
| 4. Vision loss   | No significant physical regression |
| 5. Regression  | -                                  |
| 6. Worsening   | -                                  |

diagnosis. Table 2 shows the specialty and clinical diagnosis while agranulocytosis was the main complication of medical treatment seen in 6 (2.6%) patients. Compliance was ascertained in 145 (63.4%) patients. Table 3 highlights the outcomes of therapy in each specialty.

## Discussion

The treatment modalities for hyperthyroidism include ATD,

RAI and Total thyroidectomy with all exhibiting a similar level of effectiveness as initial treatment [15] albeit with varied rates of relapse [16]. Although our review is multidisciplinary, our data indicates a high and rising prevalence of hyperthyroidism in UCH Ibadan consistent with initial reports [17-20]. Although Graves' disease is reported to have a low prevalence amongst blacks [21], it accounts for majority (73%) of cases of hyperthyroidism seen in our practice. This is similar to figures quoted by other authors [22,23]. Similarly thyroid dermopathy (pretibial myxedema) a rare manifestation of Graves' disease, occurred in only 3.3 % of our patients, akin to the reported occurrence rate of 1-4% reported in literature [24]. While most patients with dermopathy usually have coexisting ophthalmopathy [25] this was not observed in our retrospective review. Toxic multinodular goiter accounted for a quarter of patients seen while solitary toxic adenoma accounted for a very small number. Less common causes of hyperthyroidism such as amiodarone-induced thyrotoxicosis, sub-acute thyroiditis, iodine-induced hyperthyroidisms were not seen.

A diagnosis of hyperthyroidism in our centre is largely based on a combination of clinical, biochemical, radiological and pathological findings with or without evaluation of thyroid antibodies while clinical and ultrasonography findings assist in diagnosing toxic multinodular goiter and solitary toxic adenoma. Our reduced emphasis on the assay of thyroid associated antibodies is borne out of the fact that they are not usually required for diagnosis or monitoring disease related activities [26] as titres may be low or undetectable in patients with Graves' disease due to exclusive intrathyroidal production or assay insensitivity [22]. Some studies also suggest a lower prevalence of thyroid antibodies in blacks [27]. We endeavour to test for thyroid auto antibodies in patients without obvious clinical manifestations suggestive of Graves' disease provided availability and affordability is not an issue. This is because more often than not payment is 'out of pocket' for our patients and emphasis is mainly on performing the basic investigations that must be done to achieve a diagnosis; this sometimes makes our practice less robust. Indeed patients, physician's preference, age, the size of the thyroid gland, spectrum of available local resources, and the severity of hyperthyroidism are determinants involved in the choice of treatment [5,28]. The availability of three treatment modalities enables patients to have options in our hospital, but at times this is biased by the referral patterns. However, inter-specialty referrals and deliberations alter the patients' choice of modality of care in select cases. With an 85% rate of diagnostic accuracy Wayne's Prognostic index is invaluable in low resource settings such as ours [29], where the most readily available and cheapest modality of diagnosis is our clinical acumen. Our low dose titrated ATDs regimen, administered for between 12-18 months achieved a remission rate of 67.8%; which is comparable and slightly better than the 61% reported by Modebe in Enugu, Nigeria [30]. We attribute the higher remission rates to improved compliance by the patients [31]. Other investigators initially advocated a block and replace regimen in order to achieve improved long term remission rates [32,33], long term studies have however showed no improved outcome from high dose therapy [34-36]. Agranulocytosis was an uncommon finding in our study. In these patients, ATD were discontinued and they were subsequently referred for either surgical or RAI therapy as this is a contra-indication to the continued use of ATDs in those who manifest it [37]. Although RAI therapy in

Ibadan is just slightly over a decade [38], its acceptance, challenges, safety and efficacy as a treatment option for hyperthyroidism has been documented [39,40]. Advantages inherent in the half-life of radionuclides for RAI allow for international sourcing; however this accounts for its prohibitive costs in our low income setting [39,40].

From a scientific and operational stand-point in the UCH Ibadan, empirical treatment with 555Mq is convenient in our setting, although successful outcomes have been reported using lower activities [41,42]. We aim to minimize the high retreatment rates associated with use of lower activities of RAI [43]. Thus the logistics and costs associated with re-treatment make initial treatment with higher activities favorable in our setting. Although multiple factors are associated with efficacy, our treatment success rate of 67% is higher in comparison with other studies [44-47].

A third of the patients had toxic nodular goiter consequently making surgery the key modality of care in this subset of patients because of cosmesis (goiter), aero-digestive inlet obstruction and the risk of malignant foci or toxicity. Moreover ATD do not induce remission in patients with toxic nodular goiter, and maintaining a euthyroid state is unlikely following discontinuation of therapy. An increased prevalence and aggression of clinical thyroid cancer in the setting of Graves' disease has been reported in this category of patients as opposed to euthyroid patients who develop thyroid cancer [48]. The prevalence of nodular toxic goiters in our setting may be explained by the two-three fold increase in nodular goiters seen in endemic goiter areas where iodine intake is moderately deficient [49]. The predominance of relatively large thyroid glands (WHO grade II and III) in our environment [50] may also negate the use of RAI in terms of the higher activities of radioactive iodine needed or need for a second treatment with RAI as well as the higher risk for adverse effect [40]. In addition, the important cosmesis requisite in these patients favors surgical ablation ultimately, even though biochemical control might have been achieved by other specialty means (RAI or ATD's). The prevalence of females in the child bearing age group in our review may also play an important role in choice of therapy for females desirous of pregnancy within 12 months because of the instruction and need to avoid pregnancy until 6 months after RAI treatment. Surgical options vary; however total thyroidectomy is the preferred in Ibadan with minimal complications [50]. It eliminates the risk of recurrence, whilst ensuring a commensurate low level of post-operative complication and achieves the aim of eliminating any foci of occult malignancy; this makes surgery a compelling component of the armamentarium in deciding which specialty takes the lead in managing these patients in our environment. Majority of patients with TAO have mild ocular symptoms and require only minimal intervention [6]. In this study, Graves' disease bore the commonest ophthalmic manifestation of hyperthyroidism in patients in Ibadan; however, the clinical profile of our patients was significantly different from that reported by Caucasian studies [14]. Practically all our patients had mild ocular disease and no single patient presented with active orbital inflammation or significant ocular motility disorder. It is noteworthy that among both male and female patients in this study, the prevalence of smoking was extremely low. It is therefore possible that the lack of severe TAO may be as a result of low prevalence of smoking in these patients, or may represent an unknown protective effect related to yet undetermined racial or cultural factors. In this

study, all our patients responded well to the systemic treatment of their hyperthyroidism in addition to topical treatment for dry eye symptoms. However, as expected, cosmetic appearance remained unchanged for the few with mild to moderate exophthalmos and periorbital fullness.

**Conclusion:** All the current therapies have both advantages and disadvantages. The presence of all modalities of care is beneficial to patients. Total thyroidectomy remains a safe and definitive treatment modality in low income countries like Nigeria

- What is already known on this topic: The clinic-pathologic profile and outcomes of care of patients with hyperthyroidism

- Graves' disease is the commonest cause of hyperthyroidism

What this study adds:

- Clinic-pathologic profile of patients with hyperthyroidism in Ibadan, Southwestern Nigeria

- Availability of various options of treatment in an interdisciplinary setting in Ibadan, Nigeria

- Outcomes of treatment with surgery, radioactive iodine and antithyroid drugs in a sub-Saharan setting

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