ORIGINAL ARTICLE

Reduced Thyrotropin In Euthyroid Goitrous Patients Suggesting Subclinical Hyperthyroidism.

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Abstract

Background: *Subclinical hyperthyroidism, a biochemical finding of low serum thyrotropin (TSH) with the serum levels of thyroxine(T_4) and triiodothyronine(T_3) within the reference range, could easily be ignored by clinicians, as it, usually, does not manifest with any thyroid specific symptoms. It is of two types: endogenous and exogenous . However, patients with the findings of low TSH, normal T_4 and T_3 develop some abnormalities in the cardiovascular system, such as atrial fibrillation, increase in left ventricular mass and diastolic dysfunction. It is believed that treatment intervention may reduce or halt the progression of the cardiac abnormalities. The main objective of the study was to determine how frequent subclinical hyperthyroidism was occurs and to serve as a reminder to the existence of the disorder.*

Methods: *It was a hospital- based study carried out at the Jos University Teaching Hospital (JUTH). Consecutive clinically euthyroid goitre patients attending the outpatient department of JUTH, were studied for various parameters including TSH, T_4 and T_3. The serum concentrations of T4and T3 were determined by enzyme-linked immunosorbent assay (ELISA) technique. The serum TSH concentration was estimated using a 2nd generation ELISA technique.*

Results: *98 patients participated in the study. Nine patients had non-specific symptoms not referable to the thyroid and found to have high levels of thyroid hormone concentration with depressed TSH and were excluded from further analysis, while 7 had subclinical hyperthyroidism giving a prevalence rate of 7.9% among these clinical euthyroid goitre patients. The subjects with this condition were mainly above 60 years of age and mainly had long -standing goitre.*

Conclusion: *Endogenous subclinical hyperthyroidism was present in 7.9% of these clinically euthyroid goitre patients mainly 60 years and above, with long - standing goitre. This high prevalence rate calls for high index of suspicion as this condition is associated with morbidities that can raise mortality.*

Key words: *Endogenous subclinical hyperthyroidism; clinically euthyroid patients; prevalence rate; cardiac morbidity and mortality.*

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INTRODUCTION

Subclinical hyperthyroidism is a biochemical finding. The hallmark of this disorder is low serum thyrotropin concentration [1,2,3]. Immunoradiometric assays of TSH have a sensitivity of between 80-100%[3,4]. ELISA techniques have an even higher sensitivity. The combination of an undetectable serum thyrotropin concentration as measured by an assay with a threshold of detection that is 0.1mU per litre or less, and a serum triiodothyronine and thyroxine concentrations within the reference range (usually, at the upper limit of the reference range) is known as subclinical hyperthyroidism [5]. The term subclinical Grave's disease is used by some researchers when subclinical hyperthyroidism is accompanied by the presence of stimulating thyrotropin receptor antibodies (TSI) or by a radioactive iodine (RAI) uptake suggestive of Grave's disease [6].

Subclinical hyperthyroidism is of two types: endogenous and exogenous types[6,7]. The endogenous type occurs when the disorder arises from within the body, i.e, it results from the thyroid gland or elsewhere in the body. Endogenous subclinical hyperthyroidism mainly results from longstanding thyroid gland disorder, which is seen more commonly in

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the elderly [6,8,9]. The causes of endogenous subclinical hyperthyroidism include multinodular goitre, silent thyroiditis, pituitary abnormalities (with suppressed free T_4), early hyperthyroidism in transition and partially treated hyperthyroidism[3]. Exogenous subclinical hyperthyroidism is said to be present when patients take thyroxine for whatever reason (particularly replacement therapy). It can also occur when patients take substances that increase thyroid hormone production but not marked enough to manifest clinically. This increase, however, may not be enough to suppress serum thyrotropin to the hyperthyroid range[3]. These substances include radiocontrast administration (e.g, intravenous urographic contrast media, barium swallow and meal), excessive iodine intake and medication that suppress thyrotropin .

Subclinical hyperthyroidism was thought to be associated with no features of thyrotoxicosis, but recently, some researchers have shown that patients with subclinical hyperthyroidism could have non-specific symptoms such as malaise, tachycardia, nervousness or anxiety[10-11]. However, symptoms depend on the state of the disorder [5], and patients with subclinical hyperthyroidism are said to have a 1-3% risk per year of developing overt hyperthyroidism [3,5,10].

The reported prevalence rate of subclinical hyperthyroidism ranges from 1% to 12%, depending on the sensitivity of the TSH assay that is employed [2,3]. TSH assay has improved since the development of monoclonal antibody technology and "two site" assay systems. The two site assays in general use, have evolved into distinct methods known as: first generation assay technique, detecting serum TSH to about 0.1mU/l, second generation detects between 0.05 and 0.08mU/ml, and third generation detects levels [3,11] between 0.01 and 0.03mU/ml.

It has been reported, however, that 25% of patients with euthyroid multinodular goitre show evidence of subclinical hyperthyroidism, and these are likely to develop overt hyperthyroidism, often, of the T_3 variety within a few years [8,9].

Subclinical hyperthyroidism has not been associated with any specific physical sign, but it has been found that patients with this condition, have a high risk for the development of atrial fibrillation [10]. Holter ECG in some of these patients showed a higher prevalence of atrial premature beats but not statistically different from that of control subjects [3]. In a related study, it has also been shown that patients with subclinical hyperthyroidism have an increase in left ventricular mass and diastolic functional impairment. These associated findings in patients with subclinical hyperthyroidism have been found to cause several morbidities that affect the qualities of life, and increase mortality from all causes [6].

Subclinical hyperthyroidism is a disorder whose prognosis is not very clear and since it is a biochemical finding, many clinicians might ignore its significance. However, a study conducted to find the views of thyroid specialists on the management of subclinical hyperthyroidism [12], showed that 66% of them favoured treatment of older women with the condition: patients with subclinical hyperthyroidism from Grave's disease should have antithyroid agents while those with subclinical hyperthyroidism from toxic nodular thyroid disease should have radioactive iodine therapy [1]. To support this point, Biondi et al[6], have found that early treatment of endogenous subclinical hyperthyroidism with antithyroid agents made some cardiac abnormalities to undergo reversibility after restoring the patients' TSH to the normal euthyroid level. They also found a reduction in left ventricular mass after treatment with biosoprolol.

The Jos University Teaching Hospital, venue of study, is located on the Jos Plateau of Nigeria. The Jos Plateau is one of Nigeria's iodine deficient areas with a prevalence of 24% in some parts of the state [13]. The persons with goitre might not know that it is a disease, for some believe it is a sign of beauty. Such patients would naturally, therefore not seek medical attention and the goitre would progress to multinodular goitre which may gradually become toxic, and a stage of subclinical hyperthyroidism may be seen in-between. Therefore, because of the high prevalence of iodine deficient goitre in Plateau State of Nigeria, there is a higher probability of the development of subclinical hyperthyroidism. Goitre patients without symptoms may not know that they have a disease and they will be unwilling to seek medical attention even if they are told that there is a problem. These patients may be unwilling to be investigated for the thyroid disorder, as these are expensive and more so, the thyroid gland is not associated with any form of pain. A study of patients with goitre was undertaken to determine the rarity of this condition. As clinicians may overlook the finding of a low serum thyrotropin in a clinically euthyroid patient, this study will highlight the fact that low serum thyrotropin needs to be monitored and, if possible treated, in goitre patients, as we now know that subclinical hyperthyroidism is associated with morbidities that can

increase mortalities.

MATERIALS AND METHODS

The Jos University Teaching hospital (JUTH), venue of the study, is situated on the Jos Plateau of Nigeria. The Jos Plateau is one of the goitre endemic areas on the West coast of Africa.

Consecutive patients, with clinically euthyroid goitre, aged 16 years and above seen in the outpatient department of JUTH over a period of one year, were evaluated after obtaining their consent. Goitre patients with features of thyrotoxicosis, hypothyroidism, decompensated cirrhosis of the liver, chronic renal failure and heart failure were excluded as these may affect the biochemistry of the thyroid gland by the euthyroid sick syndrome. Patients that met the inclusion criteria were clerked and examined for age, sex, goitre grade and duration of goitre. Weights and heights were also taken for the calculation of body mass index. These patients had blood samples taken to determine the levels of serum thyroid hormones and thyrotropin (TSH). The thyroid hormones were estimated by the Enzyme-linked immunosorbent assay (ELISA) technique. TSH estimation was carried out by second generation ELISA technique. Subclinical hyperthyroidism was diagnosed when T_3 and T_4 were within normal limits but TSH was barely detectable or undetectable i.e. TSH level was below the lowest limit of detection of the assay.Means were compared using the student's t-test. A two tailed test of significance was used, with $P< 0.05$ being considered statistically significant.

RESULTS

In a survey for the prevalence of goitre in JUTH, 124 Patients were found to have goitre out of a hospital population of 3000. Twenty-six (26) excluded from study for various complaints as their results may be influenced by their complaints. Only 98 were clinically euthyroid and participated in the study. Out of the 98 clinically euthyroid patients, nine (9) were biochemically hyperthyroid and were further excluded from analysis. Of the 89 patients that met the inclusion criteria for the study, seven (six females and one male) patients met the criteria for the diagnosis of subclinical hyperthyroidism. This gives a prevalence rate of 7.9%. All subclinically hyperthyroid patients had goirtre for over 10 years and were over 60 years of age except the only male patient who was 34 years old. The biochemically euthyroid patients were younger than those with subclinical hyperthyroidism ($P <0.05$), however there was no difference in the body mass index (BMI) of these patients ($P>0.10$). The characteristics and mean hormone concentration of these patients are summarized on table I.

Table 1: Age and goiter group distribution of the clinically euthyroid patients.

Age Group (years)	Goitre Grade (No with subclinical hyperthyroidism)				Total	%
	1	2	3	4		
<20	0	4	0	0	4	0
21-30	2 (1)	17	1	0	20 (1)	5
31-40	5	16	5(1)	0	26 (1)	3.8
41-50	2	13	10 (1)	1	26 (1)	3.8
51-60	1	12 (1)	6 (3)	3	22 (4)	18.2
Total	10	62	22	4	98	

The table shows that the Subclinically hyperthyroid patients were significantly older than the biochemically euthyroid patients($p<0.05$). The serum TSH of the subclinically hyperthyroid patients was lower than that of the biochemically euthyroid patients.patients though not statistically different ($P<0.10$). The other parameters were similar.

Some serum analytes known to be deranged in overt hyperthyroidism, were also estimated. These were similar in euthyroid and subclinically hyperthyroid patients ($P>0.10$) in all cases.

Patients with subclinical hyperthyroidism had larger goitres than the clinically euthyroid patients. No patient (euthyroid or subclinically hyperthyroid) had atrial fibrillation.

Table II: Characteristics and main hormone concentration of the biochemically euthyroid and subclinically hyperthyroid patients.

Character or Serum analyte	Mean (SD) Biochemically Euthyroid Patients (n = 82)	Subclinically Hyperthyroid patients (n = 7)	t value
Age*(years)	39.77(11.96)	50.14(8.84)	2.2147
BMI (Kg/m^2)	26.85(3.15)	26.16(1.43)	0.5640
T_3(ug/ml) Reference range (1 2.1 ug/ml)	1.95(1.70)	1.29(0.52)	1.0112
T_4 (ug/100ml) Reference range (6.0 12 ug/100ml)	12.10(6.65)	8.16(3.44)	1.5324
TSH (m.I.U./ml)* Reference range (0.5 5.0 mIU/ml)	1.42(1.24)	0.04(0.05)	2.9102

*NB: *statistically significantly different (P<0.05).*

DISCUSSION

Subclinical hyperthyroidism, a biochemical observation, may easily be ignored as it does not have symptoms. Many patients with the condition go on for a long time without untoward sequalae though some workers have shown that a few patients go into overt hyperthyroidism [6,7]. Atrial fibrillation is a frequent accompaniment of subclinical hyperthyroidism. This arrhythmia is quite dreaded because of the risk of embolism and cerebrovascular events [3,7,10]. There was no patient in this study with atrial fibrillation probably because of the small number.

The main finding of the study was that endogenous subclinical hyperthyroidism was present in 7.9% of the study subjects. There was also no patient with atrial fibrillation .

The prevalence of 7.9% in this study is similar to findings in other studies [3,6] where the prevalence rates of upto 12% were found. The patients with subclinical hyperthyroidism in the study were all above 60 years of age except the only male who was 34 years old. It also occurred in patients with bigger goitres. The finding of subclinical hyperthyroidism in older patients with bigger goitres may be due to the fact that above the age of 60 years, simple goitre, which should have been longstanding at this age in this part of Nigeria, becomes multinodular with increasing amount of autonomous tissue leading to subclinical hyperthyroidism. In studies of subjects over 60 years of age, prevalence was even higher [7,11] and the risk of atrial fibrillation also higher. The lifespan of an average Nigerian may not permit the study of subjects over 60 years of age as these are few. The serum T_4 and T_3 were statistically similar in both groups of patients. It suggests that the levels of these hormones are similar in subclinical hyperthyroidism as compared to clinically euthyroid patients, and their levels may not contribute per se to the diagnosis. The TSH was higher in biochemically euthyroid patients and barely measurable in subclinically hyperthyroid patients. Hence, it is the hormone of diagnostic importance in subclinical thyroid disease. All the serum analytes were similar in these patients. These

findings suggest that there are no changes in serum analytes associated with subclinical hyperthyroidism.

CONCLUSION

The prevalence of subclinical hyperthyroidism is 7.9% among subjects with goitre in the Jos Plateau of Nigeria, a goitre endemic area. Subclinical hyperthyroidism was found mainly among patients who were 60 years and over, with longstanding goitre of over 10 years. TSH the hormone of diagnostic importance was lower in subclinical hyperthyroid than in euthyroid patients with goitre. Patients with subclinical hyperthyroidism had bigger goitres.

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