Original Article

Spectrum of Thyroid Dysfunction among Patients Evaluated by Thyroid Function Tests at a Tertiary Clinical Laboratory in Calabar, Nigeria

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Abstract

Background: Thyroid dysfunction is one of the common abnormalities encountered in contemporary clinical endocrinology practice. There is a fairly wide spectrum of thyroid dysfunction which can be identified by patterns of thyroid function test results. Whereas overt hypothyroidism or hyperthyroidism are clinically manifest and can be distinguished by the pattern of changes in serum T_4, T_3 and TSH levels, subclinical thyroid dysfunctions are essentially laboratory-based diagnoses. **Objective:** To describe the spectrum (pattern and prevalence) of thyroid dysfunction among patients evaluated by thyroid function tests at a tertiary clinical laboratory. **Method:** The study was a retrospective study that was carried out by retrieving and reviewing archived thyroid function tests results stored in an electronic database of a fully-automated tertiary clinical laboratory. **Results:** Among the results, 68.8% indicated euthyriodism while thyroid dysfunction occurred in 31.2% of cases. The spectrum of thyroid dysfunction included: primary hyperthyroidism (13.7%), subclinical hypothyroidism (6.3%), primary hypothyroidism (4.9%), subclinical hyperthyroidism (4.1%), euthyriod sick syndrome (1.5%) and euthyriod hyperthyroxinaemia (0.3%). Primary and subclinical hyperthyroidism were more common in females while primary and subclinical hypothyroidism were more common in males. **Conclusion:** Thyroid dysfunction is a fairly common endocrine abnormality in our contemporary clinical practice and it occurs in a wide range of spectrum. Primary hyperthyroidism is the most common form of thyroid dysfunction in our environment with women of child-bearing age being the mostly affected.

Keywords: Thyroid function; Thyroid function tests; Thyroid dysfunction

Introduction

Thyroid dysfunction (TD) is one of the common endocrine abnormalities encountered in contemporary clinical endocrinology practice.[1,2] Clinicians commonly request for the laboratory assessment of thyroid function based on the suspicion of thyroid disease in patients with overt or mild clinical features that pertain to thyroid function. Some of the results obtained from the laboratory investigations may be suggestive of clear-cut TD which may be either overt hypothyroidism or hyperthyroidism.[3,4] However, the spectrum of TD based on the pattern of measured thyroid hormones may vary.

While a good number of disorders of thyroid function manifest with clear-cut signs and symptoms, several of them may not be clinically obvious with regard to their presenting symptoms and demonstrable clinical signs. These categories of TD have been referred to as subclinical thyroid dysfunctions.[5,6] Subclinical TD includes both subclinical hypothyroidism and subclinical hyperthyroidism. In both conditions, the measured serum level of both thyroxine (T_4) and triodothyronine (T_3) remain within health-associated reference limits while serum thyroid stimulating hormone (TSH) concentration is mildly elevated or suppressed respectively.[7,8]

Whereas overt hypothyroidism or hyperthyroidism are clinically manifest and can be distinguished by the pattern of changes in serum T_4, T_3 and TSH levels, subclinical thyroid dysfunctions are essentially laboratory-based diagnoses.[9] This stems from the fact that in most cases, symptoms of subclinical hypothyroidism and subclinical hyperthyroidism are vague and may not be readily distinguished from other commonplace constitutional symptoms. Thus, the clinical laboratory plays a significant role in establishing the diagnosis of overt thyroid dysfunction, and more especially those of subclinical thyroid dysfunction.[10,11] In addition to overt and subclinical hypothyroidism or hyperthyroidism, other conditions that may be diagnosed by measurement of serum TSH, T_3 and T_4 include: euthyroid sick syndrome, euthyroid hyperthyroxinaemia, and euthyroid hypothyroxinaemia.[12-14]

Cross river state of Nigeria based on her geographical location, encompasses regions of environmental and nutritional iodine

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deficiency and sufficiency. [15,16] While the northern region of the state belongs to the mountainous belt with poor soil and food iodine content, the southern region is close to the sea with the potential of environmental iodine sufficiency. Both clinical and epidemiological studies have shown that endemic goiter and its sequalae such as toxic multinodular goiter tend to be more prevalent among individuals living in areas with environmental iodine deficiency especially the women folk. [17-19] In contrast, subclinical hypothyroidism is fairly more frequent in areas of environmental iodine sufficiency. [20]

Based on the above, it can be deduced that TD is a fairly common endocrine disorder in this part of Nigeria. This has prompted the quest to review laboratory test results of thyroid function test at a tertiary clinical laboratory situated in Calabar Municipality of Cross river state. In this laboratory, the assessment of thyroid function is carried out by measurement of serum free or total T_3 and T_4 as well as serum TSH concentration, all measured using the highly sensitive immuno-chemiluminescent assays. Submitted patients samples are usually processed and analyzed the same day of receiving the sample without preanalytical preservation. Patients' results were electronically archived in a retrievable database for subsequent reference if the need arises.

The aim of this study was to review the pattern, frequency, age- and gender-distribution of TD using laboratory thyroid function test results retrieved from the electronically archived database of a tertiary clinical laboratory in Calabar, Nigeria.

Materials and Methods

Study location, design and subject selection

The study was carried out at Asiukpo diagnostic and medical centre, Calabar, Cross river state, Nigeria. The centre has a tertiary clinical laboratory that undertakes both routine and specialized biochemical and endocrinological tests, including thyroid function tests. The design of the study was retrospective. It involved the retrieval and review of archived patient's thyroid function test results from an electronically-stored database. The study protocol was approved by the Ethical Research and Review Committee of the institution.

The patients' thyroid function test results were selected for the study based on the inclusion and exclusion criteria. The following categories of patients' results were included in the study viz: (1) all previously performed thyroid function tests results carried out between 1st of January, 2014 to 30th of June, 2015, (2) thyroid function test results of patients between the ages of one day to 79 years. The exclusion criteria included: (1) patients with recorded history of anti-thyroid therapy or thyroid hormone replacement therapy, (2) patients with incomplete thyroid function test profile.

Sampling and data collection

Purposive sampling procedure was used for this study. This involved the enrollment of patients that underwent thyroid function testing between 1st January, 2014 and 30th June, 2015 at the tertiary clinical laboratory.

The sample size for the study consisted of the total number of thyroid function test results of patients that fulfilled the selection criteria. Only thyroid function test results within the period under review were selected. A proforma was designed for collection of data with respect to age and gender of the patients. The thyroid function test results consisting of either serum total thyroxine (TT_4) or free thyroxine (FT_3), total triodothyronine (TT_3) or free tridothyronine (FT_3), and thyroid-stimulating hormone (TSH) values were retrieved from the archived database.

Assay methodology for thyroid hormones profile

Serum samples of patients were tested within 1-hour of sample collection using automated immunoassay analyzer. The tests were performed using highly sensitive chemilumnescent immunoassays (CLIA). For all the parameters i.e., TT_3, FT_3, TT_4, FT_4, and TSH, both low and high quality control sera were ran together with each batch of patient samples after instrument calibration.

The reference values for the various thyroid function test parameters are given in brackets as follows: TT_3 (0.79-1.58 ng/ml), FT_3 (2.1 – 3.8 pg/ml), TT_4 (4.9-11.0 ng/ml), FT_4 (0.82-1.6 ng/dl) and TSH (0.38-4.31 mIU/L).

Definition and classification of categories of thyroid dysfunction

The categories of TD were classified based on the reference intervals for the hormones and pattern of derangement in the thyroid hormones profile. The abnormal thyroid function tests result was classified into any of the following:

- Subclinical hypothyroidism: Normal TT_3 or FT_3 and TT_4 or FT_4 with elevated serum TSH.
- Primary (overt) hypothyroidism: Suppressed serum TT_3 or FT_3 and TT_4 or FT_4 with elevated serum TSH.
- Secondary hypothyroidism: Reduced serum concentrations (below lower reference limits) of TT_3 or FT_3, TT_4 or FT_4 and TSH.
- Subclinical hyperthyroidism: Normal TT_3 or FT_3 and TT_4 or FT_4 with suppressed serum TSH.
- Primary (overt) hyperthyroidism: Elevated serum TT_3 or FT_3 and TT_4 or FT_4 with suppressed serum TSH.
- Secondary hyperthyroidism: Elevated serum TT_3 or FT_3 and TT_4 or FT_4 and TSH.
- Euthyroid hyperthyroxinaemia: Isolated elevation of FT_4 or TT_4 in the presence of TSH, FT_3 and TT_3 within reference limits.
- Euthyroid sick syndrome: Low TT_3 or FT_3 in the presence of normal TSH and FT_4 levels.

Statistical analysis

Data were analyzed to find out the frequencies of various categories of thyroid dysfunction. Data were classified into

subgroups according to age and gender so as to determine age-and gender-associated frequency of thyroid dysfunctions. The relative frequencies and ratios of each category of TD were determined. Data were analyzed using SPSS version 16 statistical package. Frequency bar charts and tables were prepared using Microsoft excel software programme. A p-value of <0.05 was considered statistically significant.

Results

This study was carried out by reviewing thyroid function test results performed between January 2014 and December 2015 (2 years) at the clinical laboratory unit of Asiukpo Medical and Diagnostic Centre located in Calabar, South-south Nigeria. Within the period under review, a total of 441 thyroid function test results were retrieved. Out of this, only 388 (88.0%) results were selected in line with the inclusion and exclusion criteria.

Table 1 shows the general summary of the thyroid function test results and the percentage frequencies of various forms of thyroid function status. Among the results, 68.8% indicated euthyroidism, while TD occurred in 31.2% of cases. The spectrum of TD included: primary hyperthyroidism (13.7%), subclinical hypothyroidism (6.3%), primary hypothyroidism (4.9%), subclincal hyperthyroidism (4.1%), euthyroid sick syndrome (1.5%) and euthyroid hyperthyroxinaemia (0.3%). The study showed that primary hyperthyroidism was the commonest form of TD with a prevalence of 13.7%.

Table 1: Spectrum of thyroid diseases among males and females (n=388).

Diagnosis	Males Frequency (%)	Females Frequency (%)	Total Frequency (%)	Chi square test	p-value
Euthyroidism	64 (16.5)	203 (52.3)	267 (68.8)	2.792	0.835
Primary hyperthyroidism	9 (2.3)	44 (11.3)	53 (13.7)		
Primary hypothyroidism	6 (1.5)	13 (3.4)	19 (4.9)		
Subclinical hyperthyroidism	3 (0.8)	13 (3.4)	16 (4.1)		
Subclinical hypothyroidism	6 (1.5)	18 (4.6)	24 (6.3)		
Euthyroid sick syndrome	2 (0.5)	6 (1.5)	8 (2.1)		
Euthyroid hyperthyroxinaemia	0 (0.0)	1 (0.3)	1 (0.3)		
Total	90 (23.2)	298 (76.8)	388 (100.0)		

Figure 1 shows the comparison of thyroid function test results between males and females. Primary hyperthyroidism and subclinical hyperthyroidism occurred more in females than in males while primary and subclinical hypothyroidism were more common in males.

Table 2 represents an age-distribution of the thyroid function test results. Generally, there is a direct relationship between age and the occurrence of TD. Higher prevalence rates of TD were found among patients aged 41 and above (50.0%) followed by those between 16 and 40 years 45.9% and 4.1% among those aged 15 years and below. The difference in the frequency of TD among age groups is statistically significant (p<0.001).

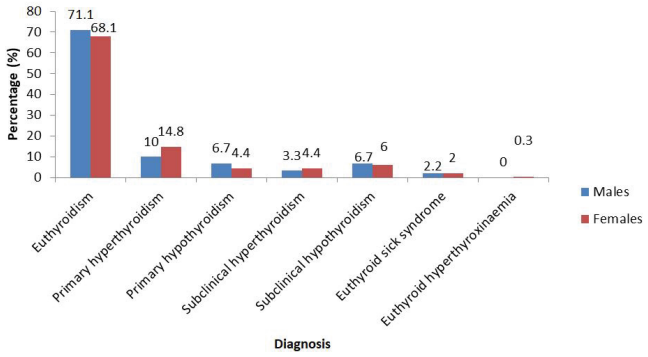

Figure 1: Comparison of subtypes of thyroid diseases between males and females.

Table 2: Spectrum of thyroid diseases in different age groups of patients (n=388).

	Age groups (years)				
Diagnosis	≤15	16-40	≥41	Fisher's Exact	p-value
Euthyroidism	5 (1.3)	124 (32.0)	138 (35.6)	1.237	<0.001*
Primary hyperthyroidism	0 (0.0)	31 (8.0)	22 (5.7)		
Primary hypothyroidism	3 (0.8)	9 (2.3)	7 (1.8)		
Subclinical hyperthyroidism	0 (0.0)	4 (1.0)	12 (3.1)		
Subclinical hypothyroidism	7 (1.8)	7 (1.8)	10 (2.6)		
Euthyroid sick syndrome	1 (0.3)	3 (0.8)	4 (1.0)		
Euthyroid hyperthyroxinaemia	0 (0.0)	0 (0.0)	1 (0.3)		
Total	16 (4.1)	178 (45.9)	194 (50.0)		

Table 3: Spectrum of thyroid diseases in different age groups of males (n=90).

	Age groups (years)				
Diagnosis	≤15	16-40	≥41	Fisher's Exact	p-value
Euthyroidism	1 (1.1)	23 (25.6)	40 (44.4)	33.235	0.09
Primary hyperthyroidism	0 (0.0)	5 (5.6)	4 (4.4)		
Primary hypothyroidism	1 (1.1)	2 (2.2)	3 (3.3)		
Subclinical hyperthyroidism	0 (0.0)	1 (1.1)	2 (2.2)		
Subclinical hypothyroidism	1 (1.1)	3 (3.3)	2 (2.2)		
Euthyroid sick syndrome	1 (1.1)	0 (0.0)	1 (1.1)		
Euthyroid hyperthyroxinaemia	-	-	-		
Total	4 (4.4)	34 (37.8)	52 (57.8)		

Table 3 shows the spectrum of TD in different age groups of males only. Apart from ESS found at the extremes of age groups and subclinical hypothyroidism that peaked in the middle-age group, there is a direct relationship between age and the occurrence of TD among males. However, the difference is not statistically significant (p=0.09).

Table 4 shows the spectrum of TD in different age groups of females. Here, the highest proportion of most TD was found in

Table 4: Spectrum of thyroid diseases in different age groups of females (n=298).

	Age groups (years)				
Diagnosis	**≤ 15**	**16-40**	**≥ 41**	**Fisher's Exact**	**p-value**
Euthyroidism	4 (1.3)	101 (33.9)	98 (32.9)	13.235	<0.001*
Primary hyperthyroidism	0 (0.0)	26 (8.7)	18 (6.0)		
Primary hypothyroidism	2 (0.7)	7 (2.3)	4 (1.3)		
Subclinical hyperthyroidism	0 (0.0)	3 (1.0)	10 (3.4)		
Subclinical hypothyroidism	6 (2.0)	4 (1.3)	8 (2.7)		
Euthyroid sick syndrome	0 (0.0)	3 (1.0)	3 (1.0)		
Euthyroid hyperthyroxinaemia	0 (0.0)	0 (0.0)	1 (0.3)		
Total	12 (4.0)	144 (48.3)	142 (47.7)		

the 16 - 40 years age group compared with the other age groups. The difference by age group among females was statistically significant ($p<0.01$).

Discussion

The spectrum of TD among Nigerian patients was evaluated by thyroid function tests at a clinical laboratory. The result of the study was conducted with 69% that indicated euthyroidism with thyroid dysfunction in 31% cases. Thyroid dysfunction included: primary hyperthyroidism (13.7%), subclinical hypothyroidism (6.3%), primary hypothyroidism (4.9%), subclinical hyperthyroidism (4.1%), euthyroid sick syndrome (1.5%) and euthyroid hyperthyroxinaemia (0.3%) in patients in Calabar, Nigeria. Primary hyperthyroidism was the most common form of thyroid dysfunction in women of child-bearing age. The higher frequency of hypothyroidism may be explained by poor iodine nutrition in areas in Nigeria. [15,16]

The high prevalence of TD seen in this study showed that TD is a fairly common endocrine abnormality in contemporary clinical practice. The prevalence found in this study is similar to those reported by previous studies. Baral and co-workers in their study conducted in eastern Nepal, reported a prevalence of approximately 30.0% while Mahato et al. in another region of Nepal found a prevalence of 36.0%. [21,22] Denge et al. in their study reported a prevalence of 31.3%. [23] Amballi et al. in their study carried out in Abakiliki South east, Nigeria obtained a prevalence of 33.9% with individuals between 36 - 45 years of age being mostly affected. [24] The relatively high prevalence of TD in our study may be explained by the geographical location, influence of age, diet and possibly the presence of environmental goitrogens. [15,16]

Furthermore, the high frequency of TD in this study may be related to high prevalence of chronic non-communicable diseases such as obesity, metabolic syndrome, diabetes mellitus (DM), chronic liver disease due non-alcoholic fatty liver disease (NAFLD) which by WHO projection accounted for 24% of deaths in the year 2015. [25] The above-mentioned chronic disease states are pathogenetically-linked and were recently reported to be associated with TD. [26-28] In Nigeria, the current population-based prevalence of DM is not known but a value of approximately 10% was reported based on guestimate. [29] With an estimated population of about 180 million, approximately 18 million Nigerians suffer from diabetes. Both local and foreign studies have reported the common association between diabetes and TD. [30-32]

Recent studies have shown that TD plays a significant role in the etiopathogenesis of NAFLD including non-alcohol steatohepatitis (NASH) and hepatic fibrosis. [33,34] Essentially both subclinical and overt hypothyroidism have been reported to be associated with NAFLD/NASH. [35] A study by Bano and co-workers observed that hypothyroid subjects had higher risk of NAFLD than their euthyroid counterparts. [36] Furthermore, hypothyroidism was found to be associated with increased risk of hepatic fibrosis among patients with early stages of NAFLD. [36] Significantly, obesity, metabolic syndrome, DM and NAFLD – interconnected dysmetabolic states with strong association with underlying insulin resistance – are linked with TD especially subclinical and overt hypothyroidism. [37,38]

In Nigeria, there is paucity of population-based studies on the epidemiology of NAFLD. However, Onyekwere et al. in their study among patients with type 2 diabetes mellitus (T2DM) reported an overall prevalence of NAFLD to be 8.7% among ungrouped subjects with 9.5% in DM patients alone and 4.5% in non-diabetics. [39] Also, Olusanya and co-workers reported prevalence rates of 16.7% and 1.2% among T2DM patients and non-diabetic controls respectively. [40] The relatively high prevalence of TD in type 2 diabetic Nigerians may thus be connected with high prevalence of NAFLD. Even though the influence of high-fat diet on the pathogenesis of NAFLD has been suggested, [41] this has not been ascertained by local Nigerian studies.

Cross river state of Nigeria, with respect to her geographical location spans through regions of environmental and dietary iodine deficiency to those of iodine sufficiency. [15,16] Both iodine deficiency and iodine sufficiency are known to be associated with various patterns of TD. While iodine deficiency is a well-known cause of TD and goiter, iodine sufficiency has been associated with high incidence of subclinical hypothyroidism. [16-20,42] The northern region of Cross river state belongs to the mountainous belt of east and west African sub-regions that are known for their association with iodine deficiency in soil, food, and water. [15] Both hypothyroidism (due to nutritional iodine deficiency) and toxic nodular or multinodular goiters (with attendant sub-clinical or primary hyperthyroidism) have been reported to occur with greater frequencies in areas of iodine deficiency. [43,44]

The pathophysiology of TD in iodine deficiency states is not far-fetched. Since iodine is essential for biosynthesis of thyroid hormones, insufficient dietary iodine and reduced supply of iodine to the thyroid gland will cause thyroid dyshormogenesis with attendant decreased synthesis, secretion and circulating levels of thyroid hormones. [18,45] This primarily causes hypothyroidism which may be subclinical or overt. Often, iodine deficiency–induced hypothyroidism causes a compensatory

increase in synthesis and secretion of TSH which in turn promotes growth and enlargement of thyroid tissue thereby causing goiter (euthyroid or hypothyroid goitre). Most iodine–deficiency goiters are associated with euthyroidism (euthyroid or simple goiters) at the initial stage. Without adequate iodine supplementation, simple goiters may progress to hypothyroid goiters with prevailing subclinicial or primary hypothyroidism. [46] This scenario is common among women of child-bearing age who are known to have increased demand for iodine and also higher prevalence of simple and hypothyroid goiters.

Our study showed that the highest frequency of TD occurred among women between the ages 16 and 40 years, who due to dietary iodine deficiency and increased iodine requirement during pregnancy and lactation, are prone to simple or hypothyroid goiters. Chronicity of iodine deficiency in patients with hypothyroid goiters causes compensatory increase in synthesis and secretion of TSH with increased stimulation of thyroid tissue growth, size, nodullarity, and function thereby causing nodular or multinodular goiters. Multinodular goitres are initially benign but may become toxic with time causing subclinical or overt hyperthyroidism. [44]

Among the spectrum of TD reported in this study, primary hyperthyroidism is the commonest with a frequency of 13.7% with females being more affected (11.3%) than males (2.3%). This particular finding is similar to reports by previous studies. Amballi et al. in a similar study carried out in Sagamu, Ogun state Nigeria, reported prevalence of 25.5% and 8.4% for hyperthyroidism and hypothyroidism respectively. [24] They further observed that primary hyperthyroidism predominated and occurred mostly among patients between 36 - 45 years of age with females being more affected than males. [24] The preponderance of TD among females was also reported by other Nigerian studies. Ogbera and coworkers in their earlier study made similar observation. [1] Again, in a later report by Salami et al, females were noted to be more affected by TD than their male counterparts. [47] Reasons for the higher frequency of TD in females have been suggested and they include: higher prevalence of autoimmune thyroid disease, pregnancy, postpartum thyroid disease, lactation and nutritional factors. [48]

Our study found a total prevalence of subclinical TD to be 10.4% with subclinical hyperthyroidism being 4.1% and subclinical hypothyroidism being 6.3%. These are at variance to findings reported by Eteudo and colleagues in Abakiliki southeast, Nigeria. [49] In their study, the overall prevalence of subclinical hyperthyroidism and sub-clinical hypothyroidism were 14.3% and 4.4% respectively. [49] Similar to our study, they reported higher frequency of TD among females with a female-to-male ratio of 5.83:1.00.49 The disparity between their study findings and ours may be due to variation in study design and sample size. While their study was cross-sectional in design, this particular study was retrospective.

The higher frequency of subclinical hypothyroidism in our study may be explained in relation to iodine nutrition. Studies have shown that sub-clinical hypothyroidism predominates in areas of iodine sufficiency compared to regions of environmental and dietary iodine deficiency. [7,42] Calabar in Cross river state of Nigeria is located near the sea. Thus, residents are likely to eat more seafoods which are known to be rich in iodine content. In addition, sub-clinical hypothyroidism was observed to occur more in males than in females in our study. This may be related to the relatively high prevalence of the metabolic syndrome as reported by previous studies. [50] Subclinical hypothyroidism has been reported to be a predominant form of TD among patients with the metabolic syndrome. [51] A recent study by Gyawali et al. in India reported an overall prevalence of TD in patient with metabolic syndrome to be 31.8% with sub-clinical hypothyroidism being the predominant form (29.3% of the 31.8%). [52]

Our study reported an overall prevalence of ESS to be 2.1% among the reviewed results. This is relatively low compared to 32.6% and 20.6% found in acute and chronic non-thyroidal illnesses among hospitalized patients. [53] Also a recent study in Nigeria reported a relatively high prevalence of ESS (33.0%) among patients with the metabolic syndrome. [54] The cause of the low prevalence in our study cannot be readily explained. However, the sample size, study design, and the outpatient status of most of the patients involved in our study may be the plausible reasons.

This study has obvious limitations. The first is its retrospective design while the second is the use of purposive sampling technique. In addition, it is an institution-based study carried out within a relatively short time period of 2 years. Large population-based well-designed epidemiological studies with robust sampling technique(s) are needed to establish the epidemiology of TD in the study locality.

Conclusion

Thyroid dysfunction is a fairly common abnormality in our contemporary clinical practice. The spectrum comprises a wide range of disorders including: primary and subclinical hyperthyroidism, primary and subclinical hypothyroidism, euthyroid sick syndrome and euthyroid hyperthyroxinaemia. Primary hyperthyroidism is the most common abnormality and women of child-bearing age were mostly affected. Primary and subclinical hypothyroidism was more common in males.

Conflict of Interest

All authors disclose that there was no conflict of interest.

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