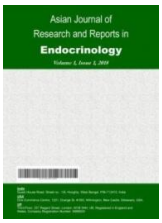

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The Importance of Laboratory Investigation of Thyroid Hormones in Various Thyroid Dysfunctions in Enugu South Eastern Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors NOE and OUO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AMI and HOO managed the analyses of the study. Authors ECE, ICI and MN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Thyroid disorder remains the disease of major public health importance in Nigeria. Clinical diagnosis in thyroid dysfunction is limited; hence diagnosis and management are dependent on accurate laboratory measurements and interpretation of results.
Objective: The present study was designed to evaluate the importance of serum total triiodothyronine (tT_3), total thyroxine (tT_4), Free triiodothyronine (fT_3) and Free thyroxine (fT_4) as reliable indicators to assess thyroid dysfunctions in Enugu Southeastern Nigeria.

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Materials and Methods: The study was conducted at Department of Chemical Pathology (Endocrine unit) University of Nigeria Teaching Hospital (UNTH) Enugu, from 2015 - 2017. It comprised of a total of 1182 participants. 336 patients (110 males, 226 females; age range 20-75 years) with hypothyroidism, 336 patients (100 males, 236 females; age range 20-75 years) with hyperthyroidism and 510 healthy subjects (200 males, 310 females; age range 20-75 years) with detailed medical history. After due consent, chest x-ray was done. Blood samples for serum analysis of tT_3, tT_4, fT_4, fT_3 and thyrotropin (TSH) were collected between 8 to 10 am using Enzyme Linked Immunosorbent Assay (ELISA) method. The Pearson correlation between tT_3, tT_4, fT_3, fT_4 and TSH was determined to identify the valuable indicator for thyroid function besides TSH.

Result: The correlations of tT_3 and fT3 with TSH were statistically significant in healthy population *P* = .003, .015 and r-values were .130 and -.108) respectively. The correlations of fT_3 and fT_4 with TSH were statistically significant in patients with hypothyroidism and (P <.0001) and r-values were -.480 and -.307 respectively. The correlation of tT_3, fT_3 and tT_4 with TSH were statistically significant in patients with hyperthyroidism and (*P*<0001) and r-values were -.459, - .337 and -.313 respectively.

Conclusion: TSH, tT_3 and fT_3 are the indicators of thyroid function in healthy population, TSH fT_3,fT_4 in hypothyroidism. TSH, tT_3 and tT_4 in hyperthyroidism.

Keywords: Laboratory; values; thyroid function; Enugu; Nigeria.

1. INTRODUCTION

Despite the advent of new techniques, highly functional sensitive methods of thyroid testing that have impacted clinical decision for detecting and treating thyroid disorders, morbidity and mortality are still on the increase in Africa, Nigeria inclusive. This continuous increase can be partly attributable to goitrogenous effect on the thyroid as a result of poorly detoxified cassava, a staple food that is commonly eaten as a source of carbohydrate. Also selenium deficiency has been reported to be contributory factor in the occurrence of endemic goiter [1].

Iodine deficiency is a major public health problem throughout Africa and is the commonest cause of thyroid disorder in the continent [2]. Thyroid disorder is commonly encountered in clinical practice and the second most common endocrine disorder in Nigeria. The UNICEF estimates state that 8% of newborns from sub-Saharan Africa including Nigeria are unprotected from learning disabilities resulting from iodine deficiency [3]. Report estimated that a total of 78 patients with thyroid disorderswere seen within a 15-month periodgiven prevalence of 1.6% in southwestern Nigeria. In this report, the estimated prevalence of hyperthyroidism and that of hypothyroidism were 1.3% and 0.1%, respectively [4].Graves disease was recorded in 80% of the subjects. A report of annual incidence of thyrotoxicosis was 8% [5]. In some parts of Nigeria, there is hardly information on the outcome of thyroid disorder and this is largely attributable to the virtual absence of thyroid registries and so underreported.

The value of clinical diagnosis is limited and can be attributed to diverse characteristics of different degree of severity and non-specific signs and symptoms of this disorder. Report has been documented that clinical management of this disorder is largely rooted in expert opinion and personal experience [6]. Considering this scenario, laboratory error is bound to occur in diagnosis with serious consequences. Having known the implications of medical error from the publications of institute of medicine (IOM) in 2000 titled: *To err is Human* [7].Medical error can cause serious harm to patient and national economy because of improper medical intervention [8]. Laboratory medicine has always been a frontier pursing this issue of evaluation. If the analysis of only patients with clearly suggestive signs and symptoms are evaluated, many of the thyroid disorder victims will remain undiagnosed or untreated leading to more morbidity and mortality. Therefore, there is need to evaluate all possible indicators of this disorder to identify such patients so that appropriate treatment can be instituted. This research work explores the best indicator of thyroid function with recent advancement in test methodology.

The thyroid is a butterfly shaped gland located in the front of the neck just above the trachea. The thyroid produces and releases into the circulation at least two potent hormones, total thyroxine (tT_4) and total triiodothyronine (tT_3), which influence basal metabolic processes by enhancing oxygen

consumption in all the tissue of the body. The thyroid hormones also influence linear growth, brain function including intelligence and memory, neural and bone development [9]. Total T_3 and tT_4 are under the influence of anterior pituitary hormone, thyrotropin (TSH) which in turn is regulated by thyrotropin-releasing hormone (TRH) [10]. It is penitent to note that the substrate for tT3 and tT_4 is iodine [11]. Different disorders may be seen due to inappropriate secretion of thyroid hormones eg hypothyroidism (a condition in which TSH concentration is high and tT_3 and tT_4 secretion is suppressed) which may cause non-toxic colloid goiter myxedema, Hashimoto thyroiditis, while hyperthyroidism (a condition in which TSH is suppressed and T3, T4 levels are high) results in toxic goiter, thyrotoxicosis, Graves' disease [12].Thyroid Stimulating hormone (TSH) regulates synthesis and secretion of thyroid hormone through the hypothalamic-pituitary-thyroid axis [13] and is considered the primary indicator to assess thyroid function.

Currently, thyrotropin (TSH), free thyroxine (fT_4), or fT_4 combined with total triiodothyronine (tT_3) is recommended for use as indicators in laboratory testing to assess thyroid function by American Thyroid Association (ATA) [6]. Report elsewhere has been documented that the recommendation was not credible enough because large demographic data was not considered [14]. The report recommended TSH and fT_4 as indicators in healthy population while tT_4 and TSH as a measuring indicator to assess thyroid function using Chinese population. The report noted that fT_4 and fT_3 have indirect measurement with no direct quantitation [14]. Evaluation of these thyroid hormones seem to be critical and urgent in Nigeria. According to the authors of ATA, the value of the existing reference wasbased relatively on limited available evidence and is a guide for future research [6].The present was designed to evaluate the correlation between tT3,tT4,fT3 and$fT_4$with TSH in healthy population and in patient with hypothyroidism and hyperthyroidism to give reliable indicator to assess thyroid function in Enugu southeastern Nigeria.

2. MATERIALS AND METHODS

2.1 Study Population and Design

2.1.1 Subjects

A total of 1182 participants (336) patients with hypothyroidism 336 patients with hyperthyroidism and 510 healthy subjects were enrolled from University of Nigeria Teaching Hospital (UNTH)Enugu from Jan. 2015 to Dec. 2017 as test subject. Three groups were analyzed;

(i) Healthy population; 20-75yrs, (200 males and 310 females); all the subjects were enrolled from hospital staff and staff of College of Medicine of the University presented with no thyroid disease as evaluated through history, blood testing and thyroid ultrasound. (ii) Hyperthyroidism all diagnosed with Graves's disease.20-70yrs; 100 males and 236 females. (iii) Hypothyroidism (all diagnosed with Hashimoto thyroiditis etc. 20-70yrs; 110males and 226 females. All patients with hyperthyroidism or hypothyroidism were outpatient of the endocrinology clinic of the hospital and without complication based on their history, physical examination, screening blood test, x-ray, electro cardiogram.

2.1.2 Exclusion criteria

Subjects on certain medications that can cause thyroid dysfunction like Lithium, amiodarone immunomodulating drugs like interferon alpha,Interleukin-2, tyrosine kinase inhibitor and medications that can interfere with thyroid laboratory measurements eg heparin, furosemide were excluded.

2.1.3 Anthropometric and laboratory blood test

BMI measurements, liver function test, urea, creatinine and fasting blood sugar.

The body weight and height were measured to the nearest 1 kg, 0.1 m respectively using standard protocols. The BMI was calculated as the ratio of the body in kg to height in meter (kg/m^2). The blood pressure was measured and the reading taken in nearest one millimeter of mercury (1 mmHg) using sphygmomanometer.

2.2 Blood Sample Collection

Four milliliter (4mls) of blood sample was collected from each participant. The blood sample was collected between 8-10am by venipuncture and was dispensed into dry plain bottles and allowed to clot, retracted and centrifuged. The serum was separated from the clot immediately and transferred into the well labeled container and store frozen at -20°c until assayed for hormones tT_3, tT_4,fT_3,$fT_4$and TSH.

2.3 Methods

2.3.1 Laboratory analysis of hormones

Determination of total triiodothyronine, total thyroxine, free triiodothyronine, free thyroxine and thyrotropin (tT_3, T_4, fT_4, fT_3 and TSH) were determined using Enzyme linked Immunosorbent Assay (ELISA) method described by [15,16]. Quality control samples which represent the lower, middle and upper ranges of the assay were used for quality control of the result. Results ±SD of the target values were considered acceptable. Only the batches with all the controls being within permissible limit were accepted. The manufacture's reference limits are tT3 (0.6-1.6 ng/ml) tT_4 (2.5-12.5 µg/dl), fT3 (1.4-4.2 ρg/ml), fT4 (0.7-2.2ng/dl) TSH (0.5-4.8 µU/ml).

2.4 Data Analysis

The version 16 of SPSS Package was used in statistical analysis (IBM SPSS 15, Inc. Chicago, IL). The results are presented as mean ± standard deviation (SD). The student independent t-test and analysis of variance (ANOVA) and post hoc analysis were used to assess significant mean differences of each data studied within groups comparison was determined.The Pearson correlation coefficient was used to assess the level of association between two variables using student t-test. P values were accepted to be significant (P<0.0001) and the absolute value of the r was close to 1.

3. RESULTS

3.1 Mean ± SD

Thyroid Hormones tT_3 (ng/ml), tT_4 (µg/dl), fT_3 (pg/ml), fT_4 (ng/dl) TSH (µU/ml), AST (U/L) ALT (U/L), Creatinine (µmmol/L), Urea (mmol/L) SBP (mm/Hg), DBP (mm/Hg) and FBS (mmol/L).

3.1and 3.2. Baseline data of the participants and concentration of Mean ± SD of T3, T4, fT4, fT3 and TSH from the three groups and normal ranges of the parameters measured are presented in Tables 3.1 and 3.2.

Table 3.2: Mean ± SD of tT3, tT_4, fT_3, fT_4 and TSH of studied population.

The post-hoc analysis showed significant increase in the mean serum $tT_4$and tT_3 concentration of hyperthyroidism patient 13.68±5.86 ug/dl and 3.35±2.78 ng/ml respectively compared with the corresponding values in hypothyroidism 3.21±2.53 ug/dl and 0.73±0.25 ng/dl. The result showed significant increase in mean serum of $fT_4$2.17± 1.46 ng/ml in hyperthyroidism compared with 0.42 ± 0.26 ng/ml in hypothyroidism.

The result reported significant increased level of TSH in hypothyroidism 10.82 ± 5.76 µn/ml compared with hyperthyroidism 0.31 ± 0.21 µn/ml and normal1.86 ± 1.28µn/ml (*P*<0.001).

Table 3.1. Baseline data of the participants from the three groups

Parameters	Groups			
	Normal (A) (n = 510)	Hypothyroidism (B) (n = 336)	Hyperthyroidism (C) (n = 336)	Normal range
Age (yr)	40.36 ± 12.39	47.53 ± 9.40	44.22 ± 9.78	
Sex Male/Female	200/310	100/236	110/226	
BMI (kg/m^2)	26 ± 1.9	27 ± 2.1	29.5 ± 1.4	
SBP mm/Hg	132.4±15.2	130±15.1	129.5±17.6	
DBP mmHg	78.6±8.3	73±8.2	72±10.6	
Creatµmol/L	68.1±10.4	62.3±9.5	58.2±12.5	45 – 195
Urea mmol/L	4.6±1.2	6.43±0.8	5.76±0.81	2.5 – 8.0
ALT U/L	7.65±1.5	8.6±2.1	8.9±4.5	3 – 15
AST U/L	5.7±2.5	5.4±3.1	7.5±3.5	5 – 18
FBSmmol/L	4.5±1.0	5.5±0.9	4.6±0.8	3.5 – 5.6
Chest X-ray		Clear		
ECG	No abnormalities			

YR: years; SBP: systolic blood pressure; DBP: diastolic blood pressure; creat: creatine; ALT: alanine aminotransferase; AST: aspartate aminotransferase;FBS: fasting blood sugar. ECG: electrocardiogram;

Table 3.2. Mean± SD of T_3, T_4, fT3, fT4, and TSH of the studied population

Parameters	Groups			
	Normal (A) (n = 510)	Hypothyroidism (B) (n = 336)	Hyperthyroidism (C) (n = 336)	Normal range
T3 (ng/ml)	1.07 ± 0.45	0.73 ± 0.25[a]	3.35 ± 2.78[ab]	0.6 – 1.6
T4 (µg/dl)	8.07 ± 2.75	3.21 ± 2.53[a]	13.68 ± 5.86[ab]	2.5 – 12.5
fT3 (ρg/ml)	4.36 ± 17.17	1.87 ± 1.15	3.38 ± 1.93[a]	1.4 – 4.2
fT4ng/ml)	1.04 ± 0.57	0.42 ± 0.26[a]	2.17 ± 1.46[ab]	0.7 – 2.2
TSH (µU/ml)	1.86 ± 1.28	10.82 ± 5.76[ac]	0.31 ± 0.21	0.5 – 4.8

[a] (P<0.0001) compared to normal; [b] compared to hypothyroidism; [c] compared to hyperthyroidism

Table 3.3: The Pearson Correlation between tT_3, tT_4, fT_3, fT_4 and TSH was determined to identify the valuable indicator for thyroid function besides TSH. The correlation of tT_3, tT_4, fT_3 and fT_4in healthy population with TSH was (P-values = .003, .105,.015, .506, r-values = .130, .072, -108, .029) respectively. The correlation of T3 and fT3 with TSH was maximum in healthy population (P=.003, r=.130) and (P=.015, r=-.108) respectively. The correlation of (fT3, fT4, tT4, and tT3) with TSH was statistically significant in patients with hypothyroidism and r-values were; - .480, -.307, -.248 and -.173respectively. The correlation of tT3, fT3, tT4 and fT4 with TSH was statistically significant in patients with hyperthyroidism and r-values were -.459, -.337, -.313 and -.224 respectively.

4. DISCUSSION

The present study observed that the correlation between tT_3, fT_3 with TSH is found to show a strong correlation in healthy subjects. Although tT_3 is the most potent of thyroid hormone but it is generally agreed that tT_3 is not a true reflection of thyroid status, since it is bound to carrier proteins and not stable, therefore it is rarely measured having been largely superseded by fT_3 [17] fT_3 is believed to be responsible for biological action. Moreover, the level of carrier proteins do alter in many clinical condition such as pregnancy, non-thyroidal illness and medications that alter the hormone. In normal thyroid function, as the concentration of carrier proteins alter, tT_3 and tT_4 change while fT_3 remains constant. Free T_3 correlates more with clinical status [18].Thyroid disease can always be ruled out when the level of TSH is normal. TSH is considered as the most important primary indicator in evaluation of thyroid function. This is attributed to central negative feedback mechanism, but in case of suggestive possible hypothalamic-pituitary disease, estimation of fT_4 is desirable [19,20]. However, in a thyroid disorder free population, high normal thyroid function test could have an effect on human health, such as atrial fibrillation. This agrees with the results of previous researchers [21,22].

Therefore thyroid function testing of healthy individual is necessary. Report of healthy individual >50years old showed that there are progressive changes in hypothalamic-thyroid axis function and these changes will affect the accurate diagnosis of thyroid function. Studies documented that there are various reasons for the changes of thyroid function in thyroid disease free population. The reasons include excessive synthesis of cytokines eg. tumor necrosis factor (TNF) α and interleukin (IL) and these cytokines can reduce the secretion of TSH, T3 and inhibit gene expression of TBG in the liver. The secretion and release of thyroid hormones from the thyroid gland occur at the normal levels in apparently healthy individuals. In the absence of factors affecting the TBG, serum thyroid hormone levels can be maintained within a certain level. Report has been documented that, in populations with normal thyroid function at the baseline, increasing fT_4 levels tend to predict long-term mortality [23]. The present study showed that the correlation between tT_3, FT_3 and TSH is the closest in healthy people. We can easily evaluate thyroid function by measuring tT_3, fT_3 and TSH levels in this study.

The present study reported significantly increased level of TSH in hypothyroidism. This signifies hypometabolic state of the thyroid gland. Most of the patients used in the study were suffering from primary hypothyroidism known as Hashimoto disease, chronic autoimmune thyroiditis in which the thyroid is destroyed by antibodies or lymphocytes that attack the gland, in addition, iodine deficiency and some drugs can interfere with the synthesis or availability of the hormone resulting in secondary hypothyroidism. It has been reported that during prolonged illness, the blood levels of selenium, tT3, tT_4 and TSH may decrease and the conversion of tT_4 to tT_3 slows down thus inducing a hypothyroid

Table 3.3. Correlation analysis of $tT_3tT_4fT_3fT_4$ and TSH of the three groups

Parameters	tT_3(ng/ml)	*P*-Value	r-value	tT_4 (µg/dl)	*P*-value	r-value	fT_3	*P*-value	r-value	fT_4	*P*-value	r-value
Groups Normal population n=510	1.07 ± 0.43	.003**	.130	8.07 ± 2.74	.105	.072	4.36 ± 17.17	.015	-.108*	1.04 ± 0.57	.506	.029
Hypothyroidism n = 336	0.73 ± 0.24	.001	-.173**	3.21 ± 2.53	.0001	-.248**	1.86 ± 1.15	.0001	-.480**	1.04 ± 0.57	.0001	-.307**
Hyperthyroidism n = 336	3.34 ± 2.78	.0001	-.459	13.68 ± 5.56	.0001	-.313	3.38 ± 1.98	.0001	-.337	2.17 ± 1.46	.0001	-.224

state [24]. An individual with high serum TSH value, serum fT_4 should be measured. The finding of a higher serum TSH concentration and a low fT_4 level confirm the diagnosis of primary hypothyroidism in this study, but an individual with high serum TSH concentration and a normal or low normal serum FT_4 level has subclinical hypothyroidism. However, secondary hypothyroidism is unlikely to be detected by a screening based on measurement of TSH [9]. The present study demonstrated that the correlation of fT_3, fT_4 with TSH was closer than the correlation of tT4, tT3 and TSH. It implies that fT_3, fT_4 and TSH are indicators for the diagnosis hypothyroidism.Free T_3 is what actually binds to thyroid receptor. An individual is considered as hypothyroid condition, if she or he has normal tT_4 level but low tT_3 level. Masking of abnormal thyroid function can also occur in both hypothyroidism and hyperthyroidism by alteration in TGB concentration so that normal reference results occur. Free T4 concentration can help in uncovering the patients' actual clinical condition [25].

The role of serum tT3 is limited, because they are generally normal in patients diagnosed with hypothyroidism. This is as a result of increased TSH and functional role generated by the increased conversion of type 2 iodinated thyronine deiodinase to residual thyroid tissue. About 80% of tT3 comes from deiodination of tT4, as tT4 level increases, tT3 should also increase at the same time, but it is not always the case. However a report elsewhere has been documented that in patients diagnosed with hypothyroidism who are treated long-term with levothyroxine (L-T4), serum T3 is usually maintained at a stable level, which suggests that energy metabolism is changed by T4 dependent pathway [26]. Therefore fT3 and fT4 are more reliable than tT3 and tT4 in assessing thyroid function in patient with hypothyroidism because they can uncover the patient clinical state.

Report documented that nonspecific binding of the blood sample and assay reagent affected the measurement of fT_3 and fT_4. [19]. Autoantibodies against T_3, T_4 and TSH have been identified in the sera of patients with autoimmune thyroid disorder as well as non-thyroid disorder leading to anomalous free and total thyroid hormone levels and TSH value but current used methods rarely have this interference [20]. The method of measurement in our study is test system which showed the least square regression equation and correlation coefficient indicates excellent method agreement with the reference. The choice of bottle container for blood collection is important, earlier report showed that anticoagulant heparin can raise serum free T4 concentration by stimulating release of free fatty acid from Triglyceride [9]. This effect was avoided in this study by using plain bottle for sample collection.

Therefore when hypothyroidism is suspected, fT4 is appropriate because tT3 and fT3 have inadequate sensitivity and specificity. The value of fT3 and fT4 are thensensitive in the evaluation of hypothyroidism. We suggest fT3 and fT4 are credible and dependable on Nigerian patients.

The present study demonstrated significantly increased level of tT3, tT4 and fT4 in hyperthyroidism. Majority of patient used in this study were women suffering from Graves' disease, an autoimmune disease characterized by the production of antibodies that activate the TSH receptor, resulting in stimulation of T_4 and T_3 production and enlargement of the thyroid. The findings of a high serum fT_4 level and a low serum TSH concentration confirmed hyperthyroidism in this study.Although, individual with hyperthyroidism have a normal fT_4 and high fT_3 concentrations, such patients have T_3-hyperthyroidism.Total T_3 is more potent than tT_4 which is regarded as a prohormone. The study reported that the correlation of fT_3 with TSH is stronger than the association of tT_4 with TSH. The tT_4 is less accurate due to the large amount of binding proteins that are bound to tT_4 compared to tT_3. However when hyperthyroidism is suspected, a tT4 estimation is appropriate because tT_3 and fT_3 have inadequate sensitivity.

The measurement of tT_4 and tT_3 do not reflect thyroid function very well. A report based on animal (Cat) suffering from hyperthyroidism, over 30% had a normal tT3, while only 10% had a normal tT4 [27,28]. Many clinicians prefer measuring tT4rather than tT3 because its better diagnostic sensitivity. This might be that when production of thyroid hormones begins to increase, this leads to a compensatory decrease of tT4 into tT3[27]. Therefore measurement of tT_3 should be done in conjunction with tT_4 in hyperthyroidism to include T3 hyperthyroidism.

5. CONCLUSION

We recommend tT3, fT3 and TSH as measuring indicators to assess thyroid function in healthy population, fT3,fT4 and TSH as a measuring indicators to assess hypothyroidism and tT3,fT3, tT4 and TSH to assess hyperthyroidism. This is a

guide for further studies.A new national strategic plan for thyroid disease is advocated to include all possible indicators for screening of thyroid function.

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CONSENT

All authors hereby declare that all written informed consent was obtained from all the patients who participated in this study

ETHICAL APPROVAL

All authors hereby declare that all experiment and procedure have been examined and approved by the appropriate board of ethics committee of University Teaching Hospital Enugu, South East Nigeria, and research have therefore been performed in accordance with the standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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