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Free Thyroxine And Free Triidothyronine As An Index For The Assessment Of Thyroid Function In Port Harcourt, Rivers State, Nigeria

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Abstract

A critical part of diagnosing thyroid disorders is the laboratory evaluation performed through blood testing. A reliable and accurate diagnosis is necessary in order to select the proper treatment options for thyroid disorder patients and help to increase workflow and efficiency. This research was carried out because of increased late diagnosis of thyroid disease in patients suffering from various thyroid disorders. The estimation of free thyroxine, fT_4, and free triodothyronine, fT_3 was done and used as an index for the differential assessment of thyroid function. A total number of nine hundred and seven (907) patients were diagnosed of various thyroid dysfunctions from the subjects that attended the various hospitals/clinics in the city of Port Harcourt, Rivers State, Nigeria, between the months of February, 2010 to April, 2013. The method of enzyme linked immuno sorbent assay (ELISA) was used in carrying out the study. Out of the 907 patients, 532 of them, representing 58.65% were females while 375 of the patients representing 41.35% were males. From the result analysis, 55.46% of the patients diagnosed of primary hyperthroidism had elevated serum levels of both total and free T_3, T_4 with low TSH values, while 3.09% of the hyperthyroid cases had normal total T_4 and T_3 but elevated values of fT_4 and fT_3. 0.88% of the patients with hypothyroidism had normal total T_4 and T_3, but with low serum levels of fT_4 and fT_3 and was diagnosed so clinically. Triiodothyronine (T_3) toxicosis with elevated fT_3 and normal fT_4 serum levels were found in 9.81% of the patients. Non thyroidal illness cases had low serum fT_4 in 9.26% of the patients. Two (about 0.22%) of the patients that were diagnosed of TSH Secreting tumours had an elevated serum fT_4 level in addition to high serum TSH levels. This study showed that fT_3 and fT_4 is actually an index in the differential diagnosis of thyroid diseases.

Keywords: Hyperthyroidism, Hypothyroidism, Toxicosis, Non –Thyroidal, Hormone, Thyroxine, Triidothyronine.

1.0 Introduction

Thyroxine (T_4), tri-iodothyronine (T_3) and calcitonin are secreted by the thyroid gland. The T_4 and T_3 are products of the follicular cells and generally influence the rate of all metabolic processes. The hormones are synthesized in the thyroid gland by the iodination and coupling molecules of the amino acid tyrosine, a process that is dependent on an adequate supply of iodide (Crook, 2006). Iodide is actively taken up by the thyroid gland under the control of thyroid stimulating hormone (TSH) via a sodium/iodide symporter. Uptake is blocked by thyiocyanate and perchlorate. The concentration of iodide in the gland is at least 20 times that in plasma and may exceed it by 100 times more (Glinoer, 2004). Secretion of the thyroid hormones is regulated by pituitary thyrotropin (TSH). TSH secretion in turn is controlled through negative feedback by the thyroid hormones. There is a negative log-linear relationship between serum free T_4 and TSH concentrations (Spencer *et al*., 1990).

Most of the plasma T_4 and T_3 is protein bound mainly (70 %) to an α-globulin, thyroxine binding globulin (TBG) and to a lesser extent (15.0 %), transthyretin with about 10-15 % bound to albumin and thyroxine binding pre albumin (TBPA). Crook, in 2001 stated that in keeping with many other hormones; the free unbound fraction is the physiologically active form, which also regulates TSH secretion from the anterior pituitary. This means that very small changes in serum free T_4 concentrations induce very large reciprocal changes in serum TSH

concentrations. As a result, thyroid function is best assessed by measuring serum TSH, assuming steady state conditions and the absence of pituitary or hypothalamic disease (Baloch *et al*., 2003).

Some of the circulating T_4 is de-iodinated by enzymes in peripheral tissues, especially in the liver and kidneys. About 80 % of the plasma T_3 is produced by the removal of an iodine atom from the outer (β) ring, the remaining 20 % is secreted by the thyroid gland. De-iodination of the inner (α) ring produces reverse T_3, which is probably inactive (Braverman *et al*., 2005).

The thyroid hormones generally affect many metabolic processes, increasing oxygen consumption. They bind to specific receptors in cell nuclei and change the expression of certain genes (Shirotani *et al.,* 2003). Thyroid hormones are essential for normal growth, mental development and sexual maturation and also increase the sensitivity of the cardiovascular and central nervous systems to catecholamine's, thereby influencing cardiac output and heart rate (Glinoer, 1997).

Assessment of thyroid hormone secretion can be made by measuring plasma TSH as well as either fT_4 or total T_4 (same as fT_3 or total T_3). Each test has its advantages and disadvantages and many laboratory thyroid assays can now measure fT_4 and fT_3 rather than total hormone concentrations (Helfand and Redfern, 1998). Plasma T_4 is more than 99 % protein bound, therefore, plasma, Total T_4 assays reflect the protein bound rather than the free hormone fraction. Total T_4 reflects fT_4 concentrations unless there are abnormalities of binding proteins. This also is applicable to plasma T_3 or fT_3 concentrations (Tate, and Tasota, 2001) .The thyroid hormones also regulate protein, fat and carbohydrate metabolism, affecting how human cells use energetic compounds. They also stimulate vitamin metabolism and therefore numerous physiological and pathological stimuli influencing thyroid hormone synthesis.

Thyroid function tests are blood tests used to evaluate how effectively the thyroid gland is working. The tests are ordered and indeed interpreted by the physician and it includes thyroid stimulating hormone (TSH) free and total thyroxine (fT_4, T_4) the free and total triiodothyronine (fT_3, T_3) depending on local laboratory policy. The thyroxine binding globulin (TBG) and the T_3 uptake tests are used to diagnose underactive thyroid (hypothyroidism) and over active thyroid (hyperthyroidism), evaluate thyroid gland activity and monitor response to thyroid therapy. This study was undertaken to assess the use fullness of fT_4 and fT_3 in the differential diagnosis of thyroid function.

1.1 Materials and Methods

1.1.1 Study area/population:

This study was carried out in Port Harcourt, Rivers State, South of Nigeria. The subjects consisted of nine hundred and seven (907) patients, male and female diagnosed of various thyroid disorders that attended the different hospitals/clinics in the city of Port Harcourt, Rivers State, Nigeria. The figure breakdown showed a total of three hundred and seventy five (41.35 %) males of different age range and five hundred and thirty two (58.65 %) females also of different age range were studied.

1.1.2 Sample Collection and Preparation:

About 10 ml of venous blood were collected from the patients in the different centres using the standard vein puncture technique and its after obtaining a consent from the patient and the centre management. This was discharged into a plain tube without additives and allowed to clot. The serum from the sample was separated after centrifugation at 3,000 rpm and stored frozen at -20 ^{o}C. Analyses of the samples were done within 7 days of collection.

1.1.3 Assay method

The method of enzyme linked immunosorbent assay (ELISA) was used in the quantitation of the various thyroid hormones. The ELISA test is based on the principle of solid phase enzyme linked immunosorbent techniques, where the antibody to be measured is incubated with specific antigen coupled to a solid phase. (Stowell *et al*., 1991)(Midgeley, 2001.)

1.1.4 Statistical analysis

The percentage tool was used in the analysis of the data.

1.2 Result

Table 1: Free thyroxine and triidothyronine as index for the assessment of thyroid function in Port Harcourt.

Hormone parameter assayed

Type of thyroid disorder	Percentage	No of Patients	TT_3	TT_4	FT_3	FT_4	TSH	TBG
Primary hyperthyroidism	55.46%	503	↑	↑	↑	↑	↓	Normal
Secondary hyperthyroidism	0.88%	8	↑	↑	↑	↑	↑	Normal
Primary hypothyroidism	15.44%	140	↓	↓	↓	↓	↑	Normal
Secondary hypothyroidism	0.22%	2	↓	↓	↓	↓	↓	Normal
T_3 toxicities	9.81%	89	↑	Normal	↑	Normal	↓	Normal
TBG excess	1.21%	11	↑	↑	Normal	↓	Normal	↑
TBG deficiency	0.55%	5	↓	↓	Normal	↑	Normal	↓
Non thyroidal illness	9.26%	84	Normal	Normal	Normal	↓	Normal	Normal
Subclinical hypothyroidism	1.10%	10	Normal	Normal	Normal	Normal	↓	Normal
TSH-Secreting tumour	0.22%	2	Normal	Normal	Normal	↑	↑	Normal
Euthyroid patient with cancer/goiter	1.88%	17	Normal	Normal	Normal	Normal	↑	Normal
*Hyperthyroid	3.09%	28	Normal	Normal	↑	↑	↓	Normal
*Hypothyroid	0.88%	8	Normal	Normal	↓	↓	↑	normal

Legend: ↑: increase,

↓: decrease.

*Hyperthyroid refers to the patient diagnosed of hyperthyroidism but had normal total T_3 and normal total T_4 but with elevated free forms.

*Hypothyroid refers to the percentage of patients diagnosed of hypothyroidism with normal total T_3 and T_4 but with decreased serum free forms.

1.2.1 Discussion

The free thyroxine (fT_4) and free triiodothyronine (fT_3) tests, commonly done simultaneously measure serum levels of fT_4 and fT_3, which is the minute portions of total T_4 and T_3 not bound to thyroxine binding globulin (TBG) and other serum proteins. These unbound hormones are responsible for the thyroids effect on cellular metabolism. Because of disagreement as to whether fT_4 or fT_3 is the better indicator, both are commonly measured in laboratory. The disadvantages of these tests include complex laboratory method, cost and its inaccessibility. The test is very useful in some patients in whom the standard total T_3 and T_4 test fail to produce diagnostic results (Dufour, 2007), particularly when the state of the pituitary or hypothalamic function is required (Kratzsch *et al*., 2005).

The evidence that fT_4 and fT_3 are better indicator for the diagnosis of various thyroid dysfunctions was shown in this study were fT_4 and fT_3 values actually confirmed the patient diagnosis. From the result, 503 patients diagnosed of primary hyperthyroidism had elevated serum levels both in total and free T_4 and T_3 and low TSH

values. While the rest 28 hyperthyroid patients had normal total T_4 and T_3 but elevated values for fT_4 and fT_3. Clinical presentations of the patients, agreed with these laboratory findings.

These were also applicable to the 8 patients diagnosed of hypothyroidism with normal total T_4 and T_3 but low serum levels of fT_4 and fT_3, and were clinically hypothyroid by this study. There were generally fT_4 involvements in the diagnosis of the other thyroid disorders. Eighty nine (89) patients diagnosed of T_3 toxicosis had normal fT_4 serum levels, eighty four (84) patients diagnosed of non-thyroidal illness had a low serum fT_4 levels and two (2) patients diagnosed of TSH secreting tumours had an elevated serum fT_4 levels in addition to high serum TSH values. These were the findings from the thyroid assay done in this locality between the months of February, 2010 and April, 2013.

It's argued in some quarters that the high sensitivity thyroid stimulating hormones (TSH) test is the most sensitive and specific screening test for thyroid disease (Ogedebe, 2007). That TSH levels change exponentially with changes in T_4 and T_3 and are less likely to be elevated or depressed by non-thyroidal illness or drugs. They concluded that the strategy is more cost-effective than a panel approach of TSH + fT_4 and TT_4 or fT_3 and TT_4. Its worthy of note that values of TSH below 0.02 miu/L requires differential diagnosis of primary hyperthyroidism which causes levels to be near undetectable from the low end of the reference range, which is only 0.4 miu/L and that normal TSH levels rules out clinical thyroid disease (Dayan, 2001). This means that low TSH levels might be as a result of primary hyperthyroidism or secondary hypothyroidism caused by the pituitary TSH deficiency. High TSH levels are caused by the pituitary TSH deficiency. High TSH level are caused by hypothyroidism or secondary hyperthyroidism resulting from pituitary adenoma. These situations therefore require (and are normally followed by) measurement of free T_4 and free T_3 to confirm the diagnosis. From the study, a patient with low TSH who has primary hyperthyroidism had an elevated T_3 and also elevated free T_4 or T_3 , a patient with a low serum TSH values caused by pituitary disease had low levels of these hormones.

Conclusion

It can be concluded therefore that measurement of free T_4 and free T_3 is more sensitive and better specific indicator in the diagnosis of thyroid diseases. However, there remain a few situations, according to Dayan (2001), in which the results of TSH, free T_4 and free T_3 assays tend to point in different directions, as well as cases in whom thyroid function test results seem clear cut but are in fact misleading. The challenge lies in applying them to the right individual at the right time.

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Author's biography

Ezeiruake Ferdinand was born on 5th of February 1966 and had a Ph. D degree in clinical biochemistry from the University of Calabar, Nigeria in 2007. He is an associate member of the Medical Laboratory Science Council of Nigeria since 1992 and became a member of the Nigeria Biochemical Society in 1993. Presently he is a Senior Lecturer in the Department of Medical Laboratory Science (chemical pathology unit), College of Health Sciences, Niger Delta University, Bayelsa State, Nigeria.

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