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Original Research Article

Assessment of Glomerular Filtration Rate (GFR) from Cystatin C in Patients with Thyroid Disorders in a Nigerian Tertiary Hospital

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Abstract: ***Background*:** Thyroid disorders (hyperthyroidism and hypothyroidism) have been known to affect renal function although studies regarding this are scanty. The goal of this study is to evaluate renal dysfunction in newly diagnosed untreated patients with hyperthyroidism and hypothyroidism using serum cystatin C. ***Methods:*** A total of 115 patients, 70 females and 45 males age 20 – 55 years with 60 cases of newly diagnosed hyperthyroidism and 55 cases of newly diagnosed hypothyroidism as well as 80 healthy controls (50 females and 30 males) matched for sex and age. Serum levels of thyrotropin (TSH), free tri-iodothyronine (fT3), free tetraiodothyronine (fT4) and cystatin C were measured in all the cases and controls. Serum fT3, fT4 and TSH was analyzed by enzyme linked immunosorbent assay (ELISA) technique using stat – fax- 2100. The serum cystatin C was evaluated using immunoturbidimetric method on TOSOH AIA 360 immuno assay machine. ***Results:*** In this study, serum cystatin C levels were significantly higher in both hyperthyroid and hypothyroid patients compared to controls (1.06 $\pm$ 0.12 vs 1.26 $\pm$ 0.27 vs 0.7 $\pm$ 0.14; P - 0.01). ***Conclusion*:** Renal dysfunction has been observed in patients with untreated thyroid disorders and therefore, there is need to screen all such patients for renal function.

Keywords: Cystatin C, fT3, fT4, TSH and Thyroid disorders.

1. INTRODUCTION

Renal disease particularly chronic kidney disease (CKD) is a global health problem, and therefore early recognition of impaired renal function and prompt intervention can slow down the progression of disease and prevent the development of complications associated with renal disease [1].

The most reliable parameter for evaluating renal function is glomerular filtration rate (GFR), which can be estimated using dependable and accurate methods using clearances of exogenous substances such as paraaminohippuric acid (PAH), iohexol, ^{51}Cr-EDTA, ^{125}I, iothalamate. These methods however, are not routinely used for diagnosis [2].

The endogenous marker of GFR most commonly used in routine laboratory practice is serum creatinine [3]. However, knowing that serum creatinine levels are influenced by factors such as age, sex, race, muscle mass and diet that are non-renal making it insufficient marker of GFR [2].

Equations based on serum creatinine are used commonly in evaluation of glomerular filtration rate [4]. The most commonly used are the Cockcroft-Gault and the modification of diet in renal disease (MDRD) and its

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modified form believed to be more precise in estimation of glomerular filtration rate [3]. Although these equations have improved routine estimations of GFR, none is ideal and unaffected by age, sex, disease and methods used to estimate serum creatinine. Recent researches have suggested that cystatin C, a low molecular weight protein produced endogenously by almost all cells, filtered by the glomerulus and completely reabsorbed by the proximal convoluted tubules, is a dependable parameter in GFR estimation. This parameter have been found superior to serum creatinine in evaluating GFR at the range of 60 – 90ml/min/ 1.73m^2 [4]. It can be used in the predictive equations for GFR evaluation, however, more emphasis should be paid on presence of pathology and appropriate laboratory method. Serum cystatin C is not influenced by non-renal factors such as race, sex, muscle mass and diet as seen with creatinine [2]. It has also been found to be superior to creatinine in GFR estimation, post-kidney transplant patients [5]. Patients with type 2 diabetes mellitus [6], patients on non-steroidal anti-inflammatory drugs (NSAIDS), anti-cancer drugs and chronic liver disease [7].

On the other hand, serum cystatin C is influenced by other non-renal factors, such as treatment with steroids and thyroid disorders [8] that limits its use in certain medical conditions. Interactions between renal and thyroid functions have been established. Thyroid hormones are essential for the growth and development of the kidney, they maintain homeostasis of fluids and electrolytes, and affect glomerular filtration rate, effective renal plasma flow and tubula function [9].

Having in mind the possible effects of thyroid function on serum cystatin C and creatinine levels regardless of renal function, one would want to see whether it is possible to accurately estimate GFR using these markers in patients with impaired thyroid function. The objective of this study is to estimate GFR in patients with thyroid disorders using serum cystatin C.

2. MATERIALS AND METHOD

2.1 Patients

A total of 115 patients, 70 females and 45 males aged 20 – 55 years with 60 cases of newly diagnosed hyperthyroidism and 55 cases of newly diagnosed hypothyroidism as well as 8 healthy controls (50 females and 30 males) matched for sex and age. The recruitment of individuals was conducted at the endocrinology clinic of the University of Maiduguri Teaching Hospital. Euthyroidism was defined as fT3 of 1.4 – 4.2pg/ml, fT4 of 0.8 – 2.0ng/dl and TSH of 0.28 – 0.53 miu/ml [10]. Patient are hypothyroids if their serum levels of fT3 is <1.4pg/ml, fT4 of <0.8ng/dl and TSH of >0.53miu/ml.

Hyperthyroidism is when their serum levels of fT3 is >4.2pg/ml, fT4>2.0ng/dl and TSH < 0.28miu/ml. The reference interval for serum cystatin C is between 0.5 – 1.03mg/L [11], values > 1.0mg/L are consistent with renal dysfunction.

Patients were excluded if they are hypertensive, diabetic, pregnant, liver, kidney and heart disease, previous history of thyroid disease, medications that affect thyroid hormone level were also excluded.

Informed consent was obtained from all participants and the study was approved by the ethical committee of the University of Maiduguri Teaching Hospital.

2.2 Measurements

Measurements of weight, height, body mass index (BMI) and blood pressure were done. Weight was estimated using a weighing scale (OHAUS pioneer PA 413) with subjects putting on light clothes and no shoes. The height was measured by stadiometer and the BMI was estimated by calculation using weight (kg) divided by height (m^2). The blood pressure was measured twice in the sitting position on the left arm using an accuson's sphygmomanometer. About 5ml of whole blood specimens were collected after an overnight fast (8 - 12 hours) from the antecubital vein observing aseptic procedures for measurements of fT3, fT4 and TSH. Serum was separated from the cells using pasteur's pipette and spun at 3,000 revolutions per minutes (rpm) for 10 minutes using swinging bucket centrifuge and store-frozen at -20^{0}c until time of analysis.

fT3, fT4 and TSH levels were estimated using enzyme linked immunosorbent assay (ELISA) kit, Perkins Elmer. The serum cystatin C was evaluated using immunoturbidimetric method employing the ST AIA – PACK CYSTATIN C using TOSOH AIA 360 autoanalyzer Tosoh Bioscience, INC. San Francisco.

3. STATISTICAL ANALYSIS

Statistical analysis was carried out using IBM SPSS statistics for windows, version 25.0 (Released 2011: IBM corp., Armonk, New York United States).

Data were expressed as mean $\pm$ SD. The Paired Student t-test was used to analyze values within the two groups. In between group differences were measured by independent sample test for the different groups. A p-value of <0.05 was deemed significant.

4. RESULT

The mean characteristics of their ages in the cases (hypo – and hyperthyroidism) were 40.10 $\pm$ 4.3 and 41.5 $\pm$ 4.6 while 42.30 $\pm$ 4.8 (p – 0.17) for the controls were statistically insignificant. The BMI mean values for hypothyroidism were 24.1 $\pm$ 4.5, hyperthyroidism of 19.1 $\pm$ 3.1, that of the control was 21.3 $\pm$ 2.4 (p – 0.09) respectively were statistically not significant. The mean systolic blood pressure was 125.3 $\pm$ 1.4 for hypothyroidism, 121 $\pm$ 1.2 for hyperthyroidism and that of the control respectively was 122.3 $\pm$ 2.1 (p – 0.07)

were statistically not significant. Their diastolic blood pressure counterparts mean values were 78.4 ± 2.1 for hypothyroidism and 82.0 ± 3.5 for hyperthyroidism, 73.6 ± 1.4 (p – 0.05) respectively were statistically not significant (table I).

Table I: This shows mean values of age, Body Mass Index and Blood Pressure

S/N	Parameters	Cases		Control	p – Value
		Hypothyroidism	Hyperthyroidism		
1	Age (years)	40.10 + 4.3	41.5 + 4.6	42.3 + 4.8	0.17
2	BMI (kg/m^2)	24.1 + 4.5	19.1 + 3.1	21.3 + 2.4	0.09
3	Systolic Blood Pressure	125.3 + 1.4	121 + 1.2	122.3 + 2.1	0.07
4	Diastolic blood pressure	78.4 + 2.1	82.0 + 3.5	73.6 + 1.4	0.05

$p < .0.05$ is considered significant

There was a significant difference in serum cystatin C level between both hypothyroid patients and controls (1.06 ± 0.12 vs 0.7 ± 0.14; p – 0.01) and hyperthyroid with their control counterparts respectively (1.26 ± 0.27 vs 0.7 ± 0.14; p – 0.01).

Mean values of fT3 for both hypothyroids and hyperthyroids and their control counterparts (1.21 + 0.9, 12.4 ± 9.1 vs 1.9 ± 0.7; p – 0.001) were statistically significant. The mean values of fT4 for both thyroid disorders and their control counterparts (0.06 ± 0.5, 20.6 ± 8.7 vs 1.4 ± 0.3; p – 0.001) were also statistically significant. TSH mean values for hypothyroids, hyperthyroids and controls (2.1 ± 1.2, 0.09 ± 0.04 vs 0.5 ± 1.7; p – 0.03) were statistically significant (Table II).

Table II: Mean values of thyroid hormones and cystatin C

S/N	Parameters	Cases		Control	p – Value
		Hypothyroidism	Hyperthyroidism		
1.	fT3(pg/ml) (Triiodothyronine)	1.21 ± 0.9	12.4 ± 9.1	1.9 ± 0.7	0.001
2.	fT4 (ng/dl) (Tetraiodothyronine)	0.6 ± 0.5	20.6 ± 8.7	1.4 ± 0.3	0.001
3.	TSH (miu/L) (Thyroid Stimulating Hormone)	2.1 ± 1.2	0.09 ± 0.04	0.5 ± 1.7	0.003
4.	Cystatin C (mg/L)	1.06 ± 0.12	1.26 ± 0.27	0.7 ± 0.14	0.01

p<0.05 is considered significant

5. DISCUSSION

Our study results show significantly higher serum cystatin C in thyroid disorders (hypo-and hyperthyroidism) when compared with their control counterparts. This is consistent with a similar study by Velibor *et al*., [12-15].

The increase in serum cystatin C level may be due to increase in production rate as a result of increase metabolic activity and altered metabolic process in hyperthyroidism [14]. Stojanoski *et al*., reported that cystatin C levels in their hyperthyroid patients remain elevated, regardless of increase in glomerular filtration rate (GFR), which may support the theory on the direct effect of thyroid hormones on increase cellular production of cystatin C [16].

Wiesli *et al*., found that even mild changes in the levels of thyroid hormones had significant effect on cystatin C levels [14]. Several other studies have shown that elevated cystatin C levels in hyperthyroid patients decrease after the euthyroid state have been restored with treatment [12, 16].

In our study, the patients with hypothyroidism had statistically higher level of cystatin C compared to their control counterparts, however, lower than their control hyperthyroid counterparts. This is in agreement with published data [13, 15]. The lower values of cystatin C in hypothyroid patients when compared to the hyperthyroids could be due to decrease metabolic activity and decrease cystatin C production due to low levels of thyroid hormones [14]. Studies that followed the effects of thyroid hormone replacement therapy on serum cystatin report that, changes in the level of cystatin C in hypothyroidism are short-lived, rise after restoration of the euthyroid state [16].

6. CONCLUSION/RECOMMENDATION

The results obtained in this study indicate that patients with hypo- and hyperthyroidism are pace disposed to renal disease, therefore the need to regularly screen these patients for renal disease to prevent its complications.

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