

The effect of thyroid hormone levels on different kidney Function tests.

Ali majeed Rasheed , Pro.Dr.Tarik H .Al- Khayat

Abstract- Thyroid dysfunction causes significant changes in kidney function. Both hypothyroidism and hyperthyroidism affect renal blood flow and glomerular filtration rate (GFR). Thirty five patients (16 male, 19 female) with primary hypothyroidism and thirty five patients (16 male, 19 female) with primary hyperthyroidism were enrolled in this study. Serum creatinine and serum urea were determined by using colorimetric method. Serum cystatin C were determined by using enzyme-linked immunosorbent Assay (ELISA).

Estimations of the GFR calculated by clearances [estimated GFR based on creatinine (CKD-EPI equation) and estimated GFR based on cystatin C]. When total thyroxine (tT4) and total triiodothyronine (tT3) are normalized in primary hypothyroid patients, creatinine decreased and creatinine- based eGFR increased significantly. In contrast, cystatin C increased and eGFR based on cystatin C decreased significantly. When total thyroxine (tT4) and total triiodothyronine (tT3) are normalized in hyperthyroid patients, creatinine increased and creatinine-based eGFR decreased significantly. In contrast, cystatin C decreased and cystatin-C based eGFR increased significantly.

Index Terms: primary hypothyroidism, Cystatin C, eGFR by creatinine, eGFR by Cystatin C, primary hyperthyroidism



1 INTRODUCTION:

There is a well-known interaction between thyroid and kidney functions. Thyroid hormones are involved in the growth, development and the physiology of the kidney [1]. Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Disorders of the thyroid and kidney may co-exist with common etiological factors. In addition, treatment strategies of one disease may affect those of the other organ. There are important and clinically relevant interactions between thyroid function and renal function, which are essential for the clinician to optimally manage the patient [2]. Cystatin C, a medium size molecule (13 k Da), is a cysteine proteinase inhibitor. It is synthesized by all nucleated cells with constant production rate, freely filterable through the glomerulus due to its small size, and metabolized by proximal tubular cells [3]. The concentration of serum Cystatin C is mainly determined by glomerular filtration, which makes Cystatin C an endogenous marker of glomerular filtration rate [4]. Hyperthyroidism results in increased RBF and GFR [5]. The effect of thyroid hormones on RBF and GFR occurs at multiple levels. Among the pre-renal factors, thyroid hormones increase the cardiac output by positive chronotropic [6] and inotropic effects [7] as well as a reduction in systemic vascular resistance [8]. In hyperthyroidism, there is increased β -adrenergic activity, accompanied by increased density of β -adrenergic receptors in the renal cortex, resulting in increased stimulation of renin - angiotensin - aldosterone system (RAAS) [9]. The effects of hypothyroidism on the kidney are usually opposite to the effects of hyperthyroidism. The RBF is reduced in hypothyroidism by decreased cardiac output (negative chronotropic and inotropic effects) [10], increased peripheral vascular resistance [11], intrarenal vasoconstriction [12], reduced renal response to vasodilators [13], and a reduced expression of renal vasodilators [14].

This study aims to find the effect of thyroid hormones on cystatin C and creatinine levels in addition to other kidney function tests in patients with hyperthyroidism and hypothyroidism both before and after treatment.

2 Materials and Methods

This study protocol was carried out in Najaf province. The collection of samples was conducted during the period from the 1st of September till the 10th June 2014 in AL-Sader and AL-Sajed hospitals in Najaf city. Case- controlled study included thirty five (16 male, 19 female) with hypothyroidism and thirty five (16 male, 19 female) with hyperthyroidism (all of them were newly diagnosed with primary hypothyroidism and primary hyperthyroidism by Endocrinologist) were taken as patient's group. These selected patients group were divided into subgroups:

- The first group included 35 patients with primary hypothyroidism (O) included 35 patients, their age ranged between (30-52) years. Before treatment referred to as (OB) and after receiving thyroxin for 8 weeks referred to as (OA) with the exclusion of people who suffer from kidney problems. The diagnosis of primary hypothyroidism was confirmed by appropriate clinical and biochemical criteria.

- The second group included 35 patients with primary hyperthyroidism (H), their age ranged between (31- 60) years. Before treatment referred to as (HB) and after receiving Carbimazole for about 8 weeks referred to as (HA) with the exclusion of people who suffer from kidney problems. the diagnosis of hyperthyroidism was confirmed by appropriate clinical and biochemical criteria. Serum creatinine were determined by using colorimetric method [15].

Serum cystatin C were determined by using enzyme-linked immunosorbent Assay (ELISA) [16]. Estimations of the GFR calculated by clearances [estimated GFR based on creatinine (CKD-EPI equation) and estimated GFR based on cystatin C] [17].

The patients were studied again after normalization of thyroid function tests. In all patients, the kidney function tests was measured at each of the 2 time points: in thyroid dysfunction (primary hypothyroidism and primary hyperthyroidism) and after therapy in euthyroidism.

Statistical Analysis:

Data are presented as means \pm SD. Values before and after treatment within the 2 groups were analyzed using the paired t test. P values less than (0.05) is considered significant while values less than (0.01) is considered highly significant.

Table 1: Biochemical features of primary hypothyroidism and hyperthyroidism groups.

Primary hypothyroidism patients	Creatinine mg/dl	Cystatin C mg/l	eGFR by Creatinine ml/min	eGFR by Cystatin C ml/min
Before treatment (OB)	1.1 \pm 0.09	0.67 \pm 0.12	70.1 \pm 18.2	102.6 \pm 10.1
After treatment (OA)	0.8 \pm 0.1	0.75 \pm 0.10	96.9 \pm 24.7	89.8 \pm 10.3
Primary hyperthyroidism patients	Creatinine mg/dl	Cystatin C mg/l	eGFR by Creatinine ml/min	eGFR by Cystatin C ml/min
Before treatment (HB)	0.64 \pm 0.07	0.95 \pm 0.14	111.3 \pm 5.3	76.3 \pm 10.6
After treatment (HA)	0.74 \pm 0.12	0.84 \pm 0.21	99.5 \pm 6.7	111.2 \pm 26.2

TABLE 1 SHOWS A HIGHLY SIGNIFICANT DECREASE IN CREATININE LEVELS IN PRIMARY HYPOTHYROIDISM PATIENTS GROUP AFTER TREATMENT IN COMPARISON WITH THE HYPOTHYROIDISM PATIENTS GROUP BEFORE TREATMENT (P>0.01).

Also, There were a highly significant increase in creatinine levels in the primary hyperthyroidism patients group after treatment in comparison with the primary hyperthyroidism patients group before treatment (P>0.01). While there was a highly significant increase in eGFR by creatinine in primary hypothyroidism patients group after treatment compared with those after treatment (P>0.01). Also, there was highly significant decrease in eGFR by creatinine 99.5 \pm 6.7 ml/min in the primary hyperthyroidism patients groups after treatment in comparison with the primary hyperthyroidism patients group before treatment 111.3 \pm 5.3 ml/min (P>0.01).

Also, table 1 shows a highly significant increase in Cystatin C level in primary hypothyroidism patients group after treatment

0.75 ± 0.10 mg/l compared with the primary hypothyroidism patients group before treatment 0.67 ± 0.12 mg/l (P>0.01). While there were a highly significant decrease in Cystatin C levels in the primary hyperthyroidism patients groups after treatment 0.84 ± 0.21 mg/l in comparison with the primary hyperthyroidism patients group before treatment 0.95 ± 0.14 mg/l (P>0.01). While there was a highly significant decrease in eGFR by cystatin C 89.8 ± 10.3ml/min in primary hypothyroidism patients group after treatment compared with the primary hypothyroidism patients group before treatment 102.6 ± 10.1 ml/min (P>0.01). Also, there were highly significant increase in eGFR by cystatin C in the primary hyperthyroidism patients groups after treatment in comparison with the primary hyperthyroidism patients group before treatment 76.3 ± 10.6 ml/min (P>0.01).

Figure (2) shows highly positive correlation between thyroid hormones and serum cystatin C in both cases before and after treatment.

Serum creatinine (mg/dl)

Serum creatinine (mg/dl)

Serum Cystatin C (mg/l)

Serum Cystatin C (mg/l)

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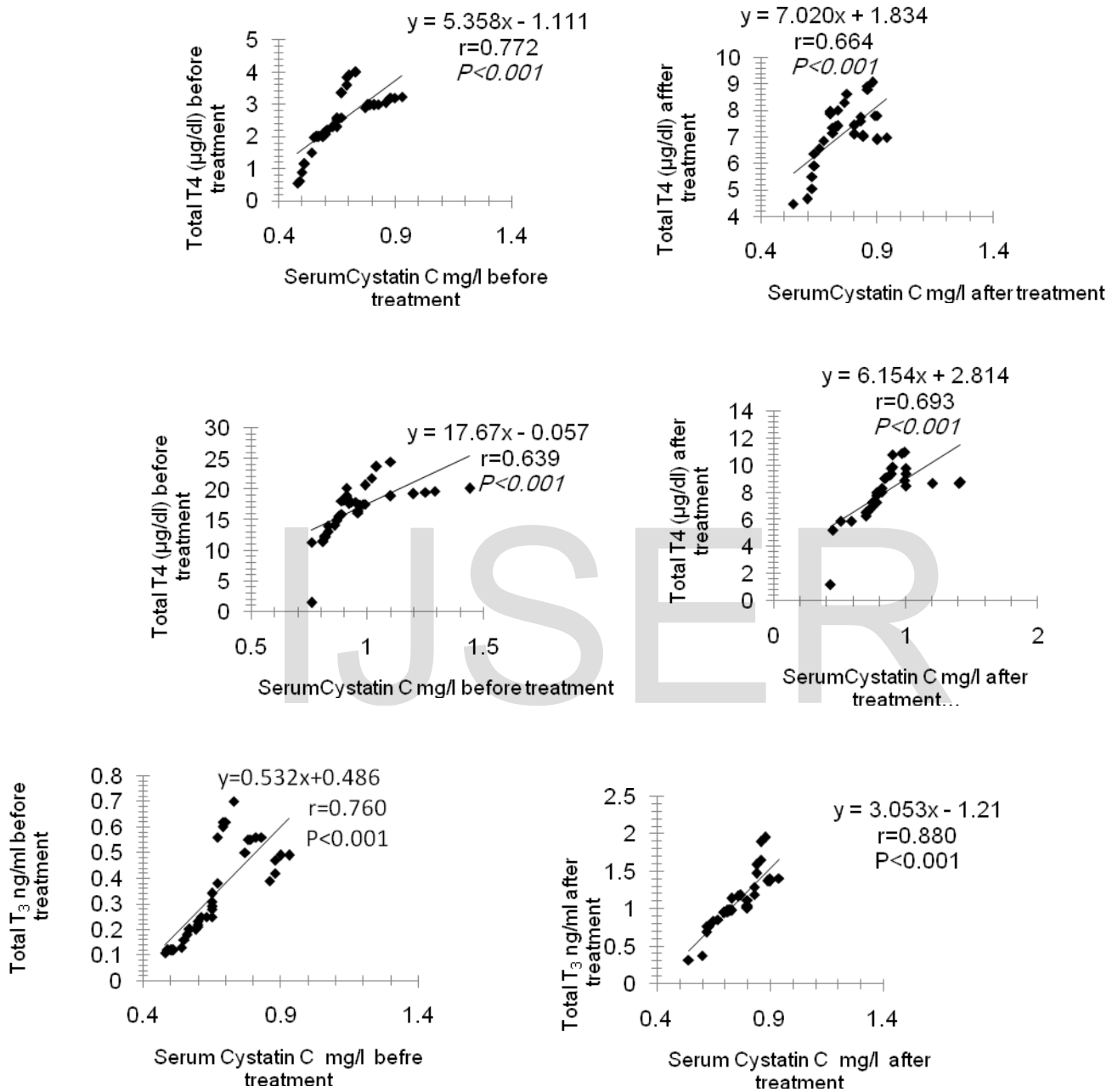
eGFR by CKD-EPI (ml/min)

eGFR by CKD-EPI (ml/min)

eGFR by cystatin C (ml/min)

eGFR by cystatin C (ml/min)

Figure (1): Creatinine based kidney function tests (creatinine and eGFR by creatinine)
and Cystatin C based kidney function tests (cystatin C and eGFR by cystatin C)



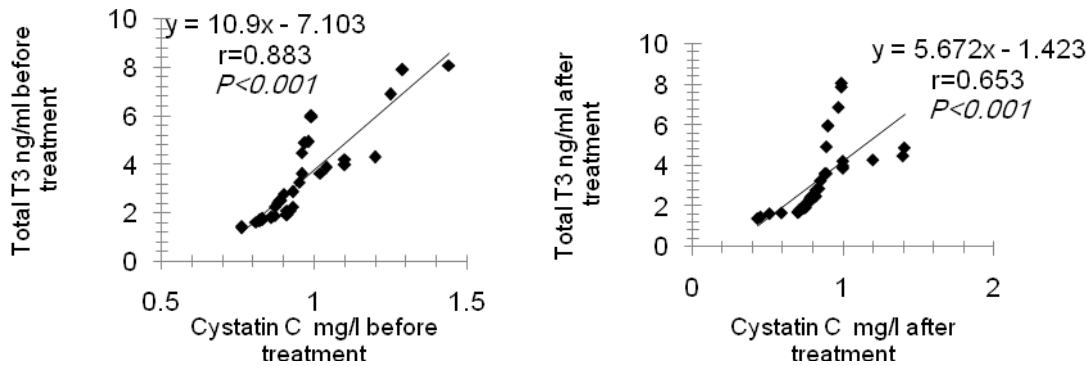


Figure (2): Correlation between serum cystatin C and Thyroid hormones.

4 Discussion

Thyroid and kidney function are known to interact, and thyroid dysfunction is known to cause significant changes in kidney function, especially to affect GFR. Previous studies showed that the effects of hypothyroidism on the kidney are usually opposite to the effects of hyperthyroidism [1]. Thyroid dysfunction affects the metabolic processes in all organs and tissues, including the kidneys. Which leads consequently to changes in the GFR, by affecting the renal plasma flow and the kidney structure.

Thyroid hormones affect the renal function by both pre-renal and direct renal effects, influencing cardiovascular system and renal blood flow. They mainly influence Na^+ reabsorption at the proximal convoluted tubule (PCT) primarily by increasing the activity of Na^+/K^+ ATPase and tubular potassium permeability. Thus thyroid dysfunction affects renal blood flow, GFR, tubular function and kidney structure [18]. Another possible mechanism of action of thyroid hormone on renal function could be explained by its influence on maturation of the renin-angiotensin system (RAAS). Plasma renin activity and plasma levels of angiotensinogen, angiotensin II and aldosterone are directly related to plasma levels of thyroid hormones [19]. Hypothyroidism is associated with low plasma renin. In contrast, hyperthyroidism is accompanied by hyperactivity of the RAAS [19]. Hyperthyroidism is considered to increase the GFR by decreasing the peripheral vascular resistance, increasing the effective renal plasma flow, vasodilatation of the renal blood vessels and the positive ino- and chronotropic effect. Those effects are reversed in the case of hypothyroidism [20].

Different kidney function tests are used in everyday clinical practice: biomarkers like serum urea, serum creatinine, serum cystatin C. and estimations of the GFR by calculated clearances [estimated GFR based on creatinine (CKD-EPI equation), estimated GFR based on cystatin C].

The results in table (1) show a significant decrease in serum creatinine concentrations in patients with primary hyperthyroidism before treatment, while patients with primary hypothyroidism showed higher values of serum cre-

atinine concentrations before treatment. This observation was reversed in those patients after treatment. This can be attributed to the fact that increased thyroid hormone levels leads to increased intracellular creatine phosphate catabolism [21]. The hypoenergetic state in hyperthyroidism blocks the process of creatine regeneration [21]. This effect together with the increased GFR, increased creatinine clearance and increased creatinine tubular secretion explain the lower values of serum creatinine in hyperthyroidism. The reverse events occur in hypothyroidism [21]. The decrease in RBF and GFR is readily reversible upon correction of thyroid hormones deficiency in the hypothyroidism and hyperthyroidism patients group after treatment with thyroxine and Carbimazole [3] [22].

In this study a newer biomarker i.e cystatin C was used for the measurements of kidney function. Cystatin C may be superior to creatinine as a marker for GFR, and a more accurate marker in acute kidney injury. Cystatin C has advantages because concentrations in blood are not influenced by muscle mass, age and gender. but several known factors, other than GFR, affect serum cystatin C levels are high-dose glucocorticoid therapy and thyroid dysfunction [23].

Thyroid hormones were shown by N Kotajima, et al [24] to affect the expression of cystatin C in thyroid disorders but this report didn't explain the effects of the corresponding hormones in the assessment of kidney function and didn't demonstrate the nature of changes in cystatin C occurring in thyroid hormones after the treatment regimens.

The results in table (1) show the significant increase in Cys C levels in the sera of patients with hyperthyroidism and a significant decrease in the patients with hypothyroidism. This is in different and opposite trend shown by creatinine in the corresponding patients. The next step is estimating the GFR by calculated clearances [calculated GFR based on creatinine by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, estimated GFR (eGFR) based on cystatin C]. In case of chronic kidney disease (GFR < 60 ml/min), the eGFR by the MDRD formulas is the best-validated approach. The widely used MDRD equations are limited to chronic kidney disease (with GFR < 60 ml/min), because of the well-known GFR underestimation in a population with normal GFR [25]. Ideally, GFR should be determined with a method that is convenient, inexpensive, and accurate. Up to date, several algorithms and methods have been proposed, but none is applicable as a valid GFR estimator in all clinical conditions [26, 27].

The results in table (1) show significant changes in eGFR in the patients with thyroid disorders. The results indicate that any change in creatinine or cystatin C are accompanied by reverse changes in eGFR in patients with hypothyroidism and hyperthyroidism both before and after treatment. These results indicate the inefficiency of cystatin C in assessment of renal function. The highly significant positive correlation between cystatin C levels and thyroid hormones indicate that cystatin C is a good biomarker of thyroid status than renal function.

eGFR based on creatinine is a better indicator of kidney function in patients with thyroid disorders, in spite of the fact that using invasive methods such as inulin clearance test and radioisotope tracers is more useful in the assessment of renal function in the corresponding patients.

Conclusions

Thyroid hormones showed diverse effects on cystatin C and creatinine in patients with thyroid disorders. The changes in creatinine and cystatin C levels lead to concomitant changes in the measured of estimation of GFR. Cystatin C is biomarker of thyroid function more than kidney function in patients with thyroid disorders.

5 References

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