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Association of Serum Creatinine in Thyroid Disorders

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Introduction: *Thyroid hormones are metabolized and eliminated through kidneys. The dysfunction of kidneys may therefore affect thyroid function and vice versa. Since no standard text mentions the changes in serum Creatinine levels in thyroid disorders, this study attempts to emphasizing the utility of periodic assessment of renal parameters in thyroid patients.*
Aims & objectives: *The present study was planned to assess the influences of thyroid dysfunction on the levels of serum Creatinine.*
Material and method: *150 subjects of age group 15-60 years visiting the out- patient department of Biochemistry for thyroid function tests were enrolled for the study. Based on T_3, T_4 and TSH levels, subjects were grouped as- euthyroid, overt hypothyroid, subclinical hypothyroid and hyperthyroid group. Serum Creatinine and serum T_3, T_4, TSH levels were estimated and analyzed. Results obtained were compared statistically.*
Result: *Mean serum Creatinine levels were significantly higher in overt cases and lowest in hyperthyroidism (P=0.00). Coefficient correlation between T_3, T_4 and serum Creatinine shows negative association r = -0.198 and r = -0.285 respectively while serum Creatinine and TSH were non-significant.*
Conclusion: *Our study shows that renal dysfunctions are often observed in cases of thyroid disorders during any time of disease process; which can be determined by the elevation in serum Creatinine levels.*
Keywords: *Hyperthyroidism, Hypothyroidism, Serum Creatinine*

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I. Introduction

Dysfunction and anatomic abnormalities of the thyroid are among the most common disease of endocrine gland[1]. Without any exception, it is affecting the general population, even the persons residing in non-goiterous too. According to the World Health Organization (WHO), about 2 billion people are iodine deficient based on urinary excretion data[2].

Thyroid gland produces and releases two potent hormones, thyroxine (T_4) and triiodothyronine (T_3), which influence basal metabolic processes, enhance oxygen consumption, linear growth, brain function including intelligence and memory, neural development, dentition, and bone development [3].

The thyroid is a common target of disease or dysfunction very frequently [4]. Thyroid disorders are classified into two major categories, hyperthyroidism (caused by an overactive thyroid gland) and hypothyroidism (due to a poorly functioning thyroid gland), depending on whether serum thyroid hormone levels (T_4 and T_3) are increased or decreased, respectively. Both hypothyroidism and hyperthyroidism have potentially fatal systemic manifestations [5].

Thyroid and kidney functions have several interactions in each other organ's disease states. Thyroid hormones affect renal development and physiology by significantly affecting RBF, GFR, tubular function, electrolytes homeostasis, electrolyte pump functions and kidney structure. Hypothyroidism is associated with reduced GFR and hyperthyroidism results in increased GFR as well as increased renin–angiotensin–aldosterone activation [6]. The most common kidney derangement associated to hypothyroidism includes elevation of serum Creatinine level [7].

Creatinine is a breakdown product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass). Serum Creatinine is an important indicator of renal health because it is excreted unchanged by the kidneys, primarily through glomerular filtration, but also by proximal tubular secretion. Little or no tubular reabsorption of Creatinine occurs. If the filtration in the kidney is deficient, Creatinine blood levels rise. Therefore, Creatinine levels in blood and urine may be used to calculate

the Creatinine clearance, which correlates with the GFR. Guanidine aminoacetic acid undergo methylation to form Creatinine. The serum creatinine can vary by 0.5 to 1.0 mg/dL according to diurnal and menstrual variations, race, and diet (and method of meat preparation)[8,9].

Thyroid hormones influence the maturation of renin angiotensin system, thus increasing concentration of renin and angiotensinogen in the serum. T_3 causes relaxation of blood vessels leading to vasoconstriction and increased peripheral resistance in hypothyroidism which results in reduced blood flow in the renal arteries. Thus, serum Creatinine is influenced by a decrease in T_3 and T_4 and increase in TSH [10].

The present study was therefore, planned to assess the influence of thyroid dysfunction on levels of serum Creatinine and also to explore the diagnostic importance in the treatment and follow up of thyroid diseases.

II. Material And Methods

The study was conducted in Department of Biochemistry in association with Department of General Medicine and Endocrinology of Mahatma Gandhi Medical College and Hospital, Jaipur after seeking approval from **Institutional Ethics Committee (IEC).** Total 150 subjects, age between 15-60 years coming for thyroid function tests were enrolled for the study. Exclusion criteria was taken to rule out patients with other co-morbid conditions such as gross hepatic or renal dysfunctions, pulmonary infarction, diabetes mellitus, hypertension, ischemic heart disease, cerebrovascular disease, rheumatoid arthritis. All patients were screened for any drug history which can affect thyroid hormone levels like statins, diuretics, NSAIDs, anti-hypertensives, steroids, oral contraceptives.

Blood samples were collected by standard aseptic technique and analyzed for serum T_3, T_4 and TSH by chemiluminescence using Vitros ECI and serum Creatinine, Blood Urea and Uric acid by using Vitros 4600-Dry Chemistry analyzer.

Based on their thyroid function, the enrolled subjects were grouped viz. euthyroid, subclinical hypothyroid, overt hypothyroid and hyperthyroid group. All results obtained were presented as mean ± SD and subjected to statistical evaluation by applying students 't' test. To compare the various parameters in the above groups, one way ANOVA test was applied. Correlation between thyroid hormones and other variables, Pearson's Correlation was applied. A P value of ≤ 0.05 was considered as statistically significant.

III. Result

The enrolled 150 subjects were grouped on the basis of thyroid function as- euthyroid (n=31), overt hypothyroid (n=64), subclinical hypothyroid (n=30) and hyperthyroid (n=25) group.

On applying 't' test, serum T_3, T_4 were found to be significant in hyperthyroid group with mean value as 2.63 ± 2.17 ng/mL and 15.25 ± 4.38 µg/dL respectively. Mean value of the serum TSH in overt hypothyroid cases was as high as 25.98 ±21.85 µIU/mL and in the subclinical hypothyroid group was 9.41 ± 4.16 µIU/mL. The standard deviation range in both subclinical and overt hypothyroid groups was reasonably high suggesting a wide range of TSH levels in both the conditions. (TABLE 1)

TABLE 2 compares serum Creatinine, blood Urea and serum Uric Acid levels among the four groups of thyroid function. A highly significant variation (p =0.00) is observed with higher serum Creatinine levels in the hypothyroid (subclinical and overt) group and are lowest in the hyperthyroid group. Similar findings were observed in serum urea and uric acid levels. Both are significantly higher in subclinical and overt hypothyroid groups while lowest in hyperthyroid subjects. The above findings suggest that the renal markers are strongly affected by hypoactivity of thyroid hormones.

Age distribution of study subjects shows that the mean age was higher in the overt and subclinical hypothyroid groups as compared to the euthyroid and hyperthyroid patients. Patients with overt hypothyroidism had the highest mean age of 45.13 ± 10.57 years.

Out of 150 patients, male: female distribution was 49: 101. The prevalence of hypothyroidism was higher among females. The increased predisposition of females was observed with 64% in subclinical hypothyroidism and 83.3% in overt hypothyroidism (TABLE 2).

TABLE 3, FIGURE 1 shows the correlation coefficient of thyroid profile with serum Creatinine levels. A highly significant negative correlation was observed between serum Creatinine and T_3 (r = -0.198), T_4 (r= -0.285). However, serum TSH levels did not show a significant correlation. This can be attributed to the wide range of serum TSH covered among the four groups.

Table no 1: Distribution of thyroid hormone levels in the group based on thyroid function

Group	n	T_3 (ng/mL)	T_4 (µg/dL)	TSH (µIU/mL)
Euthyroid	31	1.35±0.24	10.25±2.82	2.24±1.13
Subclinical Hypothyroidism	64	1.36±0.22	8.57±1.96	9.41±4.16
Overt Hypothyroidism	30	0.85±0.50	4.53±1.22	25.98±21.85
Hyperthyroidism	25	2.63±2.17	15.25±4.38	0.07±0.12
P-value		0.000	**0.000**	**0.000**

P- value as obtained on applying 't-test'.

Table no 2: Distribution of age, sex, creatinine, urea and uric acid levels in the group based on thyroid function

Group	N	Age (years)	Sex		Creatinine (mg%)	Urea(mg%)	Uric acid (mg%)
			Male	Female			
Euthyroid	31	33.29±14.93	11	20	0.58±0.15	21.55±5.99	3.90±1.27
Subclinical Hypothyroidism	64	40.5±13.40	23	41	0.91±0.47	27.48±11.83	5.03±1.96
Overt Hypothyroidism	30	45.13±10.57	05	25	1.25±1.14	37.76±24.72	5.31±1.93
Hyperthyroidism	25	36.56±11.74	10	15	0.48±0.10	21.44±5.36	3.82±1.27
P-value		0.003			**0.000**	**0.000**	**0.000**

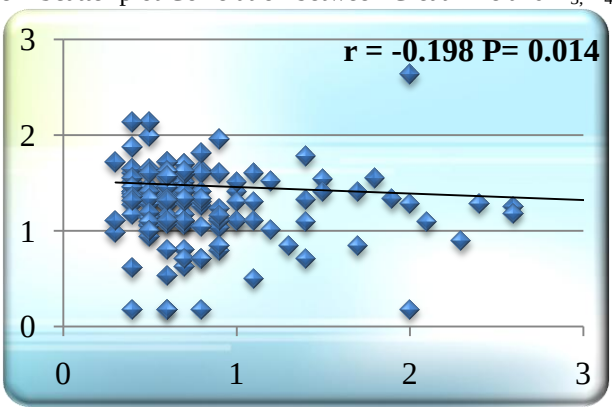
P- value as obtained on applying 't-test'.

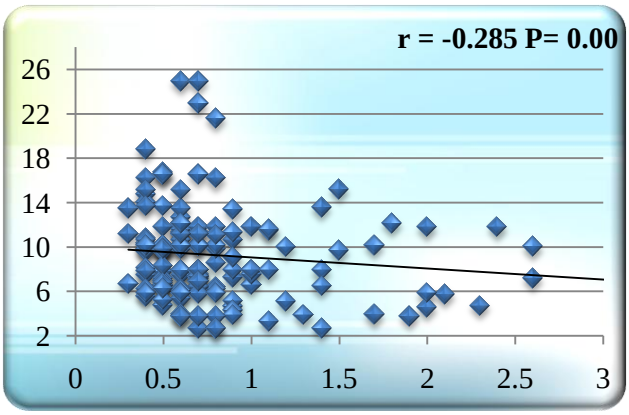
Table no 3: Correlation coefficient between Creatinine and Thyroid Function

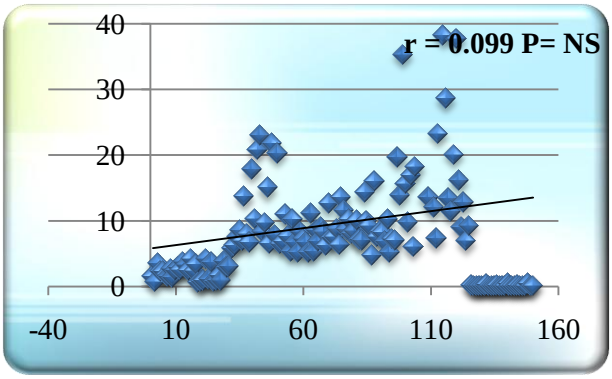
Test	Correlation coefficient (r)	P-value
Creatinine v/s T3	-0.1988	0.0147
Creatinine v/s T4	-0.2857	0.000
Creatinine v/s TSH	0.099	NS

r and P- value as obtained on applying **Pearson's correlation**

Figure 1 Scatter plot Correlation between Creatinine and T_3, T_4, TSH







IV. Discussion

Thyroid gland is located anterior to trachea and produces hormones which play a great role in control of BMR, general body metabolism, growth, development and tissue differentiation. Thyroid hormones are necessary for the growth and development of the kidney and for maintenance of water and electrolyte homeostasis[11]. On the other hand, the kidney is involved in the metabolism and elimination of thyroid hormone[12,13]. Abnormalities of these hormones frequently involve many organs. Hypothyroidism causes reduced metabolic function and may lead to neuromuscular and musculoskeletal manifestations [14]. Clinical manifestation such as overweight, fatigue, hypertension and depression is frequently seen [15,16]. It may be associated with low GFR because of hypodynamic state. It causes decreased myocardial contractility, cardiac output and peripheral oxygen consumption with increase in peripheral resistance leading to systemic and renal vasoconstriction resulting in decreased RBF causing increase in Creatinine and decreased Creatinine Clearance [17].

Thyroid function brings about a significant change in renal structure and function by affecting RBF, GFR and electrolyte homoeostasis. Elevated serum Creatinine in hypothyroid patients has been reported in previous studies of **Tejomani M, et. al., 2013; Nakahama H, et. al., 2001**[18,19].

Imtiaz MA, et. al., 2015 have observed that patients with hypothyroidism can gradually end up with renal dysfunction and myopathies[20]. The probable mechanism for this elevated Creatinine levels may be peripheral resistance leading to systemic and renal vasoconstriction resulting in decreased RBF which in turn results in increased serum Creatinine and decreased Creatinine Clearance. The RBF is reduced in hypothyroidism by decreased cardiac output (negative chronotropic and inotropic effects)[21], increased peripheral vascular resistance[22], intrarenal vasoconstriction[23], reduced renal response to vasodilators[24] and a reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) and insulin like growth factor-1 (IGF-1)[25]. In hypothyroidism, glomerular basement membrane thickening and mesangial matrix expansion may cause reduced RBF.

Hyperthyroidism leads to increased RBF and GFR[12]. Thyroid hormones increase the cardiac output by positive chronotropic[26] and inotropic effects[27], as well as reduction in systemic vascular resistance[28]. This indirectly contributes to an increase in RBF. Thus an increased intrarenal vasodilation and decreased vasoconstriction, results in net increase in RBF.

While most of the previous studies have compared the serum Creatinine activity in hypothyroidism (Imtiaz M, et. al., 2015; Tejomani M, et. al., 2013)[20,18] or hyperthyroidism patients (Attaullah S, et. al., 2015; Ranka R, et. al., 2003)[29,30], the present study is an attempt to compare the serum Creatinine levels in different conditions of hypo and hyperactivity of thyroid glands.

The present study observed lower serum Creatinine levels in the hyperthyroid subjects and levels are higher in the hypothyroid (subclinical and overt) group. The findings are similar to that of **Attaullah S, et. al., 2015** who have reported a negative correlation between serum T_3, $T_4$and serum Creatinine[29]. A study by **Kreisman SH, et. al., 1999** concluded that serum Creatinine levels show a consistent and reversible rise during hypothyroid state. The study also proposed that in certain cases the values may be reasonably abnormal [17].

In the present study, serum urea and uric acid levels were also compared in the different thyroid disorders. Serum urea levels were significantly higher in the overt and subclinical hypothyroid groups. However, the values in the hyperthyroid subjects were similar to the normal thyroid function group (Table2). In the study by S Baikunje, et. al., 2013, blood urea was consistently normal[31]. On the contrary, another study has shown significantly elevated serum urea and Creatinine levels in patients with overt and subclinical hypothyroidism which correlated positively with TSH levels[32].

Similarly, the serum uric acid levels were significantly higher in the hypothyroid groups (subclinical and overt) and slightly lower in the hyperthyroid group (Table 2). The above findings suggest that the renal markers are strongly affected by hypoactivity of thyroid hormones.

Hypothyroidism results in low cardiac output which triggers the carotid baro-receptors and consequently increases the non-osmotic ADH secretion[7]. The reduced GFR reduced sodium reabsorption and relatively increased ADH secretion and renal ADH super sensitivity mediated impaired free water clearance, all contribute to hyponatremia in hypothyroidism[33]. Hyponatremia is common among hypothyroid patients with raised serum Creatinine as among those with normal serum Creatinine.

Table 3, Figure 1 shows a highly significant negative correlation of T_3, T_4 with serum Creatinine levels. Previous studies have reported similar finding and confirmed that serum Creatinine levels are strongly influenced by hypo and hyperthyroid activity of hormones. Further, these studies have demonstrated an inverse relationship between thyroid hormones and biochemical markers of kidney[29,34].

V. Conclusion

The findings of the study indicate profound influence of thyroid hormone on renal function. It suggests that serum Creatinine have a strong correlation with thyroid function and its levels can elevate even in the absence of decline in the GFR and the concomitant elevation of blood urea. Moreover, hypothyroid-induced renal dysfunction may lead to adverse clinical consequences, especially among patients on medications cleared by the kidneys. The study therefore, recommends regular assessment of renal function in patients with impaired thyroid function. This may play a critical role in minimizing the complications of associated kidney disorders.The study further proposes the evaluation of markers of endothelial dysfunction and inflammation viz. CRP, IL-6 etc. in various thyroid disorders. With confirmation of the influence of activity of thyroid hormone on renal function, analysis of the serum electrolytes especially serum Sodium and Potassium will be interesting to explore further.

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