Association Between Renal Dysfunction Markers and Creatine Kinase Levels in Hypothyroidism.

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Abstract: Hypothyroidism is one of the most common endocrine disorders in clinical practice. It can affect the kidney function through various mechanisms, such as decreased cardiac output, increased vascular resistance, intrarenal vasoconstriction, reduced production and activity of hormones that regulate blood pressure and fluid balance, and altered kidney structure and feedback. Hypothyroidism can reduce renal plasma flow, glomerular filtration rate, and glomerular transcapillary pressure, which are important for kidney function. Hypothyroid myopathy is a common clinical feature in patients with hypothyroidism. The study was taken up to determine the influence of thyroid hormone on renal dysfunction markers, serum creatinine and cystatin C and on myopathy marker total creatine kinase levels and to evaluate the association between these dysfunction markers in hypothyroid cases. Serum T3, T4, TSH, Total Creatine Kinase, Cystatin C and Creatinine levels were estimated. Creatinine Clearance was calculated by using the Cockcroft-Gault formula and eGFR by using the MDRD formula. The elevation of serum creatinine in the study may be attributed to an increase in total creatine kinase levels which may be due to hypothyroid myopathy or decreased clearance by the kidneys. In contrast to creatinine concentrations, Cystatin C levels are lower in the hypothyroid cases suggesting a paradoxical relationship between them, though both are renal dysfunction markers. Hence interpretation of Cystatin C must be cautiously done in hypothyroidism.

Keywords: Creatinine, creatinine clearance, cystatin C, eGFR, hypothyroidism, renal dysfunction, myopathy, thyroid hormone, total creatine kinase.

Introduction

Thyroid dysfunction has been proven to alter the function of all organ systems in the body such as the heart, muscles, and brain. Thyroid status has an impact on renal function as well. The thyroid hormone is produced and secreted by the thyroid gland under the control of the anterior pituitary hormone: thyroid stimulating hormone (TSH), which in turn is regulated by hypothalamic thyrotropin-releasing hormone. Thyroxine (T4) is produced only by the thyroid gland, whereas triiodothyronine (T3), the more biologically active form of thyroid hormone, is produced primarily through local deiodination of T4 by the enzyme 5'- deiodinase in other tissues, including kidney [1]. The kidney contains the D1 isoform of this enzyme, which becomes less active in uremia. The thyroid hormone exerts its effect primarily by binding to thyroid hormone nuclear receptors, which can affect gene transcription by binding to thyroid hormone response elements of target genes [2]. Thyroid hormones can also exert nongenomic effects by binding to elements on the plasma membrane and cytoplasm.

The thyroid hormone directly influences the expression and/or activity of a number of ion channels and transporters. The impact of thyroid dysfunction on renal function is highlighted by studies substantiating that clinical hypothyroidism is common in patients with an estimated GFR, 60 ml/min per 1.73 m2 [3]. Renal function deterioration secondary to hypothyroidism involves diverse mechanisms including hemodynamic defects including the negative inotropic effect on the heart, reduced circulating intravascular volume and increased peripheral resistance with renal vasoconstriction [4]. Myopathy may be the exclusive clinical manifestation of hypothyroidism in some cases along with a rise in serum creatine kinase level, lactate dehydrogenase and aldolase levels. The skeletal muscle could be the major source of the increase in plasma CK in hypothyroidism. Total CK level is considered to be a sensitive and excellent biochemical marker for the diagnosis of neuromuscular diseases. Hypothyroidism is a common cause of endocrine myopathy and should be considered in patients with unexplained persistent elevation of serum muscle enzymes, which are found to be higher in patients with hypothyroidism.

Thyroid hormones are necessary for the growth and development of the kidneys in addition to the maintenance of water and electrolyte homeostasis. The kidney is involved in the metabolism and elimination of thyroid hormones. The decline in kidney function is accompanied by changes in the process of synthesis, secretion, metabolism and elimination of thyroid hormone. Thyroid hormone affects the tubular transport of sodium and potassium via their actions on the sodium–potassium ATP pump (Na+ /K+ ATPase) and permeability of potassium in the membrane of proximal tubules [5]. Thyroid dysfunction can bring about significant changes in renal function by affecting renal blood flow, GFR, tubular function, electrolytes homeostasis, electrolyte pump functions and kidney structure. The most common kidney derangement associated with hypothyroidism includes an elevation of serum creatinine level [6].

Cystatin C is a cysteine proteinase inhibitor and is produced at a constant rate by most nucleated cells, freely filtered at the glomerulus. Cystatin C is reabsorbed and metabolized by proximal tubular epithelial cells. Serum cystatin C (Cys C) is a novel marker for kidney function that has been claimed to be superior to serum creatinine [7]. The aim of the study was to determine the influence of thyroid hormone on creatine kinase level and to estimate renal dysfunction markers, serum creatinine and cystatin C in hypothyroidism and to evaluate the association between them. The study would further help to interpret the differences in serum creatinine and cystatin C levels in hypothyroidism.

MATERIALS AND METHODS

The study population consisted of about 40 clinically suspected and biochemically confirmed hypothyroid patients who visited the outpatient clinic of the Department of Medicine and Endocrinology, MS Ramaiah Hospital, Bangalore. The control group included 40 healthy euthyroid subjects who attended the hospital for a routine health check-up or blood bank. A detailed history including if any drug regimen was followed was taken from the patients.

Inclusion Criteria

Clinically diagnosed and biochemically confirmed hypothyroid cases in the age group of 25 to 55 years of both genders. Patients were considered as hypothyroid based on T3, T4 and TSH values (Normal reference range: - T3: 1.08–4.14 nmol/L, T4: Males: 59- 135 nmol/L, Females: 65-138 nmol/L, TSH: 0.5-4.3 µIU/ml). Raised serum TSH levels with normal or low T3 and T4 levels were categorized as hypothyroid cases.

Exclusion Criteria

Patients with impaired renal function (Serum creatinine > 1.2 mg/dl in females and >1.4 mg/dl in males), ischemic heart disease, cerebrovascular disease, hypertension, diabetes mellitus, rheumatoid arthritis, Duchenne's muscular dystrophy, polymyositis, and other causes for the transient increase in CK were excluded from the study.

Informed consent was taken before the collection of the sample from cases and controls. The control subjects had the same exclusion criteria as the cases and were not on any drug regimen which could influence the study. Ethical clearance was obtained for the study. Blood samples after overnight fasting were collected from cases and controls. About 5 ml of blood sample was collected in a red vacutainer, devoid of any anticoagulant. The samples were centrifuged, and the serum was separated at the earliest. The serum sample was used for the estimation of T3, T4, TSH, cystatin C, creatinine, and total creatine kinase levels.

Serum T3, T4 and TSH were estimated on the autoanalyzer Roche/Hitachi COBAS e601 (Elecsys) by electrochemiluminescence (ECLIA). Serum total creatine kinase level was estimated by IFCC NAC – Activated method. Serum creatinine was estimated by modified Jaffe's reaction and serum Cystatin C was estimated by the immunoturbidimetric method.

Creatinine clearance was calculated by using Cockcroft Gault Formula. Creatinine clearance (ml/min/1.73m²) = (140- Age X mass in kg X [0.85 if female]) / [72 X serum creatinine (mg/dl)] [7].

eGFR (estimated Glomerular Filtration Rate) was calculated, using MDRD (Modification of diet in renal disease) formula.eGFR (ml/min/1.73 m2) = 186 x (Plasma/serum creatinine mg/dl)-1.154 x (age)-0.203x (1.210 if black) x (0.742 if female) [8]. eGFR greater than 90ml/min/1.73 m^2 was considered normal.

The results are expressed in Mean ± SD. Significance was assessed at 5 % level of significance. Student t-test (two tailed, independent) has been used to find the significance of the study parameters. The Pearson correlation coefficient was used to study the relation between the various study parameters.

RESULTS AND DISCUSSION

The data of the euthyroid controls and hypothyroid cases were compared with respect to serum T3, T4 (thyroid hormones), TSH (thyroid stimulating hormone), Total CK activity, cystatin C, creatinine and creatinine clearance and glomerular filtration rate as eGFR. The distribution of age in cases and controls is shown in Table 1. Hypothyroidism was found more common among the 25-35 years age group. The prevalence of hypothyroidism was higher among females as is observed world over (Table 1). Hypothyroids in the study had more body weight when compared to controls (Fig 1). TSH was found nearly ten times higher in cases when compared to controls (Fig 2). Thyroid profile in hypothyroids and euthyroids are shown in Figure 2. There is a significant decrease in T3, T4, and increase in TSH levels as shown in Table 2. The total CK levels were highly significant in hypothyroids in comparison to controls (Fig 3). Fig 3). A significant rise in serum creatinine levels was seen in hypothyroid cases as compared to controls ($p<0.001$) (Fig 4). The creatinine clearance was decreased in cases when compared with controls (Fig 5). eGFR was decreased in cases as compared to controls (Table 2). There was a decrease in cystatin C levels in hypothyroid cases as compared to euthyroid controls (Fig 6).

Table-1: **Comparison of demographic profiles between hypothyroid cases and euthyroid controls**

Demographic profiles	Hypothyroid Cases (n=40)	Euthyroid Controls (n=40)
Age in years	33.96±10.17	41.85±11.91
Gender		
Males	17(42.9%)	6(15.4%)
Females	23(57.1%)	34(84.6%)
Weight(kgs)	64.36±8.95	56.92±7.3(p value 0.027*)

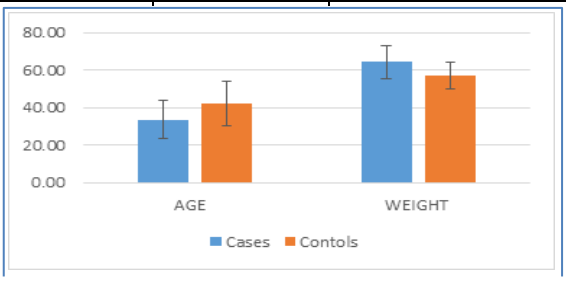

Fig-1: Age (years) and weight (kg) in hypothyroid cases and euthyroid controls.

Table-2: Comparison of biochemical profiles in hypothyroid cases and euthyroid controls

Biochemical Profiles	Hypothyroid Cases (n=40)	Euthyroid Controls (n=40)	P value
S. T3 nmol/L	0.60±0.34	1.88±0.38	<0.001**
S. T4 nmol/L	20.51±19.28	111.29±22.4	<0.001**
S. TSH uIU/ml	214.85±43.16	2.67±1.19	<0.001**
S. Total CK IU/L	544.70±90.86	59.75±34.33	<0.001**
S. Creatinine mg/dl	1.14±0.22	0.81±0.18	<0.001**
Creatinine Clearance ml/min	79.90±16.5	91.19±40.99	0.350
eGFR ml/min	69.62±14.84	95.20±38.72	0.030*
S. Cystatin C mg/L	0.73±0.34	0.95±0.32	0.098+

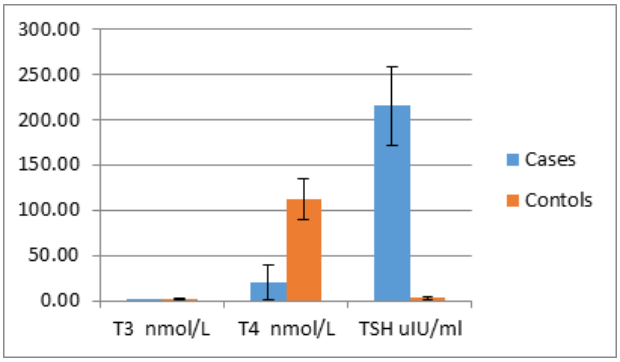

Fig-2: Thyroid profile in hypothyroid cases and euthyroid controls

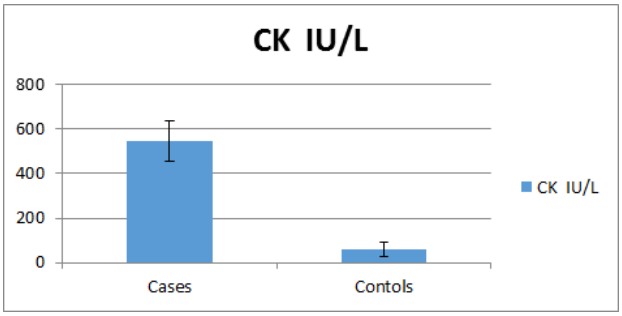

Fig-3: Serum Total CK (IU/L) in hypothyroid cases and euthyroid controls

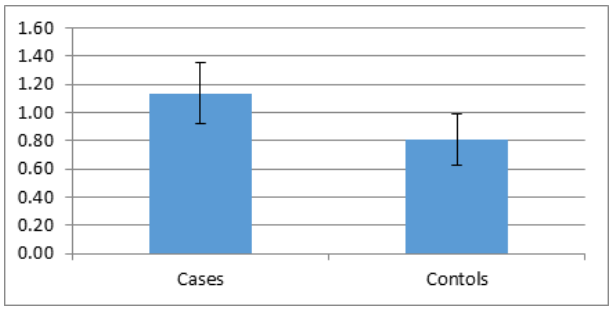

Fig-4: Serum Creatinine (mg/dl) in hypothyroid cases and euthyroid controls

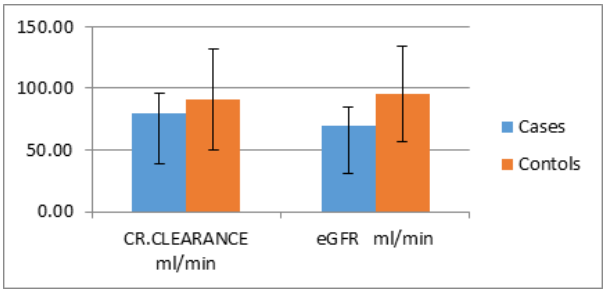

Fig-5: GFR (ml/min) and creatinine clearance (ml/min) in hypothyroid cases and euthyroid controls

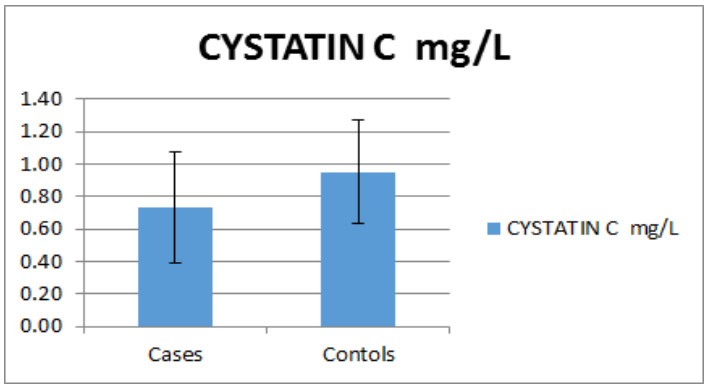

Fig-6: Serum Cystatin C (mg/L) in hypothyroid cases and euthyroid controls

The correlation of T3 with T4 , TSH along with total CK, cystatin C and creatinine was studied. T3 is the active hormone that has a shorter half-life and did not directly correlate with the measured parameters, hence may exert its action via T3 receptors as in Table 3.

Table-3: Pearson correlation of T_3 with T_4, TSH, Total CK, S. Creatinine, Creatinine clearance and eGFR in Hypothyroids

Pair	Hypothyroid Cases	
	r value	p value
T_3 nmol/L vs T_4 nmol/L	**0.52**	**0.05+**
T_3 nmol/L vs TSH µIU/ml	0.08	0.78
T_3 nmol/L vs Total CK IU/L	-0.26	0.36
T_3 nmol/L vs S.Creatinine (mg/dl)	-0.44	0.11
T_3 nmol/L vs Creatinine clearance (ml/min)	-0.06	0.83
T_3 nmol/L vs eGFR(ml/min)	-0.12	0.68
T_3 nmol/L vs S. Cystatin C (mg/dl)	- 0.40	0.15

There is a significant correlation between TSH and total CK in the study indicating TSH levels can influence the development of myopathy and the release of muscle enzymes in hypothyroidism as in Table 4.

Table-4: Pearson correlation of TSH with Total creatine kinase, S. creatinine, Creatinine clearance and eGFR in hypothyroids

Pair	Hypothyroid Cases	
	r value	p value
TSH µIU/ml vs Total CK level IU/L	0.66	0.01+
TSH µIU/ml vs S. creatinine (mg/dl)	- 0.11	0.70
TSH µIU/ml vs Creatinine clearance (ml/min)	0.14	0.63
TSH µIU/ml vs eGFR (ml/min)	-0.19	0.51
TSH µIU/ml vs S. Cystatin C	-0.37	0.19

There is negative correlation of total CK with creatinine, eGFR and creatinine clearance as in Table 5.

Table-5: Pearson correlation of Total CK level with S.creatinine, Creatinine clearance and eGFR in hypothyroids

Pair	Hypothyroid Cases	
	r value	p value
Total CK level (IU/L) vs S. creatinine (mg/dl)	-0.50	0.06
Total CK level (IU/L) vs Creatinine clearance (ml/min)	0.22	0.44
Total CK level (IU/L) vs eGFR (ml/min)	-0.30	0.29
Total CK level (IU/L) vs S. Cystatin C (mg/L)	-0.55	0.04

There is significant correlation of eGFR with creatinine clearance as in table 6.

Table-6: Pearson correlation of eGFR with other profiles in Hypothyroids

Pair	Hypothyroid Cases	
	r value	p value
eGFR(ml/min) vs T_3 (nmol/L)	-0.12	0.68
eGFR(ml/min) vs T_4 (nmol/L)	-0.27	0.35
eGFR(ml/min) vs TSH (µIU/ml)	-0.19	0.51
eGFR (ml/min) vs Total CK level (IU/L)	-0.30	0.29
eGFR (ml/min) vs S. creatinine (mg/dl)	-0.68	<0.01**
eGFR(ml/min) vs Creatinine clearance (ml/min)	-0.76	<0.01**
eGFR (ml/min) vs S. Cystatin C (mg/L)	-0.01	0.97

Hypothyroidism is a common endocrine disorder associated with decreased myocardial contractility, cardiac output and increase in peripheral vascular resistance. The increase in peripheral resistance can predispose to the alteration in renal hemodynamics such as reduced renal blood flow and diminution of glomerular filtration rate resulting in a decrease in the clearance of certain substances like creatine kinase, creatinine, and others in hypothyroidism[9]. Hypothyroidism may be contributing to the low GFR in some of the hypothyroid cases [10]. Renal function deterioration secondary to hypothyroidism involves heterogeneous

mechanisms which include a negative inotropic effect on the heart, reduced circulating intravascular volume and increased peripheral resistance with renal vasoconstriction [4]. The elevation of total CK level in hypothyroids in the study could be due to the release of CK from the skeletal muscles (Table 2). The pituitary gland releases TSH in response to a suboptimal level of thyroid hormones, similarly, the muscles may also respond by releasing creatine kinase into the circulation in hypothyroidism. Several authors have also reported an elevation of serum CK activity correlating with the severity ofhypothyroidism. Hypothyroids have increased levels of CK, due to increased CK-MM isoenzyme which indicates skeletal muscle as the major source of the increased plasma CK level. Skeletal muscles are more receptive to alteration in TSH level as compared to renal system.

The study shows an elevation in serum total CK level in hypothyroids as compared to controls (Fig 3). The CK level is increased ten folds in hypothyroids as compared to controls. The increase in total CK level may be due to an increase in the concentration of the enzyme in circulation as a result of leakage of the enzyme from muscle cells. There may be a decrease in renal blood flow thereby affecting the clearance of CK from circulation. Serum muscle enzyme elevations in hypothyroidism, which occur in the absence of weakness, myalgias or structural muscle abnormalities,could be due to changes in muscle cell membrane permeability, although the basis for this change is unknown [11]. There may be a decrease in renal blood flow thereby affecting the clearance of CK from the circulation. Reduced clearance of creatine kinase (CK) probably also plays a role in hypothyroidism [12].

A positive correlation observed between TSH and CK levels in hypothyroids in the study indicates the influence of TSH on myopathy, though therise in CK level was nearly ten times higher (Table 4). The presence of T_3 receptors on the mitochondrial membrane of skeletal muscles suggests a direct effectof thyroid hormones on oxidative metabolism inmuscles and may be one of the causes for muscle dysfunction in hypothyroidism [13]. The hypo-metabolic state of hypothyroidism can cause a reduction in glycolysis and oxidative phosphorylation thereby reducing ATP concentrations beyond a critical limit. Mitochondrial defect and reduction in oxidative phosphorylation may contribute to impaired oxygen use in hypothyroidism resulting in increased lactate concentration [14]. It has been reported, alteration in sarcolemmal membranes can cause increased cell permeability and leakage of CK from cells. High serumCK concentration in hypothyroidism may be due tomuscle fiber degeneration, altered muscle energy metabolism and decreased clearance of CK fromcirculation [15].

The effects of hypothyroidism on the renal system include changes in water and electrolyte metabolism, notably hyponatremia and alterations of renal hemodynamics including decrements in renal blood flow, GFR and single nephron GFR [16]. The decreases in renal plasma flow and glomerular filtration rate (GFR) that accompany hypothyroidism are believed to be related to the generalized hypodynamic state of the circulatory system in hypothyroidism. Elevation of serum creatinine levels is not generally mentioned as anabnormality that occurs in association with hypothyroidism. Thyroid dysfunction may alter creatinine, which has been found to be increased inhypothyroidism and decreased in hyperthyroidism. The study was taken up to evaluate whether changes in Cys C and creatinine are similar during the diagnosis of hypothyroidism. Serum cystatin C is a low molecular weight and a basic protein that functions as a physiological inhibitor of cysteine proteinases and is produced at a constant rate by most nucleated cells [17].Cystatin C gene is of the housekeeping type and the production of Cys C is not influenced by inflammatory states. The protein is freely filtered at the glomerulus and practically completely reabsorbed and catabolized by tubular cells [18]. In comparison to serum creatinine, Cys C has a lower inter-individual variability and is not correlated to lean tissue mass, gender, and age. Cys C has proved to be a reliable marker of glomerular filtration rate (GFR) in healthy adults and children. A highly significant correlation between cystatin C and TSH was not observed in the study (Table 4) This further indicates Cystatin C, a novel marker for renal dysfunction, when estimated and used for calculating glomerular filtration rate, the results have to be interpreted with caution as decreased thyroid hormone levels and other clinical conditions can influence their serum levels. The hypothyroid cases in the study did not have very evident renal failure. The cases recruited for the study were not treated for renal dysfunction.

The study shows a significant increase in serum creatinine in hypothyroids (p value <0.001) when compared with controls (Table 2). Tayal *et al*. have alsoreported significant elevation in serum creatinine levels in hypothyroids [19]. There is correlation between TSH and CK level in hypothyroid cases but correlation between TSH and creatinine was not very significant, may be due to involvement of skeletal muscle before renal dysfunction (Table 4).

The renal involvement in hypothyroidism isevident by the significant correlation of eGFR with serum creatinine and creatinine clearance in hypothyroids (Table 5). Kreisman *et al*. have reported that the rise in serum creatinine level can be due to a decrease in the GFR and is a reversible condition [20]. The cause for a decrease in GFR can be due to hypodynamic circulation in hypothyroidism. The cause for the elevation of serum creatinine can be either due to decrease in GFR or due to decrease in renin levels consequently reducing the level of renin-angiotensin system [21]. There isdecreased sensitivity to β-adrenergic stimulus and decreased renin release, along with decreased angiotensin II levels and impaired RAAS activity resulting in decreased filtration rate [22].

The rise in serum creatinine levels in hypothyroids can be partly due to the influence of T_3, T_4 and TSH on renal function and also due to rise in CKlevel. Increased serum creatinine level, decreased eGFRand a decline in creatinine clearance are observed in hypothyroidism. The reduction of cystatin C levels in hypothyroids may be due to the involvement of muscle cells associated with an increase in creatine kinase level. The rise in CK and serum creatinine levels could be eitherdue to reduced clearance or overproduction or both.

CONCLUSION

The elevation of serum creatinine in hypothyroidism may be associated with an increase in totalcreatine kinase level either due to myopathy or due to decreased clearance by the kidneys. There is a paradoxical relation between the elevated serum creatinine and the decreased serum cystatin C levels in hypothyroidism, which warrants the use of cystatin C as a renal dysfunction marker in hypothyroidism with caution. However, further studies are required with a larger population to verify the utility of serum cystatin C as a renal dysfunction marker in hypothyroids and in whom, otherwise, serum creatinine may be a better indicator of renal function impairment.

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