Relevance of Creatine Kinase Activity and Serum Creatinine Levels in Hypothyroidism

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Research Article

Abstract: **Background:** Hypothyroidism is the most common endocrine disorders. Musculoskeletal and renal dysfunctions are often observed in cases of hypothyroidism during any time of disease process. **Objectives:** To determine the influence of thyroid hormone on creatine kinase activity and serum creatinine level in hypothyroids and to determine the extent of musculoskeletal and renal involvement. **Materials and Methods**: Serum T_3, T_4, TSH, Total CK activity and S. Creatinine levels were estimated. Creatinine clearance was calculated using Cockcroft Gault formula and eGFR by using MDRD formula. **Results and Conclusion:** The rise in total CK activity in hypothyroidism can be either due to increased leakage from muscles, increased turnover of muscle proteins or can be due to decreased clearance from the circulation. Increased serum creatinine level, decreased GFR and decline in creatinine clearance were obvious in overt hypothyroids. The elevation in serum creatinine levels in hypothyroidism can be due to skeletal muscle dysfunction with associated renal involvement.

Keywords: Creatinine, creatinine clearance, creatine kinase activity, eGFR, hypothyroidism, myopathy, TSH.

Introduction

Hypothyroidism is one of the most common endocrine disorders in the world resulting from insufficient production or diminished action of thyroid hormone. There are various causes for hypothyroidism and the clinical presentation depends on patient's age, gender, physical condition and others. The symptoms of the disease are often too vague to confirm the diagnosis and even those with overt hypothyroidism may present with subtle clinical presentation. Thyroid hormones are required for normal growth, development and function of nearly all the tissues with major effect on oxygen consumption. Thyroid hormone plays a crucial role in cell differentiation and helps to maintain metabolic homeostasis in the body. Thyroid stimulating hormone is a very sensitive and specific parameter for assessing thyroid function and has significance in early detection or exclusion of thyroid disorder [1]. Any alteration in the levels of thyroid hormone has profound influence on metabolic processes, consequently damaging various tissues and organs. Hypothyroidism causes reduced metabolic functions in the body such as decreased protein turnover, impaired carbohydrate metabolism and others. Hypothyroidism causes systemic effects either due to derangements in metabolic processes or due to myxoedematous infiltration including accumulation of glycosaminoglycans in the tissue of different organs including skeletal muscle, renal and others thereby causing organ dysfunction. Neuromuscular and musculoskeletal manifestations are often observed in cases of hypothyroidism during any time of the disease process [2]. Myopathy may be the sole clinical manifestation of hypothyroidism in some cases with rise in serum creatine kinase activity and rise in lactate dehydrogenase and aldolase levels [3]. Skeletal muscle may be the major source of increased plasma CK activity in hypothyroidism. Total CK activity is considered to be a sensitive and excellent biochemical marker for diagnosis of neuromuscular diseases [4]. An increase in the level of these enzymes represents an index of cellular necrosis and tissue damage. Hypothyroidism is a common cause of endocrine myopathy and should be considered in patients with unexplained persistent elevation of serum muscle enzymes, which are higher in patients with overt hypothyroidism and lower in subclinical hypothyroidism. Thyroid hormones are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. Kidney is involved in the metabolism and elimination of thyroid hormone. The decline in kidney function is accompanied by changes in the process of synthesis, secretion, metabolism and elimination of thyroid hormone. Thyroid hormone affects 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 change 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 to hypothyroidism includes elevation of serum creatinine level [6]. The aim of the study was to determine the influence of thyroid hormone on the creatine kinase activity and serum creatinine level in hypothyroidism and to determine the extent of renal involvement. The study

would further help to decipher whether the alteration in serum creatinine level is due to renal dysfunction or due to skeletal muscle involvement.

Materials and Methods

The study population consisted of about 50 clinically suspected and biochemically confirmed hypothyroid patients who visited the out-patient clinic of Department of Medicine and Endocrinology, M S Ramaiah Teaching Hospital, Bangalore. The control group included 50 healthy euthyroid subjects who attended the hospital for routine health check-up. A detailed history including drug history was taken from the patient.

Inclusion Criteria

1. Clinically diagnosed and biochemically confirmed hypothyroid cases in the age group of 25 to 55 years of either sex.
2. Patients were sub grouped based on T_3, T_4 and TSH values (Normal *reference range:* - T_3: 1.08–4.14 nmol/L, T_4: Males: 59-135 nmol/L, Females: 65-138 nmol/L, TSH: 0.5-4.3 μIU/ml). Group 1**:** Subclinical Hypothyroids included patients with normal T_3, T_4 but with raised TSH levels. Group 2**:** Overt Hypothyroids included patients with low T_3, T_4 and raised TSH levels.

Exclusion Criteria

Patients with impaired renal function (Serum creatinine > 1.2 mg/dl in females and >1.4 mg/dl in males), Patients with ischemic heart disease and cerebrovascular disease, Patients with hypertension and diabetes mellitus, Patients with rheumatoid arthritis, Duchenne's muscular dystrophy, polymyositis and other causes for transient increase in CK. Patients on drugs like statins, diuretics, antihypertensives, non-steroidal anti inflammatory drugs, steroids, oral contraceptives, lithium and amiodarone were excluded from the study

An 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 regimens which could influence the study. The ethical clearance was obtained from the institutional Ethical Review Board of the hospital. In the study population, demographic details were recorded, physical examination was done and anthropometric measurements were recorded. Blood samples after overnight fasting were collected from cases and controls in yellow vacutainers, devoid of any anticoagulant and contained clotting agent to hasten the process of clotting. The samples were centrifuged and the serum was separated at the earliest. The serum was used for the estimation of serum T_3, T_4, TSH, creatinine and total creatine kinase activity.

Serum T_3, T_4, TSH was estimated on the autoanalyser Roche/Hitachi COBAS e601 (Elecsys) by the electrochemiluminescence (ECLIA). Serum total Creatine kinase activity was estimated by IFCC NAC – Activated method. Serum Creatinine was estimated by Modified Jaffe's reaction. 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)]. eGFR (estimated Glomerular Filtration Rate) was calculated, using MDRD (Modification of diet in renal disease) formula. eGFR (ml/min/1.73 m^2) = 186 x (Plasma/serum creatinine mg/dl) $^{-1.154}$ x $(age)^{-0.203}$x (1.210 if black) x (0.742 if female) [7]. eGFR greater than 90ml/min/1.73 m^2 were considered to be normal.

Statistical analysis

The results are expressed as Mean ± SD. Significance was assessed at 5 % level of significance. Student t test (two tailed, independent) and analysis of variance (ANOVA) was used to find the significance of study parameters. Pearson correlation was used to study the relation between the various parameters.

Results

The data of the euthyroid controls and hypothyroid cases was compared with respect to serum T_3, T_4 (levels of thyroid hormone), TSH (thyroid stimulating hormone), Total CK activity, serum creatinine and creatinine clearance and glomerular filtration rate as eGFR. Depending on the value of TSH, T_3 and T_4, the hypothyroids were further sub grouped into overt and subclinical hypothyroidism. The distribution of age in cases and controls are shown in Table 1. The mean age of hypothyroids and controls were nearly same (Table 2). However, hypothyroidism was found more common in 25-35 years age group. The prevalence of hypothyroidism was higher among females (Fig 1). The increased predisposition of females is observed in overt and subclinical hypothyroids (Table 3). TSH was nearly ten times higher in overt cases when compared to subclinical cases (Table 5). TSH levels were nearly five folds higher in subclinical cases as compared to controls (Table 4, 5). The CK activity was highly significant in overt hypothyroids in comparison to its activity in subclinical cases ($p<0.001$) and controls (Table 6). But there was no significant change in CK activity between subclinical hypothyroids and controls ($p = 0.243$). A significant rise in serum creatinine levels was seen in overt cases as compared to subclinical cases and controls ($p<0.001$) (Table 6). The overt cases had serum creatinine levels towards the higher side of the physiological range as compared to other groups (Table 6). The creatinine clearance was significantly decreased in overt cases with mean value of 83.23±17.29 ml/min when compared to subclinical cases and controls ($p = 0.001$). eGFR was significantly decreased in overt cases as compared to subclinical cases and controls and are highly significant

with p value <0.001, which further substantiates for the decline in renal function in overt hypothyroids (Table 6). There was a significant correlation between T_3 and T_4 ($p<0.001$) in overt hypothyroids, indicating the fall in T_3 level is directly dependent on T_4 level of thyroid hormones (Table 7). In overt cases there was decrease in circulating levels of both hormones leading to significant increase in TSH secretion. There was a significant negative correlation between T_3 and total CK activity ($p<0.001$), T_3 and S. creatinine ($p = 0.007$) in overt and subclinical cases indicating decrease in T_3 levels may cause muscle and renal dysfunction (Table 7). There was highly significant negative correlation between T_4 and TSH in overt hypothyroids (Table 8). Due to decrease in T_4 levels there was increase in TSH secretion in overt cases. There was highly significant negative correlation of T_4 with S. creatinine ($p=0.005$) and CK ($p<0.001$) in overt cases indicating decrease of T_4 is associated with renal dysfunction and myopathy (Fig 2). There was highly significant positive correlation between TSH and CK activity in the study with p value<0.001 in both overt and subclinical cases (Table 9). With the rise in TSH level in hypothyroids an increase in serum CK activity was observed (Fig 3). However, the rise in CK activity was many folds higher in overt cases as compared to subclinical cases. There was a positive correlation also between S.creatinine and TSH, though only statistically significant in overt cases (p value = 0.010). There was a significant positive correlation between total CK activity and serum creatinine in overt cases with p value < 0.001 indicating the rise in S. creatinine may be due to rise in CK levels (Table 10) (Fig 4). There was significant negative correlation between eGFR and serum creatinine with p value < 0.001 (Table 11). Due to decrease in filtration rate increase in serum creatinine level is found in overt and subclinical hypothyroids. A significant positive correlation between eGFR and creatinine clearance in hypothyroids was noted indicating decrease in creatinine clearance is due to reduced filtration rate.

Discussion

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. Hypothyroids have decreased myocardial contractility, cardiac output and peripheral oxygen consumption with increase in peripheral vascular resistance. The increase in peripheral resistance can predispose to the alteration in renal hemodynamic such as reduced renal blood flow and diminution of glomerular filtration rate resulting in decrease in the clearance of certain substances like creatine kinase, creatinine and others in hypothyroidism. The decrease in T_3 level has been found to be associated with markers of inflammation like hsCRP, IL-6, malnutrition, increased endothelial dysfunction and cardiovascular mortality. The study shows elevation in serum total CK activity in hypothyroids as compared to controls (Table-6). The CK activity is four folds higher in overt hypothyroids as compared to subclinical hypothyroids. Hekimsoy *et al* have reported increased prevalence of skeletal muscle dysfunction in overt hypothyroids as compared to subclinical hypothyroids [8]. The increase in total CK activity may be due to increase in concentration of the enzyme in circulation as a result of leakage of the enzyme from muscle cells [9]. Nitric oxide synthase activity in hypothyroidism is found to be reduced in large vessels with increase in vascular tone. There may be decrease in renal blood flow thereby affecting the clearance of CK from the circulation [10]. A highly significant negative correlation is observed between T_3 and Total CK activity in overt hypothyroids (Table 7). The presence of T_3 receptors on the mitochondrial membrane of skeletal muscles suggests a direct effect of thyroid hormones on oxidative metabolism in muscles and may be one of the causes for muscle dysfunction in overt hypothyroidism [11]. The hypo-metabolic state of hypothyroidism can cause 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 [12, 13]. Robinson et.al have reported alteration in sarcolemmal membranes can cause increased cell permeability and leakage of CK from cells [14]. High serum CK concentration in hypothyroidism may be due to muscle fiber degeneration, altered muscle energy metabolism and decreased clearance of CK from circulation. Though high serum myoglobin concentrations have been reported in hypothyroid patients, the degree of elevation is considerably lower than that of serum creatine kinase. The slight elevation in CK activity in subclinical hypothyroids in the study may be due to release of CK from the skeletal muscles (Table 6). The pituitary gland releases TSH in response to suboptimal level of thyroid hormones, similarly the muscles may also respond by releasing CK into the circulation in subclinical hypothyroidism. Khaleeli *et al* have also reported elevation of serum CK activities correlating with the severity of hypothyroidism [15]. Hypothyroids had increased activity of CK, due to increased CK-MM isoenzyme which indicates skeletal muscle as the major source of the increased plasma CK activity [16]. A significant positive correlation was observed between TSH and CK activity in both overt and subclinical hypothyroids in the present study which indicates the influence of TSH on myopathy, though the rise in CK activity was nearly 4-5 times more in overt cases (Table

9). Skeletal muscles are more receptive to alteration in TSH level as compared to renal system. Long term stimulation of the thyroid gland by TSH leads to a decrease in the secretary response of the thyroid gland. This process of desensitisation can be due to decrease in the stimulation of adenylyl cyclase, exhaustion of the apical membranes available for macro pinocytosis or due to down regulation of the TSH receptors. However, significant negative correlation between T_3 and T_4 with CK activity in the study is indicative of the predominant role of decreased thyroid levels over and above the influence of TSH level in overt hypothyroids thereby influencing the release of CK from skeletal muscles (Table 7, 8). There is impaired glycogenolysis and impaired mitochondrial oxidative metabolism in hypothyroidism[12]. In subclinical hypothyroids, the process of mitochondrial oxidative dysfunction in skeletal muscle is initiated. Subclinical hypothyroids have less severe manifestations of myopathy and symptoms resolved with correction of hypothyroidism [17].

The effects of hypothyroidism on renal system includes changes in water and electrolyte metabolism, notably hyponatremia and alterations of renal hemodynamics including decrements in renal blood flow, GFR and single nephron GFR [18, 19]. Plasma renin activity, plasma levels of angiotensinogen, angiotensin II and aldosterone are on the lower side in hypothyroidism as their levels are directly related to plasma levels of thyroid hormones [20, 21]. Hypothyroidism is associated with negative inotropic and chronotropic effect on cardiovascular system with increased vascular resistance due to reduced nitric oxide synthase activity. High vascular resistance and low cardiac output in hypothyroidism results in reduced renal blood flow [10]. The study shows a significant increase in serum creatinine in overt hypothyroids (p value <0.001) when compared with controls and subclinical hypothyroids (Table 6). Tayal *et al* have also reported significant elevation in serum creatinine levels in hypothyroids but elevation being more in overt hypothyroids as compared to subclinical hypothyroids [22]. In the present study, there is significant correlation between T_3 and T_4 with S.creatinine in overt cases (Table 7, 8). This shows the influence of T_3 and T_4 is more relevant than the influence of TSH on renal function. There is significant correlation between TSH and CK activity in both overt and subclinical cases but correlation between TSH and creatinine is not very significant, indicates there is skeletal muscle involvement before renal dysfunction. The renal involvement in hypothyroidism is evident by a highly significant correlation of eGFR with serum creatinine and creatinine clearance in both overt and subclinical hypothyroids (Table 11). Kreisman *et al* have reported the rise in serum creatinine level can be due to a decrease in the GFR and is a reversible condition [23]. The cause for decrease in GFR can be due to hypodynamic circulation in hypothyroidism. In the study there is decrease in GFR in overt hypothyroids as compared to other groups (Table 6). The cause for elevation of serum creatinine can be either due to decrease in GFR or due to decrease in renin levels consequently reducing the activity of renin angiotensin system [24, 25]. The other mechanisms involved in hypothyroidism-associated kidney derangements includes direct effect of thyroid hormone on the cardiovascular system (increased peripheral resistance and reduction of myocardial contractility and stroke volume) and indirect effect via paracrine or endocrine mediators, such as insulin-like growth factor type 1 (IGF-1) and vascular endothelial growth factor [26]. There is decreased sensitivity to β-adrenergic stimulus and decreased renin release, along with decreased angiotensin II levels and impaired RAAS activity resulting in decreased filtration rate [24, 27, 28]. The rise in serum creatinine levels in overt hypothyroidism can be partly due to the influence of T_3, T_4 and TSH on renal function and also due to rise in CK activity. A highly significant correlation between thyroid hormone and total CK activity in overt hypothyroidism is indicative of the decisive role, the thyroid hormones have on oxidative metabolism in muscles. The renal dysfunction in hypothyroidism can be due to decrease in renal plasma flow and associated reduction in glomerular filtration rate [10, 23]. Increased serum creatinine level, decreased eGFR and decline in creatinine clearance are observed in hypothyroidism and are more obvious in overt hypothyroids. Due to reduction in GFR, there is decrease in clearance of creatinine and creatine kinase in hypothyroidism. The rise in CK activity and serum creatinine could be either due to reduced clearance or due to overproduction or both [8, 9, 28].

Conclusion

An alteration in thyroid hormone levels influences the function of skeletal muscle with associated decreases in renal perfusion and filtration capacity. The skeletal muscle involvement precedes renal dysfunction in hypothyroidism. The elevation of serum creatinine levels in hypothyroidism is due to skeletal muscle dysfunction with associated increase in total creatine kinase activity and also partly due to renal involvement. However, further studies are required in large population to provide better understanding of the biological significance of the effect of changes in thyroid hormone levels will have on musculoskeletal and renal dysfunction.

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Table 1: Age distribution of hypothyroids and controls (Mean ± SD)

Age in years	Hypothyroids		Controls	
	No	%	No	%
25-35	29	58.0	23	46.0
36-45	13	26.0	16	32.0
46-55	8	16.0	11	22.0
Total	50	100.0	50	100.0
Mean ± SD	35.40±9.41		36.84±10.44	

Table 2: Comparison of age in overt and subclinincal hypothyroids (Mean ± SD)

Variables	Hypothyroids		P value
	Overt	Subclinical	
Age in years	32.86±9.74	37.55±8.73	0.079+

Table 3: Gender distribution in overt and subclinical hypothyroids

Gender	Hypothyroid Cases (sub group)			
	Overt		Sub clinical	
	No	%	No	%
Male	9	39.1	2	7.4
Female	14	60.8	25	92.6
Total	23	100.0	27	100.0

Table 4: Comparison of thyroid profiles in hypothyroids and controls (Mean ± SD)

Thyroid parameters	Hypothyroids	Controls	P value
T_3 nmol/L	1.21±0.54	1.82±0.32	<0.001**
T_4 nmol/L	57.91±34.13	103.12±20.22	<0.001**
TSH µIU/ml	58.24±59.75	2.54±0.81	<0.001**

Table 5: T_3, T_4 and TSH levels in overt and subclinical hypothyroids (Mean ± SD)

Thyroid parameters	Hypothyroids		P value
	Overt	Subclinical	
T_3 nmol/L	0.69±0.20	1.64±0.30	<0.001**
T_4 nmol/L	24.72±14.66	86.19±14.44	<0.001**
TSH µIU/ml	113.24±45.60	11.39±3.56	<0.001**

Table 6: Comparison of biochemical parameters in overt and subclinical hypothyroids and controls (Mean ± SD)

Biochemical parameters	Overt	Subclinical	Controls	p value		
				Overt-Controls	Subclinical-controls	Overt-subclinical
Total CK activity IU/L	549.10±121.24	86.70±19.96	62.52±30.67	<0.001**	0.243	<0.001**
S.creatinine mg/dl	1.05±0.21	0.74±0.12	0.74±0.15	<0.001**	0.996	<0.001**
Creatinine clearance (ml/min)	83.23±17.29	104.91±23.75	109.24±32.11	0.001**	0.784	0.001**
eGFR (ml/min)	75.39±16.49	99.88±22.53	104.64±26.76	0.001**	0.682	<0.001**

Table 7: Pearson correlation of T_3 with T_4, TSH, CK, S. Creatinine, Creatinine clearance and eGFR in overt and subclinical hypothyroids

Pair	Overt		Sub clinical	
	r value	p value	r value	p value
T_3 nmol/L vs T_4 nmol/L	0.902	<0.001**	0.199	0.320
T_3 nmol/L vs TSH µIU/ml	-0.791	<0.001**	-0.175	0.381
T_3 nmol/L vs CK activity IU/L	-0.785	<0.001**	0.060	0.767
T_3 nmol/L vs S.creatinine (mg/dl)	-0.543	0.007**	-0.140	0.485
T_3 nmol/L vs Creatinine clearance (ml/min)	0.048	0.823	0.306	0.121
T_3 nmol/L vs eGFR(ml/min)	0.254	0.243	0.339	0.084+

Table 8: Pearson correlation of T_4 with TSH, CK, S.creatinine, Creatinine clearance and eGFR in overt and subclinical hypothyroids

Pair	Overt		Sub clinical	
	r value	p value	r value	p value
T_4 nmol/L vs TSH µIU/ml	-0.791	<0.001**	-0.893	<0.001**
T_4 nmol/L vs CK activity IU/L	-0.836	<0.001**	-0.628	<0.001**
T_4 nmol/L vs S.creatinine (mg/dl)	-0.566	0.005**	0.065	0.747
T_4 nmol/L vs Creatinine clearance (ml/min)	0.019	0.931	-0.102	0.614
T_4 nmol/L vs eGFR (ml/min)	0.234	0.283	0.042	0.835

Table 9: Pearson correlation of TSH with CK, S.creatinine, Creatinine clearance and eGFR in overt and subclinical hypothyroids

Pair	Overt		Sub clinical	
	r value	p value	r value	p value
TSH µIU/ml vs CK activity IU/L	0.832	<0.001**	0.734	<0.001**
TSH µIU/ml vs S. creatinine (mg/dl)	0.528	0.010*	-0.043	0.833
TSH µIU/ml vs Creatinine clearance (ml/min)	0.011	0.960	0.070	0.730
TSH µIU/ml vs eGFR (ml/min)	-0.251	0.247	-0.004	0.986

Table 10: Pearson correlation of CK activity with S.creatinine, Creatinine clearance and eGFR in hypothyroids

Pair	Overt		Sub clinical	
	r value	p value	r value	p value
CK activity (IU/L) vs S. creatinine (mg/dl)	0.632	<0.001**	0.208	0.298
CK activity (IU/L) vs Creatinine clearance (ml/min)	0.034	0.876	-0.060	0.765
CK activity (IU/L) vs eGFR (ml/min)	-0.265	0.222	-0.088	0.664

Table 11: Pearson correlation of eGFR with other profiles in Overt and Subclinical hypothyroidism

Pair	Overt		Sub clinical	
	r value	p value	r value	p value
eGFR(ml/min) vs T_3 (nmol/L)	0.254	0.243	0.339	0.084+
eGFR(ml/min) vs T_4 (nmol/L)	0.234	0.283	0.042	0.836
eGFR(ml/min) vs TSH (µIU/ml)	-0.251	0.247	-0.004	0.986
eGFR (ml/min) vs CK activity (IU/L)	-0.266	0.222	-0.080	0.664
eGFR (ml/min) vs S.creatinine (mg/dl)	-0.715	< 0.001**	-0.869	<0.001**
eGFR(ml/min) vs Creatinine clearance (ml/min)	0.775	<0.001**	0.916	<0.001**

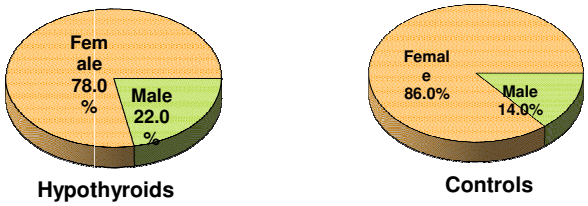

Figure 1: Gender distribution in hypothyroid cases and controls

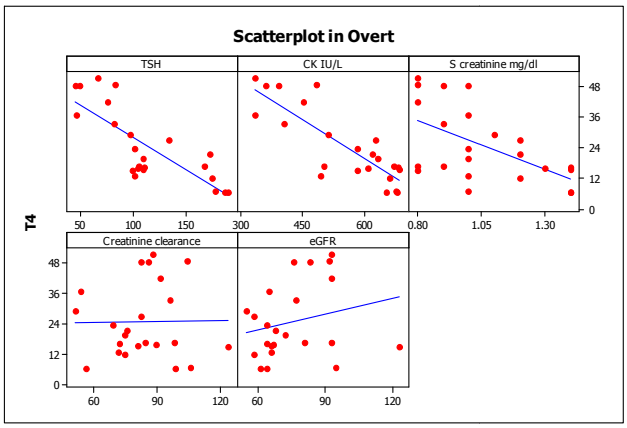

Figure 2: Scatter plot of T_4 with TSH, CK, S. Creatinine, Creatinine clearance and eGFR in overt hypothyroids

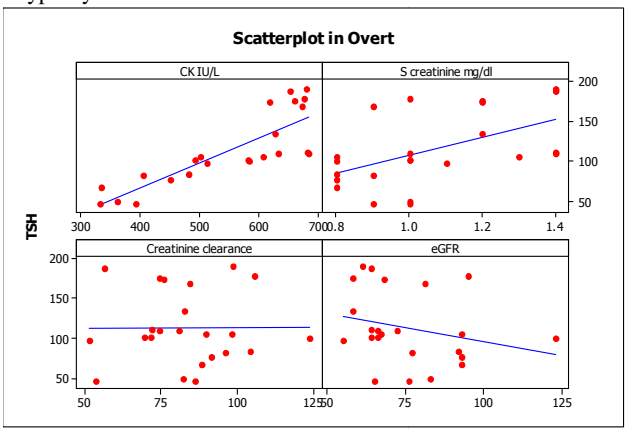

Figure 3: Scatter plot of TSH with CK, S. creatinine, Creatinine clearance and eGFR in overt cases

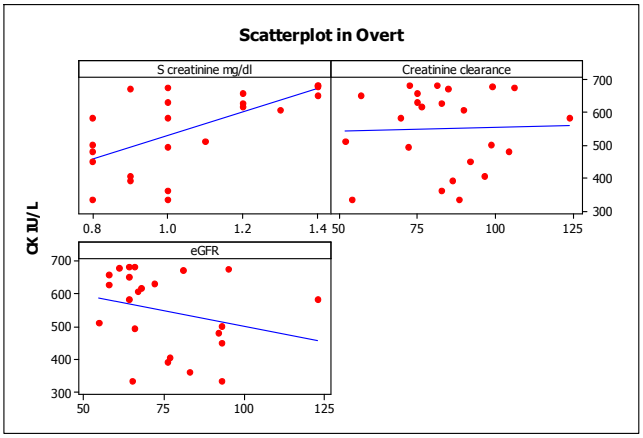

Figure 4: Scatter plot between CK activity and S. Creatinine, Creatinine clearance and eGFR in overt hypothyroid cases