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Original Research Article

Degree of Renal Dysfunction in Patients of Subclinical and Overt Hypothyroidism

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Abstract
Background: *Thyroid hormones deficiency may lead to impaired renal function either directly or indirectly. Impaired renal function is characterized by increased serum creatinine and decreased creatinine clearance. This study was intended to evaluate the level of serum creatinine and creatinine clearance in both subclinical and overt hypothyroid patients.*
Materials and Methods*: 104 hypothyroid patients were divided in two equal groups namely subclinical and overt hypothyroids based on their serum TSH levels. 52 age, sex and weight matched euthyroid controls were used for comparison.*
Result: *Significantly raised serum creatinine was found in overt hypothyroids as compared to both subclinical hypothyroids and controls. Creatinine clearance was found significantly low in overt hypothyroids as compared to controls.*
Conclusion: *Decrease in creatinine clearance was found more profound as compared to increase in serum creatinine in hypothyroids. Thus creatinine clearance is better early marker for renal dysfunction in hypothyroids.*

Introduction

Hypothyroidism may result in significant reversible changes in renal function.

Hypothyroidism causes hypodynamic state which may lead to impairment in the concentrating and diluting capacities of the distal tubules. There is decreased sodium resorption in the proximal tubules which causes hyponatremia leading to low blood pressure and a decrease in renal blood flow and GFR. A decrease in myocardial contractility and cardiac output is seen in hypothyroidism which causes increased peripheral resistance resulting in systemic and renal vasoconstriction. This also leads to decreased renal blood flow causing decrease in GFR, increase in serum creatinine and a decrease in creatinine clearance. There is thickening of basement membrane which again causes reduced blood flow to the kidneys, so there is decreased creatinine clearance.[1]

Thyroid hormones increase the concentration of renin and angiotensinogen in the serum which influence the maturation of renin angiotensin system. Hypothyroidism leads to vasoconstriction and increased peripheral resistance leading to reduced blood flow in the renal arteries.[2] Hypothyroid myopathy may lead to increased release of creatinine from muscles resulting in a high level of serum creatinine in the circulation without altering GFR.[3]

Thyroid hormones are responsible for the growth and development of the kidneys. Hypothyroidism affects the transportation of substances through the membrane and modifies the electrolyte metabolism leading to deficit in renal function. Low thyroid hormone level can also cause glomerulopathy (nephrotic or nephritic syndr-ome), chronic kidney disease, which may worsen the prognosis in these patients.

Hypothyroidism can also result in kidney derangements through paracrine or endocrine mediators such as insulin like growth factor type 1 and vascular growth factors. It has also been seen that most kidney abnormalities caused by hypothyroidism can be reverted after supplementation with thyroxin.[4]

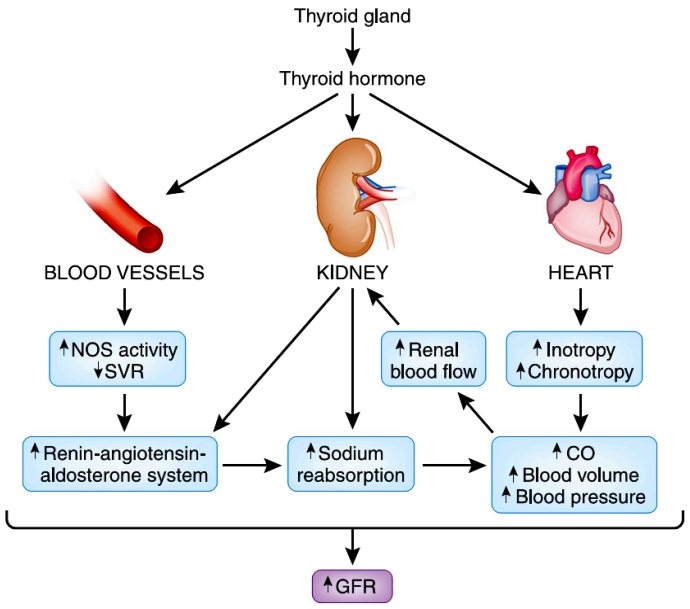

Figure 1: Multiple direct and indirect effects of thyroid hormone on GFR[5] NOS- nitric oxide synthase; SVR- systemic vascular resistance; CO-cardiac output

Aim

Our study was aimed to compare the serum creatinine and creatinine clearance of subclinical and overt hypothyroid patients. An effort was also done to correlate the levels of serum creatinine and creatinine clearance with T3, T4 and TSH in subclinical and overt hypothyroid patients.

Material and Methods

The present study was conducted in the Department of Biochemistry of Govt. medical college, Nagpur with cooperation from Medicine Department of the institute during period of May 2014 to October 2015. The study was approved by institutional Ethics Committee for research work. It was a Cross sectional comparative study.

The study consisted of 3 groups of 52 subjects each between 18-72 years of age as follows:

1. Subclinical hypothyroidism (TSH 3.6-10 µlU/mL)
2. Overt hypothyroidism (TSH >10µlU/mL)
3. Age, sex and weight matched controls (Table1,2,3)

Patients with severe infections, renal diseases, hepatobiliary diseases, diabetes mellitus, heart diseases, past history of hyperlipidemia, myopa-thies, pregnancy, patient taking lipid lowering agents, alcohol users and smokers were excluded from the study.

Serum T3, T4 and TSH were measured by quantitative solid phase enzyme linked immunsorbent assay. Serum creatinine was estimated by Modified Jaffe's reaction (Initial rate). Creatinine clearance was calculated by using Cockcroft Gault formula and expressed in ml/min/1.73m².

Data was analyzed using Analysis of Variance (ANOVA), Bonferroni test, Karl pearsons correlation and Chi square test. $P < 0.05$ was considered to be statistically significant and $P < 0.001$ was taken as statistically highly significant.

Results

Table 1: Age distribution of study subjects

	Controls (n=52)	Subclinical hypothyroids (n=52)	Overt hypothyroids (n=52)	ANOVA F value	*P* value
Age (yrs.) Mean ± SD	37.75 ± 9.85	38.19 ± 9.53	39.84 ± 11.46	0.59	0.55

Table 2: Sex distribution of study subjects

Gender	Controls	Subclinical hypothyroids	Overt hypothyroids	Chi square value	*P* value
Females	42 (80.8%)	43 (82.7%)	44 (84.6%)	0.2687	0.874
Males	10 (19.2%)	9 (17.3%)	8 (15.4%)		
Total	52	52	52		

Table 3: Weight distribution of study subjects

	Controls (n=52)	Subclinical hypothyroids (n=52)	Overt hypothyroids (n=52)	ANOVA F value	*P* value
Wt. (Kg)	57.96 ± 7.77	58.13 ± 8.41	58.51 ± 8.46	0.062	0.939

Table 4: Comparison of T3, T4 and TSH among controls, subclinical and overt hypothyroids (by using ANOVA test)

	Controls (n=52)	Subclinical hypothyroids (n=52)	Overt hypothyroids (n=52)	ANOVA F value	*P* value
T3 (ng/ml)	0.87 ± 0.27	0.77 ± 0.30	0.59 ± 0.27	12.8	<0.001
T4 (µg/dl)	8.42 ± 2.38	7.15 ± 2.68	4.91 ± 3.13	21.66	<0.001
TSH (µIU/ml)	2.13 ± 1.13	6.18 ± 1.48	19.83 ± 5.55	390.85	<0.001

Table 5: Comparison of mean of serum creatinine and creatinine clearance in the study groups (ANOVA test)

	Controls (n=52)	Subclinical hypothyroids (n=52)	Overt hypothyroids (n=52)	ANOVA F value	*P* value
Serum creatinine (mg/dl)	0.77 ± 0.13	0.8 ± 0.12	0.87 ± 0.14	6.95	0.001
Creatinine clearance (ml/min)	94.8 ± 17.2	90.8 ± 17.65	82.82 ± 16.05	6.7	0.001

Table 6: Pairwise comparison of the mean difference of serum creatinine and creatinine clearance among the study groups (by using Bonferroni test)

	Compared Groups		Mean difference	*P* value
Serum creatinine (mg/dl)	Controls	Subclinical hypothyroids	-0.03	0.831
		Overt hypothyroids	-0.1	0.001
	Subclinical hypothyroids	Overt hypothyroids	-0.07	0.035
Creatinine clearance (ml/min)	Controls	Subclinical hypothyroids	4	0.695
		Overt hypothyroids	11.98	0.001
	Subclinical hypothyroids	Overt hypothyroids	7.98	0.053

Table 7: Correlation of serum creatinine & creatinine clearance with T3, T4 and TSH in the study groups

	Groups	T3		T4		TSH	
		r value	*P* value	r value	*P* value	r value	*P* value
Serum creatinine	Controls	-0.065	0.647	-0.2089	0.137	0.0013	0.992
	Subclinical hypothyroids	-0.0382	0.788	0.1296	0.359	-0.0083	0.953
	Overt hypothyroids	0.052	0.714	-0.0589	0.678	0.1824	0.195
Creatinine clearance	Controls	0.0048	0.973	0.0421	0.766	-0.0214	0.88
	Subclinical hypothyroids	0.1414	0.317	-0.0914	0.519	0.0533	0.707
	Overt hypothyroids	-0.0989	0.485	0.2503	0.073	-0.2709	0.052

Discussion

There is generalized hypodynamic state of the circulatory system in hypothyroidism. It results in decreased renal plasma flow and associated reduction in GFR. Due to reduction in GFR, there is decrease in clearance of creatinine. The rise in creatinine could be due to reduced clearance. The present study shows that there was statistically significant increase in serum creatinine among overt hypothyroids as compared to both controls and subclinical hypothyroids (Table 6) which is in accordance with the study of Tayal et al[2], Claus et al[6] and Ledo et al[7]. Rodrigo et al[8] observed several cases of acute renal failure in untreated hypothyroidism. Still the exact pathogenesis is unclear and thought to be multifactorial. The principal mode of kidney injury is thought to be the reduced plasma flow and reduced glomerular filtration rate due to the hypodynamic circulation. It leads to a pre-renal insufficiency and this may be aggravated by other systemic effects of hypothyroidism such as low volume state, reduced cardiac output, hyponatraemia with associated hemodynamic changes and increased peripheral resistance due to arterial wall stiffness. There is primary glomerular and tubular dysfunction in hypothyroidism with thickening of glomerular and tubular basement membranes and inclusions in cell cytoplasm with supportive histological evidence from biopsy specimens. Another rare manifestation of hypothyroidism is rhabdomy-olysis that can also result in acute kidney injury. These changes are reversible with thyroxine treatment.

There was no statistical significance in the mean difference of serum creatinine between controls and subclinical hypothyroids (Table 6). This finding is in accordance with the study done by Park et al[9] which emphasizes that though glomerular and tubular function is influenced by thyroid status, it is very unusual to have a significant rise in serum creatinine in patients with subclinical hypothyroidism, but the finding is in contrast to study of Adrees et al[10] in which serum creatinine was found to be higher and estimated glomerular filration rate was reduced in women with subclinical hypothyroidism than normal subjects. No statistically significant correlation was found between serum creatinine and thyroid profile in both groups of hypothyroids (Table 7).

Study showed that there was a statistically significant decrease in creatinine clearance among overt hypothyroid subjects than controls (Table 6). This finding is in accordance with findings reported by Claus et al[6] and Rio et al[3]. There was no significant change in creatinine clearance in subclinical hypothyroids as compared to controls (Table 6). This is in contrast to earlier studies of Muhammad et al[11] which illustrates that renal dysfunction can be seen across the whole spectrum of severity of hypothyroidism including subclinical hypothyroidism. The mean difference of creatinine clearance between subclinical and overt hypothyroids was also not found statistically significant (Table 6). No statistically significant correlation was found between creatinine clearance and thyroid profile in both groups of hypothyroids (Table 7). In this study, both

increase in serum creatinine and decrease in creatinine clearance were found highly significant in overt hypothyroids as compared to controls. Though serum creatinine was increased significantly in overt hypothyroids as compared to controls but still its level was found in the normal range. However creatinine clearance in overt hypothyroids was found below normal range. This shows that creatinine clearance is a more sensitive marker for the renal dysfunction.

Conclusion

Study concludes that overt hypothyroidism leads to impaired renal function which is manifested by changes in serum creatinine and creatinine clearance. If a hypothyroid patient is having normal serum creatinine level, that doesn't mean that he is not having any amount of renal dysfunction. As creatinine clearance falls much before there is a rise in serum creatinine level, it can be used as an early marker of renal dysfunction in hypothyroids. Beside, if a person has normal serum creatinine level but decreased creatinine clearance without any obvious signs and symptoms of renal disease, hypothyroidism may be the cause and thyroid function test should be done.

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