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ABNORMALITIES OF THYROID FUNCTION IN SUBJECTS WITH CHRONIC KIDNEY DISEASE

General Medicine

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ABSTRACT

Background: The relation between severity of renal failure and thyroid dysfunction is not clear. Thus we aimed to study the abnormalities of thyroid function in patients with chronic kidney disease.
Methodology: This hospital based observational analytical case control study included 100 subjects with CKD early stage 1, 2 and 3a in group 1 and 100 subjects with CKD late stage 3b, 4 and 5 as defined by criteria for CKD. Subject with early CKD and late CKD were compared for demographic data, clinical features, examination findings and thyroid function tests.
Results: Significantly higher frequency of symptoms specific for thyroid dysfunction was noted in late CKD subjects. Also renal function tests and thyroid function test were found to be significantly deranged in subjects in late CKD stages.
Conclusion: Symptoms of hyperthyroid state are significantly frequent in early stages of CKD while, hypothyroidism is more frequent in late stages.

KEYWORDS

Chronic kidney disease, End stage renal disease, Hypothyroidism, Hyper-thyroidism.

Introduction

Chronic kidney disease (CKD) is a major and prevalent health problem worldwide, affecting millions.[1] The disease includes a spectrum of distinct pathophysiological processes associated with abnormal kidney function and a progressive reduction in glomerular filtration rate [2,3]. 1 The Global Burden of Disease (GBD) study 20152 ranked chronic kidney disease 17th among the causes of deaths globally (age standardised annual death rate of 19·2 deaths per 100 000 population). In India, GBD 2015 ranks chronic kidney disease as the eighth leading cause of death.[4] In India Deaths due to renal failure constituted 2·9% of all deaths in 2010–13 among 15–69 year-olds.[5]

CKD occurs due to irreversible loss of renal function leading to metabolic, endocrine, excretory and synthetic function resulting in accumulation of non – protein nitrogenous substances, a reason for metabolic derangements. End stage renal disease is described as a terminal stage of chronic kidney disease that without any replacement therapy patients could not survive would result in death.[6] In spite of diverse etiologies, CKD is the final common pathway of irreversible loss of nephrons finally resulting in alteration of "milieu interior" affecting every system in the body including thyroid hormonal system. The functions of thyroid and kidney are interrelated.[6-8]

The thyroid hormones are essential for growth and development of the kidney and for maintaining electrolyte and water homeostasis. Excretion of iodine is reduced in advanced renal failure leading to elevated serum levels of inorganic iodide that potentially blocks thyroid hormone production resulting in —Wolff Chaikoffll effect.[9] CKD is associated with low levels of serum total and free T3 concentration and normal reverse T3 and free T4 levels. The TSH levels are almost normal in most patients and found to be in euthyroid state. Previous studies have reported abnormalities like hypothyroidism, hyperthyroidism and euthyroid state have been reported in the studies done previously.[6-13] Variable levels of serum T3 and T4 despite normal TSH levels have been reported in most patients of CRF. The incidence of goitre has also been variably reported in literature.[13-17] A study had reported reversion of thyroid function to normal after successful renal transplantation.[14]

Exact relationship between thyroid diseases and CKD remains to established under the light of various stages of CKD and thyroid dysfunction. Further, the lack of data is highlighted in this very region of Central India. Thus we aimed to study the abnormalities of thyroid function in patients with chronic kidney disease.

Material and methods

This hospital based observational analytical case control study with cross sectional data collection was performed in the Department of Medicine, in Shri Balaji Institute of Medical Science, Raipur. The study included 100 subjects with CKD early stage 1, 2 and 3a in group 1 and 100 subjects with CKD late stage 3b, 4 and 5 as defined by criteria for CKD. All subjects with symptoms of uraemia for 3 months or more, elevated blood urea, serum creatinine and decreased creatinine clearance, ultra sound evidence of chronic renal failure, supportive laboratory evidence of CRF like anaemia, low specific gravity, changes in serum electrolytes, etc and radiological evidence of renal osteodystrophy were included in the study. Patients with nephrogenic range of proteinuria, low serum protein especially albumin, other conditions like acute illness, Recent surgery, trauma or burns, diabetes mellitus, liver diseases, drugs altering thyroid profile like amiodarone, steroids, dopamine, phenytoin, beta-blocker, estrogen pills, iodine-containing drugs or those undergoing peritoneal dialysis or haemodialysis were excluded from the study.

After obtaining informed written consent details history was sought and relevant examination was performed. Investigations present with the subjects were assessed which was followed by routine and microscopic urine examinations, peripheral smear for anemia and burr cells investigation. Blood urea, serum creatinine, creatinine clearance (using Cockroft-Gault formula), Serum electrolytes including calcium and phosphorous, serum cholesterol, 24 hour urine protein and serum protein were performed using clinical chemistry analyser using manufacturer's protocol. Serum triiodothyronine (T3), serum thyroxine (T4) and serum thyroid stimulating hormone (TSH) was performed by electrochemiluminiscenceanalyzer using manufacturer's protocol.

Data was expressed as percentage ,mean ± S.D and Median (Range). Kolmogorove-Smirnove analysis was performed for checking linearity of the data.Student's t test was used to check the significance of difference between two parameters in parametric data and Mann Whitney U test was used to check the significance of difference between two parameters in non parametric data.Fischer's exact test or Chi square test was used to analyze the significance of difference between frequency distribution of the data.Relative risk/odd's ratio was calculated. P value <0.05 was considered as statistically significant.SPSS© for windows™ Vs 17, IBM™ Corp NY and Microsoft excel™ 2007, Microsoft® Inc USA was used perform the statistical analysis.

Results and observations:

Distribution of study subjects in severity of CKD is mentioned in Table 1. Maximum subjects (70 subjects, 35%) were in stage 1. 100 Subjects were in early CKD stage while rest 100 subjects were in late CKD staging. **(Table 1)**

Table 1: Frequency of various stages of CKD in study subjects

		Frequency	Percent
CKD stages	1	70	35.0
	2	27	13.5
	3a	3	1.5
	3b	29	14.5
	4	44	22.0
	5	27	13.5
CKD staging	Early	100	50.0
	Late	100	50.0

Both groups were found to be matched for gender distribution and occupation. Symptoms of hyperthyroidism were found to be significantly frequent in subjects with early CKD. Slow movement (p=0.010), delayed ankle reflex (p=0.019), Coarse skin (p=0.028), peri orbital puffiness (0.001) and cold skin (p=0.034) we found to be significantly higher in subjects with late CKD. **(Table 2)**

Table 2: Baseline characteristics of study subjects

		CKD		Total	P value
		Early	Late		
Age (years)	</=4	42	14	56	**<0.0001**
		42.0%	14.0%	28.0%	
	41-50	21	31	52	
		21.0%	31.0%	26.0%	
	51-60	23	26	49	
		23.0%	26.0%	24.5%	
	61-70	8	21	29	
		8.0%	21.0%	14.5%	
	>70	6	8	14	
		6.0%	8.0%	7.0%	
Gender	Female	49	46	95	**0.389**
		49.0%	46.0%	47.5%	
	Male	51	54	105	
		51.0%	54.0%	52.5%	
Socioeconomic status	Lower	4	9	9	**0.027**
		4.0%	9.0%	4.5%	
	Upper lower	34	22	56	
		34.0%	22.0%	28.0%	
	Lower middle	27	33	60	
		27.0%	33.0%	30.0%	
	Upper middle	35	33	68	
		35.0%	33.0%	34.0%	
	Upper	0	3	3	
		0.0%	3.0%	1.5%	
Occupation	Businessman	17	18	35	**0.382**
		17.0%	18.0%	17.5%	
	Executive	20	11	31	
		20.0%	11.0%	15.5%	
	Housewife	33	41	74	
		33.0%	41.0%	37.0%	
	Labourer	0	1	1	
		0.0%	1.0%	0.5%	
	Service	8	5	13	
		8.0%	5.0%	6.5%	
	Unemployed	22	24	46	
		22.0%	24.0%	23.0%	
Symptoms	Diminished sweating	3	8	11	**0.107**
		3.0%	8.0%	11.0%	
	Hoarseness	2	6	8	**0.306**
		2.0%	6.0%	8.0%	
	Paraesthesia	21	29	50	**0.126**
		21.0%	29.0%	50.0%	
	Dry skin	18	26	44	**0.116**
		18.0%	26.0%	44.0%	
	Constipation	31	39	70	**0.150**
		31.0%	39.0%	70.0%	
	Symptoms of hyperthyroidism	12	1	13	**0.001**
		12.0%	1.0%	13.0%	
Signs	Impairment of hearing	3	4	7	**0.5**
		3.0%	4.0%	7.0%	
	Weight gain	18	21	39	**0.361**
		18.0%	21.0%	39.0%	
	Slow movements	7	19	26	**0.010**
		7.0%	19.0%	26.0%	
	Delayed ankle reflex	11	23	34	**0.019**
		11.0%	23.0%	34.0%	
	Coarse skin	11	22	33	**0.028**
		11.0%	22.0%	33.0%	
	Peri orbital puffiness	15	35	50	**0.001**
		15.0%	35.0%	50.0%	
	Cold skin	16	34	50	**0.003**
		16.0%	34.0%	50.0%	

Serum urea (p<0.0001) and serum creatinine (p<0.0001) were found to be significantly raised, while Creatinine clearance was found to be significantly low in subjects with late CKD. While T3 and T4 were found to be significantly lower in late CKD stages (p<0.0001 and p=0.010 respectively), TSH levels were found to be matched. **(Table 3)**

Table 3: Comparison of renal function tests in early and late CKD subjects

		CKD	Mean	S.D	S.E Mean	T	P value
Renal function tests	Serum Urea (mg/dl)	Early	24.58	6.83	0.68	-19.40	**<0.0001**
		Late	67.61	21.11	2.11		
	Serum creatinine (mg/dl)	Early	0.73	0.29	0.03	-22.17	**<0.0001**
		Late	2.69	0.83	0.08		
	Creatinine clearance	Early	114.05	50.66	5.07	17.30	**<0.0001**
		Late	24.29	11.24	1.12		
Thyroid function test	T3 (ng/ml)	Early	1.0041	.47432	.04743	3.781	**<0.0001**
		Late	.7859	.32860	.03286		
	T4 (mcg/dl)	Early	10.2520	9.68112	.96811	2.607	**.010**
		Late	7.6550	2.35051	.23505		
	TSH	Early	5.3080	12. 76298	1. 27630	-.403	**.687**
		Late	5.9878	11. 00338	1. 10034		

Significant association was observed indicating higher frequency of hyperthyroid state in early CKD and hypothyroid state in late CKD (p=0.014). **(Table 4)**

Table 4 : Association between Thyroid status and CKD staging

Thyroid status		CKD		Total	P value
		Early	Late		
	Hyperthyroid	8	1	9	0.014
		8.0%	1.0%	4.5%	
	Euthyroid	76	72	148	
		76.0%	72.0%	74%	
	Hypothyroid	16	27	43	
		16.0%	27.0%	21.5%	
Total		100	100	200	
		100.0%	100.0%	100.0%	

Discussion:

In our study early CKD subjects were showing higher frequency in youger age groups, indicating that CKD staging increases with age. The groups were found to be matched for gender distribution thus excluding any bias related to gender. It was noted that socioeconomic status has impact on staging of kidney disease. While no such impact was visible in case of occupation and groups were found to be matched for occupation. While other symptoms viz. diminished sweating, hoarseness, paresthesia, dry skin, constipation were found to be matched between both early and late CKD groups, Symptoms of hyperthyroidism were found to be significantly frequent in early CKD. Serum urea and serum creatinine were found to be significantly raised, while Creatinine clearance was found to be significantly low in subjects with late CKD. These findings are as per expected. In this study while T3 and T4 were

found to be significantly lower in late CKD stages, TSH levels were found to be matched. Significant association was observed between Thyroid status and CKD staging indicating higher frequency of hyperthyroid state in early CKD and hypothyroid state in late CKD. In late CKD stages, the mean values of both serum T3 & T4 were significantly low. This is comparable to Ramirez *et al*.[13]and Lim VS *et al*.[17]study. In our study, out of 50 patients 27 patients (54%) had low T3 syndrome. The prevalence of low T3 in stage 1- 3 is 20 %, for stage 4 is 38%, and stage 5 is 70%. This observation is consistent with Sang Heon Song *et al*.[11] in which the prevalence of low T3 will be increased according to the increase in stage of CKD. In our study there is a positive correlation between Total T3 , indicating serum T3 levels were associated with severity of CKD even in the normal TSH level.

Our observation is consistent with Joseph *et al*.[18] who studied 175 patients of CRF who had low T3, T4, fT4 but had high TSH levels suggested maintenance of pituitary thyroid axis. 48 patients i.e. 96% reported normal level of serum TSH ≤5 µIU/ml out of which, 25 patients had normal level of serum TSH in spite of low serum T3 level. They demonstrated abnormality in the hypophyseal mechanism of TSH release in uremic patients as the TSH response to TRH was blunted. These results are consistent with study of Spector *et al*[15] and Ramirez *et al*[13] reported normal level of serum TSH in patients of CRF in spite of low serum T3 levels. In Mehta H.J. *et al*.[18] study, low T3, FT3 and T4 values are seen in clinically euthyroid CKD patients. However finding of normal T4 values and TSH would indicate functional euthyroid status. It can be presumed that free T4 values would fall if these patients develop hypothyroidism and TSH values would rise simultaneously. Thus Free T4 and TSH levels combined can be used for the diagnosis of hypothyroidism in presence of CKD.

Ramirez *et al*[13] reported high prevalence of goiter in CRF patients especially those on chronic dialysis. Incidences were increased in end stage renal disease. The possible explanation is due to accumulation of iodides in thyroid gland due to decreased renal clearance in CRF patients. Study conducted by Hegedus *et al*[19] showed thyroid gland volume was significantly increased in patients with CRF. Dudani *et al*[20] and Karunanidhi *et al*[21] also depicted abnormality in hypophyseal mechanism of TSH release in uraemic patients as the TSH response to the TRH was blunted. Beckett *et al* [22], Ajil Singh *et al*[23], P Iglesias and JJ Diez[9] and many others reported low T3 values in CKD patients Previous studies by Quion verdeet[24] reported high preponderance of hypothyroidism in CKD. It was estimated to be about 5% in patients with terminal stage of renal failure. Elaborated study by Kaptein*et al* [7,25] estimated the prevalence of primary hypothyroidism was about 2.5 times much frequent in chronic kidney disease and dialysis. The hypothyroidism in CKD was estimated to range between 0 and 9.5%. Kaptein study also estimated the presence of anti thyroid antibody titer in 6.7% of CKD. Kayima *et a l*[26] and Giordano *et al* [27] have showed 90 studies regarding effect of dialysis on CKD patients with thyroid dysfunction. These studies showed no significant improvement in thyroid profile after repeated hemodialysis. But in the patients who have undergone renal transplant surgery, most of the thyroid function parameters returned to normal with TSH below normal.[28]

Conclusion:

The authors conclude that socioeconomic status has an impact on CKD staging while CKD staging is not influenced by occupation. Symptoms of hyperthyroid state are significantly frequent in early stages of CKD while, serum T3 and serum T4 are significantly lower in late CKD stages. Also, hyperthyroidism is more frequent in early stages of CKD wile hypothyroidism is more frequent in late stages.

Conflict of interest: Authors declare that there is no conflict of interest.

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