ISSN: 0975-3583, 0976-2833 VOL15, ISSUE8, 2024

EVALUATION OF THYROID HORMONES AND ITS CORRELATION WITH RENAL FUNCTIONS IN UNDIALYZED CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Background: To study the correlation of thyroid hormone profile with biochemical markers of renal function in patients with undialyzed chronic kidney disease. A lot of data is available for dialysis patients but only a few studies on undialyzed patients in our country.

Method- A cross sectional study was done at Rajindra Hospital, Patiala on 100 undialyzed CKD patients above 18 years of age and excluded patients with existing thyroid disorder, taking drugs affecting thyroid function, pregnant females and previous history of dialysis. Renal functions and thyroid hormone levels were analysed and correlated.

Result- Major proportion of the patients was in CKD stage 5 (53%). Mean age of the patients was 59.21±14.23 years. Mean FT3 levels were 2.92 ± 1.28, FT4 levels were 10.06 ± 7.51, and TSH values were 3.60 ± 3.28. In present study, 38% patients had euthyroidism, 13% had overt hypothyroidism, 38% had sick euthyroidism, and 11% had subclinical hypothyroidism. Out of those in CKD 5, 41.5% had sick euthyroidism followed by euthyroidism (34%), overt hypothyroidism (15.1%), and subclinical hypothyroidism (9.4%).

Conclusion-. There is direct proportionate relationship between the incidence of low T3, T4 syndrome and increasing severity of the kidney disease. No correlation was found between the serum levels of T3 and T4 and the severity of CRF. Our data supports that renal disease leads to significant changes in thyroid hormone levels that unlocks the significance of thyroid hormone quantification in CKD patients.

1. INTRODUCTION

Chronic kidney disease (CKD) is characterised as anomalies of renal function lasting for more than or equal to 3 months.[1] Thyroid hormones have an important role in renal development and there is a relation between renal function and thyroid hormones.[2,3] Thyroid hormone affects the ratio of the functioning renal mass to the body mass with direct proportion to thyroid levels.

The earliest dysfunction in patients is low levels of T3[4] because of metabolic acidosis, fasting, protein malnutrition, decreased peripheral conversion of T3 from T4 and iodothyronine deiodination. The inflammatory cytokines like TNF alpha and interleukin –1(IL-1) inhibits the expression of type 1 5' deiodinase that is required for conversion of T3 from T4 peripherally. One should keep the possibility of T4 thyrotoxicosis if T4 is high and T3 being on lower side

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because of suppressed levels of serum T3 in low T3 syndrome and T4 levels remain unaffected.[6]

In CKD patients there occurs initial drop in total T3 and T4 despite TSH being low to normal. CKD affects the thyroid by decreasing the sensitivity of TSH secretion to T3, T4 and impaired nocturnal release of TSH in pulses because of reduced TRH secretion [6-8] The thyroxine and TBG binding are inhibited by the protein and non-protein inhibitors. [6, 9] There is alteration in the T4 binding site's structure which is acquired intrinsically [10] and reduced concentration of TBG. [5,6] In uremia, there is no change in the thyroid hormones action at the nuclear level. There is evidence of increased receptor expression to preserve tissue euthyroid state. [11] Recent studies have shown a rise in the prevalence of hypothyroid state in CKD. [12] Both the hypothyroid state and CKD share common clinical symptoms and signs. So, it should be mandatory to screen all the CKD patients for hypothyroid.

The burden of the thyroid dysfunction that occurred in patients fulfilling the criteria for chronic kidney disease, in general reflects the severity of the illness.[13] The low serum levels of T3, T4, TSH are associated with poor prognosis. Studies have shown that there is reverse of thyroid function abnormalities in CKD patients after renal transplantation.

2. MATERIALS AND METHODS

A hospital based cross sectional study was conducted in the department of Medicine at Rajindra Hospital, Patiala on 100 undialyzed CKD patients above 18 years of age, after obtaining informed consent and ethical clearance.

Chronic kidney disease was diagnosed as per the criteria of existence of kidney abnormality lasting longer than three months in terms of either structure or function. One or more of the following are included in this: 1) GFR <60 mL/min/1.73 m2; 2) albuminuria (urine albumin ≥30 mg/24 h or urine albumin-to-creatinine ratio [ACR] ≥30 mg/g); 3) anomalies in urine sediment, histology, or imaging indicating renal damage; 4) renal tubular diseases; or 5) kidney transplant history.

We excluded patients with existing thyroid disorder, taking drugs affecting thyroid function e.g. amiodarone, lithium, methimazole, propylthiouracil etc., pregnant females and previous history of dialysis. A thorough history was taken and blood samples were analyzed for renal functions and thyroid hormone levels. GFR was calculated by Modification of Diet in Renal Disease Study formula.

We distributed CKD stages into groups

- Group A includes CKD stage 5 (Egfr ≤15)
- Group B includes CKD stage 4 (Egfr 16-29)
- Group C includes CKD stage 3b (Egfr 30-44) and 3a (Egfr 45-60)
- Group D includes CKD 2 (Egfr 60-89) and stage 1 (Egfr ≥90)

Statistical analysis was done using IBM statistical package for social sciences (IBM SPSS) software version 22. Continuous variables were reported as Mean ± Standard Deviation (SD) while categorical variables were expressed as absolute values and percentages. P-value <0.05 was considered statistically significant.

3. RESULTS

Table 1: Distribution of CKD groups

CKD Groups	Frequency	Percent
A	53	53.0

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B	20	20.0
C	21	21.0
D	6	6.0
Total	100	100.0

Table 2: Mean value of thyroid profile

Thyroid profile	**N**	**Mean±SD**
FT3	100	2.92±1.28
FT4	100	10.06±7.51
TSH	100	3.60±3.28

Table 3: Distribution of mean value of age and thyroid profile parameters according to CKD groups

Variables	CKD groups				Total
	A	B	C	D	
Age (In years)	58.96±13.54	60.35±11.16	63.66±13.69	42.00±20.86	59.21±14.23
T3	2.71±1.14	3.29±1.10	3.09±1.55	2.99±1.93	2.92±1.28
T4	9.92±7.62	11.45±7.64	9.67±7.45	8.02±7.38	10.06±7.51
TSH	3.24±2.69	2.87±1.65	5.0160±2.19	4.27±2.81	3.60±2.28

Test applied: One-way ANOVA

Table 4: Distribution of thyroid profile according to CKD groups

		CKD Groups				Total	p-value
		A	B	C	D		
	Euthyroid	18	12	5	3	38	>0.05
		34.0%	60.0%	23.8%	50.0%	38.0%	
	Overt Hypothyroid	8	2	2	1	13	
		15.1%	10.0%	9.5%	16.7%	13.0%	
	Sick Euthyroid	22	5	9	2	38	
		41.5%	25.0%	42.9%	33.3%	38.0%	
	Subclinical Hypothyroid	5	1	5	0	11	
		9.4%	5.0%	23.8%	0.0%	11.0%	
Total		53	20	21	6	100	
		100.0%	100.0%	100.0%	100.0%	100.0%	

Test applied: Chi-square test

Table 5: Correlation of various renal parameters with thyroid profile

		FT3	FT4	TSH
Creatinine	Pearson Correlation	.123	-.113	-.064
	Sig. (2-tailed)	.221	.263	.525
	N	100	100	100

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Urea	Pearson Correlation	-.008	-.175	-.023
	Sig. (2-tailed)	.937	.082	.819
	N	100	100	100
Egfr	Pearson Correlation	-.062	.165	.105
	Sig. (2-tailed)	.537	.101	.300
	N	100	100	100
HB	Pearson Correlation	.024	.081	.048
	Sig. (2-tailed)	.814	.423	.633
	N	100	100	100
PLT	Pearson Correlation	.091	.048	-.088
	Sig. (2-tailed)	.366	.636	.386
	N	100	100	100
Na	Pearson Correlation	.003	-.121	.071
	Sig. (2-tailed)	.976	.231	.484
	N	100	100	100
K	Pearson Correlation	-.089	.106	-.203*
	Sig. (2-tailed)	.376	.293	.043 (Sig.)
	N	100	100	100
CA	Pearson Correlation	.150	.136	-.097
	Sig. (2-tailed)	.136	.178	.339
	N	100	100	100
PO4	Pearson Correlation	.104	-.070	-.023
	Sig. (2-tailed)	.304	.490	.823
	N	100	100	100
S.ALB	Pearson Correlation	.018	-.171	.018
	Sig. (2-tailed)	.863	.089	.859
	N	100	100	100
24hr U.P.	Pearson Correlation	.117	.091	.018
	Sig. (2-tailed)	.248	.367	.858
	N	100	100	100

Majority of the patients were in CKD group A (53%) followed by group C (21%), group B (20%), and group D (6%). Mean age of patients in group A was 58.96±13.54 years, group B was 60.35±11.16 years, group C was 63.66±13.69 years, group D was 42.00±20.86. Overall mean age was 59.21±14.23 years. The association of mean age levels with CKD grades was found statistically significant (p-value<0.05). Mean FT3 levels were 2.92 ± 1.28, FT4 levels were 10.06 ± 7.51, and TSH values were 3.60 ± 3.28. In present study, 41.5% had sick euthyroidism followed by euthyroidism (34%), overt hypothyroidism (15.1%), and subclinical hypothyroidism (9.4%) in CKD group A. In group B, 60% followed euthyroidism followed by sick euthyroidism (25%), overt hypothyroidism (10%), and subclinical hypothyroidism (5%). In group C, 42.9% followed sick euthyroidism followed by euthyroidism (23.8%), subclinical hypothyroidism (23.8%), and overt hypothyroidism (9.5%). In group D, 50% followed euthyroidism followed by sick euthyroidism (33.3%), and overt hypothyroidism (16.7%). The p-value (>0.05) suggests that the distribution of thyroid status do not differ significantly across CKD grades in this dataset. There were no statistically significant differences in FT3, FT4, or TSH levels between the groups of age and eGFR within each variable category.

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4. DISCUSSION

Major proportion of the patients was in CKD group A (53%) followed by group C (21%), group B (20%), and group D (6%) in present study. In present study, major proportion of the patients visiting hospital belonged to group A and B (73%) as compared to group C and D (26%). Contrary to this, major proportion of the patients (82%) belonged to group A, B and C in study done by Singh H et al. [14] Similar results were found in study done by Bhatele P et al. [15]
Overall, mean age of the patients was 59.21±14.23 years. Mean age of patients with group A was 58.96±13.54 years, group B was 60.35±11.16 years, group C was 63.66±13.69 years, group D was 42.00±20.86. The association of mean age levels with CKD grades was found statistically significant (p-value<0.05). In study conducted by Singh H et al,[14] mean age was 57.08±10.35 years. In study conducted by Vanani BL et al,[16] mean age was 48.55 ±6.65 years. Mean FT3 levels were 2.92 ± 1.28, FT4 levels were 10.06 ± 7.51, and TSH values were 3.60 ± 3.28 in current study. FT4 shows higher variability compared to FT3 and TSH, suggesting a wider range of thyroid function across the individuals sampled. There were no significant differences observed in T3 levels (A: 2.71±1.14, D: 2.99±1.93, p>0.05), T4 levels (A: 9.92±7.62, D: 8.02±7.38, p>0.05), and TSH levels (A: 3.24±2.69, D: 4.27±2.81, p>0.05) among the CKD grades. These findings suggest that thyroid hormone levels do not vary significantly with various stages of chronic kidney disease based on this dataset. However, further investigation with larger sample sizes or different populations may be warranted to confirm these results and explore relation between thyroid function and CKD progression. In study done by Khatiwada S et al,[17] no significant association of CKD grades with FT3 and FT4 levels (p-values=0.131 ad 0.175, respectively) but found significant association with TSH values (p-value<0.001).
In present study, 41.5% had sick euthyroidism followed by euthyroidism (34%), overt hypothyroidism (15.1%), and subclinical hypothyroidism (9.4%) in CKD group A. In group B, 60% followed euthyroidism followed by sick euthyroidism (25%), overt hypothyroidism (10%), and subclinical hypothyroidism (5%). In group C, 42.9% followed sick euthyroidism followed by euthyroidism (23.8%), subclinical hypothyroidism (23.8%), and overt hypothyroidism (9.5%). In group D, 50% followed euthyroidism followed by sick euthyroidism (33.3%), and overt hypothyroidism (16.7%). The p-value (>0.05) suggests that the distribution of thyroid status does not significantly differ across CKD grades in this dataset. This analysis highlights the prevalence of various thyroid statuses within various CKD grades, providing insights into their co-occurrence but indicating no strong association based on the current data.
In present study, 38% patients had euthyroidism, 13% had overt hypothyroidism, 38% had sick euthyroidism, and 11% had subclinical hypothyroidism. In study done by Khatiwada S et al,[18] 61.4% patients had Euthyroidism, 27.2% had subclinical hypothyroidism, 8.1% had overt hypothyroidism and 3.3% had subclinical hyperthyroidism. The relation of euthyroidism and subclinical hypothyroidism was found statistically significant with CKD grades but found non-significant in case of overt hypothyroidism and subclinical hyperthyroidism. Subclinical hypothyroidism was shown to be present in 24.8% of end-stage renal failure (ESRD) patients in an Indian study.[19] In a Taiwanese peritoneal dialysis (PD) patient study, Ng et al. found that 5 (4.1%), 19 (15.6%), and 98 (80.3%) of the patients had subclinical hyperthyroidism, hypothyroidism, and euthyroidism.[20] The high incidence of thyroid autoimmunity in our study sample, excessive or insufficient iodine intake, and the inclusion of participants with non-thyroidal illnesses could all be contributing factors to the high rate of thyroid dysfunction in CKD patients.[17,21]

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We found that there were no statistically significant differences in FT3, FT4, or TSH levels with age. Concordance finding reported by Singh H et al.[22]

In Falhi AK et al [23] study, 50 CKD patients between the ages of 20 and 50 were examined; the results revealed that, in comparison to controls, there was a highly significant decrease ($P < 0.01$) in T3 and T4 levels and an increase in TSH. In contrast, the study by Khatiwada S et al. found that CKD patients had a significant increase in TSH levels but a non-significant decrease in T3 and T4 levels.[17] In comparison to controls, Rajagopalan B et al. (2013) discovered a substantial drop in T3 and T4 with unaltered TSH in CKD patients.[24] A prior study conducted in Iraq on CKD patients receiving either conservative therapy or routine haemodialysis revealed a significant decrease in TT3 and TT4, but no significant changes in TSH levels were seen when compared to the control group.[25] Toda A et al. found a statistically significant link in 2019, while Alshammari F et al. found a non-significant correlation between the incidence of hypothyroidism and a decline in GFR.[26,27]

Mehta HJ et al in 1991 studied levels of total and free thyroid hormone in chronic renal failure. They discovered that there was a strong correlation between growing renal injury and large decreases in TT3, FT4, and FT3 levels.[28] In a Nepalese investigation, the researchers discovered that CKD patients had aberrant thyroid function. They discovered a strong correlation between subclinical hypothyroidism and CKD, as well as a link between thyroid function abnormalities and the advancement of CKD.[17] Ramirez et al. conducted a groundbreaking study in which they compared two groups of patients with renal failure—one without dialysis and the other with dialysis—with normal people. When compared to normal persons, they found that both renal failure groups had significantly lower T3. Nevertheless, only the haemodialysis group experienced a statistically significant decrease in T4.[5] The non-haemodialysis renal failure group did not show a drop in thyroid binding globulin, which suggests a pathophysiology independent of binding proteins.

In many nations, patients suffer from some of the most common medical problems, including CKD and thyroid issues. Along with the treatment of CKD, clinicians—including nephrologists—must take into account the risks associated with thyroid disease and the best ways to treat it. Significant alterations in renal function are brought about by thyroid dysfunction, and thyroid abnormalities can also be linked to kidney illnesses. Consequently, CKD and thyroid dysfunction are mutually influencing conditions.[29]

5. CONCLUSION

There is a high incidence of thyroid disorder especially hypothyroidism in CKD patients and it requires both the clinical evaluation and biochemical testing to diagnose the hypothyroid state in CRF patients. There is direct proportionate relationship between the incidence of low T3, T4 syndrome and increasing severity of the kidney disease. No correlation was found between the serum levels of T3 and T4 and the severity of CRF. Our data supports that renal disease leads to significant changes in thyroid hormone levels that unlocks the significance of thyroid hormone quantification in CKD patients. The participants' iodine level was not investigated, thyroid problems, particularly subclinical hypothyroidism, may be exacerbated by excessive iodine nutrition or iodine deficit in these areas.[17] Also, we did not evaluate the research population's thyroid autoimmunity status. The current study's high rate of thyroid abnormalities may have been influenced by the presence of thyroid autoimmunity.

Subsequent research ought to investigate plausible causative pathways linking chronic kidney disease (CKD) to elevated TSH and decreased thyroid function. These pathways may

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encompass the functions of autoimmunity and excess iodine, as well as the mechanism of dyslipidaemia in CKD patients.

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