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A Study of Prevalence and Clinical Significance of Low T3 in Non-Dialysis Patients with Chronic Kidney Disease

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Abstract

Background: In this study, we wanted to evaluate the prevalence and clinical significance of low T3 in non-dialysis patients with chronic kidney disease. **Material and Methods:** This was a hospital-based observational, cross-sectional study conducted among 50 patients who presented with chronic kidney disease on conservative therapy, to Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, for 6 months, after obtaining clearance from the institutional ethics committee, and written informed consent from the study participants. **Results:** The mean value of T3 in stage 5 and stage 4 CKD was lower than the mean value of T3 in stage 3 depicting a linear correlation between low T3 and the severity of CKD. In patients with non-dialysis CKD, thyroid dysfunction was very common accounting for about 68%. In the prevalence of low T3 in non-dialysis CKD patients, low T3 was present in 29 patients accounting for 58%. In the prevalence of low T3 syndrome in CKD patients, 26 (52%) patients had low T3 values. **Conclusion:** Low T3 syndrome was seen in 32% and low T4 syndrome was seen in 8% of patients. Low T3 syndrome was common in older patients with CKD. The lower the eGFR, the lower is the T3 value. Significance is that as the disease severity increases, the T3 values fall progressively depicting a direct relation between eGFR and T3.

Keywords: Prevalence, Clinical, Significance, Low T3, Non-Dialysis, Patients, Chronic Kidney Disease.

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Introduction

The 2015 Global Burden of Disease Study has reported a stupendous increase in life expectancy globally between the years 1980 and 2015. This enormous improvement in global statistics is due to the decline in mortality from various communicable, non-communicable and nutritional diseases. Chronic kidney disease is one of the most common non-communicable diseases in the world with significant mortality and morbidity. It is a spectrum disease of various pathophysiological processes associated with an abnormality in renal

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function and a progressive decline in the glomerular filtration rate. Chronic kidney disease is loosely defined as an abnormal kidney structure or function that lasts for more than three months with associated health implications in the form of synthetic, hormonal, metabolic, excretory, and endocrine abnormalities eventually leading to the accumulation of waste products leading to several homeostatic derangements. Patients with end-stage renal disease (ESRD) have a poor quality of life and die at an early age. However, due to improvements in the health sector and improved methods of screening the disease early, there is a decrease in the mortality rate of dialysis patients and there is also a decline in the rate of progression to ESRD due to novel therapies and correction of risk factors. Several factors contribute to the high prevalence of CKD in India. Hypovitaminosis A and other nutritional deficiencies during pregnancy can lead to a smaller kidney volume of the offspring and a lower eGFR. Consanguineous marriage and genetic inbreeding can increase the risk of congenital anomalies of the kidney and urinary tract. Poverty, poor environmental sanitation, pollution, water contamination, overcrowding, and known and unknown nephrotoxins (including heavy metals and plant toxins in indigenous medical practices) may lead to glomerular and interstitial renal diseases. Added to these, hypertension and diabetes mellitus are the major burdens leading to ESRD. By the end of 2030, India is expected to have the world's largest population of diabetic patients. Over 50% of patients with advanced CKD are first seen when the eGFR is <15 ml/min per 1.73 m2. This highlights the need for widespread screening programs for those people who are at risk of CKD. The aetiology of CKD varies throughout India. Parts of the states of Andhra Pradesh, Telangana, Odisha, and Goa have high levels of CKD of unknown aetiology designated as CKD presenting as chronic interstitial nephropathy with insidious onset and slow progression. Irrespective of the cause, chronic kidney disease is the final pathway of permanent loss of the functional unit of the kidneys, the nephrons, which results in disturbance in the normal homeostasis of the body thereby affecting every system. The thyroid gland is no exception to this rule. Thyroid hormones are an important determinant of somatic and brain development in children and adults. Thyroid hormones affect the function of every other organ of the body and they should be constantly available for the normal functioning of the body. The kidneys play a vital role in the metabolism, degradation and excretion of thyroid hormones. So, impairment of renal function will lead to abnormalities of thyroid physiology. Iodine is excreted mainly by kidneys and an impaired kidney function leads to increased levels of serum iodine which impairs thyroid hormone synthesis – popularly called the Wolff-Chaikoff effect. All the levels of the hypothalamic–pituitary–thyroid axis can be involved resulting in disturbances in hormone synthesis, metabolism, distribution and excretion. The thyroid gland on the other side has a significant role in the development and function of kidneys. It plays a pivotal role in the moderation of renal blood flow thereby controlling GFR. There is considerable overlap in symptoms related to CKD and hypothyroidism. Hence it is vital to differentiate them and to establish a link between two different conditions.

Aims and Objectives

- To study the prevalence and clinical significance of low T3 in CKD patients who are not on dialysis.
- To study the different non-thyroid illness patterns occurring in non-dialysis CKD patients.
- To find the clinical significance of low T3 in CKD.
- To establish a correlation between low T3 and severity of CKD.

Methodology

This was a hospital-based observational, cross-sectional study conducted among 50 patients who presented with chronic kidney disease on conservative therapy, to Institute of Internal

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Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, for 6 months, after obtaining clearance from the institutional ethics committee, and written informed consent from the study participants.

Inclusion Criteria

Age greater than 18 years.
Patients with chronic kidney disease of different stages who are not on dialysis.
Criteria to say a case as chronic kidney disease:
Uremic symptoms for more than three months.
Elevated blood urea, creatinine and reduced eGFR.
Ultrasonographic evidence of renal parenchymal disease or loss of corticomedullary differentiation.
Supportive evidence like hypocalcaemia, anaemia, hyperphosphatemia etc.

Exclusion Criteria

CKD patients who are on renal replacement therapy.
Pregnant patients.
Patients who are known cases of primary hypothyroidism.
Post-Surgical patients.
Patients taking drugs that alter thyroid function.
Age less than 18 years.

Statistical Methods

Data was entered in MS Excel and analysed using SPSS software. Results were presented as tables.

RESULTS

Table 1:

			T3_group		**Total**
			Low	**Normal**	
Age group	20-40 years	Count	8	8	16
		% within T3_group	27.6%	38.1%	32.0%
	41-60 years	count	15	7	22
		% within T3_group	51.7%	33.3%	44.0%
	Above 60 years	Count	6	6	12
		% Within T3_group	20.7%	28.6%	24.0%
Total		Count	29	21	50
		% within T3_group	100.0%	100.0%	100.0%
Distribution of age and serum T3 among the cases					
Pearson Chi-Square=1.672, P=0.433					
			T3_group		total
			low	normal	
sex	male	count	15	10	25
		% within T3_group	51.7%	47.6%	50.0%
	female	count	14	11	25
		% within T3_group	48.3%	52.4%	50.0%
Total		Count	29	21	50
		% within T3_GROUP	100.0%	100.0%	100.0%

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Distribution of sex and serum T3 among cases					
Pearson Chi-Square P=0.774					
			T4_group		Total
			Low	Normal	
Age group	20-40 Years	Count	7	9	16
		% within T4_group	41.2%	27.3%	32.0%
	41-60 Years	Count	5	17	22
		% within T4_group	29.4%	51.5%	44.0%
	Above 60 Years	Count	5	7	12
		% within T4_group	29.4%	21.2%	24.0%
Total		Count	17	33	50
		% within T4_group	100.0%	100.0%	100.0%
Distribution of age and serum T4 among cases					
Pearson Chi-Square=2.238 P=0.327					

Table 2:

			T3_group		**Total**
			Low	**Normal**	
TSH_group	Normal	Count	26	20	46
		% within T3_group	89.7%	95.2%	92.0%
	High	Count	3	1	4
		% within T3_group	10.3%	4.8%	8.0%
Total		Count	29	21	50
		% within T3_group	100.0%	100.0%	100.0%
Distribution of low T3 with different levels of TSH					
Pearson Chi Square=0.516, P=0.473					
			T4_group		Total
			Low	Normal	
TSH_group	Normal	Count	14	32	46
		% within T4_group	82.4%	97.0%	92.0%
	High	Count	3	1	4
		% within T4_group	17.6%	3.0%	8.0%
Total		Count	17	33	50
		% within T4_group	100.0%	100.0%	100.0%
Distribution of low T4 with different levels of TSH					
Pearson Chi-Square=3.257 P=0.071					
			T3_group		Total
			Low	Normal	
Creatinine group	0-4	Count	11	20	31
		% within T3_group	37.9%	95.2%	62.0%
	4.1-8.0	Count	8	0	8
		% within T3_group	27.6%	0.0%	16.0%
	8.1-12.0	count	8	1	9
		% within T3_group	27.6%	4.8%	18.0%
	12.1-16.0	Count	2	0	2
		% within T3_group	6.9%	0.0%	4.0%
Total		Count	29	21	50
		% within T3_group	100.0%	100.0%	100.0%

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Distribution of serum creatinine and serum T3
Pearson Chi-Square=17.218**p=0.001

Table 3:

			T3_GROUP		**Total**
			Low	**Normal**	
EGFR group	<15	count	20	7	27
		% within T3_Group	69.0%	33.3%	54.0%
	15-30	count	8	4	12
		% within T3_Group	27.6%	19.0%	24.0%
	>30	count	1	10	11
		% within T3_Group	3.4%	47.6%	22.0%
Total		count	29	21	50
		% within T3_Group	100.0%	100.0%	100.0%
Distribution of serum T3 in various EGFR groups					
Pearson Chi-Square=1.776, P=0.412					
			T4_group		Total
			Low	Normal	
EGFR group	<15	Count	11	16	27
		% within T4_Group	64.7%	48.5%	54.0%
	15-30	Count	4	8	12
		% within T4_Group	23.5%	24.2%	24.0%
	>30	Count	2	9	11
		% within T4_Group	11.8%	27.3%	22.0%
Total		Count	17	33	50
		% within T4_Group	100.0%	100.0%	100.0%
Distribution of T4 in various EGFR groups					
Pearson Chi-Square=1.776 P=0.412					
			T3_group		total
			low	normal	
stage	4.00	Count	8	4	12
		% within T3_Group	27.6%	19.0%	24.0%
	5.00	Count	20	7	27
		% within T3_Group	69.0%	33.3%	54.0%
	3A	Count	1	3	4
		% within T3_Group	3.4%	14.3%	8.0%
	3B	Count	0	7	7
		% within T3_Group	0.0%	33.3%	14.0%
Total		Count	29	21	50
		% within T3_Group	100.0%	100.0%	100.0%
Distribution of low T3 in various stages of CKD					
Pearson Chi-Square=14.689** P=0.002					

Table 4:

		T4_group		**Total**
		Low	**Normal**	
stage	Count 4.00	4	8	12
	% within T4_Group	23.5%	24.2%	24.0%

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	Count 5.00	11	16	27
	% within T4_Group	64.7%	48.5%	54.0%
	Count 3A	1	3	4
	% within T4_Group	5.9%	9.1%	8.0%
	Count 3B	1	6	7
	% within T4_Group	5.9%	18.2%	14.0%
Total	Count	17	33	50
	% within T4_group	100.0%	100.0%	100.0%
Distribution of low T4 in various stages of CKD				
Pearson Chi-Square=1.906 P=0.592				

			T3_group		Total
			Low	normal	
Diabetes	Yes	count	10	10	20
		% within T3_Group	34.5%	47.6%	40.0%
	No	count	19	11	30
		% within T3_Group	65.5%	52.4%	60.0%
Total		count	29	21	50
		% within T3_Group	100.0%	100.0%	100.0%
Distribution of diabetics in study cases					
Pearson Chi-Square=0.876 P=0.349					

		T3_Group		Total
		Low	Normal	
Symptoms	Count	10	7	17
	Yes % within T3_Group	34.5%	33.3%	34.0%
	Count	19	14	33
	No % within T3_Group	65.5%	66.7%	66.0%
Total	Count	29	21	50
	% within T3_GROUP	100.0%	100.0%	100.0%
Distribution of hypothyroid symptoms in low T3 group				
Pearson Chi-Square=0.007 P=0.933				

Table 5:

			T4_Group		**Total**
			Low	**Normal**	
T3_GROUP	Low	Count	13	16	29
		% within T4_group	76.5%	48.5%	58.0%
	Normal	Count	4	17	21
		% within T4_group	23.5%	51.5%	42.0%
Total		Count	17	33	50
		% within T4_group	100.0%	100.0%	100.0%
Distribution of T3 and T4 in cases					

			T3_Group		T4_Group		Total
			Low	Normal	Low	Normal	
TSH group	Normal	Count	26	20	14	32	46
		%	89.7%	95.2%	82.4%	97.0%	92.0%
	High	Count	3	1	3	1	4
		%	10.3%	4.8%	17.6%	3.0%	8.0%
Total		Count	29	21	17	33	50

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		%	100.0%	100.0%	100.0%	100.0%	100.0%
Distribution of T3, T4 and TSH							
	T3_ngdl						
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	Minimum	Maximum
					Lower Bound / Upper Bound		
4.00	12	.6583	.40555	.11707	.4007 / .9160	.20	1.40
5.00	27	.6074	.51210	.09855	.4048 / .8100	.20	1.90
3A	4	.7000	.37417	.18708	.1046 / 1.2954	.20	1.10
3B	7	1.0143	.37161	.14046	.6706 / 1.3580	.60	1.70
Total	50	.6840	.46963	.06642	.5505 / .8175	.20	1.90
Mean T3 value in various stages of CKD							

Distribution of thyroid dysfunctions in various stages of CKD

In this study, 50 patients with non-dialysis CKD were studied. Among them, thyroid dysfunction was very common accounting for about 68%. Among the various thyroid function alterations, low T3 syndrome was the most common accounting for 32%. About 20% of the cases had both low T3 and low T4 values. Primary hypothyroidism accounted for 6 %. Low T4 syndrome and subclinical hypothyroidism accounted for 8% and 2% respectively. The mean value of T3 in stage 5 and stage 4 CKD was lower than the mean value of T3 in stage 3 depicting a linear correlation between low T3 and the severity of CKD. Prevalence of low T3 in non-dialysis CKD patients: In this study which consisted of 50 patients in different stages of CKD, low T3 was present in 29 patients accounting for 58%. But, 3 patients had low T3, low T4 and high TSH which lead to the diagnosis of primary hypothyroidism in these patients and hence excluded from the low T3 syndrome group. Hence 26 patients (52%) had low T3 values. Among these only 16 (32%) patients had low T3 syndrome. Prevalence of low T3 syndrome in CKD patients: Among 50 patients included in this study, 26 (52%) patients had low T3 values. In this low T3 group, 9 patients had low T4 values too. So the patients with decreased serum T3, normal serum T4 and normal serum TSH i.e., low T3 syndrome were 16 patients accounting for 32% of the study sample.

DISCUSSION

Of 50 patients, 27 patients in this study had eGFR calculated by CKD-EPI formula, below 15ml/minute. 12 patients had eGFR between 15 and 29ml/dl. Seven patients had an eGFR between 45 and 59 ml/dl consistent with stage 3A. Four patients came under stage 3B with eGFR between 30 and 44 mg/dl.

So, in this study most of the patients i.e., 54% belonged to stage 5 CKD. Ultrasound done in the subjects revealed renal parenchymal disease grade 3 in 78%, and renal parenchymal disease grade 2 in 2%. Corticomedullary differentiation was lost in 10 patients amounting to a total of 20%. In this study, 40 patients had features of anaemia supported by a completed hemogram. Serum calcium was also measured in these patients that revealed hypocalcemia in 12 patients accounting for 24% and normal calcium levels in 26 patients accounting for 52% and high calcium levels in 14 patients accounting for 28 %. Serum phosphorous was high in 16 patients amounting to 32 % and normal in 34 patients accounting for 68%. In this study which consisted of 50 patients in different stages of CKD, low T3 was present in 29 patients accounting for 58%. But, 3 patients had low T3, low T4 and high TSH which lead to the diagnosis of primary hypothyroidism in these patients and hence excluded from the low T3 syndrome group. Hence 26 patients (52%) had low T3 values. Among these only 16 (32%) patients had low T3 syndrome. Out of the 50 patients, low T4 was present in 17 patients, but

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three patients had both low T3 and high TSH suggestive of primary hypothyroidism and were excluded from the low T4 group. So, 14 patients (28%) had low T4 values. Among these, only 4 patients had low T4 syndrome. Both low T3 and low T4 syndromes were present in 10 patients (20%). In this study, 46 patients had normal TSH values, and 4 patients had high TSH values. Among those four patients, one had normal T3 and T4 suggesting subclinical hypothyroidism. 3 patients (6%) had primary hypothyroidism.

Among the three patients with primary hypothyroidism, two patients had creatinine clearance below 15 ml/dl and one patient belonged to stage 3A. There was one patient with subclinical hypothyroidism who belonged to stage 5 CKD. Excluding primary hypothyroid patients, the mean TSH in this study was within normal limits across various stages of CKD. So, it did not show any relation to the severity of the disease. Among 50 patients in this study, 16 patients had no abnormality of thyroid status. 17 patients included in this study had symptoms of hypothyroidism such as lethargy, constipation, dry skin, cold intolerance etc. Out of this all three from the primary hypothyroidism group had such symptoms. Delayed ankle jerk was present in one patient and goitre was seen in two patients who had primary hypothyroidism. 33 patients (66%) did not complain of symptoms suggestive of hypothyroidism. One patient with subclinical hypothyroidism did not have symptoms suggestive of hypothyroidism. In the low T3 group, 10 patients had symptoms of hypothyroidism and 19 did not have so. According to previous studies conducted by Kaptein et al,[1] the prevalence of hypothyroidism in CKD was 2.5 times higher than in the general population. In this study, it was found to be only 6%. The diagnosis of hypothyroidism can be made only when the TSH values are high and T3, T4 values are low.

In the low T3 group, among 29 patients, 15 patients belonged to the ages 41 to 60 years, 6 patients above 60 years, and 8 patients aged between 20 and 40 years. The number of patients above 60 years in this study was 11, so approximately half of them had low T3. Among 29 patients who had low T3, 20 of them had eGFR less than 15 ml/dl and 8 patients had eGFR between 15 and 30 ml/dl. So, this shows that the prevalence of low T3 is more in end-stage renal disease. In the same way, out of 17 patients with low T4, 11 patients had eGFR which is consistent with stage 5 CKD. The mean T3 value in this study was reduced in stage 5 and stage 4 CKD whereas the mean value of T3 in stage 3 CKD was higher. We could not correlate the mean values T3 in stage 4 and stage 5 probably because of the smaller sample size. So it shows a direct linear correlation between T3 level and eGFR.

This was supported by studies done in the past by, Hasegawa et al,[2] Ramirez et al, P Iglesias et al,[3] Plikat K, Langgartner et al,[4] which showed a linear correlation of serum T3 and severity of kidney disease. A study conducted by Quin Ver Deet et al. concluded a high prevalence of hypothyroidism in CKD.

Another study by Kaptein et al,[5,6] found a prevalence of hypothyroidism to be 2.5 times high in CKD and dialysis. In this study, the prevalence of primary hypothyroidism was 6%. Several studies by Karunanidhi et al, Ramirez et al, and Dudani et al,[7] found an abnormality in the hypophyseal mechanism of TSH release in CKD. This is consistent in this study also.

CONCLUSION

Alteration of thyroid functional status is common among CKD patients. It is very important to screen all patients with CKD for thyroid disorders as about 68% have some form of thyroid disorder according to this study. The alteration in the thyroid function in CKD is probably an adaptive mechanism to help conserve protein. This study was made on 50 patients who were diagnosed to have CKD and who were not on renal replacement therapy. Among these patients, 29 patients (58%) had low T3 values and 32% had low T3 syndrome. As observed in this study, the number of patients with low T3 and T4 increased with the severity of CKD. The risk of primary hypothyroidism is increased in CKD. In this study, 6% had TFT

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suggestive of primary hypothyroidism. Low T3 syndrome was seen in 32% and low T4 syndrome was seen in 8% of patients in this study. Low T3 syndrome was common in older patients with CKD in this study. The lower the eGFR, the lower is the T3 value. So this shows the significance that as the disease severity increases, the T3 values fall progressively depicting a direct relation between eGFR and T3.

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