Section: General Medicine

Original Research Article

PREVALENCE OF SUBCLINICAL/OVERT HYPOTHYROIDISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Chronic kidney disease (CKD) is increasingly recognized as a major public health problem. The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. It is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology. The present study was undertaken to assess the clinical and biochemical profile of thyroid abnormalities in chronic kidney disease.

Material and Methods: The present cross-sectional study was carried in Department of Medicine, Surat Municipal Institute of Medical Education and Research, Suart. A total of 100 patients with chronic kidney disease were included in the study based on the definition of The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation.

Results: Out of 100 patients, 68% were males and 32 % were females, accounting a male to female ratio of 1.84:1. Majority of patients 58(63.74%) were in the age group of 46 to 60 years. Majority of patients were in stage IV CKD 42 (46.158%). In all the 91 (100%) patients the commonest symptom was tiredness and weakness. The next common symptom was dry skin in 78(85.71%). In present study, the commonest sign of thyroid dysfunction was coarse skin (62.64%). Raised TSH was noted in 14 (15.38%) patients, 5 (5.49%) had below normal FT4 and 6 (6.59%) had below normal FT3.

Conclusion: Based on the Zulewski's score for the assessment of hypothyroidism considering clinical signs and symptoms 7.69% patients were diagnosed to have clinical hypothyroidism. Of the 91 patients with chronic kidney disease the biochemical profile considering FT3, FT4 and TSH levels 14 (15.38%) patients had thyroid abnormalities of which, 7 (7.69%) each had hypothyroidism and subclinical hypothyroidism.

Keywords: Chronic kidney disease; Hyperthyroidism; Hypothyroidism; Thyroid abnormalities; Zuwelski's score.

INTRODUCTION

Chronic kidney disease (CKD) is increasingly recognized as a major public health problem worldwide and in south Asia too.[1,2] Based on internationally accepted definitions CKD is diagnosed when structural or functional abnormalities of the kidneys persist for more than or equal to three months. The disease is categorized into five stages of increasing severity.[3,4]

Data derived from the national health and nutrition examination survey iii (NHANES iii) show the total crude (i.e., not age-standardized) CKD prevalence estimate for adults aged >20 years in the United States was 16.8%.[5] estimates in Asia and Australia indicate that the problem is of the same magnitude in these countries.

The number of patients with CKD and the subsequent need for renal replacement therapy (RRT) has reached epidemic proportion and is anticipated to rise further. Worldwide, it is estimated that over 1.1 million patients with end-stage renal disease (ESRD) currently require maintenance dialysis, and this number is increasing at a rate of 7% per year.[6]

This figure excludes developing countries, where there is less availability for access to dialysis services, and is therefore an underestimate of the true demand and also there is lack of documentation and economic constraint among patients.

There is coherent, undisputable evidence that treatment can prevent or delay kidney disease progression and the resulting cardiovascularcomplications,[7-14] but this knowledge has rarely been translated into public health policies. Moreover, early detection can prevent or delay progression to end-stage renal disease (ESRD).

The Kidney Normally Plays an Important Role in the Metabolism, Degradation, And Excretion of Several Thyroid Hormones. It Is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology. All levels of the hypothalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion.

The evaluation of thyroid function in systemic illness remains complex because the changes occur at all levels of the hypothalamic-pituitary-thyroid axis. During illness, a decrease in triiodothyronine (T3) and pulsatile thyroid stimulating hormone (TSH) release and increases in reverse T3 Occur. This Constellation of Findings Is Termed the Low T3 Syndrome, The Euthyroid Sick Syndrome or Non-Thyroid Illness.[15]

Thyroid hormone synthesis is controlled by two fundamental mechanisms. The first, based on the thyroid-stimulating hormone (TSH), thyroxine(T4) and triidothyronine(T3) feedback loop. The second, based on the extra thyroidal generation of T3 from T4; this mechanism is of major relevance because about 80% of the T3 produced results from 5'-deiodination of T4 in peripheral tissues by two t4-5' deiodinases.[16] Together with liver, kidney is the organ endowed with the most abundant deiodinase activity.[16] Due to reduce deiodinase activity, tissue and circulating levels of the active form of the thyroid hormone, T3 is low in kidney failure5. Because of reduced renal excretion, inorganic iodide generated by residual deiodinase activity accumulates in stage 4 and 5 CKD, which in turn dampens thyroid hormone synthesis.[16,17]

Low T3 is the most frequent alteration of thyroid hormone profile observed in CKD. Low T3 associates with endothelial dysfunction, a `harbinger of atherosclerosis, in stage 3 and 4 CKD,[18] as well as with cardiomyopathy,[19] and a high risk of death in stage 5 CKD patients.[20]

Some studies showed an increased incidence of subclinical hypothyroidism in CKD patients and high prevalence of hypothyroidism in patients with terminal renal failure.[21]

When hypothyroidism becomes more severe it can cause reduced cardiac function and lead to progressively worsening kidney functions. Thus the prevalence of subclinical hypothyroidism in patients with CKD might be risk factor for both cardiovascular disease and progressive kidney disease.[22]

This study is designed to determine the prevalence of thyroid dysfunction in CRF patients in order to intervene at an early stage depending upon the hormone abnormalities and reduce both the cardiovascular risk and progressive worsening of kidney function.

Although similar studies for assessment of prevalence of hypothyroidism in CRF patients have been conducted in other country, there is very much less data available for Indian population.

Some studies have shown that thyroid hormone replacement in chronic renal failure patients preserve renal functions,[25] and reduce the cardiovascular morbidity, thus early detection of hypothyroidism in chronic renal failure patient may help the patient for retarding the progression of stages of CKD and may reduce cardiovascular risk.

However, previous studies,[23-26] have only stressed on the levels of thyroid Hormones in chronic renal failure, but have not explored clinical and biochemical profiles of thyroid abnormalities together. Hence, the present study was undertaken to assess the clinical and biochemical profile of thyroid abnormalities in chronic kidney disease.

MATERIALS AND METHODS

Present Cross sectional observational study performed at OPD and indoor facility of department of General Medicine, Surat Municipal Institute of Medical Education and Research, Surat City for the period of one year. Study was be conducted after obtaining clearance from institutional ethical committee, Surat Municipal Institute of Medical Education and Research. 100 cases of chronic renal failure that either visit OPD or admitted to SMIMER hospital medicine department will be taken for study. Informed written consent for allowing their clinical data to be used for study purpose – will be obtained from all the patients. Detailed clinical evaluation, as per the annexed proforma, will be done in all adult patients with preference to thyroid and renal disease. After selecting the patients, following investigations will be performed. Fasting blood sample for Serum thyroid profile. Components of thyroid profile in this study are serum free triidothyronine(FT3), serum free thyroxine (FT4), serum thyroid stimulating hormone (TSH). Renal parameters like blood urea, serum creatinine and creatinine clearance (using cockeroft- gault formula).

Cockcroft-Gault: CrCl (mL/min)	=	140 – age (years) x weight (kg) x [0.85 if female]
		(72 sCr (mg/dL)

1. Serum calcium and phosphorus and uric acid.
2. Peripheral smear for anemia and burr cells.
3. Urine protein and serum protein.

4. USG abdomen for evidence of chronic renal failure.

Other routine blood investigations including complete blood count, renal function test, liver function test and ECG (if required) will be done.

Inclusion Criteria

Patients who fulfill the criteria for CKD.

Criteria for CKD:

1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either:
   - ➢ Pathological abnormalities; or
   - ➢ Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging test
2. GFR <60mL/min/1.73 m2 for ≥3 months, with or without kidney damage

* Supportive laboratory evidence of CRF like anemia (male: <13gm%, female < 12gm%, pregnancy <11gm%), changes in serum electrolytes, blood urea, serum creatinine etc. urine protein ≥+1, RBC cast and broad cast in urine, B/L decreased kidney size or poor coritcomedullary differentiation.

- MDRD (Modification of Diet in Renal Disease)formula for GFR calculation is as under:

eGFR (mL/min per 1.73 m2) = 186.3 x PCr (e–1.154) x age (e–0.203) x (0.742 if female) x (1.21 if black).

Exclusion Criteria

- ➢ Patients who have been diagnosed to be having thyroid disorder.
- ➢ Patients on drugs altering thyroid profile like amiodarone, steroids, dopamine, phenytoin, estrogen pills, and iodine containing drugs.
- ➢ Patient on thyroid hormone replacement or on antithyroid drugs.

Based on guidelines of the National Kidney Foundation [Kidney Dialysis Outcomes Quality Initiative (KDOQI)], in which stages of CKD are defined according to the estimated GFR.

Stages of Chronic Kidney Disease (CKD)	
Stage	GFR, mL/min per 1.73 m2
0	**>90**[a]
1	90[b]
2	60–89
3	30–59
4	15–29
5	<15

TSH	**Free T4**	**Free T3**	**Interpretation**
Normal (0.35-5.5 µIU/mL)	Normal (0.89 – 1.76 ng/dL).	Normal (2.3 – 4.2 pg/mL)	Normal thyroid function
Elevated	Low	Low	Overt hypothyroidism
Elevated	Normal	Normal	Subclinical hypothyroidism

Patient will be classified as under into subclinical or overt hypothyroidism.

During the clinical examination the patients were interviewed for the Clinical symptoms of thyroid abnormalities. The interpretation of clinical signs and symptoms was done based Zulewski's clinical score for hypothyroidism. The 14 symptoms and signs identified by earlier study were evaluated. Two features, i.e., pulse rate and cold intolerance, had positive and negative predictive values below 70%, and were excluded. A score >5 points defined hypothyroidism, a score of 3 to 5 was defined as intermediate state while a score of 0-2 points defined euthyroidism. The most sensitive features were delayed ART (77%) and dry skin (76%), while the most specific were slow movements (98.7%) and diminished hearing (97.5%). A positive predictive value was highest for slow movements (96.5%) and puffiness (94.2%). On the other hand, a negative predictive value was highest for ART (80.3%) and dry skin (72.7%).

Statistical Analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2019) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were described as means and standard deviations or median and interquartile range based on their distribution. Qualitative variables were presented as count and percentages. For all tests, confidence level and level of significance were set at 95% and 5% respectively.

RESULTS

Out of the 100 patient's majority of patients (71%) were in the age group of 41 to 60 years, followed by 22% patients in the age group greater than 60 years and 7% patients in age group less than 40%. Out of 100 patients, 68% were males and 32% were females, accounting a ratio of male to female was 2.12:1. Majority of patients were in stage 5 CKD (52%), 38% patients in stage 4 and 10% patients were in stage 3 CKD.

Table 1: Prevalence of Thyroid Dysfunction

Impression	Cases			
	Numbers	Percent	Male	Female
Hypothyroidism	15	15%	10	5
Subclinical Hypothyroidism	6	6%	6	0
Some Other Thyroid Abnormality (Low T3)	8	8%	5	3
Normal	71	71%	47	24
Total	100	100%	68	32

Out of 100 patients, 15% patients had hypothyroidism, 6% had subclinical hypothyroidism, 8% had (Low T3) and 71% patients had normal thyroid function test.

Table 2: Relationship Between Duration of Hemodialysis and Thyroid Dysfunction

	Hypothyroidism		Subclinical Hypothyroidism		Some Other Thyroid Abnormality		Total
	Numbers	Percent	Numbers	Percent	Numbers	Percent	
NIL	0	0%	0	0%	1	1%	1
Up to 12	10	10%	3	3%	7	7%	20
13 to 24	5	5%	3	3%	0	0%	8
Total	15	15%	6	6%	8	8%	29
Chi square value		6.82			Statistically not significant		

Out of 15% patients with hypothyroidism 10% patients were on hemodiaylisis for up to 12 months and 5% patients were on hemodialysis for 13 to 24 months, out of 6% with subclinical hypothyroidism 3% patients were on hemodiaylisis for up to 12 months and 3% patients were on hemodialysis for 13 to 24 months, out of 8% with some other thyroid abnormality (Low T3)1% patients were on conservative treatment for CKD and 7% were on hemodiaylisis for up to 12 months. However, this correlation is statistically not significant.

Table 3: Symptoms of Thyroid Dysfunction

	Cases	
	Numbers	Percent
Tired/Weakness	100	100%
Diminished Sweating	56	56%
Hoarseness Of Voice	2	2%
Parasthesia	6	6%
Dry Skin	91	91%
Constipation	11	11%
Impaired Hearing	0	0%
Weight Gain	55	55%
Hair loss	12	12%

Out of 100 patients the commonest symptom was tiredness and weakness (100%). The next common symptom was dry skin in 91%, diminished sweating in 56%, weight increase in 55%, hair loss in 12%, parasthesia in 6%, constipation in 11% and hoarseness of voice in 2%. However, no patients reported impairment of hearing. In the present study, the commonest sign of thyroid dysfunction was coarse skin (67%). Cold skin was observed in 18% patients, periorbital puffiness of face in 6%, delayed ankle jerk in 6% patients and slow movements in 4%.

Of 15% patients with hypothyroidism10% were male and 5% were female, of 6% with subclinical hypothyroidism all were male (6%), of 8% with some other thyroid abnormality (low t3) 5% were male and 3% were female.

Table 4: Relationship Between Thyroid Dysfunction and CKD Stages

Thyroid Dysfunction	CKD Stages					
	3		4		5	
	No.	%	No.	%	No.	%
Hypothyroidism	0	0%	1	3%	14	27%
Subclinical Hypothyroidism	0	0%	0	0%	6	11.5%
Some Other Thyroid Abnormality	0	0%	2	5%	6	11.5%
Normal	10	100%	35	92%	26	50%
Total	10	100%	38	100.00%	52	100%
Chi square Value		24.59	Statistical significant			

Out of 100 patients in study group, 58 patients had stage 5 CKD. Of which 27% patients had hypothyroidism when compared to stage 4 (3%) and stage 3(0%). 11.5% of patients with stage 5 CKD had subclinical hypothyroidism when compared to stage 4(0%) and stage 3(0%). 11.5% patients with stage 5 CKD had some other thyroid hormone abnormality (lt3) when compared to stage 4(5%)

and stage 3(0%). So, higher the stage of CKDhigher was the prevalence of thyroid hormone dysfunction.

Table 5: Relationship Between Zulewski Score and Thyroid Dysfunction

Thyroid Dysfunction	Zulewski Score					
	0 To 2 (Euthyroid)		3 To 5 (Intermediate)		>5 (Hypothyroid)	
	No.	%	No.	%	No.	%
Hypothyroidism	0	0%	9	15%	6	75%
Subclinical Hypothyroidism	0	0%	5	8%	1	13%
Some Other Thyroid Abnormality(Low T3)	2	6%	6	10%	0	0%
Normal	31	94%	39	66%	1	13%
Total	33	100%	59	100%	8	100%
Chi square value	136.5		Statistically significant			

Patients with score of 0-2, none had hypothyroidism and subclinical hypothyroidism. In patients with a score of 3-5, 15% patients had hypothyroidism, 8% had subclinical hypothyroidism and 10% had low ft3. In patients with a score of >5, 75% patients had hypothyroidism, 13% had subclinical hypothyroidism. This correlation between zulewski score and thyroid function test is statistically significant.

Table 6: Stage of CKD, Zulewski Score and TSH

Stage of CKD	Zulewski score	Raised TSH		LT3 With Normal TSH	
		Number	Percent	Number	Percent
1	0 to 2	0	0	0	0
	3 to 5	0	0	0	0
	>5	0	0	0	0
	Total	0	0	0	0
2	0 to 2	0	0	0	0
	3 to 5	0	0	0	0
	>5	0	0	0	0
	Total	0	0	0	0
3	0 to 2	0	0	0	0
	3 to 5	0	0	0	0
	>5	0	0	0	0
	Total	0	0	0	0
4	0 to 2	0	0	1	12.5%
	3 to 5	1	5%	1	12.5%
	>5	0	0	0	0
	Total	1	5%	2	25.0%
5	0 to 2	0	0	1	12.5%
	3 to 5	13	62%	5	62.5%
	>5	7	33%	0	0
	Total	20	95%	6	75.0%
Total		21		8	

There were no patients in stage 1 and 2 in our study. In the patients with stage 3 none of the patients had either a score of greater than 5 nor did any patient have low T3 levels. Among patients with stage 4, 2 (25%) had low T3 levels of which, 1(12.5%) had score between 0 to 2 and 1(12.5%) had a score between 3 to 5. In those with stage 5, 6(75%) had low T3 Levels. Among this 1(12.5%) patient had a score between 0 to 3, and 5 (62.5%) had a score between 3 to 5.

In the patients with stage 3 none of the patients had either a score of greater than 5 nor did any patient had raised TSH levels. Among patients with stage 4, 1 (5%) had raised TSH levels with score between 3to 5. In those with stage 5, 20(95%) had raised TSH levels. Among these 13(62%) patients had a score between 3 to 5and 7 (33%) had a score greater than 5.

Blood urea and serum creatinine level increased As Stage of CKD increases and also in patients with thyroid function test showing hypothyroid compared to normal patients.

DISCUSSION

The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. It is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology. All levels of the hypothalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion.[4,5,6]

In our study majority of patients 71% were in the age group of 41to 60. In a similar study,[7] done in India most of the patients were in the age group of 38 to 64 years.

In our study Majority of patients (52%) were in stage 5 CKD, 38% patients in stage 4 and 10% patients were in stage 3 CKD. No patients were in stage 2 or stage 1 chronic kidney disease. In a

similar study,[8] done in Italian population majority of patients were in stage 2 CKD (57.8%) and (16.0%) were in stage 3 CKD, 0.4% in stage 4 CKD. In another study,[10] done in Korea majority of patients 1042 (45.62%) patients were in stage 1, 1025 (44.87%) patients were in stage 2, 183 (8.01%) patients were in stage 3, 20(0.8%) patients were in stage 4 and 14 (0.61%) patients were in stage.[5]

In our study 70 % patients were on maintenance hemodialysis. Out of which 55% patients were on hemodialysis for up to 12 months,15% patients were on hemodialysis for a period between 13 to 24 months.30% patients with CKD were either on conservative line of treatment or were not on maintenance haemodialysis. In our study 71% had TSH within normal limits, 15% patients had hypothyroidism and 6% had subclinical hypothyroidism. 8 % patients had low free T3 level with normal TSH. None of the patients had TSH below normal limits. None patients had isolated below normal FT4. None of the patients had a FT3 and FT4 above the normal limits. Similar study done in Kenya8a 10% patients had hypothyroidism and 5% had subclinical hypothyroidism. 14 % patients had low free T3 level. Quion-verde et al have also reported higher prevalence of up to 5% of frank hypothyroidism in patients with chronic renal failure, in comparison with hospitalized patients with normal renal function (0.6%).[13] In our study, the levels of Free T3was found to be low and these were noted to decrease as the renal insufficiency progresses. This is primarily related to diminished peripheral tissue conversion of T4 to T3. These low Free T3 levels have been reported in other studies.[10,12] Carrero et al found low free T3 levels to be independent predictors of cardiovascular mortality in CKD patients and low free T3 as sensitive predictor of mortality in CKD than free T3.[18]

Out of 15% Patients with Hypothyroidism, 10% Patients Were on Hemodiaylisis for Up to 12 Months and 5% Patients Were on Hemodialysis for 13 To 24 Months. Out of 6% With Subclinical Hypothyroidism, 3% Patients Were on Hemodiaylisis for Up to 12 Months and 3% Patients Were on Hemodialysis for 13 To 24 Months. Out of 8% with Some Other Thyroid Abnormality (Low T3),1% Patients Were on Conservative Treatment for CKD and 7% Were on Hemodiaylisis for Up to 12 Months.

In our study of 100% patients the commonest symptom was tiredness and weakness. The next common symptoms was dry skin in 91% diminished sweating in 56%, weight increase in 55%, hair loss in 12 %, parasthesia in 6 %, constipation in 11% and hoarseness of voice in 2%. However, no patients reported impairment of hearing. Studies reporting clinical profile of thyroid abnormalities in chronic kidney disease are few. In a study,[7] done in Indian population The Billewicz score20 was used. 2 (6.66%) patients of chronic renal failure had clinical sign symptom index scores suggestive of hypothyroidism. One patient had hypothyroidism index score of +44 and another patient had +32.

The most sensitive features were delayed ART (77%) and dry skin (76%), while the most specific were slow movements (98.7%) and diminished hearing (97.5%). A positive predictive value was highest for slow movements (96.5%) and puffiness (94.2%). On the other hand, a negative predictive value was highest for ART (80.3%) and dry skin (72.7%).[21]

In our study, using the zulewski score 33% patients and a score between 0 to 2 (euthyroid state), 59% had a score between 03 to 05 (intermediate) and 8% had a score of above 5 (hypothyroid state). No patients were found to have hyperyhyroidism. In our study, in patients with zulewski score 0 to 2, 2(6%) patients had Low T3 but none patients had hypothyroidism (raised TSH). With score 3 to 5, 10% patients had LowT3, 8 % patients had subclinical hypothyroidism and 15% patients had overt hypothyroidism. With score >5 none had Low T3, 13% patients had subclinical hyopothyroidism and 75% patients had overt hypothyroidism. Thereby suggesting that clinical hypothyroidism is more commonly associated with thyroid function test abnormality.

There were no patients in stage 1 and 2 in our study. In the patients with stage 3 none of the patients had either a score of greater than 5 nor did any patient had raised TSH levels. Thus, some of the symptoms of CRF tend to be overlap with hypothyroidism and may pose difficulty in diagnosis merely on the basis of clinical symptoms.

In our study, 27% of stage 5 CKD patients had hypothyroidism when compared to Stage 4 (3%) And Stage 3(0%). 11.5%patients of stage 5 patients had subclinical hypothyroidism when compared to no patients in stage 3 and stage 4. 11.5% Patients with Stage 5 CKD Had Some Other Thyroid Hormone Abnormality (LT3) When Compared to Stage 4(5%) and Stage 3(0%). So, Higher the Stage of CKD Higher Was the Prevalence of Thyroid Hormone Dysfunction. Out of 21 patients with raised TSH, 20(95%) patients had stage 5 and 1(5%) patient had stage 4 CKD. Out of 8 patients with Low T3, 6(75%) patients had stage 5 and 2(7%) patients had stage 4 CKD. In another study,[24] it was shown that that in patients on dialysis, mean serum T4 and T3 levels are lower than normal. Despite the recent considerable improvements in renal replacement therapy, cardiovascular disease still remains the main cause of morbidity and mortality in CRF patients.[25] It is evident from various studies conducted by Lindner, et.al,[26] Stenvinkel et.al,[27] Cheung, et.al,[28] and etc. Bradley et al found that in clinically overt primary hypothyroidism, the significant manifestation of renal function change is hyponatremia that results from impairment in the renal diluting capacity resulting in water retention.[29]

Decreased cardiac output resulting from overt hypothyroidism may also contribute to renal

hemodynamic alterations leading to progressive decline in GFR. Thus, as hypothyroidism becomes more severe it may cause reduced heart function which in turn leads to progressively worsening kidney function.

CONCLUSION

Excluding hypothyroidism and subclinical hypothyroidism, the mean TSH level in our study is within normal limits which indicate abnormality in hypophyseal mechanism of TSH release in uremic patients as the as the TSH response to the TRH was blunted. Considering the fact that clinical features of thyroid dysfunction are often masked with uremic state it may be necessary to conduct periodic screening of thyroid function in CKD patients because early diagnosis and treatment of thyroid disease significantly reduces morbidity and mortality.

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