International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Study of Thyroid Profile in Diabetic Versus Non - Diabetic Chronic Kidney Disease Patients

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Abstract: ***Objectives: Chronic kidney disease (CKD) and its progression is associated with a number of complications, including thyroid dysfunction, in particular hypothyroidism. The objective of the study was to compared the thyroid profiles in diabetic and non - diabetic chronic kidney disease. Also, thyroid profiles were compared in different stages of CKD and in dialyzed versus non - dialyzed patients. Methods: An observational study was conducted among 150 CKD patients at DY Patil Hospital, Nerul.75 of the patients were of diabetic kidney disease. Demographic features, medical history of diabetes mellitus, hypertension and renal disease of each patient were noted, and blood samples were analyzed for free triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH). Results: Thyroid dysfunction was found in 48.7 % CKD patients, the most common was subclinical hypothyroidism (45.3%). When compared to non - diabetic chronic kidney disease patients, diabetic kidney disease patients had higher prevalence of subclinical hypothyroidism (32% vs 58.6%). Stage 4 and 5 CKD patients had higher prevalence of having subclinical hypothyroidism as compared to stage 3 patients (54.1% vs 48.9% vs 30.5% respectively). Subclinical hypothyroidism was found to be more in patients undergoing hemodialysis as compared to those not under hemodialysis (61.5% vs 32.65%). Conclusions: CKD patients of diabetic origin were more prone to thyroid abnormalities as compared to CKD patients of non - diabetic origin. Stage 4 and 5 CKD patients had significantly higher risk of having thyroid dysfunction as compared to stage 3 patients. Thyroid dysfunction was found to be more in patients undergoing hemodialysis as compared to those not under hemodialysis***

Keywords: Chronic kidney disease, diabetic kidney disease, Subclinical hypothyroidism, Thyroid dysfunction

1. Background

Chronic kidney disease (CKD) is defined by irreversible renal dysfunction that accumulates nitrogenous waste products and causes excretory, metabolic, and systemic failure. It also presents with a wide range of clinical symptoms, including reduced creatinine clearance. End - stage renal disease (ESRD) is a clinical condition in which the patient's endogenous renal function has irreversibly failed, leaving them permanently dependent on renal replacement treatment to prevent potentially fatal uremic consequences. [1]

Thyroid hormone peripheral metabolism and the hypothalamus - pituitary thyroid axis are both impacted by CKD. Low levels of circulating thyroid hormone, changes in peripheral hormone metabolism, inadequate binding to carrier proteins, decreased tissue thyroid hormone content, and modified thyroid gland iodine storage are just a few of the ways that chronic kidney disease (CKD) impacts thyroid function. Thus, in CKD, thyroid hormone metabolism is impaired [2]

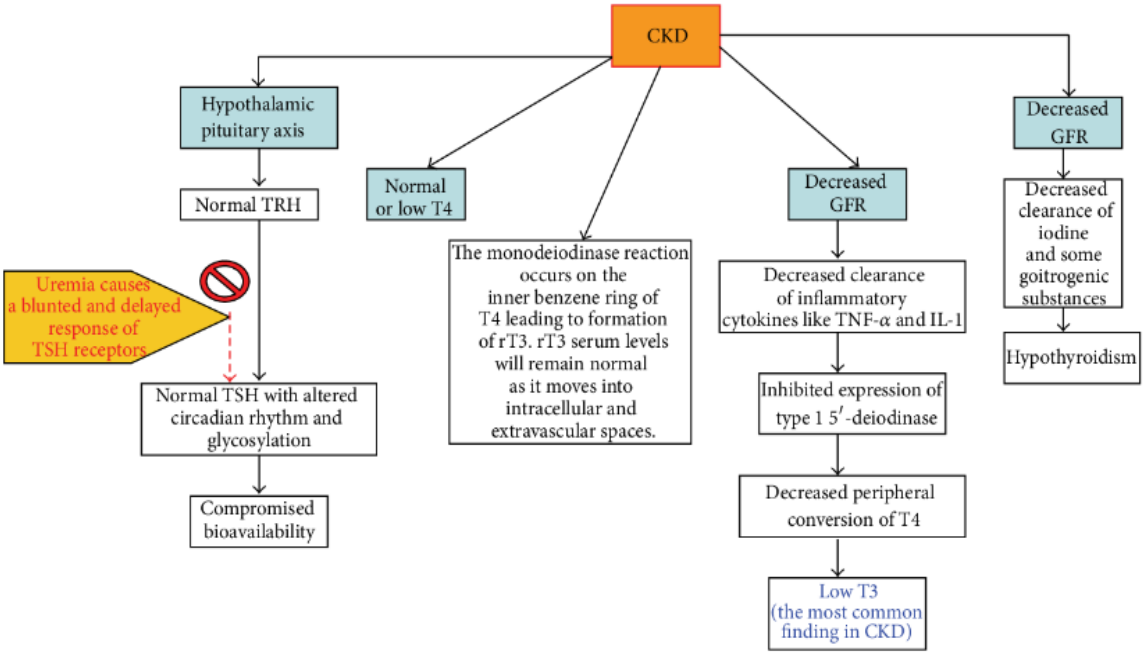

Figure 1: Effects of Chronic Kidney Disease state on Thyroid hormone metabolism

Diabetes mellitus is the primary factor associated with end - stage renal disease. Both Type 1 and Type 2 diabetes mellitus are directly linked to chronic kidney disease (CKD), which is now graded based on GFR and albuminuria excretion rates. Classic diabetic nephropathy is still associated with increased albuminuria. Compared to people without diabetes, persons with diabetes with CKD have all CKD consequences at a younger age and with a higher degree of severity [3]

According to a research, 10.2% of the general population had CKD, and the two main risk factors for CKD were diabetes mellitus and age [4].

Numerous studies have demonstrated the link between thyroid issues and declining renal function in individuals with chronic kidney disease. Nonetheless, limited information is currently available to demonstrate thyroid disorders in diabetic kidney diseases. This study was done to estimate prevalence of thyroid disorders in diabetic kidney disease and its comparison with non - diabetic chronic kidney disease.

2. Methods

An observational cross - sectional study was conducted among 150 CKD patients in DY Patil hospital including newly diagnosed and known CKD cases (stage 3 to stage 5).75 patients included were patients of diabetic kidney disease. Primary objective of the study was to compare thyroid profile in diabetic versus non - diabetic chronic kidney disease patients. Secondary objectives were to compare thyroid profiles in different stages of CKD and amongst dialyzed and non - dialyzed patients.

Inclusion Criteria
All patients of CKD who had given consent and age >18 years and patients with Diabetes Mellitus

Exclusion Criteria
Patients diagnosed with thyroid disorders before developing CKD, patients on medications that could interfere with thyroid hormone levels (eg. amiodarone, corticosteroids, beta blockers, anti - convulsant, androgens, anabolic steroids, dopamine agonists and iodine), Patients with autoimmune thyroid disorders, patients with acute kidney injury (AKI)

Definitions
CKD was defined and staged according to KDIGO guidelines wherein CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health [5]

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

Figure 2: KDIGO 2024 guidelines for classification of Chronic Kidney Disease

American Diabetes Association criteria were utilized for diabetes diagnosis (fasting blood glucose level > 126 mg/dL, a 2 - hour post prandial blood glucose level of >/=200 mg/dL, or a HbA1c of >/=6.5%) [6]

Diabetic Kidney Disease [7 - 10] diagnosis was made if the following conditions were satisfied

- Albuminuria: macroalbuminuria (>300 mg of albumin/g of creatinine or Urinary Albumin Excretion (UAE) >300mg/d) or microalbuminuria (30 - 300 mg of albumin/g of creatinine OR UAE 30 - 300mg/d) persistently over 3 - 6 months
- >5 years duration of type 1 diabetes mellitus and for type 2, from the time of diagnosis
- Associated with diabetic retinopathy
- Alternative diagnosis was considered when
- Severely elevated albuminuria (UAE >/= 300mg/d) within 5 years of onset of type 1 diabetes or prior to onset of type 2 diabetes
- RBC / WBC cast or dysmorphic RBC in urine routine microscopy
- Presence of other systemic diseases

- Sudden increase in albuminuria (>5 - 10 times over a period of less than 1 - 2 years) or rapid decline in eGFR (>5ml/min/1.73m² / year)

Thyroid profiles were classified according to American Thyroid Association (ATA) and American Association of Clinical Endocrinology (AACE)

Serum TSH	Serum Free T4	Serum Free T3	Assessment
Normal	Normal	Normal	Euthyroid
High	Normal	Normal	Subclinical Hypothyroidism
High	Low	Low	Clinical Hypothyroidism
Low	Normal	Normal	Subclinical Hypothyroidism
Normal or Low	High	High	Clinical Hypothyroidism

Figure 3: Classification of thyroid profiles of the patients in the study

Patients with known thyroid disorders, on medications affecting thyroid function were excluded from the study. Demographic features (age and sex) and medical history of diabetes mellitus, hypertension of each patient were noted, and blood samples (2 ml) were collected. Blood was analyzed for triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH). Serum free T3, free T4 and TSH were measured by using the Maglumi 1000 fully - auto chemiluminescence immunoassay (CLIA) analyzer. reference range were as follows: free T3 (1.21–4.18 pg/mL), free T4 (8.9–17.2 pg/mL) and TSH (0.3–4.5mIU/L).

Thyroid profiles of the patient were divided as depicted in figure 3. Descriptive statistics such as frequencies, mean, standard deviation and proportion for quantitative variable was calculated and association were established using chi square test with p - values. P - values of < 0.05 were taken as significant.

3. Results

A total of 150 patients who were newly diagnosed or known cases of CKD were enrolled in the study. The mean age of participants was 59.6 years. (mean, SD) = 57.24 ± 16.37 out of which 43% were males and 57% were females. Various clinical and biochemical characteristics of the study participants is illustrated in table 1

Associated co - morbidities	Frequency (n=150)	Percentage (%)
History of Diabetes	81	54
Duration (Mean ±SD) (years)	13.42 ± 7.64	
Using anti - diabetic medication	81	54
Diabetic Kidney Disease	75	50
Non - diabetic Chronic Kidney Disease	75	50
History of hypertension	99	66
Duration of hypertension (Mean ±SD) (Years)	9.384 ± 7.145	
Using anti - hypertensive drugs	81	54
History of CKD	119	79.3
Duration (Mean ± SD) (Years)	1.89 ± 2.35	
On Hemodialysis	52	34

Table 1: Associated Co - Morbidities Among Study Participants (N = 150)

Vital Signs & Clinical Features	Frequency (n= 150)	Percentage (%)
Pulse rate (bpm) (Mean ± SD)	86.89 ± 9.739	
Systolic blood pressure, (Mean ± SD) (mmHg)	131.33 ± 20.156	
Diastolic blood pressure (Mean ±) (mmHg)	80.03 ± 11.057	
Presence of pallor	129	86
Presence of edema	81	54
Diabetic Retinopathy	71	94.6
Estimated GFR (ml/ min/1.73m^2)		
Stage 3a	8	5.3
Stage 3b	27	18
Stage 4	26	17.3
Stage 5	89	59.3

Table 2: Laboratory Parameters among Diabetic and Non - Diabetic Chronic Kidney Disease Participants (N = 150)

Laboratory variables	Diabetic, (n= 75)	Non - diabetic CKD (n=75)	P value
	Mean ± SD	Mean ± SD	
HbA1C (gm/dl)	9.76 ± 2.119	6.00 ± 0.00	0.282
Current urea (mg/dl)	111.96 ± 56.51	132.14±67.24	0.13
Last 3 months urea (mg/dl)	93.82 ± 50.22	91.72 ± 44.03	0.89
Current creatinine (mg/dl)	5.16 ± 4.02	6.79 ± 5.25	0.069
Last 3 months creatinine (mg/dl)	4.15 ± 3.043	5.04 ± 4.237	0.216
Urinary Albumin Excretion (mg/d)	257 ± 120	211 ± 153	0.611
T3 (pg/ml)	2.76 ± 1.886	2.46 ± 0.944	0.376
T4 (pg/ml)	11.64 ± 3.443	12.43 ± 3.214	0.072
TSH (IU/ml)	10.22 ± 15.847	4.70 ± 5.243	0.06

Table 3: Comparison between thyroid profile among Diabetic (N=75) and Non - Diabetic Chronic Kidney Disease (N = 75) participants

Thyroid profiles	Diabetic (n= 75)	Non – diabetic CKD (n=75)	P value
Euthyroid	28	49	0.001
Subclinical Hypothyroid	44	24	0.001
Overt Hypothyroid	2	1	0.56
Overt Hyperthyroid	0	1	0.36
Sick Euthyroid	1	0	0.56

Stage 3, stage 4 and stage 5 CKD patients were 23.6 % (n = 36), 15.7 % (n = 24) and 60.5 % (n = 92) Subclinical hypothyroidism got significantly more common with CKD progression. Comparison of thyroid profiles in different stages has been tabulated in table 4

Table 4: Comparison between thyroid profile among different stages of Chronic kidney disease (CKD of all participants (N=150) in frequency

Thyroid profile	Stage III (a)	Stage III (b)	Stage IV	Stage V	P value
Euthyroid	5	18	10	45	0.18
Subclinical hypothyroid	2	9	13	45	0.29
Overt hypothyroid	0	1	0	2	0.77
Overt hyperthyroid	1	0	0	0	<0.001
Sick - euthyroid syndrome	0	0	1	0	0.75

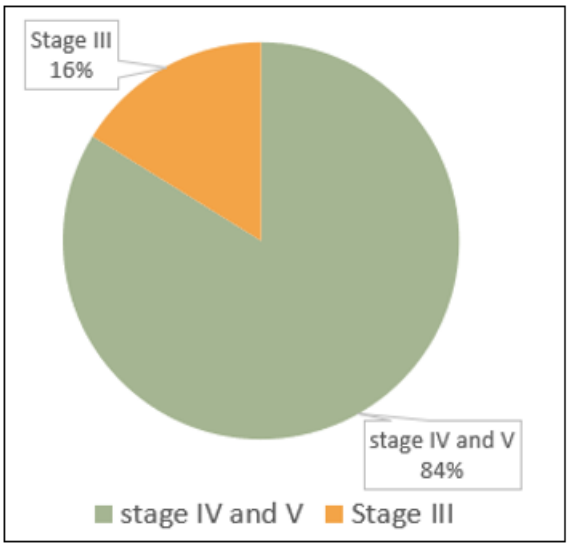

Figure 4: Comparison between subclinical thyroid subjects in stage IV and V and stage III (P=0.05)

Subclinical hypothyroidism was also common in dialyzed patients (n=52) as compared to those who were not under dialysis (n=98), which is illustrated in figure 5

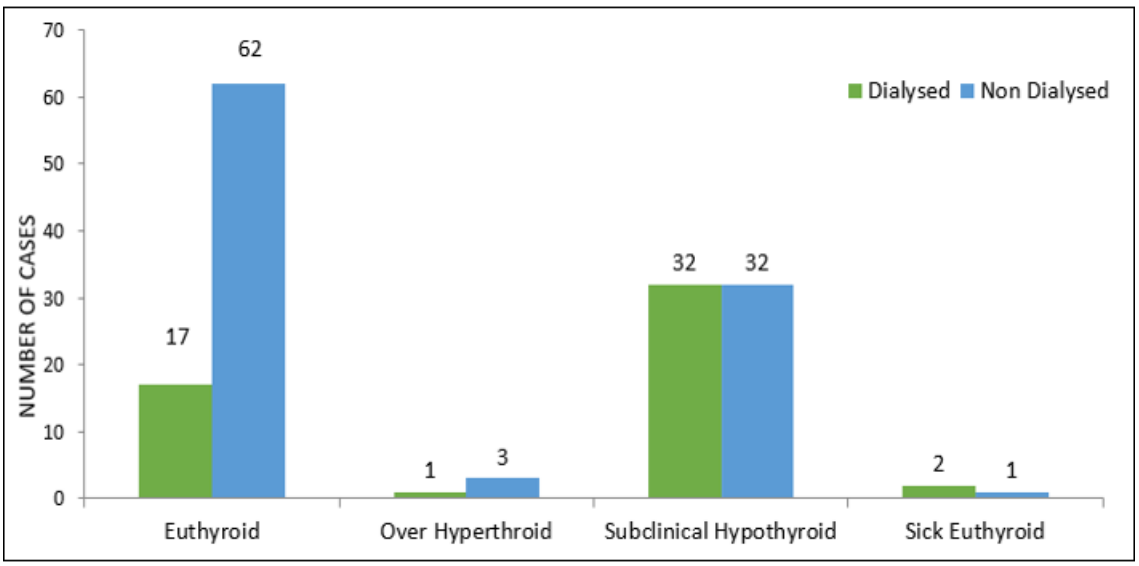

Figure 4: Comparison between thyroid profile among hemodialyzed (N=52) and non - hemodialyzed (N=98) patients (49.3% VS 20.7%, p=0.001)

4. Discussion

The present study identifies thyroid dysfunction as a common disorder in CKD patients. Thyroid dysfunction was found in 48.7 % CKD patients, the most common being subclinical hypothyroidism (45.3%). Among the participants, the prevalence of chronic kidney disease was more common in advancing age. similar findings were seen in study conducted by Nathan R. Hill in 2016 in which estimated prevalence for each age the sample population was divided by mean age into deciles. Studies measuring 5 stages of CKD mean (95%CI) were—30s: 137% (108, 166%), 40s: 120% (99, 141%), 50s: 160% (135, 184%), 60s: 276% (267, 285%), 70s: 343% (319, 367%) respectively [(11)]

Amongst the thyroid abnormalities, the most common was subclinical hypothyroidism (51.34 %) findings of which are similar to study titled Thyroid dysfunction and dyslipidemias in chronic kidney disease patients done by Khatiwada et al in the year 2015 in which thyroid dysfunction was found in 38.6 % CKD patients, the most common being subclinical hypothyroidism (27.2 %), followed by overt hypothyroidism (8.1 %) [(12).] Increased prevalence of subclinical hypothyroidism (51.34 %) was seen in patients with reduced eGFR which was similar to 14, 623 participants in NHANES III survey in which there was a higher prevalence of hypothyroidism seen (defined as TSH > 4.5 mIU/L or receipt of exogenous thyroid hormone) with increasing severity of kidney dysfunction and 56% of them were due to subclinical disease [(13)]

In an original article published by Mao Zheng et al in 2019, titled " The association between thyroid dysfunction (TD) and diabetic kidney disease (DKD) in type 2 diabetes

mellitus (T2DM) " in which it was seen that Subclinical hypothyroidism was more prevalent in T2DM patients with DKD than in T2DM patients without DKD [14]. In our study, similar results were observed. The prevalence of subclinical hypothyroidism was higher in patients of diabetic kidney disease (n=75, 28.67%, p=0.001) as compared to that of non - diabetic etiologies of CKD (n=75, 15.33%, p=0.001).

In study done by Prajapati P et al published in Journal of Indian Medical Association, titled 'Correlation between severity of chronic kidney disease and thyroid dysfunction' It is concluded that thyroid dysfunction occurs in patients with chronic kidney disease. Mean values of TT3, FT3, TT4, FT4 reduced and that of TSH increased as severity of renal failure increased. [15].

Study by Lo et al. found that the prevalence of hypothyroidism increased with lower levels of GFR (in units of mL/min/1.73 m2), occurring in 5.4 % of subjects with GFR greater than or equal to 90, 10.9 % with GFR 60–89, 20.4 % with GFR 45–59, 23.0 % with GFR 30–44, and 23.1 % with GFR < 30 (p < 0.001 for trend). They reported that 56 % of hypothyroidism cases were subclinical [16]

Comparable to this conclusion, we observed increasing trend for TSH level across CKD stages 3–5, which suggest that TSH level increases with the progression of renal impairment (which is indicated by a decrease in GFR). Prevalence of subclinical hypothyroidism was much common in stage 5 (29.3 %), than stage 4 (8.6 %) and stage 3 (7.3%) patients, which clearly demonstrates the parallel rise in subclinical hypothyroidism with CKD progression where it was pronounced in patients in stage 4 (eGFR between 15 - 30 ml/min/1.73 m2) and stage 5 (eGFR <15 ml/min/1.73 m2) which was statistically significant (p= 0.05). Thus, we found that stage 4 and 5 patients had significantly high risk for thyroid dysfunction as compared to stage 3 patients.

Thyroid dysfunction was found to be more in patients undergoing hemodialysis as compared to those not under hemodialysis (59.6 % vs 32.6%, p< 0.001).

However, in an article titled 'Thyroid function in end stage renal disease and effects of frequent hemodialysis", which was published by Joan C. LO et al in 2017, it was concluded that frequent in - center and nocturnal hemodialysis did not significantly change (baseline to month 12) TSH, FT4, or FT3 concentrations in patients with endogenous thyroid function (14). Also, a study in undialyzed CKD patients found that both T3 and T4 were significantly reduced whereas TSH remains to be unchanged in patient group compared to controls [17].

We found some other important outcomes in our study.

With respect to the clinical profile of the patient, anemia which was represented by presence of pallor was prevalent in CKD from stage 3 onwards (86%) results of which were similar to a research article published by Melissa E. Stauffer ([18], but the causes of anemia in the study could not be further evaluated.

Strength of the study

Few studies have been published which compare thyroid profile in different etiologies of CKD especially of diabetic versus non - diabetic origin and this study helped to compare the same

5. Limitations of the study

This study was done in a single hospital setting, so whether result of this study can be generalized to all population cannot be ascertained Follow up of the patients could not be done to look for prognostic value of thyroid levels. This is a small study and larger studies with greater power from multiple centers are needed. The study is observational, and no cause of thyroid disorders could be looked into.

6. Conclusions

In summary, the present study finds thyroid dysfunction to be very common in CKD patients and reveals the significant association between CKD progression and thyroid dysfunction. We can also conclude that elderly subjects of diabetic kidney disease are more prone to develop subclinical hypothyroidism as compared to non - diabetic kidney disease. From these findings it is imperative that thyroid screening programs, especially among the elderly population in diabetic kidney disease patients, should be put in the place and needs to be effective and sustained

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