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ORIGINAL RESEARCH

Prevalence of subclinical and overt hypothyroidism in diabetic and non-diabetic chronic kidney disease (CKD) and effect of treatment on glomerular filtration rate (GFR)

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ABSTRACT

Background: Primary hypothyroidism is common in CKD due to the well-established interaction between thyroid and kidney,impacting renal function.The objective of study was to evaluate the prevalence of subclinical (SCH) and overt hypothyroidism (OH) in patients with CKD and to compare the prevalence of hypothyroidism among patients with or without diabetic mellitus (DM). **Methods:** This observational prospective cohort study was conducted on patients aged ≥18 years of either sex with confirmed CKDfrom April 2015 to August 2016. **Results:** A total of 144 patients were included in the study, with a mean age of 48.92 years. Among them, 48.61% belonged to the age group of 41-60 years. Of the total study population, 47.22% had CKD with DM, and 52.78% had CKD without DM. The meaneGFR was comparable in patients of CKD with or without DM (16.34 ml/min/1.73m² vs 14.80 ml/min/1.73m²). Hypothyroidism was detected in 47.06% of CKD patients with DM, including 21.88% with OH and 78.13% with SCH. In CKD patients without DM, 48.68% had hypothyroidism, among those 32.43% had OH and 67.57% had SCH.The eGFR significantly increased for CKD patients on thyroid hormone replacement therapy (THRT) at both 3 and 6 months compared to baseline ($p < 0.001$). **Conclusion:** Hypothyroidism is substantially more common in CKD patients, and THRT has been shown to improve renal function, indicating its promise as a therapeutic intervention for CKD patients with hypothyroidism, regardless of DM status.

Keywords: overt hypothyroidism, subclinicalhypothyroidism, diabetic, estimated glomerular filtration rate, intact parathyroid.

INTRODUCTION

Chronic kidney disease (CKD) is a rising global health issue that burdens healthcare systems with significant costs due to its associated morbidity and mortality. The presence of CKD in individuals with multiple comorbidities complicates the identification of significant prognostic predictors within this challenging population [1]. Thyroid disorders, notably hypothyroidism, characterized by elevated serum thyroid-stimulating hormone (TSH) levels alongside low or normal thyroxin (T4) levels, both overt and subclinical, are widespread among individuals with CKD [2].The thyroid's activity impacts kidney function starting from the embryonic phase. Thyroid hormones play a role in overall tissue growth, tubular functions, electrolyte regulation, and neural input [3]. Both hyper- and hypo-functioning of the thyroid indirectly affect mature kidney function by influencing the cardiovascular system and renal blood flow [4], and directly impact glomerular filtration, electrolyte pumps, tubular secretory and absorptive capacity, as well as kidney structure. In individuals

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with type 2 diabetes mellitus, the risk of nephropathy and cardiovascular events increases with subclinical hypothyroidism (SCH) [3,5].

Various factors, such as autoimmunity, iodine excess, and the impact of retained solutes like organic acids and guanidino compounds, have been proposed as contributors to the association between CKD, increased TSH, and reduced thyroid function [6]. However, the precise mechanisms underlying this relationship remain unclear. This is exacerbated by the lack of comprehensive global data on the screening and prevalence of thyroid dysfunction in CKD patients. Therefore, this study aimed to determine the prevalence of SCH and OH in CKD and also, to compare the prevalence of hypothyroidism between diabetic and non-diabetic patients with CKD.

METHODS

Study design and ethical consideration

This observational prospective cohort study was conducted at M. L. N. Medical College and its associated S. R. N. Hospital, Allahabad from April 2015 to August 2016.This study was conducted in accordance with ethical principles that are consistent with the Declaration of Helsinki and was approved by the institutional ethics committee and review board. A written informed consent was taken from all the participants in the study.

Inclusion criteria and exclusion criteria

All patients aged ≥18 years of either sex with a confirmed diagnosis of CKD according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [7] were included in the study, along with those meeting the diagnostic criteria for diabetes mellitus as per the American Diabetes Association (ADA) guidelines [8]. Patients with a known case of thyroid dysfunction or those receiving concurrent treatment with drugs that could contribute to hypothyroidism (such as lithium, amiodarone, or iodine) were excluded from the study.

Data collection

Data collection included demographic information and the patient's detailed medical history, encompassing hypertension, diabetes mellitus, previous episodes of acute kidney damage, and symptoms of uremia. Clinical examinations involved blood pressure monitoring and baseline investigations, incorporating biological and radiological indicators, which were collected for further analysis.

Study intervention

The enrolled patients were then divided into two groups, chronic kidney disease patients with diabetic mellites (DM) and without DM, diagnosed with hypothyroidism (both overt (OH) and subclinical (SCH) and qualifying for treatment recommendations) [9], were initiated on thyroid hormone replacement therapy (THRT) with levothyroxine at 1.6 µg/kg body weight (dose adjusted according to comorbidities) in both groups. Patients on THRT were then followed up at three and six months after starting the treatment, and their thyroid profile and estimated glomerular filtration rate (eGFR) were re-investigated.

Study outcomes

The outcomes of the study were to determine the prevalence of subclinical (SCH) and overt hypothyroidism (OH) in patients with CKD and to compare the prevalence of hypothyroidism among patients with or without diabetic mellites (DM). The study also aimed to assess results after three and six months of treatment of hypothyroidism on progression of CKD in either group.

Statistics

Descriptive analysis was utilized to present the study outcomes, with continuous variables described as mean and standard deviation (SD), and categorical variables presented as numbers and percentages. Group comparisons involving continuous data utilized the independent sample 't' test when appropriate, and the Z-test for normally distributed data if the population variance was known. Categorical data group comparisons employed the Chi-squared test, while comparisons involving continuous dependent variables and categorical independent variables utilized analysis of variance (ANOVA). The linear correlation between two variables was assessed using the pearson correlation coefficient, and a significance level of $P < 0.05$ was considered statistically significant.

Definitions

1. The reference range for serum TSH in the general adult population is between 0.4 and 4.0 mU/L; fT3 2.2 – 5 ng/mL; fT4 0.7 – 2.5 ng/dL.

Hypothyroidism was defined as a TSH level >4 mU/L.

SCH was defined by a TSH >4 mU/L with normal fT3 level.

The normal reference range for TPO antibody was <0.5 IU/mL.

2. CKD-EPI equation GFR=141×min(Scr/k, 1)α× max(Scr/k, 1)-1.209 × 0.993 Age Multiple by 1.018 for women, Multiple by 1.159 for African ancestry, where Scr is serum creatinine in mg/dL, k is 0.7 for females and 0.9 for males, α is - 0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.

3. The American Diabetes Association criteria 2015 was used for diagnosis of diabetes mellitus [8]:

(a) Hb A1C ≥6.5%

(b) Fasting plasma glucose ≥126 mg/dL

(c) 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test; 75-g glucose load should be used

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(d) Random plasma glucose concentration ≥200 mg/dL in persons with symptoms of hyperglycemia or hyperglycemic crisis

RESULTS

A total of 144 patients with CKD were included in the study, with a mean age of 48.92 years. Among them, 48.61% belonged to the age group of 41-60 years, followed by 27.08% in the 10-40 years age group. The majority of patients (54.64%) were in stage 5 of CKD, while 32.64% were in stage 4 of CKD. The mean eGFR levels increased with increasing age of the CKD patients. [Table 1].

Of the total study population, 47.22 % of the patients were presented with DM. Of which majority (55.88%) of the patients belonged to the age group of 41-60 years. Non-diabetic CKD patients were significantly younger in age than diabetic CKD patients (p =0.0001). The mean eGFR (16.34 mL/min/1.73m² vs 14.80 mL/min/1.73m²) was comparable in patients of CKD with and without DM. Systolic blood pressure (155.47 mmHg vs. 156.80 mmHg, p=0.792) and diastolic blood pressure (90.08 mmHg vs. 89.42 mmHg, p=0.686) showed no significant difference between patients with and without DM. The mean change in haemoglobin (8.45 gm/dL vs 8.12 gm/dL, p=0.332) and serum intact parathormone (311.73 pg/mL vs. 338.61 pg/mL, p=0.526) was insignificant between patients with and without DM. The mean serum protein (6.4 gm/dL, vs 6.54 gm/dL, p=0.214) was comparable between patients with and without DM [Table 2].

Among the total patient population, 47.92% were diagnosed with hypothyroidism, of which 72.46% had SCH, and 27.54% had OH. Prevalence of hypothyroidism increased with increasing severity of CKD.

Hypothyroidism was detected in 47.06% of patients with DM, including 21.88% with overt and 78.13% with subclinical hypothyroidism. In patients without DM, 48.68% had hypothyroidism, among which 32.43% had overt and 67.57% had subclinical hypothyroidism [Figure 1].

The mean eGFR significantly increased for patients on THRT at both after 3 months (14.18 vs 17.86 mL/min/1.73m^2, $p < 0.001$) and 6 months (14.18 vs. 22.61 mL/min/1.73m^2, $p < 0.001$) compared to baseline. The mean eGFR showed significant improvements in patients with DM, who were on THRT at both after 3 months (13.05 vs. 18.46 mL/min/1.73m^2, $p < 0.001$) and 6 months (13.05 vs. 22.63 mL/min/1.73m^2, $p < 0.001$) compared to baseline. The mean eGFR showed significant improvements in patients without DM, who were on THRT at both after 3 months (14.93 vs. 17.46 mL/min/1.73m^2, $p = 0.026$) and 6 months (14.93 vs. 22.60 mL/min/1.73m^2, $p < 0.001$) compared to baseline [Table 3].

The improvement in eGFR was significant in both groups after THRT, but there was no significant difference between patients with DM and without DM regarding the improvement in renal function at baseline (p=0.570), after 3 months of THRT (p=0.565), or 6 months of THRT (p=0.995). The increment of eGFR in patients with and without DM after 3 months of THRT was 5.41 mL /min/1.73m^2 and 2.53 mL /min/1.73m^2 respectively and after 6 months was 9.58 mL/min/1.73m^2 and 7.67 mL /min/1.73m^2 respectively. [Figure 2].

Table 1: Baseline demographic characteristics of patients

Parameter	Number of patients (N=144)
Age (years), mean (SD)	48.92 (15.45)
Gender	
Male	91 (63.0)
Female	53 (36.8)
Age distribution (years)	
18 – 40	39 (27.08)
41 – 60	70 (48.61)
61 – 80	34 (23.61)
> 80	1 (0.7)
Stage wise distribution of CKD cases	
Stage 3a	6 (4.17)
Stage 3b	8 (5.5)
Stage 4	47 (32.64)
Stage 5	83 (54.64)
Mean eGFR levels, mean (SD)	
18 – 40	14.44 (10.68)
41 – 60	15.24 (10.64)
61 – 80	17.04 (10.74)
> 80	28.9
Data presented as n (%), unless otherwise specified CKD, chronic kidney disease; eGFR**,** estimated glomerular filtration rate; SD, standard deviation.	

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Table 2: Comparison of parameters between CKD patients with diabetic and without diabetic

Parameter	CKD with DM (n=68)	CKD without DM (n=76)	P value
Age group (in years)			
18 – 40	7 (10.29)	32 (42.10)	
41 – 60	38 (55.88)	32 (42.10)	
61 – 80	23 (33.82)	11 (14.47)	
> 80	0	1 (1.31)	
Mean eGFR (ml/min/1.73m^2)	16.34 (11.82)	14.80 (9.58)	0.3898
Mean SBP (mmHg)	155.47 (19.93)	156.80 (24.98)	0.792
Mean DBP (mmHg)	90.08 (9.00)	89.42 (10.44)	0.686
Mean Hb (gm/dL)	8.45 (1.91)	8.12 (2.14)	0.332
Mean iPTH (pg/mL)	311.73 (253.19)	338.61 (253.98)	0.526
Mean serum protein (gm/dL)	6.4 (0.84)	6.56 (0.70)	0.214

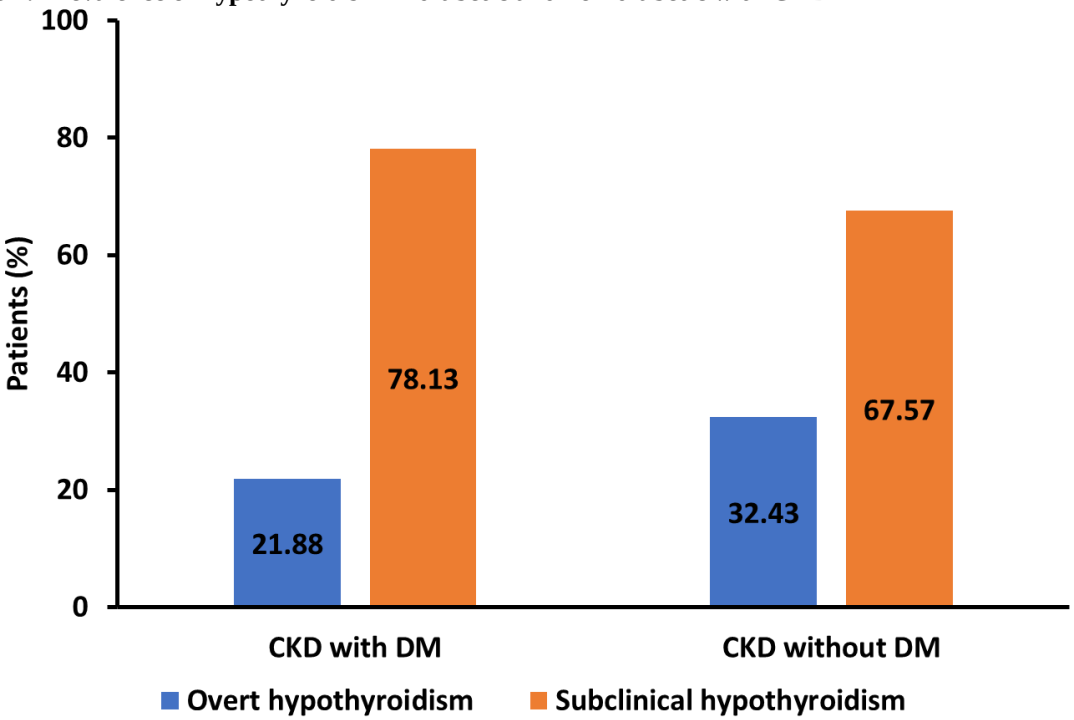
Data presented as mean (SD), unless otherwise specified.
CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellites;eGFR, estimated glomerular filtration rate; Hb, hemoglobin; iPTH, intact parathormone; SBP, systolic blood pressure.

Table 3: Improvement in eGFR from baseline to 6 months in patients on THRT

	eGFR (mL/min/1.73m^2)			P value	
	Baseline	After 3 months	After 6 months	Baseline vs 3 months	Baseline vs 6 months
CKD patients with hypothyroidism	14.18 (10.07)	17.86 (8.82)	22.61 (10.85)	0.001	< 0.001
CKD with DM	13.05 (10.13)	18.46 (9.26)	22.63 (10.75)	< 0.001	< 0.001
CKD without DM	14.93 (10.07)	17.46 (8.82)	22.60 (9.68)	0.026	< 0.001

Data presented as mean (SD).
CKD, chronic kidney disease; DM, diabetes mellites;eGFR, estimated glomerular filtration rate; THRT, thyroid hormone replacement therapy.

Figure 1: Prevalence of hypothyroidism in diabetic and non-diabetic with CKD



CKD, chronic kidney disease; DM, diabetes mellites

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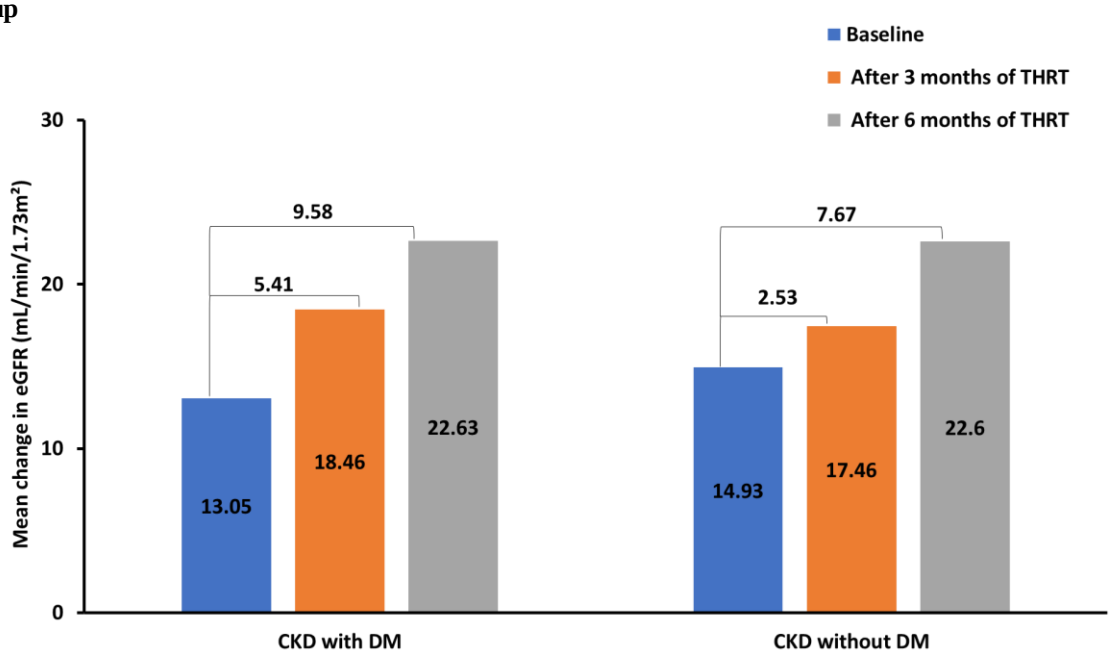
Figure 2: Comparison of improvement in eGFR after THRT between diabetic and non-diabetic CKD group



CKD, chronic kidney disease; DM, diabetes mellites; eGFR, estimated glomerular filtration rate; THRT, thyroid hormone replacement therapy.

DISCUSSION

The present study sheds light on the prevalence of SCHand OH in patients with CKD and also compared the prevalence of hypothyroidism among diabetic and non-diabetic patients with CKD.

In the present study majority of the patients were from the age group of 41-60 years.Patients with non-diabetic CKD were found to be significantly younger in age compared to those with diabetic CKD. Zhang et al. [10] found that patients with CKD and DM were older compared to those without DM.

The mean eGFR showed an increasing trend with age in the present study. This is consistent with the findings from the study by Pani et al.[11]. The mean eGFR was comparable in patients of CKD with and without DM. Similar results were observed by Osawa et al.[12] and Zhang et al.[10] in their studies. The mean change in haemoglobin and serum intact parathormone was insignificant between patients with and without DM.

Of the total study population, 47.22 % of the patients were presented with DM, while remaining 76(52.78%) patients were having non-diabetic CKD.

Nearly half (47.92%) of the total patient population in our study was diagnosed with hypothyroidism, with the majority (72.46%) having SCH and the remaining (27.54%) having OH. Furthermore, we observed that the prevalence of hypothyroidism increased with the severity of CKD. Similar observations were also reported by Chandra A. in the cross-sectional study from North India [13] and also in study by Bajaj et al.[14]. Hypothyroidism was prevalent in 47.06% of patients with DM, out of which 21.88% hadOH and 78.13% having SCH. A study by Bajaj et al. underscores the prevalence of hypothyroidism in diabetic kidney disease patients [15].A study by Khassawnehet al[16] revealed an overall prevalence of thyroid disorders at 26.7% among patients with DM, with SCH being the most common.

In patients without DM, the prevalence of hypothyroidism was 48.68%, with 32.43% having OH and 67.57% having SCH. Similar to these findings Bajaj et al. reported an increased prevalence of SCH at 41.1% and OH at 2.7% in their study.Consistent with previous study [17], present study findings affirm that SCH is not a rare disorder among CKD patients.

Following THRT, both diabetic and non-diabetic patients demonstrated a significant improvement in eGFR at both, 3- and 6-months follow-up. However, there was no statistically significant difference between the two groups in terms of renal function improvement at baseline (p=0.570), after 3 months of THRT (p=0.565), or 6 months of THRT (p=0.995).A recent study conducted by Shin et al. [18] revealed that thyroid hormone treatment not only preserved renal function but also emerged as an independent predictor of renal outcomes. This underscores the potential positive impact of thyroid hormone treatment on renal health and suggests its relevance as a factor influencing renal outcomes independently. The results from the study by Bajaj et al. demonstrate that THRT significantly improved renal function among nondiabetic CKD patients with hypothyroidism [14], and also among diabetic CKD patients with hypothyroidism [15] as evidenced by the mean eGFR (ml/min/1.73 m²).The increase in eGFR following THRT was consistent in both the diabetic (p=0.000) and non-diabetic (p=0.000) CKDgroups. However, there was no significant difference between

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the two groups in terms of eGFR increment at baseline, three months after THRT, or six months after THRT.

CONCLUSION

Hypothyroidism emerges as significantly more prevalent among CKD patients. Thyroid hormone replacement therapy demonstrates promising outcomes by improving renal function, suggesting its potential as a therapeutic intervention for CKD patients with hypothyroidism, irrespective of DM status. These findings underscore the importance of recognizing and addressing thyroid dysfunction in CKD management, emphasizing the potential benefits of THRT in improving renal function regardless of the presence of DM.

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