Study of Prevalence of Hypothyroidism and Effect of Treatment with L-thyroxine in Patients of Chronic Kidney Disease

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ABSTRACT

Objective: There is scarcity of literature regarding prevalence and severity of thyroid abnormalities in chronic kidney disease (CKD) patients. This study (i) estimated the prevalence of hypothyroidism in CKD patients, (ii) investigated the effect of thyroid hormone replacement therapy (THRT) on changes in estimated glomerular filtration rate (eGFR) in CKD patients. **Material and methods:** This was a descriptive longitudinal study conducted in MLB Medical College, Jhansi over a period of 1 year, on patients with CKD. A total of 120 CKD patients with serum creatinine levels available at least two times in previous 6 months were enrolled, screened for thyroid function and those detected with hypothyroidism were treated with L-thyroxine. Before and after treatment, comparisons were made and for statistical analysis, paired *t*-test was used for association. **Results:** Out of 120 study subjects, maximum patients were in the age group of 51-60 years (36.67%) with 65% being males and 35% females. Twenty-one (17.5%) were found to have hypothyroidism, 18 (15%) had subclinical hypothyroidism and 3 (2.5%) had overt hypothyroidism. The stage-wise distribution of hypothyroidism in CKD patients was 15.6% in stage III, 16.67% in stage IV and 20% in stage V. The rate of decline in eGFR over 6 months was significantly reduced from 3.05 ± 2.02 mL/min/1.73 m^2 before the THRT to 1.02 ± 2.5 mL/min/1.73 m^2 after giving thyroid hormone replacement ($p < 0.001$). Among the patients given thyroid hormone replacement for 6 months, 61.9% showed slower decline in eGFR, 19% showed unchanged decline, 9.5% patients showed a faster decline in eGFR and 9.5% patients showed an improvement in eGFR after THRT. **Conclusion:** Hypothyroidism (15% subclinical and 2.5% overt) is a relatively common condition in CKD patients. Prevalence of hypothyroidism increased with progressively lower levels of GFR i.e., declining renal function. THRT attenuated the rate of decline in renal function in CKD patients with hypothyroidism, suggesting that THRT may delay reaching end-stage renal disease in these patients.

Keywords: Hypothyroidism, chronic kidney disease, estimated glomerular filtration rate, thyroid hormone replacement therapy

Thyroid hormones are important in cellular growth and differentiation, and modulation of physiological functions in all human tissues including the kidney. They also play a role in maintenance of water and electrolyte homeostasis. Therefore, thyroid dysfunction, either hypothyroidism or hyperthyroidism is accompanied by alterations in the metabolism of water and electrolytes, as well as cardiovascular function. On the other hand, the kidney is an important target organ for thyroid hormone actions and for the metabolism and elimination of the thyroid hormones. Derangement in kidney function is associated with abnormalities in the thyroid hormone physiology.[1]

Chronic kidney disease (CKD) affects both hypothalamus-pituitary-thyroidal axis and thyroid hormone peripheral metabolism. The effects of impaired kidney function may lead to hypothyroidism, hyperthyroidism and nonthyroidal illness, which are associated with deranged cardiovascular function, which will adversely affect the prognosis of CKD.[2]

Replacement of thyroid hormone is fundamental to the treatment of primary hypothyroidism. It relieves the symptoms of hypothyroidism and also alleviates the deleterious effects of overt hypothyroidism on the kidney.[3] Even though previous studies have demonstrated that L-thyroxine improves cardiac

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function and dyslipidemia in patients with subclinical hypothyroidism (SCH),[4,5] there is still a lack of consensus in current guidelines on whether to treat SCH patients with thyroid hormone or not.[6] In particular, little is known about the effect of thyroid hormone replacement on the changes in glomerular filtration rate (GFR) in CKD patients with SCH. The direct impact of thyroid hormone treatment on the changes in GFR in the same individuals with SCH could not be evaluated.[7]

In the present study, we compared the changes in GFR before and after thyroid hormone replacement in the same population of adult CKD patients with hypothyroidism. This study was done to simplify the importance of interactions between thyroid functions and kidney disease. This information is essential as it shows a link between two separate conditions. Information obtained from this study will help to increase clinical knowledge and enable clinicians to provide better management for their patients who have thyroid or kidney dysfunction.

AIMS AND OBJECTIVES

- To estimate the prevalence of hypothyroidism in CKD patients.
- Effect on progression of chronic renal failure after treatment of hypothyroidism in CKD patients.

MATERIAL AND METHODS

Study Design

This was a descriptive longitudinal study and patients detected with hypothyroidism were subjected to before and after comparison studies.

Study Site and Population

This study was conducted on 120 patients of CKD, selected randomly; attending the Nephrology Clinic and admitted in wards of Dept. of Medicine, MLB Medical College, Jhansi, Uttar Pradesh between March 2014 and April 2015. There were no dropouts or deaths during the study.

Methodology

Inclusion Criteria

- Patients with CKD, between 20 and 75 years of age with serum creatinine levels available at least two times in previous 6 months before the start of study.
- Informed consent.

Case Definition

Kidney damage for >3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, that can lead to decreased GFR, manifest by either: Pathologic abnormalities *or* markers of kidney damage, including abnormalities in the composition of the blood or urine, abnormalities in imaging tests.

Estimated GFR (eGFR) <60 mL/min/1.73m^2 for >3 months, with or without kidney damage.[8] Estimation of eGFR done using the 4-variable Modification of Diet in Renal Disease (MDRD) formula:

$$GFR\ (mL/min/1.73\ m^2) = 175 \times (Standardized\ SCr\ [\mu mol/L])^{-1.154} \times (age\ [years])^{-0.203} \times 1.212\ (if\ black) \times 0.742\ (if\ female)$$

Exclusion Criteria

- Decline consent.
- Patients <20 or >75 years of age.
- Patients with heavy proteinuria including nephrotic syndrome or terminal malignancy.
- Patients who experienced acute exacerbation of underlying renal insufficiency due to dehydration, radiocontrast dye, urinary tract obstruction, etc.
- Patients previously being treated for thyroid disease.

Thyroid Function Test and Definition: In all patients, serum free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) concentrations were measured. These levels were determined by chemiluminescent microparticle immunoassay. The diagnosis of SCH was solely based upon the results of a thyroid function test and was defined as a normal serum FT4, but elevated TSH levels, irrespective of clinical symptoms of hypothyroidism. Normal reference changes FT3 = 2.30-4.20 pg/mL FT4 = 0.89-1.75 ng/dL, TSH = 0.55-4.780 IU/mL.

Treatment of Hypothyroidism and CKD: All the patients with SCH took L-thyroxine, initially administered at lowest doses necessary to normalize serum TSH levels, which was 25 µg daily. Patients with overt hypothyroidism were prescribed L-thyroxine at 50 µg daily dose. The dose of L-thyroxine was adjusted every 3 months according to the follow-up levels of TSH. The treatment of CKD was continued as before the start of study: the patients on conservative management were prescribed oral hematinics, calcium supplements and antihypertensives and oral hypoglycemic agents (OHAs)

if required, and the patients who were earlier on hemodialysis were continued with the same.

Statistical Analysis

Statistical analysis was performed using SPSS trial version. The data was entered into Microsoft Excel Software. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as number (percentage). We compared patients clinical and biochemical parameters at following time points: 6 and 3 months before L-thyroxine, time of initiation of thyroid hormone supplement and at 3 and 6 months after L-thyroxine treatment. For association, paired *t*-test was applied and p value <0.001 was considered statistically significant.

OBSERVATIONS AND RESULTS

The distribution of study subjects was done according to the age (20-75 years) with maximum study subjects in the age group of 51-60 years (36.67%), with 65% being males and 35% females, stage-wise distribution of study subjects (Table 1) showed majority of participants in stage IV (40%) followed by stage III and V (36.67% and 33.33%, respectively). None of the study subjects included was in stage I or II. Among the study subjects, 75% were on conservative management and 25% were on hemodialysis.

The primary disease process, leading to CKD was diabetes mellitus type II (DM II) (36.67%), followed by hypertension (25%), obstructive uropathy (15%), glomerulonephritis (11.67%), cystic diseases (3.33%) and other causes (8.33%). Twenty-one subjects out of 120 study subjects were found to have hypothyroidism (17.5%) out of which 3 were overt hypothyroid (2.5%) and 18 were subclinical hypothyroid (15%) (Table 2).

The distribution of hypothyroidism stage-wise in CKD showed an increasing prevalence of hypothyroidism with decline in eGFR - 15.6% in stage III, 16.67% in stage IV and 20% in stage V (Table 1).

Hypothyroidism was found to be more common in females (19.04%) as compared to males (16.66%) (Table 3). The prevalence of hypothyroidism was 18.88% in patients with conservative management and 13.33% in study subjects on hemodialysis. The rate of decline in eGFR over 6 months was significantly reduced from 3.05 ± 2.02 mL/min/1.73 m^2 before the thyroid hormone replacement therapy (THRT) to 1.02 ± 2.5 mL/min/1.73 m^2 after giving thyroid hormone replacement ($p < 0.001$) (Tables 4 and 5; Fig. 1).

Table 1. Stage-wise Distribution of Hypothyroidism in CKD Patients

	Stage I	Stage II	Stage III	Stage IV	Stage V
Total no. of subjects	0	0	32	48	40
No. of hypothyroid subjects	0	0	5	8	8
Percentage of hypothyroidism	0	0	15.6	16.67	20.0

Table 2. Thyroid Profile in CKD Patients

	Euthyroid	Overt hypothyroid	Subclinical hypothyroid
No. of subjects	99	3	18
Percentage (%)	82.50	2.50	15.0

Table 3. Gender Distribution of Hypothyroidism in CKD Patients

Gender	Total no. of subjects	No. of hypothyroid subjects	Percentage of hypothyroidism
Male	78	13	16.66
Female	42	8	19.04

Table 4. Changes in eGFR Over Time in CKD Patients

	-6	-3	0 Baseline	+3	+6
eGFR mL/min/1.73 m^2	25.45 ± 11.15	23.92 ± 11.56	22.39 ± 11.63	21.76 ± 12.14	21.35 ± 13.2

Table 5. Comparison of Rate of Decline in eGFR Before and After THRT

	6 months before THRT (-6 to 0 months)	6 months after THRT (0 to 6 months)	P value
Rate of decline of eGFR in mL/min/1.73 m^2 in 6 months	3.05 ± 2.02	1.02 ± 2.5	<0.001

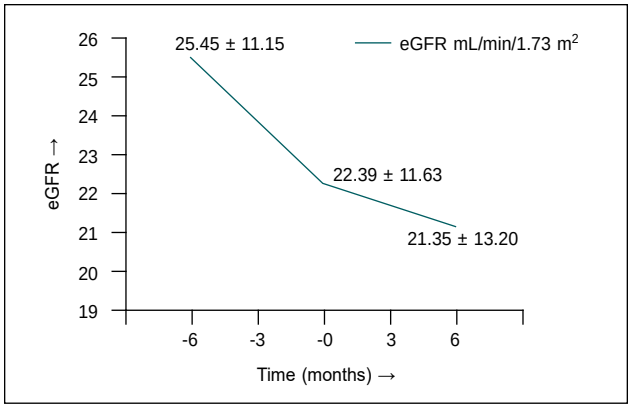

Figure 1. Changes in eGFR over time in CKD patients.

DISCUSSION

The presented study was conducted in Dept. of Medicine, MLB Medical College, Jhansi on 120 subjects from March 2014 to April 2015. The subjects were of CKD, distributed according to the age groups starting from 20 years of age, up to 75 years of age, with maximum study subjects in the group of 51-60 years (36.67%). Of these, 78 (65%) were males and 42 (35%) were females. Classification of CKD into different stages in this study was done as per National Kidney Foundation guidelines, with eGFR using the four-variable MDRD formula.[8] Majority of the participants were CKD stage IV (40%). Number of participants in CKD stage III and V were 26.67% and 33.33%, respectively. None of the participants sampled were in CKD stage I or II. This could be attributed to delay in seeking medical treatment; hence, patients were seen when the disease has progressed to more severe stages. According to the 2003-2006 NHANES (National Health and Nutrition Examination Survey) data of US adults >20 years age, 15.32% is the most recent CKD prevalence with estimated stage-wise prevalence - stage I - 4.1%, stage II - 3.2%, stage III - 6.5% and stage IV + V - 0.6%.[9] Among the 120 patients of CKD included in the study, 90 subjects (75%) were on conservative management and 30 subjects (25%) were on hemodialysis.

Among the primary disease processes leading to CKD, the most common cause was found to be DM II (36.67%), followed by hypertensive nephrosclerosis (25%), glomerulonephritis (11.67%), obstructive uropathy (15%), cystic disease (3.33%) and other causes including human immunodeficiency virus (HIV) infection, pyelonephritis and cardiomyopathies included (8.33%). These results were in concordance with NHANES 2003-2006 data of US, except the percentage prevalence of obstructive uropathy, which was found to be higher in our study subjects of Bundelkhand region.

In our study, the prevalence of hypothyroidism was found to be 17.5% i.e., 21 subjects including 18 subjects of SCH (i.e., 15%) and 3 subjects of overt hypothyroidism (i.e., 2.5%). The stage-wise distribution of hypothyroidism in CKD patients showed the prevalence of hypothyroidism to be 15.6% in stage III, 16.67% in stage IV and 20% in stage V. We concluded that the prevalence of hypothyroidism increased with lower levels of eGFR. This was in concordance with previous study done by Lo et al[10] who used data from NHANES III and revealed the prevalence of hypothyroidism, occurring in 10.9% of patients with stage II CKD, 21% with stage III CKD and 23.1% with stage IV or V CKD. Among these hypothyroidism patients, 56% were considered subclinical. Moreover, Chonchol et al[11] showed that the prevalence of SCH increased from 7% at an eGFR >90 mL/min/1.73 m^2 to 17.9% at an eGFR <60 mL/min/1.73 m^2 in 3,089 outpatient adults.

In our study, the prevalence of hypothyroidism was found to be more in females (19.04%) as compared to males (16.66%). This was not in concordance with previous studies. Study among 137 subjects concluded at Kenyatta National Hospital, Kenya concluded that there was no statistically significant difference between prevalence of hypothyroidism in males and females. A study conducted by Allawi et al[12] on prevalence of hypothyroidism concluded it to be more in males (20%) as compared to females (6%). In relation to the type of treatment in CKD, the prevalence of hypothyroidism was found to be 18.88% on patients with conservative management and 13.33% in patients on hemodialysis.

At the time of commencement of thyroid hormone therapy in 21 hypothyroid subjects, the baseline characteristics were as shown in Table 6. The overall rate of decline in eGFR over 6 months was significantly blunted from 3.05 ± 2.02 to 1.02 ± 2.5 (mL/min/1.73 m^2) ($p < 0.001$) by THRT (Tables 4 and 5). The numbers of patients who had a slower fast or unchanged eGFR decline after THRT were determined, 61.9% patients had a slower decline in eGFR, 19% had unchanged decline, 9.5% had a faster decline and 9.5% patients showed an improvement in eGFR after thyroid replacement.

Among the patients who had a slower decline and improvement in eGFR, 20% (i.e., 3 patients) were of DM II, 53.3% (i.e., 8 patients) had systemic hypertension and 26.7% patients had other etiologies. These results were in concordance with the previous studies conducted.

A study conducted by Shin et al[13] on 113 CKD patients with SCH showed similar results with rates of decline in eGFR significantly attenuated by THRT (-4.31 ± 0.5 vs. -1.08 ± 0.36) ($p < 0.001$), but there was no significant

Table 6. Baseline Characteristics of Hypothyroid Patients

	Total (n = 21) (mean ± SD)
Age	44.1 ± 8.41
Men	13
Women	8
DM II	4
HTN	11
Obstructive uropathy	2
Others	4
SBP	136.57 ± 19.15
DBP	82.19 ± 9.44
Thyroid function test	
FT3	2.33 ± 0.49
FT4	0.89 ± 0.32
S. TSH	9.32 ± 3.52
S. creatinine	3.56 ± 1.39
eGFR	22.39 ± 11.63
S. albumin	3.34 ± 0.42

change in serum FT3 and T4 levels. Slower decline in eGFR was seen in 63.7% patients in this study. A similar study by Shin et al[7] conducted previous to the above mentioned study also demonstrated that thyroid hormone replacement preserved renal function, but in that study, the changes in eGFR were just compared between two different study populations, SCH patients with and without THRT.

A study by Hataya et al[14] showed that eGFR increased rapidly over first 6 months after THRT in CKD patients, followed by a plateau. The improvement in eGFR was up to 30% overall.

CONCLUSION

The present study concluded that thyroid impairment in the form of hypothyroidism is common in CKD patients with SCH being more common and the prevalence of hypothyroidism increases with decline in eGFR levels. Since, thyroid dysfunction can cause significant changes in renal and cardiovascular functions, there is an increasing need to detect hypothyroidism earlier in CKD patients and to initiate early treatment to prevent morbidity and mortality associated. This study emphasized the role of THRT in patients of CKD with subclinical and overt hypothyroidism, as this alleviates the rate of decline in eGFR in these patients and may delay reaching end-stage renal disease in these patients.

REFERENCES

1. Asvold BO, Bjøro T, Vatten LJ. Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study. Eur J Endocrinol. 2011;164(1):101-5.
2. Iglesias P, Díez JJ. Thyroid dysfunction and kidney disease. Eur J Endocrinol. 2009;160(4):503-15.
3. den Hollander JG, Wulkan RW, Mantel MJ, Berghout A. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol (Oxf). 2005;62(4):423-7.
4. Caraccio N, Ferrannini E, Monzani F. Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab. 2002;87(4):1533-8.
5. Monzani F, Di Bello V, Caraccio N, Bertini A, Giorgi D, Giusti C, et al. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. J Clin Endocrinol Metab. 2001;86(3):1110-5.
6. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291(2):228-38.
7. Shin DH, Lee MJ, Kim SJ, Oh HJ, Kim HR, Han JH, et al. Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 2012;97(8):2732-40.
8. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266.
9. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489-99.
10. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int. 2005;67(3):1047-52.
11. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2008;3(5):1296-300.
12. Allawi AAD. Prevalence of hypothyroidism in CKD among sample of Iraqi patients. J Fac Med Baghdad. 2013;55(2):97-101.
13. Shin DH, Lee MJ, Lee HS, Oh HJ, Ko KI, Kim CH, et al. Thyroid hormone replacement therapy attenuates the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism. Thyroid. 2013;23(6):654-61.
14. Hataya Y, Igarashi S, Yamashita T, Komatsu Y. Thyroid hormone replacement therapy for primary hypothyroidism leads to significant improvement of renal function in chronic kidney disease patients. Clin Exp Nephrol. 2013;17(4):525-31.