Original Research Paper

Volume-9 | Issue-6 | June-2019 | PRINT ISSN No. 2249 - 555X

Endocrinology

EFFECT OF THYROID HORMONE REPLACEMENT IN CHRONIC KIDNEY DISEASE PATIENTS WITH HYPOTHYROIDISM

Siva Kalyani Jyotula	Postgraduate, Department of Endocrinology, Andhra Medical College, Visakhapatnam, Andhra Pradesh
B Vivekanand	Assistant Professor, Department of Endocrinology, Andhra Medical College, Visakhapatnam, Andhra Pradesh
A Mythili	Associate Professor, Department of Endocrinology, Andhra Medical College, Visakhapatnam, Andhra Pradesh
Jayanthy Ramesh	Professor, Department of Endocrinology, Andhra Medical College, Visakhapatnam, Andhra Pradesh
Dr K A V Subrahmanyam*	Professor and HOD, Department of Endocrinology, Andhra Medical College, Visakhapatnam, Andhra Pradesh *Corresponding Author

ABSTRACT

Context: There is a lack of data on whether treatment of subclinical hypothyroidism will improve estimated glomerular filtration rate (eGFR) in CKD.

Aim: To study the effect of thyroid hormone replacement on the progression of CKD.

Materials and Methods: A prospective cohort study was done on 180 CKD patients attending a tertiary care hospital in South India, who were screened for primary hypothyroidism and the hypothyroid patients were started on Thyroid Hormone Replacement (THR). Three months after achieving the target TSH, reassessment of eGFR was done.

Results: Out of the 180 patients, 12.2% had primary hypothyroidism among whom, 11.1% had subclinical hypothyroidism and 1.1% had overt hypothyroidism. There were 3 (13.63%) hypothyroid cases in stage 3A, 5 (22.72%) in stage 3B, 12 (54.54) in stage 4 and 2 (9.09%) in stage 5. The mean eGFR has increased from 26.36 10.82 ml/min/1.73 m2 at baseline to 33.85 15.35 ml/min/1.73 m2 3 months after THR.

Conclusions: Primary hypothyroidism, especially subclinical hypothyroidism is commonly associated with CKD. THR significantly improved the renal function.

KEYWORDS : Primary hypothyroidism, Chronic Kidney Disease, Thyroid Hormone Replacement

INTRODUCTION

The interplay between the thyroid gland and the kidney in each other's functions is known for many years(Kaptein EM, 1986). Thyroid dysfunction affects renal physiology and development, whereas renal disease could result in thyroid dysfunction. Thyroid hormones have pre-renal and intrinsic renal effects by which they increase the renal blood flow and the glomerular filtration rate.

CKD has been known to affect the pituitary-thyroid axis and the peripheral metabolism of thyroid hormones. The prevalence of primary hypothyroidism increases consistently with a decline in eGFR(Lo, Chertow, Go, & Hsu, 2005). The most common thyroid function abnormality in CKD patients is a "low T3 syndrome" and free T4 levels vary from being low to normal, which is similar with that observed in several nonthyroidal illnesses (NTIs).

However, unlike other NTI states, in CKD there is no increase in total rT3 levels(Basu & Mohapatra, 2012) and the thyroid stimulating hormone (TSH) levels are elevated(Basu & Mohapatra, 2012)(Singh, Bobby, Selvaraj, & Vinayagamoorthi, 2006).This raises the possibility of benefit from thyroid hormone supplementation in CKD. The impact of thyroid hormone replacement has not been extensively studied in CKD patients with hypothyroidism, especially subclinical hypothyroidism. In this context, we have studied the effect of THR on the progression of CKD.

PATIENTS AND METHODS

This is a prospective, single-center study done in the Department of Endocrinology in a tertiary care hospital in Visakhapatnam, Andhra Pradesh from April 2017 – December 2018. The study included 180 CKD patients with age ≥18 years. CKD was confirmed as per Kidney Disease Outcomes Quality Initiative guidelines. Patients with known thyroid dysfunction or subjects receiving drugs that could contribute to hypothyroidism or subjects with acute illness, recent surgery, trauma, burns or patients undergoing peritoneal dialysis or hemodialysis or those with nephrotic range of proteinuria were excluded.

Informed consent was taken from all patients at enrollment into the study. Institutional ethics committee clearance from Andhra Medical College/KGH was taken. A detailed history with physical examination was conducted. Blood samples were collected for renal function tests, complete blood picture, and thyroid function tests. eGFR was calculated by using Modification of Diet in Renal Disease (MDRD) equation.

$$eGFR([mL/min]/1.73m^2) = 175 \times (\text{serum creatinine})^{-1.154} \times age^{-0.203} \times sex$$; where sex=1 for men or 0.742 for women.

CKD was classified based on NKF - KDOQI (National Kidney Foundation - Kidney Disease Outcome Quality Initiative Guidelines(Hogg et al., 2003).

Serum T3, T4, and fT4 were analyzed on Beckman Coulter machine using Chemiluminiscence Immunoassay (CLIA) and TSH by Immunometric assay.

Reference ranges for Serum levels of thyroid hormones

T3: 0.6-1.8 ng/ml, T4: 4.5-12.6 mcg/dl, fT4: 0.7-1.9 ng/dl, TSH: 0.35-4.5 mU/L

Overt Hypothyroidism (OH) was defined by an elevated TSH level with low fT4 and Subclinical Hypothyroidism (SCH) by an elevated TSH level with normal fT4. These hypothyroid patients are treated with THR and reassessment of eGFR was done 3 months after achieving the target TSH level.

The Statistical analysis was performed using SPSS software (Trial version 21). Categorical variables were represented as proportions or percentages and quantitative variables were represented as the mean ± standard deviation of the mean, and median with Interquartile Range (IQR). Chi-square test/ Fisher Exact test, Wilcoxon signed rank test, Mann-Whitney U test and Kruskal Wallis tests were applied to the data whenever applicable to find out a significant association. P value < 0.05 was considered statistically significant.

RESULTS

The mean age of the study population was 49.5 ± 7.7 years (range 23 – 72 years) with 74.4 % (134) patients being males. In the cohort, the mean value of eGFR was 26.5 ± 11.6 ml/min per 1.73 m^2. Out of the 180 CKD patients enrolled, 22 (12.2%) patients were hypothyroid with 20 (11.1%) patients having subclinical hypothyroidism and 2 (1.1%) patients having overt hypothyroidism. Table 1 shows a comparison of baseline parameters between hypothyroid and non-hypothyroid CKD patients.

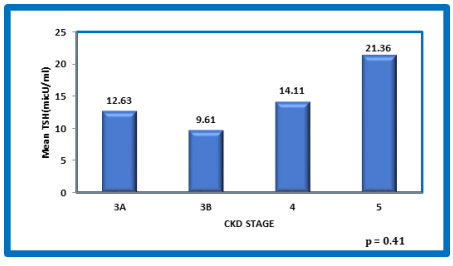
Table 1: Comparison of baseline parameters between non-hypothyroid and hypothyroid patients

On CKD stage wise analysis, the prevalence of hypothyroidism was found to be 23.1%

Variable	Mean ± SD			P-value
	Total (n=180)	Non-hypothyroid (n=158)	Hypothyroid (n=22)	
Age (years)	49.5 ± 7.7	49.70 ± 7.42	48.32 ± 9.79	.38
SBP (mm Hg)	137.6 ± 13.8	137.03 ± 13.52	141.36 ± 15.21	.20
DBP (mm Hg)	85.1 ± 9.8	84.8 ± 10.0	86.8 ± 7.8	.37
Hb (%)	8.7 ± 1.4	8.68 ± 1.42	9.22 ± 1.49	.11
24hr urine protein (g)	1.1 ± 0.6	1.04 ± 0.54	1.15 ± 0.65	.56
Bl. Urea (mg/dl)	60.6 ± 17.0	60.44 ± 16.68	61.59 ± 19.59	.93
S. Creatinine (mg/dl)	2.9 ± 0.9	2.91 ± 0.90	2.90 ± 1.12	.74
eGFR (ml/min/1.73 m2)	26.5 ± 11.6	26.03 ± 11.22	26.36 ± 10.82	.84
S.T3 (ng/dl)	121.3 ± 35.0	123.07 ± 35.80	108.73 ± 25.75	.08
S.T4 (mcg/dl)	8.1 ± 1.8	8.25 ± 1.74	7.11 ± 1.71	.01
S. fT4 (ng/dl)	1.1 ± 0.2	1.12 ± 0.21	1.01 ± 0.21	.07
S.TSH (mU/l)	3.7 ± 4.8	2.31 ± 1.05	13.55 ± 8.44	<0.001

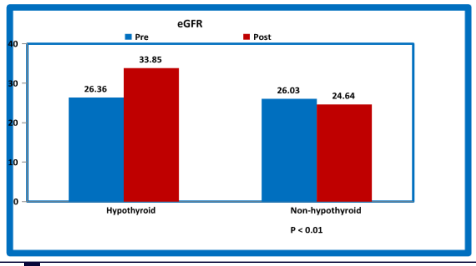
(N=3), 12.2 % (N=5), 11.8% (N=12) and 8.7% (N=2) among CKD patients in Stage 3A (n=13), Stage 3B (n=41), Stage 4 (n=102), and Stage 5 (n=23) respectively. Across various stages of CKD as the eGFR declines, there was an increasing trend in the TSH levels, though significance was not achieved (figure 1).

Figure 1: Association between eGFR and mean serum TSH across various stages of CKD in hypothyroid patients



Effect of thyroid hormone replacement on renal function In hypothyroid CKD patients, there was a significant increase in the eGFR after treatment when compared to the baseline (p=<0.001) whereas, in non-hypothyroid patients, eGFR significantly declined from the baseline (p<0.01). Figure 2 shows the comparison of eGFR values at baseline and after thyroid hormone replacement in hypothyroid and non-hypothyroid patients.

Figure 2: eGFR values at baseline and after thyroid hormone replacement in hypothyroid patients in comparison to patients without hypothyroidism



When separately analyzed based on the gender, in males, there was a significant increase in the eGFR after treatment compared to the baseline (p=<0.001), but in females though there was an increase in the eGFR after treatment, it was not significant (p=0.23).

DISCUSSION

Our study showed a prevalence of hypothyroidism of 12.2% in the CKD patients. Thyroid hormone replacement in patients with hypothyroidism resulted in significant improvement in the eGFR from the baseline. The prevalence of hypothyroidism in CKD patients in the present study was less when compared to the previous studies(Lo et al., 2005)(Unnikrishnan A. et coll., 2013) but still higher than the prevalence in the general population (11%) in India (Unnikrishnan A. et coll., 2013). This was especially reflected with male CKD patients (12.7%) showing much higher prevalence compared to the male general population (6.2%). But prevalence in female CKD patients (10.9%) was almost similar compared to the female general population (11.4%) and it could be due to lesser number of total female CKD patients resulting in gender bias. CKD affects the thyroid function in multiple ways. The reduction in T3 levels has been linked to a decrease in the peripheral synthesis of T3 from T4. This is attributed to chronic metabolic acidosis, fasting and chronic protein malnutrition which affect iodothyronine deiodination as well as protein binding of T3. In addition, inflammatory cytokines inhibit the expression of type 1 deiodinase, which is required for the conversion of T4 to T3. Additionally, Wolff-Chaikoff effect occurs due to impaired renal handling of iodine.

The data of 14,623 adult participants from the third National Health and Nutrition Examination Survey, revealed that the prevalence of hypothyroidism increased with lower levels of eGFR(Lo et al., 2005). In our study, the highest prevalence was found in stage 3A which could be due to small number of patients in this stage and the prevalence we have obtained in each stage may not reflect the true prevalence. Across various stages of CKD, there was an increasing trend in the serum TSH levels as the eGFR declines. Similarly, a study done by Chonchol et al. showed a significant decrease in mean serum TSH levels across estimated GFR deciles(Chonchol et al., 2008). Previous studies——(Åsvold, Bjøro, & Vatten, 2011)(Saini et al., 2012) also showed a significant negative correlation between eGFR and TSH concentrations. The mechanisms for thyroid dysfunction in CKD that were mentioned above are likely to operate more severely across the reducing ranges of eGFR, which might have resulted in the corresponding increasing levels of serum TSH.

A recent study by Shin *et al*. demonstrated that thyroid hormone treatment not only preserved renal function but was also an independent predictor of renal outcome(Shin et al., 2012). The results of our study similarly showed that thyroid hormone replacement significantly improved the renal function. This shows a positive effect of thyroid hormone replacement in hypothyroid patients with CKD resulting in improvement or preserving the renal function, indicated by an increment in the eGFR levels. Analysis based on gender showed that in males, there was a significant improvement in eGFR after treatment whereas in females, though there was an improvement in eGFR after treatment, it was not statistically significant. This could be due to small number of female patients.

The improvement in eGFR that was seen in majority of the hypothyroid patients after treatment could be explained through various direct and indirect actions of thyroxine on the cardiovascular system. Direct action of thyroid hormones on the cardiovascular system result in improvement in the myocardial contractility and stroke volume with a simultaneous decrease in the peripheral vascular resistance. Indirect effects could be through an improvement in the expression as well as response to various factors such as IGF-1 and VEGF which are renal vasodilators. This can result in increased recruitment of the functioning glomeruli as well as further improvement in function of the working glomeruli. All these actions lead to an increase in the RBF, with the resultant increase in the GFR. But in some patients, there was no improvement or a decline in the GFR, which might be due to irreversible renal disease or progressive nature of the disease. So, these patients may not respond to the THR due to irreversible damage to the glomeruli.

Our study reaffirms that hypothyroidism is an underappreciated cause of renal impairment and the symptoms of CKD overlap with the symptoms of hypothyroidism. So, every CKD patient must be tested

for thyroid dysfunction, especially those with renal impairment of unknown cause and those CKD patients who have an unexpected deterioration of renal function. Therefore, it is worthwhile to test for hypothyroidism in CKD patients and institute appropriate thyroid hormone replacement therapy to correct the hypothyroidism induced renal impairment.

In conclusion, the prevalence of hypothyroidism is high (12.1%) in CKD patients, with increasing TSH in relation to decreasing eGFR. THR in these patients resulted in significant improvement in the eGFR.

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