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Original Research Article

Thyroid dysfunctions in patients with chronic renal failure

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ABSTRACT

Background: Chronic renal failure (CRF), or end-stage renal disease (ESRD), is a progressive, irreversible deterioration in renal function in which the body's ability to maintain metabolic and fluid and electrolyte balance fails, resulting in the development of clinical symptoms like uraemia or azotemia. Thyroid hormones have an important role in regulating metabolism, development of the kidney, maintenance of water and electrolyte homeostasis, protein synthesis and influencing other hormone function. Tri-iodothyronine (T3) and thyroxin (T4) are the two main hormones produced by the thyroid. The patients with chronic renal failure often exhibit clinical features and laboratory findings which are indicative of thyroid dysfunction, since, kidney is involved in the metabolism and elimination of TH.
Methods: This was a cross sectional single centre descriptive study, including 50 patients of either gender between the age of 45-70 years.
Results: Present study found a significant positive correlation between the TSH levels and Zulewski score in patients with CRF.
Conclusions: Since there was found to be a correlation between the TSH levels and Zulewski score, the evaluation of symptoms and signs with Zulewski score in addition to thyroid function testing in patients with thyroid dysfunction is essential, since it can be a marker for CRF.

Keywords: CRF, GFR, Thyroid hormone

INTRODUCTION

Chronic renal failure (CRF), or end-stage renal disease (ESRD), is a progressive, irreversible deterioration in renal function in which the body's ability to maintain metabolic and fluid and electrolyte balance fails, resulting in the development of clinical symptoms like uraemia or azotemia (retention of urea and other nitrogenous wastes in the blood).[1] For ESRD, the estimated prevalence in India is 200 million per inhabitant.[2]

Thyroid hormones (TH) have an important role in regulating metabolism, development of the kidney, maintenance of water and electrolyte homeostasis, protein synthesis and influencing other hormone function. Tri-iodothyronine (T3) and Thyroxin (T4) are the two main hormones produced by the thyroid.[3,4] The patients with chronic renal failure (CRF) often exhibit clinical features and laboratory findings which are indicative of thyroid dysfunction, since, kidney is involved in the metabolism and elimination of TH. Serum tri-idothyronine levels are reported to be low. Serum total and free thyroxin (T4) are reported to be either low, normal or high, while the levels of thyroid stimulating hormone are reported to be normal in most patients of CRF.[5] Thyroid dysfunction causes significant changes in kidney function. Both hypothyroidism and hyperthyroidism affect renal blood flow, glomerular

filtration rate (GFR), tubular function, electrolytes homeostasis, electrolyte pump functions, and kidney structure.[4]

Low serum tri-iodothyronine (T3) levels and subclinical hypothyroidism are common laboratory findings in CRF. Elevation of serum creatinine levels, reduction in GFR and renal plasma flow (RPF), disruption of the capacity to excrete free water and hyponatremia are the most common kidney derangements associated with hypothyroidism. The hypothyroidism has been variously attributed to reduced TSH (thyrotropin, thyroid-stimulating hormone) secretion by the pituitary and to abnormalities primarily within the thyroid itself.[3,4,6,7]

Subclinical hypothyroidism (SCH) is defined as a serum thyroid stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxin (T4) within the reference range.[8] It is frequently seen in patients with chronic kidney disease/failure.[9] Also, with the decrease in glomerular filtration rate the prevalence of subclinical hypothyroidism increases. In the United States the prevalence of subclinical hypothyroidism is 4-8.5%.[8] In a study by Santha GPS et al reported the prevalence of SCH in ESRD to be 24.8% in Indian Population with a study size of 137 patients with ESRD.[2] In a study by Lim VS the prevalence of SCH in ESRD was 0-9.5%.

Hyperthyroidism leads to the increase in Renal Blood Flow (RBF) and GFR. The increase in RBF by the thyroid hormones is due to the increase in endothelial nitric oxide in the renal cortex and medulla. The GFR also increases by 18-25% due to the increase in RBF and activation of renin-angiotensin-aldosterone system (RAAS) (by the increased density and activation of β-adrenergic receptors).

The inverse marker of GFR, serum creatinine is reduced in hyperthyroid patients due to the increase in GFR and the reduction in renal muscle mass. Glomerular hyper filtration also leads to the increase in 24-hour urine protein in hyperthyroidism.[10]

Subclinical hyperthyroidism is characterized by a low or undetectable concentration of serum thyrotropin (TSH) with free tri-iodothyronine (FT3) and free thyroxin (FT4) levels within laboratory reference ranges. A study by Verhelst et al, found decreased creatinine levels in patients with subclinical hyperthyroidism.

In spite of low levels of T3 and T4 the plasma TSH levels are not increased. It is not due to dysfunction in hypothalamo-pituitary axis but because truly hypothyroid renal failure patients can mount a high TSH response. But in some studies shows that normal TSH response is due to blunted TSH response to TRH. Suggesting probability of pituitary dysfunction as well. Duration and severity of renal failure affects the serum thyroid hormone levels. Restoration of normal functions with renal transplant resulted in normalisation of all parameters of thyroid function with exception of blunted or absent TSH response to TRH. The latter may be a direct consequence of glucocorticoid administration.

Through the changes in binding capacity of serum proteins, serum hormonal concentrations may be altered. Thus albuminuria (proteinuria) is observed in CRF. The circulating thyroid binding inhibitors increases leading to inhibition of binding of thyroid hormones to carrier proteins in CRF. This can be considered as one of the cause of hypothyroidism.

METHODS

The study was initiated after obtaining the permission from the Institutional Ethics Committee of D.Y. Patil University, School of Medicine, Nerul, Navi Mumbai, Maharashtra, India.

The study was conducted in the Department of General Medicine at the D.Y. Patil University, School of medicine, Nerul, Navi Mumbai, Maharashtra, India.

Study population

The study included patients admitted in/ and referred to the general medicine OPD in the tertiary care hospital.

Study design

It was a cross-sectional single centre study design.

Study period

The study was conducted over a period of 1 year after obtaining approval from the Institutional Ethics Committee.

Inclusion criteria

- All patients of either gender, between the age of 45 - 70 years and having a history of chronic kidney disease with serum creatinine of >5.5 mg/dl and urea >55 mg/dl.
- Patients with dipstick test positive for protein with symptoms of chronic renal failure
- Patients willing to give a valid consent form.

Exclusion criteria

- Patients with patients on treatment with estrogen, corticosteroids and phenobarbitones.
- Patients who are above 70 years and below 45 years of age are excluded from the study

Sample size

50 patients were included in this study.

RESULTS

The number of patients with positive symptoms is as follows: 12 patients complained of diminished sweating, 7 patients of hoarseness, 14 patients of paraesthesia, constipation, coarse skin and cold skin, 21 patients of having dry skin, 2 patients of impairment in hearing, 18 patients had weight increase, 13 patients of slow movements, 16 patients reported with delayed ankle reflex and 15 patients had periorbital puffiness.

Table 1: Zulewski's clinical score.

Characteristics	Number of patients with positive symptoms (out of 50)
Symptoms	
Diminished sweating	12
Hoarseness	07
Paraesthesia	14
Dry skin	21
Constipation	14
Impairment of hearing	02
Weight increase	18
Physical signs	
Slow movements	13
Delayed ankle reflex	16
Coarse skin	14
Periorbital puffiness	15
Cold skin	14
Women <55 years of age	10

Classification of patients based on Zulewski's clinical score

Table 2: Classification of patients based on Zulewski's clinical score.

Zulewski's clinical score	No. of patients
<2 (euthyroid)	09 (18%)
2-5	30 (60%)
>5 (hypothyroidism)	11 (22%)
Total	50

Out of the 50 patients 9 (18%) patients were diagnosed with euthyroid using the Zulewski score <2, 30 (60%) patients had a Zulewski score between 2-5 and 11 (22%) patients were diagnosed with hypothyroidism using the Zulewski score >5.

Correlation between TSH levels and Zulewski's clinical score in patients of CRF

Spearman's r=0.6163 (95% CI: 0.4008 to 0.7672); p<0.0001.

The correlation between TSH levels and Zulewski's clinical score in patients of CRF was calculated. It was seen that there was a significant moderate positive correlation between TSH levels and Zulewski's clinical score in hypothyroid patients with chronic renal failure (p<0.0001).

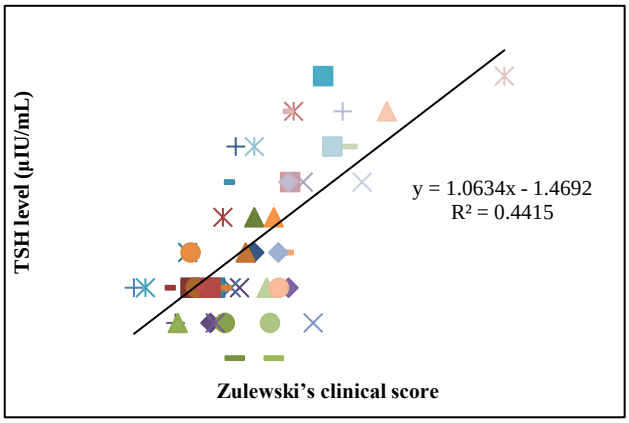

Figure 1: Correlation between TSH levels and Zulewski's clinical score in 50 patients of CRF.

Correlation between serum creatinine and T3 levels

Spearman's r = -0.3405 (95% CI: -0.5653 to -0.06861); p=0.0155.

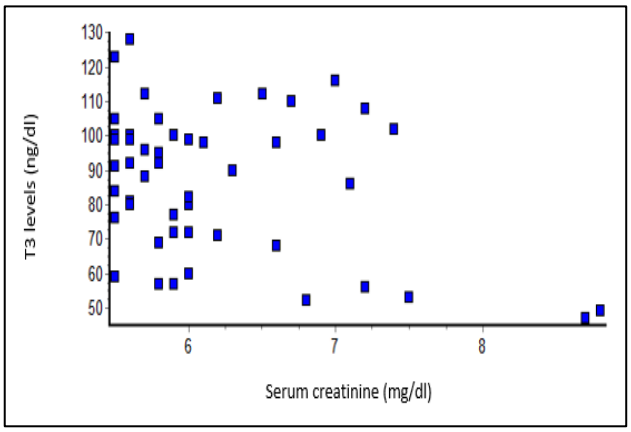

Figure 2: Correlation between serum creatinine and T3 levels in 50 patients.

The correlation between serum creatinine and T3 levels was calculated. It was seen that there was a significant moderate positive correlation between serum creatinine and T3 levels (p=0.0155).

Correlation between serum creatinine and T4 levels

Spearman's r = -0.2659 (95% CI: -0.5068 to 0.01349); p=0.00620.

The correlation between serum creatinine and T4 levels was calculated. It was seen that there was no significant correlation between serum creatinine and T4 levels as the p-value was found to be 0.0620.

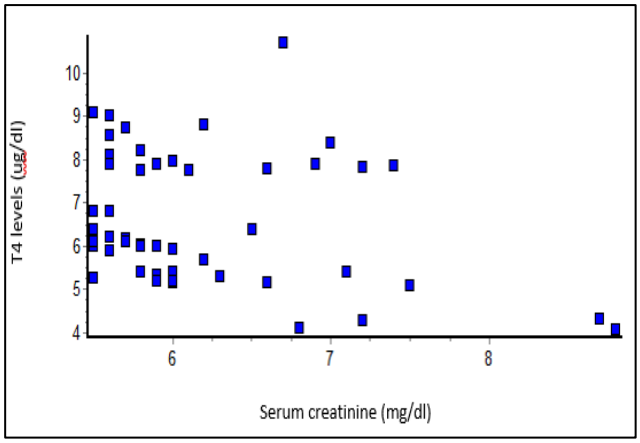

Figure 3: Correlation between serum creatinine and T4 levels in 50 patients.

Correlation between serum creatinine and TSH levels

Spearman's r = 0.4155 (95% CI: 0.1550 to 0.6219); p=0.0027.

The correlation between serum creatinine and TSH levels was also calculated. There was a very significant moderate positive correlation between serum creatinine and TSH levels (p=0.0027).

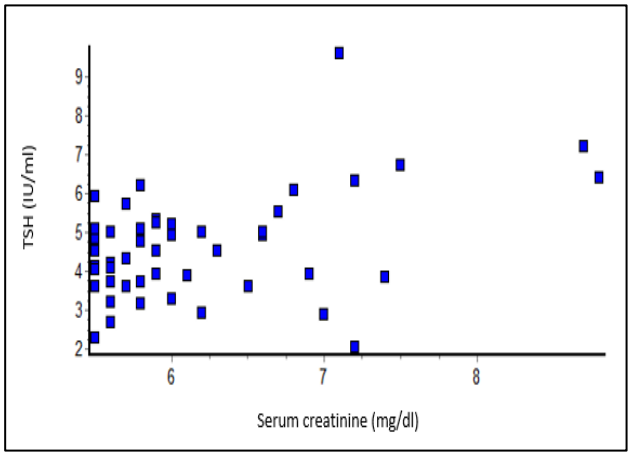

Figure 4: Correlation between serum creatinine and TSH levels in 50 patients.

DISCUSSION

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) have become worldwide public health problem. Chronic renal failure (CRF) is characterized by a persistently abnormal glomerular filtration rate. An Indian population-based study determined the crude and age-adjusted ESRD incidence rates at 151 and 232 per million population, respectively.

The function of the thyroid gland is one of the most important in the human body as it regulates majority of the body's physiological actions metabolism, development, protein synthesis, and influencing other hormone functions. The two main hormones produced by the thyroid are T3 and T4. These hormones can also have significant impact on kidney disease so it is important to consider the physiological association of thyroid dysfunction in relation to CKD.[3]

Due to reduced de-iodinase activity, tissue and circulating levels of the active form of the thyroid hormone, T3, are low in kidney failure. Because of reduced renal excretion, inorganic iodide generated by residual de-iodinase activity accumulates in stage 4 and 5 CKD, which in turn dampens thyroid hormone synthesis. Low T3 is the most frequent alteration of the thyroid hormone profile observed in CKD.

The study was conducted to study the prevalence of thyroid dysfunction in patients with chronic renal failure. The objective of the study was to evaluate the clinical profile of hypothyroid patients in chronic renal failure based on Zulewski clinical score and also to study the thyroid hormone levels in patients of chronic renal failure. This was a cross sectional single centre descriptive study with 50 patients fulfilling the conditions for inclusion criteria were included in present study. It was conducted in Department of General Medicine of D.Y. Patil University, School of Medicine, Nerul, Navi Mumbai, Maharashtra, India after obtaining Ethics Committee approval.

Out of the 50 patients enrolled in the study protocol 27 (54%) patients were males and 23 (46%) patients were females. The percentage of the males was less and that of females was more as compared to the study by Avasthi G et al, which was 22 (73%) males and 8 (26%) females.[5] However, both the studies had more number of males as compare to females, indicating that chronic renal failure is much more prevalent in males.[5]

The mean±SD age of the patients was 55.5±6.77 years. The mean age of the patients reported by Avasthi G et al, 2001 was 51.17 ± 13.53 years. The age group of our study was more or less similar to that of Avasthi G et al. There were 23 (46%) patients in the age group of 45-55 years, 21 (42%) in the age group 55-65 years and 6 (12%) in the age group 65-75 years. There were 10 women who were < 55 years of age. In a study by Shamsuddin M et al, 2014 reported 30 males between the age group of 40-70 years. Avasthi G et al reported 30 patients to be included in the age group of 22-70 years.[5] In present study there were 50 patients between the age group of 45-75 years, which was more or less similar to the study by Shamsuddin M et al, reflecting that older patients were more prone to CRF.

The mean serum creatinine and blood urea levels in the patients were reported to be 6.17±0.78 mg/dl and 94.92±14.36 mg/dl respectively. In 2014, Shamsuddin et al reported mean serum creatinine levels of 5.83±0.69 mg/dl and that of blood urea was reported to be

96.23±12.24 mg/dl. The results were more or less similar to present study suggesting severe kidney dysfunction.

The mean thyroid levels for T3, T4 and TSH were reported to be 86.98±20.48 ng/dl, 6.6±1.51 µg/dl and 4.56±1.37 µIU/ml respectively. In a study by Yee Yung NG et al reported the T3 levels to be 90.58±20.28 ng/dl, T4 levels to be 6.88±1.47 µg/dl, which were more or less comparable with our study. The TSH levels were reported to be 2.70±1.88 µIU/ml. Our study reported high levels of TSH as compared to the above study.

There were 26 (52%) patients diagnosed with euthyroid the mean T3, T4 and TSH levels of the same were 97.73±15.53 ng/dl, 7.42±1.08 ng/dl and 3.55±0.64 ng/dl respectively. Similarly, there were 16 (32%) and 8 (16%) patients diagnosed with subclinical hypothyroidism and overt hypothyroid respectively. The T3, T4 and TSH levels for subclinical hypothyroidism patients were 84.25±15.06 ng/dl, 6.20±1.46 ng/dl and 5.18±0.45 ng/dl respectively, while for patients with overt hypothyroid were 57.5±12.27 ng/dl, 4.73±0.59 ng/dl and 6.57±1.41 ng/dl respectively. There is no published data on the frequency of euthyroid, subclinical hypothyroid and overt hypothyroid and also on the levels of thyroid hormones in those patients.

The reported frequency of positive symptoms is as follows:12 (24%) diminished sweating, 7 (14%) hoarseness, 14 (28%) paraesthesia, constipation, coarse skin and cold skin, 21 (42%) dry skin, 2 (4%) impairment in hearing, 18 (36%) weight increase, 13 (26%) slow movements, 16 (32%) delayed ankle reflex and 15 (30%) periorbital puffiness. There were 10 women who were <55 years of age. In a study by Zulewski H et al, 54% reported diminished sweating, 34% reported hoarseness, 52% with paraesthesia, 48% with constipation, 60% with coarse skin, 50% with cold skin, 76% with dry skin, 225 with impairment in hearing, 54% with weight increase, 36% with slow movement, 77% with delayed ankle reflex and 60% with periorbital puffiness. The reported positive symptoms in our study were much less than that compared with the study by Zulewski et al. This indicates that our population experienced less frequency of positive symptoms.

Out of the 50 patients 9 (18%) patients were diagnosed with euthyroid with Zulewski score <2, 30 (60%) patients had a Zulewski score of 2-5 and 11 (22%) patients were diagnosed with hypothyroidism with Zulewski score >5. The correlation between TSH levels and Zulewski's clinical score in patients of CRF was calculated using correlation.

It was seen that there was a significant moderate positive correlation between TSH levels and Zulewski's clinical score in hypothyroid patients with chronic renal failure. There is no data referring to the correlation of TSH levels with Zulewski score in patients with chronic renal failure.

It is important to calculate the levels of thyroid hormones in patients with thyroid dysfunction. The review of literature shows very less data published referring to the thyroid dysfunction in patients with chronic renal failure pertaining to Indian population. This was a cross sectional single centre descriptive study carried out to determine the prevalence of same in Indian population.

Due to the nature of the study design and scope of observation it was possible to evaluate the study parameters which were as follows: serum creatinine, blood urea, thyroid hormone levels (T3, T4 and TSH), classification of patients into euthyroid, subclinical hypothyroidism and overt thyroidism, evaluation of frequency of positive symptoms presented by the patients and the correlation between the TSH levels and Zulewski clinical score.

CONCLUSION

In present study, we found patients with hypothyroidism and subclinical hypothyroidism; and no cases of hyperthyroidism were found.A positive significant correlation was found between the levels of serum creatinine with levels of T3 and TSH; whereas T4 levels were not found to have any significant correlation with serum creatinine levels.

The above study demonstrates that there was a positive correlation between the thyroid hormone levels and the presentation of positive symptoms and chronic renal failure. The evaluation of signs and symptoms with Zulewski score in hypothyroid patients with chronic renal failure can be essential in addition to thyroid function testing.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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