Correlation between Thyroid Dysfunction and Oxidative Stress in Undialyzed Chronic Renal Failure Patients

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Abstract

**Background and Aim:** Patients with chronic kidney disease (CKD) often have subclinical hypothyroidism. However, few reports have investigated changes in the status of subclinical hypothyroidism in CKD patients. This study aimed to investigate the relationship between oxidative stress and thyroid hormones status in patients with chronic renal failure (CRF).

**Methods:** Thyroid hormones and renal function parameters like serum urea, creatinine, and oxidative stress malondialdehyde (MDA) as oxidant and total vitamin-C as antioxidant were estimated and correlations between thyroid hormones, oxidative stress and renal function parameters were studied in 30 undialyzed chronic kidney disease patients’ verses 30 healthy controls.

**Results:** We found both T3 and T4 were significantly reduced (p<0.05) whereas the serum TSH concentration was increased among those with CKD patient group compared to controls (p<0.05). We also observed that urea and creatinine were significantly increased among those with CKD patient than in the controls at (p<0.05) level. In addition, patients had lower total vitamin -c than the controls at (p<0.05) level, The MDA in the CKD patients was significantly increased than in the controls at (p<0.05) level.

**Conclusion:** From our data, we concluded that renal insufficiency may lead to thyroid hormone disturbances and CKD appears to enhance the oxidative stress due increased uremia levels.

**Keywords:** chronic kidney disease, renal function markers, thyroid hormones, oxidative stress
INTRODUCTION
The endocrine abnormalities are a common feature of chronic kidney disease (CKD) [1, 2]. Renal disease leads to significant changes in thyroid function and vice versa. In one hand, thyroid hormones (TH) are necessary for growth and development of the kidney [3], and for the maintenance of water and electrolyte homeostasis [4]. On the other hand, kidney is involved in the metabolism and elimination of TH. Therefore, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism, and elimination of TH causing thyroid dysfunction [5]. Previous studies have shown that CKD patients have low triiodothyronine (T3), normal or reduced thyroxine (T4) levels, and consequently elevated thyroid-stimulating hormone (TSH) [6,7].

MATERIALS AND METHODS
The study was conducted over a period of six months. The study was done using thyroid status, renal function parameters like serum urea, creatinine and oxidative stress parameters among the subjects with CKD. The study includes 30 CKD patients with duration of CKD 5 years admitted in Department Of Nephrology, Rims Medical College, NewCo, Andhra Pradesh, India. The study was approved by the Institutional Human Ethical Committee (IHEC). Informed consent was obtained from the subjects participating in this study. They were in age group of 20-50 years. Both sexes are included. Healthy individuals were included as controls. Patients with clinically diagnosed chronic renal failure (on conservative management before dialysis) with serum creatinine levels more than 3.0 mg/dL were included in the study. The clinical history and other necessary details were obtained from the patients' medical records.

Oxidative stress defines an imbalance between formation of reactive oxygen species (ROS) and antioxidative defence mechanisms. In view of the profound biological effects of ROS, in recent years numerous clinical and experimental studies focused on detection of signs of oxidative stress in renal patients. There is good evidence indicating that uraemia in general is associated with enhanced oxidative stress [8,9], and treatment of uraemic patients with haemodialysis or peritoneal dialysis has been suggested to particularly contribute to oxidative stress and reduced antioxidant levels in these patients [10,11]. The aim of this study was to find the relationship between oxidative stress and thyroid dysfunction in patients with chronic renal failure (CRF). The levels of thyroid hormones T3, T4, TSH were measured using the method of Enzyme linked immuno sorbant Assay (ELISA). [12,13,14] Serum concentrations of creatinine are estimated by JAFFE’S method [15] and urea is estimated by GLDH-UREASE method. [16] by using commercial kits adapted to the auto-analyzer. For determination of oxidative stress Malandialdehyde (MDA) is estimated as oxidants by TBARS (Thiobarbituric acid-reactive substances) [17] and Vit-C is estimated as antioxidant by dinitrophenyl hydrazine method (DNP) [18].
STATISTICAL ANALYSIS
All continuous variables are expressed as the mean ± standard deviation (SD). We compared the data of the controls with the study group using unpaired Student's "t" test. Significance was defined at the 0.05 level of confidence $P$-value ≤ 0.05. All calculations were performed using the Statistical Package for Social Sciences Software (SPSS).[Table:1]

RESULTS
None of the patients were under dialysis. Our study showed that the serum urea values in CKD patients (107±14.32) significantly increased than in the controls (33±5.8). The serum creatinine values in CKD patients (11±3.7) significantly increased than in the controls (1±0.2). [FIG:1]
The mean serum total T3 concentration of (69±18.3) in the CKD patients was significantly lower than that in the control subjects (71±5.1). In addition, patients had lower total serum T4 concentration than the controls. The mean total T4 concentration of (6±2.0) in the CKD patients was significantly lower than that in the control subjects, (9±0.6). Finally, and the serum TSH concentration was increased in among those with CKD. The mean serum TSH concentration was (9±3.0) in the CKD patients, which was significantly increased than in the controls (3±0.9). [FIG:3,]
The mean of MDA (8±2.47) in the CKD patients was significantly increased than in the controls (4±1.9). In addition, The mean total vitamin -c of (1±0.54) in the CKD patients was significantly lower than that in the control subjects, (2±0.74).[FIG:2,]

Table 1. Comparison of measured parameters in healthy controls and chronic kidney disease patients

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PATIENTS(N=25)</th>
<th>CONTROLS(N=25)</th>
<th>$P$'-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea(mg/dL)</td>
<td>107±14.32</td>
<td>33±5.88</td>
<td>0.05</td>
</tr>
<tr>
<td>Creatinine(mg/dL)</td>
<td>11±3.76</td>
<td>1±0.22</td>
<td>0.05</td>
</tr>
<tr>
<td>T3(μg/mL)</td>
<td>69±18.35</td>
<td>71±5.12</td>
<td>0.05</td>
</tr>
<tr>
<td>T4(μg/dL)</td>
<td>6±2.06</td>
<td>9±0.64</td>
<td>0.05</td>
</tr>
<tr>
<td>TSH(μIU/mL)</td>
<td>9±3.02</td>
<td>3±0.94</td>
<td>0.05</td>
</tr>
<tr>
<td>MDA (mmol/L)</td>
<td>8±2.47</td>
<td>4±1.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Total vitamin-c(mg/dL)</td>
<td>1±0.54</td>
<td>2±0.74</td>
<td>0.05</td>
</tr>
</tbody>
</table>
DISCUSSION

Chronic kidney disease (CKD) is a growing health problem with increasing incidence. In CKD, thyroid hormone metabolism is impaired. All levels of the hypo-thalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution and excretion. Predialysis CKD patients have an increased risk of hypothyroidism. [19][20][21] Impaired conversion of T4 and T3 may be related to malnutrition and humoral factors including cytokines that are generally associated with CKD. [22] In our study, serum total T3 concentration was significantly lower than the normal range in the majority of the CKD patients in comparison with the controls. Similar findings were observed by Rajagopalan et al, Magaña et al, Gilles et al and Iglesias et al. [23][24]

Inhibitors of T4 binding to serum carrier proteins and urinary loss of TBG, albumin and pre-albumin contribute to the decreased levels of the T4 in CKD patients. [22] In our study, the CKD patients had significantly lower total serum T4 concentration than the controls. Similar findings were observed by other investigators. [24][25][26]. Serum TSH concentrations are usually normal or elevated in CKD, but its response to its releasing hormone (TRH) is generally low. [24] Both proteinuria and GFR influence the activity of the pituitary-thyroid axis. [25][27] In our study, serum TSH concentration was significantly increased in the CKD patients. Similar findings were observed by previous studies. [25] In contrast, others found serum TSH levels to be normal or unchanged in the CKD patients.

Renal dysfunction is frequently associated with oxidative stress, oxidative stress is highly present in patients with renal disease [25,28]. Several evidence suggests that antioxidant enzymes are altered as renal function declines and are profoundly impaired in patients with uremia. Investigators have also found that CKD was associated with low concentration of serum selenium and lower platelet glutathione peroxidase (GPx) activity [29]. Ceballos-Picot et al. [30] demonstrated lower serum levels of
glutathione and plasma GPx activity in renal failure patients. CKD is also associated with a profound disturbance in nitric oxide system, as it increases the concentration of endogenous NOS inhibitors.

It is known that LDL from uremic patients presents an elevated susceptibility to oxidation, being an indication of accelerated atherosclerosis in these patients. Uremic oxidative stress is characterized from a biochemical point of view as a state of reactive aldehyde and oxidized thiol group accumulation, together with depletion of reduced thiol groups, which are particularly important as part of antioxidant defense. As a consequence of diminished renal catabolism and function, uremic oxidant mediators accumulate, favoring vascular cell dysfunction and progression of atherosclerosis. In addition to the mentioned oxidized thiol groups, homocysteine accumulates in uremic patients and may contribute to atherosclerotic disease. Epidemiologic studies have correlated hyperhomocysteinemia with atherosclerotic disease not only in the general population but also in hemodialysis patients. Furthermore this CKD patients contribute to increased cardiovascular risk in uremic patients [31].

To summarize, chronic renal failure affects circulating thyroid hormone concentration. Our finding suggests that chronic renal failure patients have an increased risk of hypothyroidism. Thyroid hormones accelerate the basal metabolic rate and more especially oxidative metabolism. Excess thyroid hormones may induce tissue injury secondary to production of active oxygen species. Proteinuria results in loss of thyroid hormones, most probably caused by loss of thyroxine-binding globulin along with T4 bound to it, thus stimulating TSH production. We conclude that our data suggest that CKD results in significant changes in thyroid hormone levels and it is advisable to assess the of thyroid dysfunction in the CKD patients. Our data suggests that CKD patients may benefit from antioxidant therapy.

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