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ORIGINAL ARTICLE

# Thyroid Hormone Profile in Advanced Chronic Kidney Disease

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Abstract

*Background:* ***Interactions between thyroid hormones and renal function are complex. Both the metabolism and disposal of thyroid hormones include the kidney. Additionally, it plays a crucial role in the function of thyroid hormones.***

*Objectives:* ***To assess thyroid hormone disorders in advanced chronic kidney disease.***

*Patients and methods:* ***This cross-sectional study involved fifty chronic kidney disease patients as group I and 50 end-stage renal disease patients as group II. It was performed in the Internal Medicine Department and Nephrology Unit of El-Hussein Hospital, Al-Azhar University. Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease study (MDRD) equation. Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were measured.***

*Results:* ***24% and 1% of ESRD patients had subclinical hypothyroidism and overt hyperthyroidism, respectively. At the same time, 4% of CKD group patients had subclinical hyperthyroidism. Free triiodothyronine and free thyroxine were significantly positively correlated with GFR, while thyroid stimulating hormone was significantly negatively correlated with GFR.***

*Conclusion:* ***Both free triiodothyronine and free thyroxine levels were significantly reduced among ESRD patients and significantly correlated with GFR.***

*Keywords:* CKD; ESRD; thyroid disorders

## 1. Introduction

The prevalence of CKDD is 9.1 percent worldwide, making it a major public health concern.[1] Individuals with ESRD must undergo renal replacement therapy, which can be accomplished through hemodialysis, peritoneal dialysis, or transplantation. Dialysis serves as a transitional treatment before transplantation or as a last resort in cases where transplantation is not an option.[2]

Endocrine complications, such as aberrant thyroid function, are common in individuals with chronic renal illness and ESRD, especially those who are on dialysis. A large body of research has examined thyroid function in CKD patients. Its effects on development, renal blood flow, and homeostasis maintenance highlight its significance in kidney physiology and development.[3,4]

The effects of thyroid hormones on renal function decline have been studied using multiple lines of evidence, including data from clinical trials and epidemiological studies. Renal function and cardiovascular changes are both significantly impacted by thyroid dysfunctions.[5]

On the other hand, CKD can lead to changes in thyroid function through metabolic acidosis, altered hormonal catabolism, non-thyroidal illness, diminished peripheral conversion, disturbed binding to carrier proteins, hormonal removal during HD therapy, and increased iodine storage in the thyroid gland. [6,7]

In both non-dialysis dependent (NDD) dialysis dependent chronic kidney disease patients, hypothyroidism and other abnormalities in thyroid functional tests have been associated with an elevated risk of CVD, a low health-related quality of life (HRQOL), mortality.[8,9,10]

Research has shown that those with CKD are more likely to have subclinical hypothyroidism, as well as those at the end of their renal failure journey are more likely to have hypothyroidism overall. Up to 9.5 percent of end-stage renal disease patients may have primary hypothyroidism, compared to 0.6 to 1.1 percent of the overall population.[11]

This study aimed to assess thyroid function in individuals with severe chronic kidney disease.

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## 2. Patients and methods

This cross-sectional study was performed for 6 months, from March 2023 to September 2023, and included 100 stable patients with chronic kidney and end-stage renal disease. Patients were recruited from the Internal Medicine Department and Hemodialysis Unit at Al-Hussein Hospital, Al-Azhar University. Patients were equally divided into two groups: Group I, which included fifty CKD patients, and Group II, which included fifty end-stage renal disease patients on regular HD for more than six months.

2.1.Inclusion criteria: In this context, "patients" refers to individuals who are eighteen years old or older, and "patients with confirmed CKD" means that their estimated GFR has been below Sixty ml/min/1.732 square meters for three months or longer, & "patients with end-stage renal disease" means that they have been on regular hemodialysis for six months or longer.

2.2.Exclusion criteria: patients under eighteen years of age, patients with known thyroid disorders, personal or family history of organ-specific autoimmune diseases, patients who are too sick, patients undergoing peritoneal dialysis, patients on medications affecting thyroid function (oral contraceptives, iodine-containing drugs), and pregnant women.

2.3.Ethical consideration: The Al-Azhar University faculty of medicine's regional ethical committee approved the study. All participants—patients and controls—felt free to discontinue the research voluntarily. Personal privacy was maintained, and the data were only used for research.

Patient consent: All participants were given a thorough description of the study's benefits and risks before they were asked to sign an informed consent form.

2.4.Patient evaluation:

Demographic data and Clinical examination of medical history vital signs, Laboratory investigations, Random blood glucose (RBG)

Kidney function test (KFT): Serum creatinine blood urea nitrogen (BUN) using a fully automated chemistry analyzer (Cobas c311, Germany). Roche Diagnostics, Germany, supplied the commercial kits.

Both the estimated GFR and the stage of CKD were determined using the MDRD equation.12

Thyroid function test: Free triiodothyronine FT3, T4, and TSH using Cobs e411 (Roche analytical platform) analyzer automated chemiluminescent immunoassay (Roche Diagnostics, Mannheim, Germany).

Any deviation from the normal range in a patient's thyroid hormone levels indicates thyroid dysfunction.; levels of FT3 (4.0-8.3 pmol/L), FT4 (9.0-20.0 pmol/L), & thyroid stimulating hormone (0.25-5 mIU/L). The condition of being euthyroid was defined as thyroid hormone levels that are within the normal range. The presence of overt hypothyroidism was determined by a thyroid-stimulating hormone level above five mIU/L, FT3 levels less than 4.0 pmol/L, and FT4 levels less than nine pmol/L. To diagnose subclinical hypothyroidism, FT4 and FT3 levels had to be within the reference range, and TSH had to be above five mIU/L. Hypothyroidism in its subclinical stage was characterized by a TSH level below 0.25 mIU/L and free triiodothyronine (FT3) and free thyroxine (FT4) levels within the normal range.[1]

2.5.Statistical analysis: Results were interpreted with the help of IBM SPSS Corp., Released in 2013. Version 22.0 of IBM's SPSS Statistics for Windows. In Armonk, New York, IBM Corp., Numbers and percentages were used to describe the qualitative data. After ensuring normalcy with the Kolmogorov-Smirnov test, we utilized the median and interquartile range to characterize non-parametric quantitative data and the mean and standard deviation for parametric data. Whenever we compared two or more groups, we used the chi-square test. When comparing two independent groups, the student t-test was utilized, and one-way ANOVA was employed when comparing more than two groups. The Mann-Whitney U test was employed to compare the two separate groups. Spearman's rank-order correlation was employed to evaluate correlation.

## 3. Results

*Table 1. Comparison of demographic data & medical history among the 2 studied groups.*

| DEMOGRAPHIC DATA | | ALL PATIENTS (N = 100) | | CKD GROUP (N=50) | | ESRD GROUP (N=50) | | TEST OF SIG. | P |
|---|---|---|---|---|---|---|---|---|---|
| AGE (YEAR) | Mean±SD | 50.2 ± 10. 6 | | 48.36 ± 10.6 | | 52.04± 10.3 | | t= | 0.08 |
| | Min-Max | 24-70 | | 25-65 | | 24-70 | | -0.176 | |
| BMI ($KG/M^2$) | Median (IQR) | 25.9 (23.6-28.6) | | 25.9 (23.7-29.4) | | 25.9 (23.6-28.5) | | U= 1211.5 | 0.79 |
| | Min-Max | 19.4-40.5 | | 19.4-40.5 | | 20.5-34.5 | | | |
| | | N | % | N | % | N | % | | |
| SEX | Male | 53 | 53.0 | 25 | 50.0 | 28 | 56.0 | $\chi 2$= | |
| | Female | 47 | 47.0 | 25 | 50.0 | 22 | 44.0 | 0.36 | 0.55 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| HTN | 65 | 65.0 | 31 | 62.0 | 34 | 68.0 | $\chi2$=0.39 | 0.53 |
| DM | 27 | 27.0 | 13 | 26.0 | 14.0 | 28.0 | $\chi2$=0.05 | 0.82 |
| CVD | 38 | 38.0 | 17 | 17.0 | 21 | 42.0 | $\chi2$=0.68 | 0.41 |
| SMOKING | 10 | 10.0 | 7 | 14.0 | 3 | 6.0 | $\chi2$=1.78 | 0.18 |

CKD: Chronic kidney disease, BMI: Body mass index, DM: Diabetes mellitus, CVD: Cardiovascular disease, ESRD: End stage renal disease, HTN: Hypertension, IQR: Interquartile range, SD: Standard deviation, t: Independent t test, $\chi2$: Chi square test, U: Mann-Whitney test, p: p-value >0.05: Non-significant; p-value <0.05: Significant; p-value< 0.01: highly significant.

There wasn't statistically significant among the two groups regarding medical history & demographic.

*Table 2. Comparison of vital signs between the two studied groups.*

| VITAL SIGNS | | ALL PATIENTS (N = 100) | CKD GROUP (N=50) | ESRD GROUP (N=50) | TEST OF SIG. | P |
|---|---|---|---|---|---|---|
| SBP (MMHG) | Median (IQR) | 140 (130-150) | 130 (127.5-150) | 140 (130-150) | U= 992.5 | 0.07 |
| | Min-Max | 110-170 | 110-170 | 110-170 | | |
| DBP (MMHG) | Median (IQR) | 80 (80-90) | 90 (80-90) | 80 (70-90) | U= 1014.5 | 0.09 |
| | Min-Max | 70-110 | 70-110 | 70-100 | | |
| RBG (MG/DL) | MEDIAN (IQR) | 163.5 (140.3-227) | 161.5 (141.5-198.3) | 171.5 (139.8-239.3) | U= 1156.5 | 0.52 |

DBP: Diastolic blood pressure, RBG: Random blood glucose, SBP: Systolic blood pressure,

The difference among the two groups regarding the medical history was not statistically significant.

*Table 3. Comparison of kidney function test among the 2 studied groups.*

| KFT | | ALL PATIENTS (N = 100) | | CKD GROUP (N=50) | | ESRD GROUP (N=50) | | TEST OF SIG. | P |
|---|---|---|---|---|---|---|---|---|---|
| BUN (MG/DL) | Median (IQR) | 98 (82.3-133.8) | | 84 (49.5-95.5) | | 132.5 (104.5-160) | | U= 190.5 | 0.001* |
| | Min-Max | 14-196 | | 16-126 | | 80-240 | | | |
| SCR (MG/DL) | Mean±SD | 6.16 ± 3.8 | | 2.7 ± 0.72 | | 9.6 ± 2.94 | | t= -18.5 | 0.001* |
| | Min-Max | 1.4-14.2 | | 1.4-4.0 | | 4.4-14.2 | | | |
| GFR (ML/MIN) | Median (IQR) | 15 (8-27.8) | | 27.5 (22-42.3) | | 8.0 (5.8-10) | | U= 0 | 0.001* |
| | Min-Max | 3-58 | | 16-58 | | 3-14 | | | |
| FT4 (NG/DL) | Mean±SD | 1.01 ± 0.34 | | 1.11 ± 0.27 | | 0.9 ± 0.36 | | t= 3.28 | 0.001* |
| | Min-Max | 0.1-1.7 | | 0.6-1.7 | | 0.1-1.7 | | | |
| FT3 (PG/ML) | Mean±SD | 2.85 ± 0.78 | | 3.14 ± 0.56 | | 2.58 ± 0.87 | | t= 3.79 | 0.001* |
| | Min-Max | 1.1-4.3 | | 2.1-4.3 | | 1.1-4.3 | | | |
| TSH (MIU/L) | Mean±SD | 2.7 ± 1.48 | | 1.82 ± 0.78 | | 3.59 ±1.49 | | t= -7.46 | 0.001* |
| | Min-Max | 0.1-6.5 | | 0.3-3.6 | | 0.1-6.5 | | | |
| | | N | % | N | % | N | % | | |
| CKD STAGE | 3A | 10 | 10.0 | 10 | 20.0 | 0 | 0 | 100 | <0.001* |
| | 3B | 15 | 15.0 | 15 | 30.0 | 0 | 0 | | |
| | 4 | 25 | 25.0 | 25 | 50.0 | 0 | 0 | | |
| | 5 | 50 | 50.0 | 0 | 0 | 50 | 100.0 | | |

BUN: Blood urea nitrogen, FT3: Free triiodothyronine, FT4: Free thyroxine, SCr: Serum creatinine, GFR: Glomerular filtration rate, KFT: Kidney function test, TSH: Thyroid stimulating hormone, t: Independent student t test

The variance among the 2 groups regarding biochemical blood tests and GFR was statistically significant. Both FT4 and FT3 were significantly lower among ESRD patients, while TSH was significantly higher among ESRD patients.

*Table 4. Comparison of thyroid function according to CKD stage.*

| THYROID PROFILE TEST | | STAGE 3A (N = 10) | STAGE 3B (N=15) | STAGE 4 (N=25) | TEST OF SIG. | P |
|---|---|---|---|---|---|---|
| FT4 (NG/DL) | Mean±SD | 1.22 ± 0.37 | 1.1 ± 0.27 | 1.03 ± 0.21 | F=2.55 | 0.089 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Min-Max | 0.6-1.7 | 0.7-1.5 | 0.6-1.5 | | |
| FT3 (PG/ML) | Mean±SD | 3.81 ± 0.29 | 3.2 ± 0.56 | 2.83 ± 0.36 | F= 19 P=0.001* | $P_1$=0.001* $P_2$=0.009* |
| | Min-Max | 3.4-4.3 | 2.2-4.2 | 2.1-3.6 | | $P_3$=0.001* |
| TSH (MIU/L) | Mean±SD | 1.08 ± 0.63 | 1.49 ± 0.56 | 2.3 ± 0.58 | F=19.05 P=0.001* | $P_1$=0.089 $P_2$=0.001* |
| | MIN-MAX | 0.3-2.6 | 0.8-2.6 | 1.6-3.6 | | $P_3$=0.001* |

F: One-way ANOVA, p1: The difference between stage 3A and 3B, p2: The difference between stage 3B and 4, p3: The difference between 3A and 4,p: p-value >0.05: Non- significant; p-value <0.05: Significant; p-value< 0.01: highly significant, *: Statistically significant.

FT3 was significantly lower among stage 4 and 3B CKD patients compared to stage 3A patients, while TSH was significanlty higher among stage four CKD patients compared to stage 3A & 3B cronic kidney disease patients.

*Table 5. Comparison of thyroid disorders between the two studied groups.*

| *DIAGNOSIS* | *ALL PATIENTS (N = 100)* | | *CKD GROUP (N=50)* | | *ESRD GROUP (N=50)* | | *TEST OF SIG.* | *P* |
|---|---|---|---|---|---|---|---|---|
| | *N* | *%* | *N* | *%* | *N* | *%* | | |
| *NORMAL* | *85* | *85.0* | *48* | *96.0* | *37* | *74.0* | *χ2=16.42* | *0.001** |
| *THYROID DISORDER* | *15* | *15.0* | *2* | *2.0* | *13* | *26.0* | | |
| *SUBCLINICAL HYPOTHYROIDISM* | *12* | *12.0* | *0* | *0* | *12* | *24.0* | | |
| *SUBCLINICAL HYPERTHYROIDISM* | *2* | *2.0* | *2* | *4.0* | *0* | *0* | | |
| *HYPERTHYROIDISM* | *1* | *1.0* | *0* | *0* | *1* | *2.0* | | |

The prevalence of thyroid disease was significantly elevated among ESRD patients.

*Table 6. Correlation between thyroid profile with each of demographic and laboratory data.*

| PARAMETERS | FT4 (NG/DL) | | FT3 (PG/ML) | | TSH (MIU/ML) | |
|---|---|---|---|---|---|---|
| | R | p | r | p | r | P |
| AGE (YEAR) | -0.05 | 0.61 | 0.12 | 0.32 | 0.18 | 0.07 |
| BMI (KG/M$^2$) | 0.02 | 0.86 | 0.04 | 0.69 | -0.14 | 0.16 |
| SBP (MMHG) | -0.09 | 0.39 | -0.03 | 0.78 | 0.04 | 0.69 |
| DBP (MMHG) | 0.003 | 0.97 | -0.04 | 0.69 | -0.04 | 0.69 |
| RBG (MMHG) | -0.05 | 0.66 | 0.02 | 0.82 | 0.01 | 0.9 |
| BUN (MG/DL) | -0.27* | 0.006* | -0.36* | 0.001* | 0.58** | <0.001* |
| SCR (MG/DL) | -0.31* | 0.002* | <-0.41* | 0.001* | 0.64** | <0.001* |
| GFR | 0.43* | <0.001* | <0.57** | 0.001* | -0.73** | <0.001* |

SCr: Serum creatinine, r: Spearman correlation coefficient, *: weak correlation; **: moderate correlation; ***: strong correlation, p: p-value >0.05: non-significant; p-value <0.05: significant; p-value< 0.01: highly significant,*: Statistically significant.

Each of FT4 and FT3 were significantly negatively correlated with BUN & SCr, yet both were positively correlated with GFR. While TSH was significantly positively correlated with BUN &SCr, but negatively correlated with GFR.

## 4. Discussion

In kidney development, growth, and homeostasis, thyroid hormones (TH) are crucial. On the other hand, changes in the thyroid can impact electrolyte and water balance, glomerular filtration rate (GFR), kidney structure and function, renal blood flow, and tubular function, all of which contribute to altered kidney function.[13,14]

By our results, El Sharkia, Egypt's fifteen dialysis units, were part of a larger study of 1004 chronic kidney disease patients conducted by Ghonemy et al. The mean age of the patients was 52.03 ± 14.67 years, and there were more males (62.2 percent) than females (37.8 percent). Male and female patients aged 50 to 60 were the largest age group, accounting for 31.9 percent.[15] Additionally, Lew et al. reported the mean BMI in the study population to be 23.1 ± 3.6 kg/m2 .[16]

The prevalence of HTN was the highest (65%) among our patients, followed by CVD (38%) and DM (27%). At the same time, 10% of the total study population were smokers.

Similarly, Hassaballa et al. annual report of Egyptian data renal system (ERDS) (2020) reported HTN and DM as the most common prevalent diseases among ESRD patients (41.26%) and (13.58%), respectively.[17]

Accordingly, Peralta et al. reported that the mean SBP was 139 ± 21 mm Hg, and the mean DBP was 77± 12 millimeters mercury.[18]

Our findings indicate that Kashif et al. reported that the mean BUN was 153.94 ± 72.50 (mg/dl), while the mean SCr was 8.76 ± 3.48 (milligram/deciliter) among ESRD cases.14 While Manickam et al. reported that the majority of CKD patients were at stage 4 (76.2%), followed by stage 3 (19 %) and stage 1 (4.8%).[19]

Our results showed that both FT3 and FT4 were significantly lower among ESRD patients while thyroid-stimulating hormone was significantly increased among ESRD patients compared to chronic kidney disease patients.

Luaibi et al. found similar results when they studied fifty CKD patients aged 20 to 50 years. Compared to controls, the patients showed a highly significant reduction in T3 and T4 levels as well as an increase in TSH.[20]

Rajagopalan et al. also observed that chronic kidney disease patients, compared to controls, had significantly lower Free triiodothyronine-free thyroxine levels while maintaining an unchanged thyroid stimulating hormone.[21]

Malik conducted research in Iraq on chronic kidney disease patients who were either conservatively managed or received regular hemodialysis. The results showed a significantly lower T3 and T4 but no changes in TSH levels compared to the control group.[22]

However, according to Kayima et al., patients compared to controls had significantly lower mean T4, T3, FT4, and FT3 values. Patients also had a significantly higher mean TSH level ($P < 0.01$). There was no significant variance in any parameters among patients on hemodialysis and those receiving conservative management ($P > 0.05$).[23]

The combined prevalence of subclinical and clinical Hypothyroidism was 26.6 percent among hemodialysis patients in Western Nepal, according to Paudel.[24] Subclinical hypothyroidism was also observed to be quite common in CKD patients (27.2 percent) according to Khatiwada et al., Hypothyroidism, whether clinical or overt, raises the risk for cardiovascular disease, estimates put the incidence of subclinical Hypothyroidism in the general population at 4-10percent.[25]

The cause of the higher occurrence of Hypothyroidism in end-stage renal disease is not well understood. However, it is believed that the buildup of inorganic iodide due to decreased kidney excretion and the accumulation of other toxic substances in the body, which have effects on both the central and peripheral systems, may contribute to this phenomena.[26]

Nevertheless, some individuals have discovered that the prompt alterations in thyroid indices caused by dialysis are not enduring and may be connected to the concentration of blood or the temporary impacts of hemodialysis on the binding of thyroid hormones. Low levels of FT3 can also be observed in cases of protein malnutrition and chronic sickness. In such cases, an increase in FT3 levels may indicate an improvement in overall health rather than a direct change in thyroid function.[27]

Toda et al. discovered a direct relationship between thyroid-stimulating hormone concentration and the occurrence of CKD, as opposed to the group with lower normal TSH levels.[28]

### *4. Conclusion*

The incidence of hypothyroidism in ESRD patients was substantial. This was evidenced by a substantial decrease in the average levels of TT3 and TT4, accompanied by an increase in the average level of TSH. The notable lower in FT3 and FT4, accompanied by a substantial increase in TSH, correlated with the decline in estimated GFR.

## Disclosure

The authors have no financial interest to declare in relation to the content of this article.

## Authorship

All authors have a substantial contribution to the article

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## Conflicts of interest

There are no conflicts of interest.

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