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Evaluation of Thyroid Functions in Patients with End Stage Renal Disease in A Sample of Egyptian Populations

Ahmed Mohamed Bahaa Eldin, David Ezzat Shafik*, Inas Mohammed Sabry , Manar Abdl El Rouf Raafat, Hanan Mahmoud Ali Mahmoud

Department of Internal Medicine & Endocrinology, Faculty of Medicine, Ain Shams University, Egypt

***Corresponding author:** David Ezzat Shafik, **Mobile:** (+20) 01270102051, **E-Mail:** docdavidezzat.de@gmail.com

ABSTRACT

Background: In most cases, hypothyroidism is not linked to kidney disease. However, hypothyroidism has been shown to hasten the development of chronic kidney disease (CKD). **Objective:** The aim of the current study is to evaluate thyroid abnormalities in patients with end stage renal disease (ESRD) in a sample of Egyptian populations.

Patients and methods: A case control study was conducted on 70 Egyptian patients selected from the Nephrology Department in Theodor Bilharz Research Institute. Participants were divided into 2 groups; *Group 1* included 40 patients with ESRD, with eGFR <15 mL/min, with no history of thyroid disease or receiving any thyroid medications. *Group 2* included 30 health subjects, age and sex matched, with normal renal function, with no history of thyroid disease or receiving any thyroid medications. All subjects underwent full thyroid profile, and estimated GFR.

Results: Symptoms of thyroid dysfunction were more frequent in ESRD group; statistically significant only in muscle weakness. TSH was statistically significantly higher in *Group 1* cases with hypothyroidism. Thyroglobulin autoantibodies (**TgAbs**) were statistically significantly higher in cases with hypothyroidism. Antimicrosomal antibodies recorded only in hypothyroid cases. Free T3, TSH, TgAbs and thyroid volume had perfect diagnostic performance in diagnosing hypothyroidism among ESRD group**. Conclusion:** Frequency of hypothyroidism was higher in ESRD patients compared to the control group. Thus, it is important to keep monitoring thyroid functions in patients with advanced renal impairment that may enhance quality of life.

Keywords: Thyroid Function, End Stage Renal Disease, TSH, Thyroglobulin autoantibody.

INTRODUCTION

Chronic kidney disease (CKD) jumped from being the 27th leading cause of death in 1990 to the 18th in 2010, second only to HIV/AIDS, according to the Global Burden of Disease research conducted in 2010. Pallor, coldness, and fatigue are all signs of both hypothyroidism and chronic kidney disease [(1)].

Impairments in kidney function influence hormone production, distribution, and excretion, which in turn affects hypothalamic-pituitary-thyroid axis levels. Many occurrences of hypothyroidism in pre-dialysis CKD patients are asymptomatic, according to studies [(2)]. Up to 9.5% of ESRD patients, compared to 1.1% of the overall population, may suffer from primary hypothyroidism.

Rhee *et al.* [(3)] found that patients with CKD stages 3-5 had an estimated GFR 10 mL/min lower than those in healthy controls, resulted in 0.11 mU/l higher TSH levels and an 18% higher incidence of hypothyroidism, **Hollander *et al.*** [(4)] suggested that thyroid dysfunction is more common at advanced CKD stages. In earlier research, the incidence of hypothyroidism among ESRD patients undergoing HD varied widely. About 12% of hemodialysis patients were found to have subclinical hypothyroidism, compared to 7.14% of the control group, in one study. Patients with CKD have an increased risk of developing both subclinical hypothyroidism (SCH) and overt hypothyroidism, although the incidence of primary hyperthyroidism remains low [(5)].

Most of the time, hyperthyroidism and chronic kidney disease (CKD) are not linked. Hyperthyroidism, on the other hand, has long been known to hasten the development of CKD [(1)].

The aim of the current study is to evaluate thyroid abnormalities in patients with end stage renal disease (ESRD) in a sample of Egyptian populations.

PATIENT AND METHODS

A case control study was conducted on 70 Egyptian patients selected from the Nephrology Department in Theodor Bilharz Research Institute, during the period from July 2021 to January 2022. Age of participants ranged from 25 to 50 years old, and they were 43 males and 37 females.

Every patient parent gave their approved consent for participation in this study.

All patients approved to participate in this had been classified into two groups as the following:

• **Group 1**: It included 40 patients with ESRD, with eGFR <15 mL/min, with no history of thyroid disease or receiving any thyroid medications.

• **Group 2:** It included 30 health subjects, age and sex matched, with normal renal function, with no history of thyroid disease or receiving any thyroid medications.

Inclusion Criteria:

- Age between 25 - 50 years old.
- Both genders (male and female).

Exclusion Criteria:

- Acute illness e.g. acute infection, myocardial infarction, etc.
- Recent surgery, trauma or burns.

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- Patients taking thyroid-altering medications, such as amiodarone, steroids, dopamine, phenytoin, estrogen replacement therapy, or iodine-containing medicines, may experience adverse effects.

All patients had been subjected to the following:

1) **Full history** taking emphasis on age, sex, duration of CKD and symptoms of thyroid dysfunction (e.g., change of weight, change of bowel habits or muscle weakness)
2) **Full clinical examination** emphasis on signs of CKD, neck examination and signs of thyroid dysfunction (e.g., pallor, goiter or exophthalmos).
3) **Laboratory tests**:
   - Routine labs as CBC, kidney function tests (serum creatinine and urea), random urine sample for albumin/creatinine ratio.
   - Full Thyroid profile: Free T3, Free T4 and TSH.
   - Thyroid antibodies: Antimicrosomal antibodies and Thyroglobulin autoantibodies (**TgAbs**).
   - Thyroid ultrasound: to assess thyroid volume and presence or absence of thyroid nodules.
   - Measurement of estimated GFR by Cockroft-Gault formula.

Ethical Consent:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Ain Shams University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as means and standard deviation (SD), and independent sample t-test was used for comparison between groups. Pearson's and Spearman's correlation coefficients were employed to check for statistical significance in the observed discrepancies. The ROC curve, shorthand for receiver operating characteristic curve, was implemented. P value ≤0.05 was considered to be statistically significant.

RESULTS

Table 1 shows no statistically significant differences between patients with ESRD and control groups regarding demographic characteristics; age and sex.

Table (1): Comparing end stage renal disease (ESRD) group and control groups regarding demographic characteristics.

Variable		ESRD (N=40)	Control (N=30)	P-value
Age (years)	Mean ± SD	39.8 ± 6.2	37.8 ± 6.2	^0.187
	Range	30 - 50	27 - 50	
Sex, (n, %)	Male	26 (65%)	17 (56.7%)	#0.478
	Female	14 (35%)	13 (43.3%)	
Renal disease duration (years)	Mean ± SD	4.4 ± 2.4	---	
	Range	1 - 9		

^Independent t-test. #Chi square test.

Table 2 shows that symptoms of thyroid dysfunction were more frequent in ESRD group, the difference statistically were significant only in muscle weakness (P=0.036).

Table (2): Comparing ESRD group and control group regarding symptoms of thyroid dysfunction.

Symptoms	ESRD (N=40)	Control (N=30)	P-value
Change of weight	9 (22.5%)	2 (6.7%)	§0.100
Change of bowel habits	7 (17.5%)	2 (6.7%)	§0.283
Muscle weakness	9 (22.5%)	1 (3.3%)	§0.036*

§Fisher's Exact test. *Significant.

Table 3 shows that signs of thyroid dysfunction were more frequent in ESRD group, the difference statistically were non-significant.

Table (3): Comparing ESRD group and control group regarding signs of thyroid dysfunction

Signs	ESRD (N=40)	Control (N=30)	P-value
Neck swelling	9 (22.5%)	2 (6.7%)	§0.100
Pallor	8 (20%)	2 (6.7%)	§0.171
Goitre	6 (15%)	2 (6.7%)	§0.452
Exophthalmos	5 (12.5%)	2 (6.7%)	§0.690

§Fisher's Exact test.

Table 4 shows that there were no significant variations in thyroid profile between patients with ESRD and healthy controls.

Table (4): Comparing ESRD group and control group regarding thyroid profile

Lab		ESRD (N=40)	Control (N=30)	P-value
Free T3 (pg/dl)	**Mean ± SD**	3.8 ± 0.94	4.0 ± 0.97	^0.674
Free T4 (pg/dl)	**Mean ± SD**	1.5 ± 0.36	1.4 ± 0.33	^0.675
TSH (mIU/L)	**Mean ± SD**	5.2 ± 1.2	5.9 ± 0.9	^0.060
TgAb (IU/mL)	**Mean ± SD**	21.6 ± 5.2	18.4 ± 4.4	^0.274
Antimicrosomal antibodies		7 (17.5%)	2 (6.7%)	§0.283

^Indepednent t-test. §Fisher's Exact test.

Table 5 shows that in patients with ESRD, the volume of the thyroid was greater than in the control group (P=0.020). Thyroid nodules were statistically non-significantly more frequent in ESRD group (P=0.452).

Table (5): Comparing ESRD group and control group regarding thyroid ultrasound.

Lab		ESRD (N=40)	Control (N=30)	P-value
Thyroid volume (cm^3)	**Mean ± SD**	17.0 ± 4.12	14.3 ± 3.4	**^0.020***
Thyroid nodules		6 (15%)	2 (6.7%)	§0.452

^Indepednent t-test. §Fisher's Exact test. *Significant.

Table 6 shows that the incidence of hypothyroidism was somewhat greater in the ESRD group than in the control group (P=0.100).

Table (6): Comparing ESRD group and control group regarding incidence of hypothyroidism.

Hypothyroidism	End stage (N=40)	Control (N=30)	P-value
Hypothyroidism	9 (22.5%)	2 (6.7%)	§0.100
Euothyroidism	31 (77.5%)	28 (93.3%)	

§Fisher's Exact test.

Table 7 shows that Free T3 and Free T4 were statistically significantly lower in cases with hypothyroidism. Low thyroid function was associated with elevated TSH. Hypothyroidism was associated with statistically elevated **TgAbs**. Antimicrosomal antibodies recorded only in hypothyroid cases, the differences were statistically significant (P <0.001).

Table (7): Comparison between Hypothyroid and Euthyroid patients with ESRD as regard thyroid profile.

Lab		Hypothyroid (N=9)	Euothyroid (N=31)	P-value
FT3 (pg/dl)	**Mean ± SD**	1.7 ± 0.3	4.4 ± 1.01	**^<0.001***
FT4 (pg/dl)	**Mean ± SD**	0.5 ± 0.11	1.8 ± 0.43	**^<0.001***
TSH (mIU/L)	**Mean ± SD**	6.1 ± 0.6	2.4 ± 0.51	**^<0.001***
TGABs (IU/mL)	**Mean ± SD**	42.6 ± 7	15.5 ± 2.8	**^<0.001***
Antimicrosomal antibodies		7 (77.8%)	0 (0.0%)	**§<0.001***

Table 8 and Figure 1: Free T3, TSH, TgAbs and thyroid volume statistically had perfect diagnostic performance in diagnosing hypothyroidism among ESRD group (P <0.001).

Table (8): Diagnostic performance of Free T3, Free T4, TSH, TgAbs and thyroid volume in diagnosing hypothyroidism among end stage renal disease group.

Factors	AUC	P-value	95% CI	Cut point	Sensitivity	Specificity
FT3	1.000	**<0.001***	1.000−1.000	≤2.4	100%	100%
FT4	0.997	**<0.001***	0.975−1.000	≤0.8	100%	93.5%
TSH	1.000	**<0.001***	1.000−1.000	≤4.9	100%	100%
TGABs	1.000	**<0.001***	1.000−1.000	≥26	100%	100%
Thyroid volume	1.000	**<0.001***	1.000−1.000	≥22	100%	100%

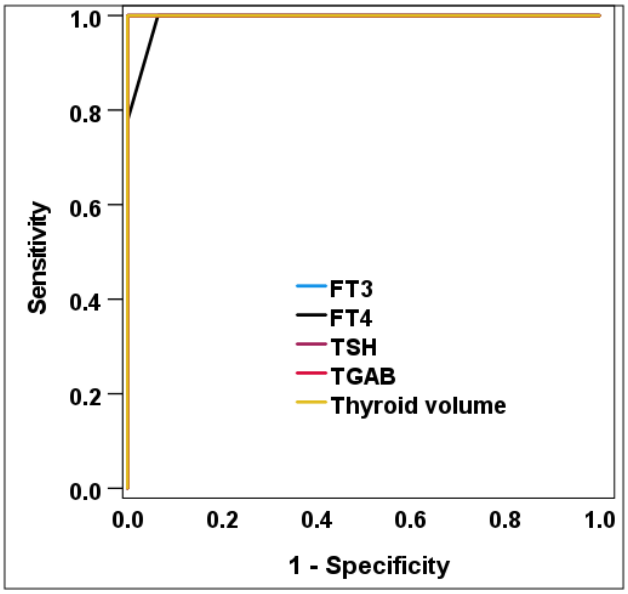

Figure (1): ROC curve for Free T3, Free T4, TSH, TgAbs and thyroid volume in diagnosing hypothyroidism among ESRD group.

DISCUSSION

Patients with chronic kidney disease have had their thyroid function assessed in great detail; however, results are inconsistent; for example, goiter was more common in studies conducted in China and Turkey, but not in the United States, Canada, Great Britain, or Australia. Chronic renal failure patients tend to have hypothyroidism, but primary hyperthyroidism is uncommon [(6)].

While patients with ESRD have normal rates of thyroid hormone synthesis, their rates of metabolic clearance of the hormone may be elevated. This finding corroborates the greater decrease in T3 than T4 seen in chronic renal failure, indicating that peripheral deiodination of T4 to T3 is inhibited and that there is preferential diversion to inactive metabolite. Unlike in other non-thyroidal diseases, low normal values of rT3 are the result of normal production and metabolic clearance rate as well as increased extra vascular binding of the hormone. Time-of-release patterns of TSH are altered in uremia patients, however at least one study shows that the pituitary-thyroid axis can be maintained even in the face of these alterations [(7)].

In the present study, it was found that **Symptoms of thyroid dysfunction** were more frequent in ESRD group the difference was statistically significant only in **muscle weakness** (P-value 0.036).

This result came in agreement with **Khatri *et al.*** [(8)] whose trial was enrolling 99 patients with late ESRD, comprising 71 male and 28 female with mean age 50.73 years. In many ways, this study demonstrated that hypothyroidism in individuals with ESRD might exacerbate neurobehavioral and neuromuscular dysfunction.

In the present study, we found that there was no statistically significant difference between the studied groups as regard **Thyroid examination** (neck swelling, exophthalmos and goiter).

This result came in agreement with **Malik *et al.*** [(9)], the research involving 21 healthy controls and 38 patients with ESRD (both on hemodialysis and conservative treatment) found the following with regards to clinical assessment of thyroid dysfunction: Eighty-one point 25% of the hemodialysis group, eighty-one point 82% of the conservatively managed group, and eighty-five point 72% of the control group had no clinical signs of potential thyroid dysfunction. One in twelve people on hemodialysis had a goiter, 4.5% of those receiving conservative treatment did, and none in the control group did. In addition, he demonstrated that exophthalmos was not more common in patients with ESRD than in controls.

In the present study, we found that there was no statistically significant difference between the studied groups as regard **thyroid profile** (P-value >0.05).

These results came in line with **Malik *et al.*** [(9)] who demonstrated that both the TT3 and TT4 of patients receiving conventional care and routine hemodialysis were significantly lower than those of control subjects. A substantial change in TSH level was not seen. Neither the conservatively managed nor the hemodialysis patients had significantly different levels of TT3 or TT4; 68.75% and 62.25 % of the H.D. patients, respectively, have TT3 and TT4 levels below normal range, while 54.5% and 72.725 % of the conservatively treated group have as well.

This result didn't come in agreement with **Khatri *et al.*** [(8)] they demonstrated that decreased Free T3 was the most prevalent thyroid malfunction in individuals with ESRD. Twenty-eight people, including 21 men and 7 women, had a low Free T3 level. Thirteen patients with a low Free T3 level were between the ages of 41 and 60, while 8 were between the ages of 16 and 40, and 7 were over the age of 60. Out of a total of 99 patients, 13 had a deficient Free T4 level; of these, 6 were between the ages of 41 and 60, 4 were between the ages of 16 and 40, and 3 were older than 60. Nine men and 4 women made up the 13 patients with low Free T4. Overall, 11 patients had abnormally low levels of both Free T3 and Free T4. Twenty-four patients had changes in their serum TSH levels. Twenty of the 24 patients had elevated TSH levels, while just 4 had low levels. Possible causes of low Free T3 include impaired peripheral T4 to T3 conversion, metabolic acidosis, urinary loss of bound and Free T4, and malnutrition-inflammatory syndrome in hemodialysis patients.

In the current study, we found that **Thyroid volume** was statistically significant higher in ESRD group, and **Thyroid nodules** were statistically non-significantly more frequent in ESRD group.

This result came in agreement with **Da Costa *et al.*** [(10)], wherein 61 patients with ESRD were compared to 43 participants with similar demographics (Mean age = 47.4 (SD 12.3) years; male to female ratio = 1:1). More people with ESRD had an enlarged thyroid (15%

vs. 14%), but there was no statistical difference between the 2 groups (P-value >0.05). The prevalence of nodules in the thyroid was higher in the ESRD group (24.1%) than in the control group (7.9%), although this difference was not statistically significant when assessed using ultrasonography.

In our study, we found that **Hypothyroidism** was statistically non-significantly more frequent in ESRD group (22.5% of 40 patients) compared to control group (6.7% of 30 patients).

This result came in agreement with **Nazzal *et al.*** [(11)] among the 209 patients with ESRD who participated in the study, 34 (6.9%) had hypothyroidism, 19 (9.6%) with overt hypothyroidism and 15 (6.7%) with subclinical hypothyroidism. There wasn't enough of a difference to warrant statistical analysis.

In our study, we found that **Thyroid antibodies** were statistically significantly higher in cases with hypothyroidism. **Antimicrosomal antibodies** recorded only in hypothyroid cases, the differences were statistically significant.

This result came in agreement with **Rhee *et al.*** [(12)] who measured TSH and antimicrosomal antibodies at cross-sectional intervals in a prospective cohort of 996 hemodialysis patients discovered that individuals with elevated antibody levels also had elevated TSH levels. These elevated TSH levels have been observed in individuals with ESRD, and they may be at least in part due to autoimmune factors.

Limitation of the current study included small sample size, lack of follow up, lack of assessment of decision changes after hypothyroidism management and their correlations with renal stage as well as assessment of survival rate of cases should be point of focus in next future studies.

CONCLUSION

CKD and hypothyroidism share a common spectrum of symptoms. However, frequency of hypothyroidism was higher in ESRD patients compared to control group. So, it is important to keep monitoring thyroid functions in patients with advanced renal impairment that may enhance quality of life.

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