

# Frequency and relation of thyroid dysfunction and inflammation in chronic kidney diseases in the Nephrology Unit, Zagazig University

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## Context

Thyroid hormones play an important role in renal development, functioning renal mass, and early renal function. Pituitary–thyroid axis and metabolism of the peripheral thyroid hormones have been affected by chronic kidney disease (CKD).

## Aims

The aim was to evaluate the frequency and relationship between thyroid disorders and high-sensitivity C-reactive protein (Hs-CRP) among CKD patients including hemodialysis (HD).

## Settings and design

In Zagazig University Hospital.

## Participants and methods

A case–control study that included 150 adult participants who were divided into: group I which included 50 patients with an estimated glomerular filtration rate (eGFR) of  $41.8 \pm 23.6$  ml/min/1.73 m<sup>2</sup>. Group II included 50 patients with an eGFR of  $11.3 \pm 4.2$  ml/min/1.73 m<sup>2</sup>. Group III included 50 participants with normal eGFR. All participants were evaluated for serum creatinine and albumin, complete blood count, estimation of GFR by modification of diet in renal disease (MDRD) equation, and serum thyroid-stimulating hormone (TSH), free T3, free T4, and Hs-CRP.

## Statistical analysis

Using the Statistical Package for the Social Sciences under windows version 20. Qualitative variables were expressed by frequency and percentage, mean  $\pm$  SD,  $\chi^2$ -test, Student's *t*-test, analysis of variance (*F*-test), and correlation analysis.

## Results

The frequency of subclinical hypothyroidism (46%) and overt hypothyroid (42%) in groups I and II, respectively, has been much higher in CKD patients. There was a strong significant negative correlation of Hs-CRP with eGFR, FT3, FT4 ( $P < 0.001$ ), highly significant positive correlation with serum creatinine, TSH ( $P < 0.001$ ) in non-HD patients, but in HD patients there was high statistically significant negative correlation of Hs-CRP with hemoglobin, albumin, FT3 ( $P < 0.001$ ), FT4, and significant positive correlation with dialysis duration ( $P < 0.001$ ) and TSH.

## Conclusion

the frequency of thyroid disorders mostly subclinical hypothyroid (46%) and overt hypothyroid (42%) is common in CKD patients and is highly correlated with Hs-CRP in these patients. So we recommend a thyroid investigation in chronic kidney patients for early detection and reduction of its morbidity and mortality.

## Keywords:

chronic kidney disease, Egypt, Zagazig University, hemodialysis, thyroid dysfunction

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## Introduction

Thyroid function disorder affects kidney development and normal physiology. Also chronic kidney diseases (CKDs) may affect thyroid function. Both have common etiological factors [1] And are commonly observe in CKD patients with nonimmune primary hypothyroidism. Especially, subclinical hypothyroidism prevalence increases with a decline in glomerular filtration rate (GFR). Usually low T3 level (total more than free T3) is the first thyroid manifestation in that patients [2]. Thyroid disorders are discovered to be a risk factor for CKD progression, and vice versa [3].

So, this study aimed to evaluate the frequency and relationship between thyroid dysfunction and high-sensitivity C-reactive protein (Hs-CRP) among CKD patients including hemodialysis (HD).

## Participants and methods

A cross-sectional study had been carried out in the inpatient ward of the Internal Medicine

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Department and Nephrology and Hemodialysis Unit of Zagazig University Hospitals, from January 2015 to January 2016 in Egypt. Written informed and oral consents were taken from the patients who participated in the study in addition to the approval for performing the study that was obtained from Internal Medicine Department after taking the Institutional Review Board (IRB) approval. Human rights were preserved according to the declaration of Helsinki guidelines. We applied this study on 150 participants who were divided into group I including 50 CKD patients with a mean estimated glomerular filtration rate (eGFR) of  $41.8 \pm 23.6$  ml/min/1.73 m<sup>2</sup> (25 men and 25 women); 12 of them are diabetic and 18 of them are hypertensive diagnosed by the kidney disease improving global outcomes (KDIGO) criteria, and group II included 50 CKD patients on HD with an eGFR of  $11.3 \pm 4.2$  ml/min/1.73 m<sup>2</sup> (22 men and 28 women); 22 of them are diabetic and 41 of them are hypertensive and group III included 50 participants (24 men and 26 women); two of them are diabetic and eight of them are hypertensive with an eGFR of greater than or equal to 90 ml/min/1.73 m<sup>2</sup>. Inclusion criteria: age equal or more than 20 years, HD patients have 4h, three times per week, dialysis session. Exclusion criteria: age less than 18 years, patients refusing to enter the study, presence of known thyroid disorder or liver disease, evidence of current infection or inflammation (other than renal cause), blood diseases, blood transfusion or malignancy, pregnancy, lactation or taking contraceptive pills and those taking drugs affecting thyroid function; consent was taken from all persons shared in this study after complete explanation of the procedure steps and nature of the research.

All persons included in this study were subjected to the following:

- (1) Complete clinical history and physical examination, lab investigation: like complete blood count, serum albumin (Alb) and creatinine, FT3, FT4, thyroid-stimulating hormone (TSH), Hs-CRP, eGFR calculated by MDRD4 equation.
- (2) All blood sample withdrawals were performed by the dialysis unit nursing staff on the day of the dialysis session for all patients on HD before the intervention and other participants when they were fasting.

#### Data management

The collected data were revised, verified, edited on PC, and then analyzed statistical using the Statistical Package for the Social Sciences (SPSS) under windows version 20 (SPSS Inc., Chicago, Illinois, USA).

The following statistical tests were used: qualitative variables were expressed by frequency and percentage. Description of quantitative variables in the form of mean $\pm$ SD.  $\chi^2$ -test, and Fisher's exact was used for comparison of qualitative variables with each other. Comparison between quantitative variables was carried out using Student's *t*-test of two independent samples. For comparison of more than two quantitative groups one-way analysis of variance *F*-test was used for categorical data. The significance level (*P*) was expressed as follows: *P* value greater than 0.05 is not significant. *P* value less than 0.05 is significant. *P* value less than 0.001 is highly significant. Pearson's correlation coefficient was used to calculate the correlation between quantitative variables.

**Table 1 Clinicodemographic data of the studied population (N=150)**

	CKD group (N=50) [n (%)]	HD group (N=50) [n (%)]	Control (N=50) [n (%)]	Test	<i>P</i>
Sex					
Male	25 (50)	22 (44)	24 (48)	0.4*	0.829
Female	25 (50)	28 (56)	26 (52)		
Age (years)	48.3 $\pm$ 13.5	43.1 $\pm$ 11.5	43.6 $\pm$ 11.8	6.6 <sup>b</sup>	0.066
Body weight (kg)	82.3 $\pm$ 15.8	76.6 $\pm$ 18.5	73 $\pm$ 14.1	7.3 <sup>b</sup>	0.026
DM					
Yes	12 (24.0)	22 (44.0)	2 (4.0)	24.8 <sup>a</sup>	<0.001
No	38 (76.0)	28 (56.0)	48 (96.0)		
HTN					
Yes	18 (36.0)	41 (82.0)	8 (16.0)	49.8 <sup>a</sup>	<0.001
No	32 (64.0)	9 (18.0)	42 (84.0)		
Overt hypothyroid	0 (0.0)	21 (42.0)	0 (0.0)		
Normal	27 (54.0)	29 (58.0)	50 (100.0)	97.3 <sup>a</sup>	<0.001
Subclinical hypothyroid	23 (46.0)	0 (0.0)	0 (0.0)	97.3 <sup>a</sup>	<0.001

CKD, chronic kidney disease; DM, diabetes mellitus; HD, hemodialysis; HTN, hypertension. <sup>a</sup> $\chi^2$ -test. <sup>b</sup>One-way analysis of variance.

## Results

Table 1 shows that there were high statistically significant differences between different groups as regards body weight, diabetes mellitus (DM), hypertension, and thyroid disorder, while there were no statistically significant differences as regards age and sex.

Table 2 shows that there were high statistically significant differences between different groups as regards serum creatinine, eGFR, blood hemoglobin (Hb), serum Alb, Hs-CRP, FT3, FT4, and TSH.

Table 3 shows that there was negative correlation between Hs-CRP and body weight, eGFR, Hb, Alb, FT3, and FT4 while positive correlation between Hs-CRP and creatinine (Cr), TSH, age and there was statistically high significance between Hs-CRP and Cr, eGFR, FT3, FT4, TSH, while there was a statistically nonsignificant difference between Hs-CRP and age, body weight, Hb, and Alb.

There was negative correlation between FT3 and Cr, Hb, Hs-CRP, TSH, while positive correlation between FT3 and age, body weight, eGFR, and

FT4 and there was statistically high significance between FT3 and eGFR, Hs-CRP, FT4, TSH, while there was significant difference between FT3 and Cr, body weight and there was statistically nonsignificant difference between FT3 and age, Hb, and Alb.

Table 4 shows that there was negative correlation between Hs-CRP and body weight, eGFR, Hb, Alb, FT3, and FT4 while positive correlation between Hs-CRP and age, HD duration, Cr, TSH, and there was statistically high significant difference between Hs-CRP and HD duration, Alb, FT3, and FT4, TSH while there was statistically nonsignificant difference between Hs-CRP and age, body weight, Cr, eGFR and there was statistically significant difference between Hs-CRP and Hb.

There was negative correlation between FT3 and age, HD duration, Cr, Hb, Hs-CRP, TSH, while positive correlation between FT3 and body weight, eGFR, Alb, FT4, and there was statistically highly significant difference between FT3 and HD duration, Hs-CRP, FT4, TSH while it is statistically nonsignificant between FT3 and age, body weight, Cr, eGFR, Hb, and Alb.

**Table 2 Baseline laboratory values data of the studied population and comparison of basal laboratory values among the different groups**

	CKD group (non-HD)	HD group	Control	F	P
Cr (mg/dl)	3.1±1.9 <sup>a,b</sup>	8.8±2.4 <sup>c</sup>	0.9±0.2	128.2	<0.001
eGFR (ml/kg/h)	41.8±23.6 <sup>a,b</sup>	11.3±4.2 <sup>c</sup>	100.9±9.6	122.1	<0.001
Hb (g/dl)	10.2±2.3 <sup>b</sup>	9.7±1.7 <sup>c</sup>	14±1.5	79.3	<0.001
Alb (mg/dl)	2.8±0.7 <sup>a,b</sup>	3.9±0.5 <sup>c</sup>	4.4±0.6	85.0	<0.001
Hs-CRP (mg/dl)	14.7±13.8 <sup>a</sup>	8.4±8.2 <sup>c</sup>	1.9±0.8	47.0	<0.001
FT3 (pmol/l)	5±1.3 <sup>a</sup>	3.8±2.1 <sup>c</sup>	5.1±1.3	10.9	0.004
FT4 (pmol/l)	16.5±3.7 <sup>a</sup>	13.2±5 <sup>c</sup>	16.5±3.6	15.4	<0.001
TSH (IU/ml)	6.5±5 <sup>b</sup>	12.1±4.5 <sup>c</sup>	2.4±1.5	25.4	<0.001

Alb, albumin; CKD, chronic kidney disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HD, hemodialysis; Hs-CRP, high-sensitivity C-reactive protein; TSH, thyroid-stimulating hormone. <sup>a</sup>When comparing group CKD with HD. <sup>b</sup>When comparing group CKD with control. <sup>c</sup>When comparing group HD with control.

**Table 3 Correlations between certain studied parameters with high-sensitivity C-reactive protein, FT3, FT4, and thyroid-stimulating hormone in the chronic kidney disease group (non-HD)**

	Hs-CRP (mg/dl)		TSH (IU/ml)		FT4 (pmol/l)		FT3 (pmol/l)	
	r	P	r	P	r	P	r	P
Age (years)	0.114	0.433	0.043	0.769	-0.105	0.466	0.036	0.803
Body weight (kg)	-0.158	0.272	-0.356	0.011	0.225	0.116	0.359	0.010
Cr (mg/dl)	0.552	<0.001	0.556	<0.001	-0.523	<0.001	-0.388	0.005
eGFR (ml/kg/h)	-0.567	<0.001	-0.656	<0.001	0.552	<0.001	0.554	<0.001
Hb (g/dl)	-0.169	0.241	-0.109	0.451	0.242	0.091	-0.029	0.841
Alb (mg/dl)	-0.029	0.842	0.084	0.560	-0.155	0.283	-0.211	0.142
FT3 (pmol/l)	-0.533	<0.001	-0.571	<0.001	0.520	<0.001		
FT4 (pmol/l)	-0.612	<0.001	-0.658	<0.001				
TSH (IU/ml)	0.698	<0.001						

Alb, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HD, hemodialysis; Hs-CRP, high-sensitivity C-reactive protein; TSH, thyroid-stimulating hormone.

**Table 4 Correlations between certain studied parameters with high-sensitivity C-reactive protein, FT3, FT4, and thyroid-stimulating hormone in the hemodialysis group**

	Hs-CRP (mg/dl)		TSH (IU/ml)		FT4 (pmol/l)		FT3 (pmol/l)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age (years)	0.243	0.090	0.035	0.812	0.005	0.972	-0.194	0.177
Body weight (kg)	-0.036	0.803	-0.138	0.340	0.201	0.162	0.212	0.139
HD duration (years)	0.481	<0.001	0.409	0.003	-0.421	0.002	-0.516	<0.001
Cr (mg/dl)	0.187	0.193	0.080	0.579	0.066	0.649	-0.001	0.996
eGFR (ml/kg/h)	-0.114	0.432	-0.042	0.770	-0.001	0.993	0.134	0.353
Hb (g/dl)	-0.287	0.043	0.316	0.025	-0.149	0.301	-0.271	0.057
Alb (mg/dl)	-0.999	<0.001	-0.118	0.413	0.094	0.515	0.167	0.246
FT3 (pmol/l)	-0.696	<0.001	-0.760	<0.001	0.723	<0.001		
FT4 (pmol/l)	-0.623	<0.001	-0.790	<0.001				
TSH (IU/ml)	0.781	<0.001						

Alb, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HD, hemodialysis; Hs-CRP, high-sensitivity C-reactive protein; TSH, thyroid-stimulating hormone.

**Table 5 Relation between thyroid profile and high-sensitivity C-reactive protein in the chronic kidney disease group (nonhemodialysis)**

	Hs-CRP negative [26 (52)] [ <i>n</i> (%)]	Hs-CRP positive [24 (48)] [ <i>n</i> (%)]	Total	$\chi^2$	<i>P</i>
Overt hypothyroid	0 (0.0)	0 (0.0)	0 (0.0)	46.1	<0.001
Normal	26 (100)	1 (4.2)	27 (54.0)		
Subclinical hypothyroid	0 (0.0)	23 (95.8)	23 (46.0)		

Hs-CRP, high-sensitivity C-reactive protein.

**Table 6 Relation between thyroid profile and high-sensitivity C-reactive protein in the hemodialysis group**

	Hs-CRP negative [26 (52)] [ <i>n</i> (%)]	Hs-CRP positive [24 (48)] [ <i>n</i> (%)]	Total	$\chi^2$	<i>P</i>
Overt hypothyroid	0 (0.0)	21 (95.5)	21 (42)	42.9	<0.001
Normal	28 (100)	1 (4.5)	29 (58)		
Subclinical hypothyroid	0 (0.0)	0 (0.0)	0 (0.0)		

Hs-CRP, high-sensitivity C-reactive protein.

Tables 5 and 6 show that there was positive relation between Hs-CRP and thyroid disorder where 95.8% of CKD was subclinical hypothyroid (SHT) and 95.5% of HD was overt hypothyroid.

## Discussion

CKD describes a group of different disturbances changing the function and structure of the kidney [4]. Alterations in thyroid hormones may occur in CKD patients in the absence of an underlying intrinsic thyroid disorder, known as the nonthyroidal illness syndrome [5,6].

We found in the present study a high rate of inflammation in both non-HD (95.8%) and HD (95.5%) groups. There was statistically high significant positive correlation between Hs-CRP and Cr and negative correlation of Hs-CRP with eGFR FT3, FT4 in chronic renal patients, our result is in accordance of Vanholder *et al.* [7], Vanholder *et al.* [8], and Abraham *et al.* [9].

The most important links between thyroid disorders and CKD was uremia [10], as it is associated with a

state of immune dysfunction and immune depression that contribute to increased incidence of infections, resulting in inflammation [11].

Also, accumulation of uremic toxins may lead to endothelium injury in CKD stages 1–3 [12], and vascular calcification in CKD stages 3–5 that may be the causes for higher Hs-CRP levels [13]. Hs-CRP negative correlated with FT3 and FT4 levels due to chronic illness adaption that minimizes catabolism [14].

Hs-CRP levels in CKD patients correlated inversely with serum Alb ( $P<0.01$ ) and blood Hb; this is due to the malnutrition inflammation complex and low levels of erythropoietin. The same results were observed with Ortega *et al.* [15], while Abraham *et al.* [9] reported no correlation between hemoglobin levels and Hs-CRP levels.

As regards age, Hs-CRP is found to have positive correlation but not significant with the patients' age. This is because morbidity increases with increasing age,

this is in agreement with Naseem *et al.* [16] who stratify SHT in CKD patients according to age; 22.7% of patients were younger than 30 years, 20.8% between 30 and 40 years and 46.2% were above 40 years.

Dialysis duration was significantly positively correlated with Hs-CRP here in the study; circulation of the blood during dialysis increases the release of inflammatory mediators. The same result was reported by Naseem *et al.* [16] who tell us that 4.5% of patients on HD for 2 years or less had SHT; 25.9% on HD for 3–5 years, and 60.9% on HD for more than 5 years had SHT.

In this study, DM was detected in 24.0% and 44.0% of CKD patients in groups 1 and 2, respectively, and also, hypertension was reported in 36.0% and 82.0% of groups 1 and 2, respectively. Similar results were obtained by Abraham *et al.* [9] and Chandra [17], who have shown a high rate of SHT and overt hypothyroid was found in DM associated with CKD groups. This is inconsistent with Miulescu *et al.* [18] who recruited 23 patients in the predialysis phase with CKD and diabetes mellitus for detecting the associations between thyroid dysfunction and CKD. The thyroid malfunction especially hypothyroid (low T3 syndrome, SHT and overt hypothyroid) is highly frequent in DM with CKD more than DM without CKD.

Chronic renal failure patients in the study have low serum T3 and T4 levels; this is due to the increase in thyroid protein binding, peripheral tissue metabolism, and decrease of peripheral conversion of T4 to T3 due to the decreased clearance of the inflammatory cytokines such as tumor necrosis factor- $\alpha$  and interleukin-1.

Also, there is increased level of TSH in some HD patients due to the direct effect on the pituitary–thyroid axis and decrease in renal function, which lead to an ineffective clearance of abnormal serum constituents which affected the levels of thyroid hormones [10]. Also, there was decrease in clearance and an increase in half-life of TSH [19], these findings were in agreement with Miulescu *et al.* [18] and Rajeev *et al.* [20].

Regarding the current study, the most prevalent thyroid dysfunctions were associated with CKD groups: 42% overt hypothyroidism in the HD group and 46% subclinical hypothyroidism in the non-HD group, associated with increasing Hs-CRP and decreasing eGFR. This is in harmony with Gupta *et al.* [3] who observed a high prevalence of SCH in CKD patients (25%). SCH is an additional risk factor in CKD and is significantly associated with CKD progression. A study by Lo *et al.* [21] included data

of 14 623 adult participants. He correlated hypothyroidism with different levels of estimated GFR according to the National Kidney Foundation CKD staging. The results showed increased prevalence of hypothyroidism from 5.4% in those with an eGFR of less than or equal to 90 ml/min/1.73 m<sup>2</sup> to 23.1% in those with an eGFR of less than 30 ml/min/1.73 m<sup>2</sup>. Also, Chonchol *et al.* [22], in a study included 3089 adult participants, concluded that subclinical hypothyroidism prevalence increased from 7 to 17.9% in individuals whose eGFR has decreased from 90 to 60 ml/min. Khatiwada *et al.* [23] identified that CKD patients have a rate of thyroid dysfunction due to excess iodine nutrition or deficiency, thyroid autoimmunity or inclusion of participants with nonthyroidal illness.

### Conclusion and recommendation

From the aforementioned results of this study, it could be conclude that hypothyroidism was the most prevalent thyroid dysfunction associated with CKD HD patients, and subclinical hypothyroidism commonly affects non-HD CKD patients due to the high prevalence of inflammation. So we advise to performing thyroid function tests in patients with CKD and following them with progressing kidney function to protect against cardiovascular risk changes.

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### Conflicts of interest

There are no conflicts of interests.

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