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A Study of Thyroid Dysfunction in Patients with End Stage Renal Disease on Hemodialysis

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Abstract
Background: Progression of chronic kidney disease (CKD) is associated with having a number of complications, including thyroid dysfunction. CKD affects the thyroid function by lowering levels of circulating thyroid hormones, interfering with hormones binding to protein carriers, disrupting metabolism and elimination of thyroid hormones.**Aim of the study**: We aimed to evaluate and compare thyroid functions among patients on chronic hemodialysis (HD) and healthy participants. **Methods:** This is a cross- sectional study conducted in the dialysis unit of Baghdad teaching hospital from (May 2015 to November 2015). A total of 45 known CKD cases (stage 5) older than 18 year were included in the study. Patients with known thyroid disorders, on medications affecting thyroid function were excluded from the study. All subjects were clinically euthyroid, they were investigated with laboratory tests to determine blood urea, serum creatinine, body mass index, estimated glomerular filtration rate (eGFR), thyroid function including: serum triiodothyronine (T3), thyroxin (T4), free T3, free T4, and thyroid- stimulating hormone (TSH).Results were compared with the same measurements in 20 normal subjects as a control group.**Results:** Of total sample of patients, 22(48.9%) were male, 23(51.1%) were female; with mean age of 50.96± 14.26 years. In control group; 12 (60%) were male, 8 (40%) were female with mean age of 40.25± 11.86 years. In HD group; we found statistically significant lower mean values of T3 (1.54± 0.67, p= 0.009), free T3 (2.65± 0.92, p <0.001), and higher frequency of low T3 syndrome in 73. 33% (n=33) vs. 5% (n= 1) with (p <0.001). Subclinical hypothyroidism was found in control group only, in 20% (n= 4), (p <0.001). There was a strong correlation between S. creatinine with free T_3, correlation coefficient (- 0.378). In patients on HD for equal or more than a year; we found statistically significant lower mean values of T3 (1.07± 0.23) vs. (1.66± 0.69), (p= 0.016), in spite of significant increase in mean eGFR of (9.00± 4.82) vs. (6.39± 3.08), (p= 0.05). There was a statistically significant association between total T_4 and presence of DM, (P= 0.044).**Conclusions:** We observed that functional thyroid gland disorders are more common among patients on chronic hemodialysis compared with healthy subjects, and reveal their link with time on dialysis. Low T3 syndrome (Euthyroid sick syndrome)is the most frequently thyroid function disorder.
Keywords: Triiodothyronine, Hemodialysis, Low T3syndrome, Euthyroid sick syndrome.

1. Introduction

1.1 Thyroid Hormone Metabolism.

The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. All levels of the hypothalamic- pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion. Thus, decline of kidney function is accompanied by a characteristic disturbance in thyroid physiology. As a result, abnormalities in thyroid function tests are frequently encountered in uremia. [1]

The kidney normally contributes to the clearance of iodide, primarily by glomerular filtration. Thus, iodide excretion is diminished in advanced renal failure, leading sequentially to an elevated plasma inorganic iodide concentration and an initial increment in thyroidal iodide uptake.[2]

Increases in total body inorganic iodide can potentially block thyroid hormone production (the Wolff-Chaikoff effect). Such a change may explain the slightly higher frequency of goiter and hypothyroidism in patients with chronic kidney disease.[3]

1.2 Hypothalamic- Pituitary Dysfunction.

CKD affects the hypothalamus- pituitary-thyroid axis and the peripheral metabolism of thyroid hormone. TSH levels are usually normal with an altered circadian rhythm (comprised of TSH bioactivity), the pituitary receptor response to TRH is blunted causing a decrease in TSH release and the response of TSH to TRH is delayed because of the decreased clearance and the increase of half- life of TSH.[4]

1.3 Subclinical Hypothyroidism.

Subclinical hypothyroidism is defined as an elevation in serum TSH concentration (normal range 5–10 μIU/mL) in conjunction with a normal serum free T4 concentration. With the decline in GFR, the prevalence of subclinical hypothyroidism increases consistently. The prevalence of subclinical primary hypothyroidism

increased from 7% to 17.9% in individuals whose GFR has decreased from ≥ 90 mL/min to 60 mL/min.[5]

1.4 Low T3Levels.

Low free T3has emerged as a potent biomarker in ESRD in several studies and represents the main finding of non thyroidal illness syndrome (NTIS) in renal disease.[6] CKD has been known to affect the peripheral metabolism of thyroid hormones. Low T3 levels are the most common laboratory finding followed by subclinical hypothyroidism in CKD patients. Hyperthyroidism is usually not associated with CKD but has been known to accelerate it.[1]

In an issue of the European Journal of Endocrinology, Iglesias P and Diez JJ published in 2009 a review article entitled: "Thyroid dysfunction and kidney disease " in which they report that "Serum TSH concentrations are usually normal or elevated in CKD. Free and total T3 and T4 concentrations are usually normal or low in patients with CKD. This reduction in T3concentrations has been linked to a decrease in the peripheral synthesis of T3 from T4. This abnormality is not associated with increased conversion of T4 to the metabolically inactive reverse T3 (rT3), since plasma rT3 levels are typically normal. This finding differentiates the uremic patient from patients with chronic illness . In the latter setting, the conversion of T4 to T3 is similarly reduced, but the generation of rT3 from T4 is enhanced.[7]

The prevalence of the low T3 syndrome is in comparison remarkably high ,being reported in more than 70% of patients with ESRD. [8] Low levels of total T3 may also reflect metabolic acidosis and reduced protein binding. [9]

Low plasma free T3 levels may also be associated with the presence of the malnutrition-inflammation syndrome. The latter is a common chronic condition in dialysis patients associated with markedly increased cytokine levels. [10] Low T3 levels in CKD may also be due to the decreased clearance of the inflammatory cytokines such as TNF-alpha and IL-1. These cytokines inhibit expression of 1 5′- deiodinase that helped convert T4 to T3. [11]The plasma concentration of (TSH) is usually normal in chronic kidney disease. However, the TSH response to exogenous thyrotropin- releasing hormone (TRH) is often blunted and delayed, with a prolonged time required to return to baseline levels.[12] Reduced renal clearance may contribute to delayed recovery, since TSH and TRH are normally cleared by the kidney. However, the blunted hormone response also suggests disordered function at the hypothalamic-pituitary level that may be induced by uremic toxins. When compared to normals, patients with CKD have an attenuated rise in TSH levels during the evening hours and the normally pulsatile secretion of TSH is smaller in amplitude.[13]

Despite these perturbations, TSH release responds appropriately to changes in the circulating level of thyroid hormones. Exogenous T3 lowers TSH levels and can totally suppress the secretory response to exogenous TRH. On the other hand, TSH production increases appropriately in response to thyroid ablation. The latter response is important clinically, since TSH levels should rise (as in normals) when a uremic patient develops hypothyroid.[14]

1.5 Effects Of Hemodialysis On Thyroid Function.

HD is associated with alterations in the concentration of circulating TH, usually to a reduction in serum total and free T3 concentrations. Low TH may be a protective adaptation for nitrogen conservation and therefore inappropriate TH supplementation can result in excessive protein nitrogen wasting in these patients. HD influences the cellular transport of TH. This effect could act as a compensatory mechanism to neutralize the thyroid dysfunction in order to maintain euthyroid status.[15]

1.6 Clinical Significance

Low T3 concentrations, although initially thought to be an adaptive response to chronic illness, have been associated with all- cause and cardiovascular mortality in uremic patients. As an example, in one study of 210 hemodialysis patients, low T3 concentrations, particularly if persistent throughout the 38 month study, were associated with a higher risk of all- cause and cardiovascular mortality, with hazard ratios of 2.7 and 4.0, respectively.[16] A low T4 but not TSH, was also associated with all- cause and cardiovascular mortality. A number of studies have consistently shown that low T3 concentrations are inversely correlated with markers of systemic inflammatory response and are an independent predictor of mortality in euthyroid patients with ESRD,[17] and in dialysis populations, having a stronger association with cardiovascular death.[18]

Low T3 has been additionally linked to impaired cardiac function and geometry,[19] coronary artery calcification,[20] increased intima- media thickness, flow-mediated vasodilatation (FMD),and measures of systemic arterial stiffness.[21]

In general, there is substantial clinical overlap between chronic kidney disease and hypothyroidism. In addition to low total and plasma free T3 levels, there are a number of symptoms that are common to both conditions including cold intolerance, puffy appearance, dry skin, lethargy, fatigability, and constipation. Furthermore, the frequency of goiter is markedly increased in end-stage renal disease. Despite these findings,

most uremic patients are considered to be euthyroid as evidenced by normal plasma concentrations of TSH and free T4, and normal basal metabolic rate and tendonrelaxation time.[22]

Finally the observational nature of the studies reporting these results emphasizes the importance of verifying whether uremic patients without primary thyroid dysfunction would benefit from thyroid hormone therapy. So far, there is insufficient evidence to recommend routine provision of thyroid hormone replacement in CKD with low T3 alone.[23]

Aim of the study.

To evaluate and compare thyroid functions among patients on chronic hemodialysis (HD) and healthy participants.

2. Patients &Methods.

2.1 Study design and sample selection

This is a cross sectional observational study conducted in the dialysis unit of Baghdad Teaching Hospital/ medical city in Baghdad from (May 2015 to November 2015). Forty- five patients older than 18 year with CKD stage 5 were included in this study; all of them were on regular hemodialysis.

CKD stage 5 was defined on the basis of National Kidney Foundation guidelines of having an estimated glomerular filtration rate (eGFR) < 15 ml/min/1.732 m^2 for more than 3 months. The Modification of Diet in Renal Disease study (MDRD) equation was used to calculate eGFR.[24]

Patients were dialyzed three times weekly, using a two needle system, low- flux polysulphone dialyzer 1.6-1.8 m^2, bicarbonate dialysis solution with dialysate flow 500ml/ min and blood flow rate 300ml/ min. Equilibrated Kt/ V was checked monthly and targeted above 1.2, in accordance with K/DOQI guidelines (National Kidney Foundation 2006). The dialysis population studied was unselected but patients with severe acute complications requiring hospitalization at the time of sampling were not included in the analysis. For the sake of the study; hemodialysis patients were divided into two subgroups according to duration of time on dialysis: (those < 1y and those ≥ 1y). Twenty healthy volunteers with normal renal function and no previous history of thyroid dysfunction were included in this study as a control group.

2.2 Clinical and Laboratory Evaluation

All patents and control were assessed for possible thyroid dysfunction depending on clinical bases and physical examination.

*2.*3 Exclusion Criteria are:

1. A family history of goiter or altered thyroid function.
2. A personal and family history of other organ- specific autoimmune diseases particularly of insulin- dependent diabetes, pernicious anemia, vitiligo, and myasthenia gravis.
3. History of intake of iodine- containing medications, such as amiodarone, lithium carbonate.
4. History of thyroid surgery or radioactive iodine intake.
5. Goiter± bruit.
6. Eye signs (exophthalmos, lid retraction….. etc).
7. Pretibial myxedema.
8. Delayed reflexes.

Pallor, weight loss, palpitation, tremor, neurological symptoms and other manifestations of thyroid dysfunction may also occur in uremia, so they are not regarded as signs of possible thyroid dysfunction in the study group. All those included in the study underwent estimations of serum total (T3) and serum total (T4) , serum (TSH), serum free T3(fT3) and serum free T4(fT4) were performed by (TT3 ELFA kit REF: 30 459), (TT4 ELFA kit REF: 41 634), (TSH ELFA kit REF: 23 634),(fT3 ELFA kit REF:12 987), (fT4 ELFA kit REF:56 342), respectively; these systems provide direct quantitative in vitro administration of L-3,5,3- tri-iodothyronine (T3), thyroxin (T4), (TSH) in human, serum (fT3) and serum (fT4).

Serum fT3, fT4 and TSH were measured by using fluorescent immunoassay (VIDAS, biomeriux SA, France). As heparin may interfere with competitive assays, blood was drawn just before the start of hemodialysis procedure from the inserted dialysis needle, before contact of blood with dialyzer and before heparin administration. This ensured that there was an interval of at least 48 hours since the last heparin application.We made sure that all patients and control group did not receive furosemide before taking blood samples as it is known to influence thyroid function.

General information regarding age, gender, occupation, and address of the patients and the control group were taken. Informationabout duration, etiology of renal failure, type and duration of dialysis, medical history of type 2 diabetes mellitus and hypertension were also recorded. Result of basic laboratory investigations which include packed cell volume (PCV), blood urea, serum creatinine, fasting blood sugar (FBS), total serum protein (TSP) and serum albumin, body mass index (BMI), glomerular filtration rate (GFR) were integrated in

this study

Reference ranges for the biochemical variables of interest are these:

TSH (0.25- 5.0 mIU/L)
T3 (0.92- 2.33 nmol/L)
Free T3 (4- 8.3 pmol/L)
T4 (60- 120 nmol/L)
Free T4 (9- 20 pmol/L).

2.4 Definitions.[25]

Euthyroidism was defined as normal TSH and T3 and T4.
Hypothyroidism was defined as TSH > 5 mIU/L and free T4 <9 pmol/L.
Hyperthyroidism was defined as TSH <0.25 mIU/L and T3 > 2.33 nmol/L or T4 > 120 nmol/L.
Subclinical hypothyroidism was defined as TSH > 5 mIU/L and normal free T4.
Euthyroid Sick Syndrome ESS or non thyroidal illness syndrome refers to patients with severe chronic illnesses like starvation, sepsis, end stage renal disease, myocardial infarction and others, in whom a decrease in serum thyroid hormone levels is observed without any identifiable primary thyroid disease. It is considered when free T3< 4 pmol/L and normal TSH.[26]
Severe ESS was definedas free T3< 4 pmol/L, free T4 < 9 and normal TSH.[27,28]

TSH	T4	T3	Interpretation
High	Normal	Normal	(subclinical) hypothyroidism
High	Low	Low or normal	clinical Hypothyroidism
Low	Normal	Normal	(subclinical) hyperthyroidism
Low	High or normal	High or normal	Clinical Hyperthyroidism
Normal	normal	low	Low T3 syndrome

Hypertension is considered if the recorded systolic blood pressure ≥ 140 mmHg and or diastolic blood pressure ≥ 90 mmHg, or if the patient was on current antihypertensive therapy.[29]
Diabetes is defined as the use of insulin or glucose- lowering medication on admission, or a diet for diabetes documented in medical history.[30]
The study protocol was approved by the scientific council of internal medicine, Iraqi Board of Medical specializations, consents were obtained from each patient and control group.

2.5 Statistical analysis.

All data follow normal distribution (Anderson Darling test was used to test the normality); continuous data were presented using mean and standard deviation, while discrete variables were presented using number and their percentages. Histogram used to represent the data, while pie gram used to represent the prevalence, and scatter plot used for representing linear regression module.Student t test (independent 2 samples) was used to assess the statistical significance between means when appropriate. Chi square test (if the table was 2x2 then Fisher exact test used instead) used to analyze discrete variables. Linear regression analysis used to test the correlation between thyroid panel parameters and eGFR, creatinine, duration of both renal failure and time on dialysis and spearman correlation coefficient used to assess the correlation.P. value (2 tailed) was considered to be significant if was below 0.05 (level of significance). All data were analyzed using SPSS (20), and figures were drown using Microsoft Excel.

3. Results.

3.1 Basic patient's characteristics.

As shown in Table 1, total sample of patients was 45, of them 23 (51.1%) were females and 22 (48.9%) were males. The control group consists of 20 normal persons, of them 8 (40%) were females and 12 (60%) were males. There was no statistically significant difference between two groups regarding gender with (P. value = 0.434). Mean age of patients was (50.96± 14.26) years while mean age of controls was 40.25± 11.86 years with statistically significant difference (P. value = 0.003).

Table 1: Demographic variables in patients and control groups.						
Variables		Patients (n= 45)		Control (n= 20)		P. value
		No	%	No	%	
Gender	Female	23	51.1	8	40	0.434
	Male	22	48.9	12	60	
Age		Mean± SD*		Mean± SD		0.003
		50.96±14.26		40.25±11.86		

SD*, Standard deviation

3.2 Laboratory variables in patients and control groups.

As shown in Table 2, the mean duration of time with renal failure was 2.7± 1.76 years and mean duration of time on dialysis was 7.72± 4.04 months. Mean values of PCV, TSP, albumin, BMI and eGFR were all significantly lower in patients compared to normal subjects with (P. value <0.001) and mean values of FBS, urea, creatinine were all significantly higher in patients compared to control with (P. value <0.001).

Table 2: Descriptive data of continuous variables in patients and control groups.			
Variables	Patients (n= 45)	Control (n= 20)	P. value
	Mean± SD	Mean± SD	
Duration of renal failure (yr)	2.70± 1.76	-	-
Time on dialysis (mo)	7.72± 4.04	-	-
Packed cell volume (PCV)	28.60± 4.28	42.35± 4.86	**<0.001**
Fasting blood sugar (FBS, mg/dL)	117.07± 38.40	94.40± 6.98	**<0.001**
Blood Urea (mg/dL)	172.27± 47.90	29.45± 5.39	**<0.001**
Serum Creatinine (mg/dL)	8.58± 2.79	0.83± 0.11	**<0.001**
Total serum protein (TSP, g/L)	62.13± 3.65	71.70± 3.88	**<0.001**
Albumin (g/L)	29.69± 2.07	41.10± 3.51	**<0.001**
Body mass index/ BMI (kg/ m^2)	20.66± 2.35	27.97± 2.69	**<0.001**
eGFR* (mL/min/1.73m^2)	6.91± 3.59	101.50±21.01	**<0.001**

* Estimated glomerular filtration rate

As shown in Table 3, mean value of TSH in patients was 2.65± 1.53 mIU/l while it wasn3.59± 1.48 mIU/l in control group with a statistically significant difference with (p value 0.025). Mean values of both total and free T_3 were lower (1.54± 0.67 and 2.65± 0.92) in patients than healthy participants (1.89± 0.36 and 6.49± 2.25) with a statistically significant difference (p. values 0.009 and <0.001respectively). While there was no statistically significant difference between patients and healthy participants regarding total and free T_4 values (p. values 0.477 and 0.13 respectively).

Table 3: Descriptive data of thyroid function test in patients and control.				
Variables	Patients/ Mean± SD*	Reference range	Control/ Mean± SD	P. value
TSH**(mIU/L)	2.65±1.53	0.25-5.0	3.59±1.48	**0.025**
T_3§(nmol/L)	1.54±0.67	0.92-2.33	1.89±0.36	**0.009**
Free T_3(pmol/L)	2.65±0.92	4.0-8.3	6.49±2.25	**<0.001**
T_4† (nmol/L)	89.78±19.60	60-120	86.74±13.80	0.477
Free T_4 (pmol/L)	14.51±5.94	9.0-20.0	12.61±3.88	0.13

* Standard deviation,**Thyroid stimulating hormone,§Ttiiodothyronine, † Thyroxin

As shown in Fig. 1, 42 (93%) patients out of 45 study groupshowed low free T_3level and 6 (13%) patients showed low free T_4level. It is also shown that 40 (90%) patients showed normal level of TSH, and 4 (9%) showed high TSH. None showed high free T_3, while 8 (18%) patients showed high free T_4.

Figure 1: Distribution of thyroid parameters according to their reference range

3.3 Etiology of CKD in hemodialysis patients.

Table 4 shows that hypertensive renal disease was the most common underlying cause of CKD fond in 17(37.8%) patients, followed by diabetic nephropathy which was present in 16 (35.6%) patients, unidentified cause in 8 (17.8%), obstructive uropathy in 7 (15.6%) and lupus nephritis in 4 (8.9%) patients.

Table 4: Etiology of CKD in hemodialysis patients.

Variables	No	%
Hypertensive renal disease	17	37.8
Diabetic nephropathy	16	35.6
Unidentified	8	17.8
Obstructive uropathy	7	15.6
Lupus nephritis	4	8.9

3.4 Thyroid function test parameters correlation with other variables.

As shown in table 5, eGFR and serum creatinine shows good correlation with total T_3 and free T_3 respectively, and the correlation between serum creatinine with free T_3 was stronger (- 0.378) than the correlation between GFR with total T_3 (-0.316); both of them inversely correlated as shown in figures 2&3.

Table 5: linear correlation between GFR and creatinine and thyroid panel.

Variables	eGFR		Creatinine	
	Correlation coefficient	P value	Correlation coefficient	P value
TSH	-0.107	0.484	0.155	0.308
T_3 total	-0.316	0.035 [SD]	0.261	0.083
T_3 free	0.173	0.257	-0.378	0.011 [SD]
T_4 total	0.202	0.184	-0.257	0.089
T_4 free	0.211	0.164	-0.254	0.092

Pearson correlation was used, p value < 0.05 were significant, SD: significant difference

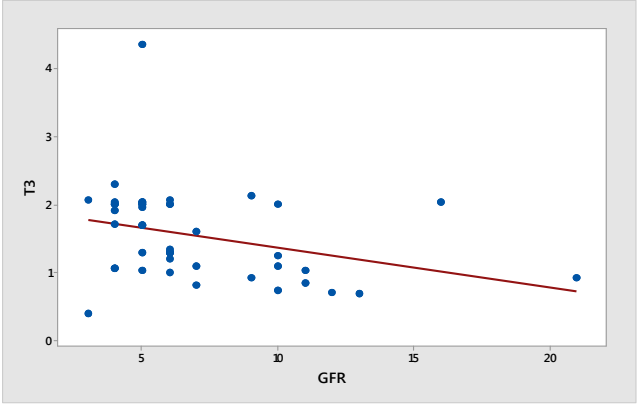

Figure 2: Scatter plot of total T_3 and eGFR showing linear regression line

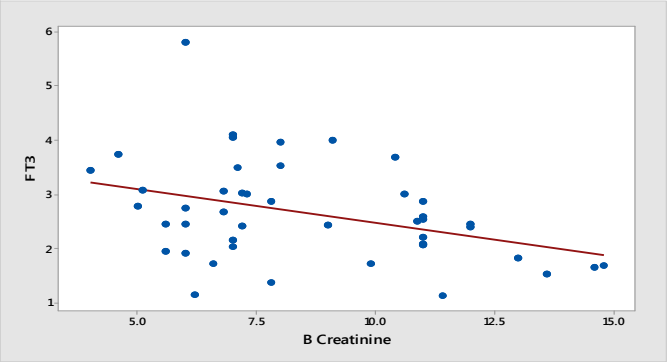

Figure 3: Scatter plot of free T_3 and serum creatinine showing linear regression line

3.5 Thyroid dysfunction and duration of time on dialysis.

As shown in Table 6, patients with duration of time on dialysis more than one year showed lower total T_3 values compared to those less than a year with statistically significant difference (P. value 0.016) while other thyroid parameters didn't show such effect. It is also shown that mean values of B. urea and S. creatinine were significantly lower in those on dialysis more than a year with (P. values 0.021 and 0.017 respectively) and mean value of eGFR was significantly more after one year of dialysis with (P. value 0.05).

Table 6: Descriptive data of continuous variables in subgroups of patients.

Variables	On dialysis < a year Mean± SD	On dialysis ≥ a year Mean± SD	P. value
TSH(mIU/l)	2.72±1.59	2.35±1.30	0.523
T_3(nmol/l)	1.66±0.69	1.07±0.23	**0.016**
Free T_3(pmol/l)	2.59±0.84	2.86±1.24	0.442
T4(nmol/l)	88.69±19.14	94.12±21.96	0.464
Free T4(pmol/l)	15.05±5.86	12.37±6.10	0.231
Blood Urea (mg/dL)	180.42±48.87	139.67±26.02	**0.021**
Serum Creatinine (mg/dL)	9.07±2.91	6.62±0.70	**0.017**
eGFR(mL/min/1.73m^2)	6.39±3.08	9.00±4.82	**0.05**

3.6 Rate of thyroid function disorders in patients (total and subgroups).

In this study, no patient was diagnosed with hypothyroidism or hyperthyroidism. As shown in table 7 and figure 4, Euthyroid Sick Syndrome (ESS) was found in 33(73.3%) of patients compared with 1(5%) of control. Severe ESS was found in7 (15.6%) patients, subclinical hypothyroidism was found only in 4(20%) of control group and only 5 (11.1%) patients were euthyroid. All correlations were statistically significant with (P. value<0.001).

Table 7: Distribution of study sample according to thyroid status

Variables	Patients		Control		P. value
	No	Percent %	No	Percent %	
ESS	33	73.33	1	5	<0.001
Euthyroid	5	11.11	15	75	
Severe ESS	7	15.56	0	0	
Subclinical hypothyroidism	0	0	4	20	
Chi square analysis used					

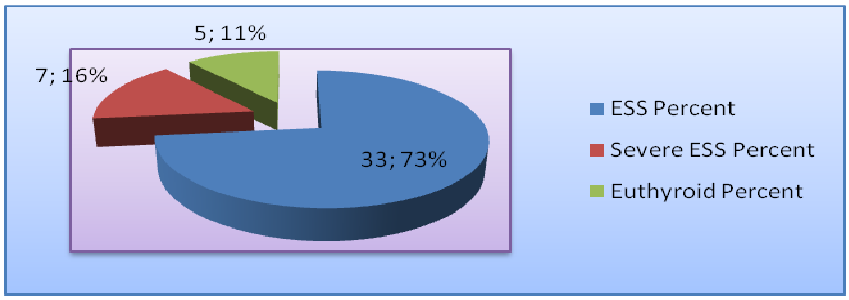

Figure 4: Rate of thyroid function disorders in hemodialysis patients.

3.7 Thyroid parameters in patients according to DM and HTN.

As shown in table 8, there was no statistically significant difference regarding mean value of free T_3 in diabetic and non diabetic patients, the same for HTN, while it was significant between total T_4 and presence of DM with (P. value 0.044).

Table 8: Comparison of mean serum thyroid panel in patients divided according to DM and HTN

Variables		TSH		T_3		Free T_3		T_4		Free T_4	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DM	Negative	2.68	1.31	1.61	.74	2.55	0.99	85.43	17.59	14.06	5.24
	DM	2.59	1.90	1.42	0.51	2.83	0.78	97.66	21.11	15.33	7.15
	P value	0.864		0.35		0.345		***0.044***		0.497	
HTN	Negative	2.64	1.35	1.67	0.72	2.55	0.83	87.56	18.39	13.75	4.89
	HTN	2.66	1.83	1.34	0.53	2.81	1.07	93.43	21.51	15.76	7.35
	P value	0.957		0.116		0.366		0.336		0.276	

Independent t test (2 sample), all p value were 2 tailed
DM: diabetics mellitus, HTN: hypertension

4. Discussion.

We aimed to assess spectrum of thyroid function disorders in CKD stage (5) patients on chronic hemodialysis. The present study identifies thyroid dysfunction as a common disorder in hemodialysis patients. lowT_3 syndrome, as part of ESS or non- thyroidal illness was found in 42 (93.3%) patients.

In addition; both total serum T3 and serum freeT3 concentration in patients on chronic HD were significantly lower (1.54,and 2.65) than control (1.89 and 6.49) with p-value (0.009 and<0.001) respectively .These results confirm earlier observations of several authors that most of patients with chronic renal failure have low level of total T3 level.[31,32,33]

A study by Lo et al. found that the prevalence of hypothyroidism increased with lower levels of GFR (in units of mL/min/1.73 m^2), occurring in 5.4 % of subjects with GFR greater than or equal to 90, 10.9 % with GFR 60–89, 20.4 % with GFR 45–59, 23.0 % with GFR 30–44, and 23.1 % with GFR < 30 ($p < 0.001$ for trend). They reported that 56 % of hypothyroidism cases were subclinical.[34]

In this study, none of the HD patients showed subclinical hypothyroidism while it was found in20% of control group knowing that the prevalence of subclinical hypothyroidism in general population is about 4 to 8.5%.[35] This finding is not in consistent with other studies. Saroj et al found that prevalence of subclinical hypothyroidism in stage 5 was 43.3 %.[36]

Another study in India among (ESRD) patients, found that the prevalence of subclinical hypothyroidism was 24.8 %.[37]

Another study in hemodialysis patients in Nepal found the combined prevalence of subclinical and clinical hypothyroidism in 26.6 % patients.[38]

Association with hyperglycemia.

In our study, although there was no significant low T3 among type 2 diabetic patient compared to non diabetic but there was significant association between T_4 and presence of DM.

In a recent study in Baghdad, (20%) of patients with type 2 DM have abnormal thyroid function tests compared to (3.33%) of control group.[39]

Several other studies revealed higher incidence of thyroid dysfunction in diabetic type 2 patients comparing to general population. A prevalence of 12.3% was reported among Greek diabetic type 2 patients[40] and 16% of Saudi patients with type 2 diabetes were found to have thyroid dysfunction.[41]

In Jordan, a study reported that thyroid dysfunction was present in 12.5% of type 2 diabetic patients. [42]

In Al Wazzan*et al* study, sick euthyroid syndrome constituted 15.7% of those with abnormal thyroid function in diabetic type 2 patients. [43] This can be explained by the fact that in diabetic patients, the nocturnal TSH peak is blunted or abolished, and the TSH response to TRH is impaired in addition to impairment in peripheral conversion of T4 to T3 that normalizes with improvement in glycemic control.

In this study, total T3 shows significant inverse good correlation with eGFR; (- 0.316) with P-value0.0035 as shown in figure 1, in which total T3 and GFR showing linear regression line and figure 2, in which freeT3 and serum creatinine showing linear regression line, free T3 show good correlation with serum creatinine and it was inverse value 0.011.

This can be explained by the fact that since the kidney contributes to the clearance of iodide, plasma iodide retention in CKD favors thyroidal iodide uptake and potentially blocks thyroid hormone production by negative feedback mechanism. In addition, systemic acidosis, time on dialysis, markers of endothelial damage,

and inflammation from HD are associated with low T3 levels. [44]

Finally because this study is cross-sectional, the present analysis is limited in its ability to establish causal or temporal relationships between thyroid dysfunction and kidney disease.

5. Conclusion.

Our study showed that functional thyroid gland disorders are more common among patients on chronic hemodialysis compared with healthy subjects, and reveal their link with time on dialysis. Low T3 syndrome (Euthyroid sick syndrome)is the most frequently thyroid function disorder.

6. Recommendations.

Clinicians, including nephrologists, need to consider the dangers of thyroid disease and its appropriate treatment in conjunction to treating CKD. Future prospective studies are necessary to study the effect of low T3 as a prognostic indicator of mortality and to test the causal implication ofT3 in major clinical outcome in CKD.

References.

1. Mohamedali M, Maddika SR, Vyas A, Iyer A, Cheriyath P. Thyroid Disorders and Chronic Kidney Disease. International Journal of Nephrology, Volume 2014, Article ID 520281, 6 pages.Published 13 April 2014.
2. Mariani LH, Berns JS. The renal manifestations of thyroid disease, J Am Soc Nephrol 2012; 23: 22-26.
3. Singh PA, Bobby Z, Selvaraj N, Vinayagamoorthi R. An evaluation of thyroid hormone status and oxidative stress in undialyzed chronic renal failure patients. Indian J PhysiolPharmacol 2006; 50: 279–284.
4. G. Basu and A. Mohapatra, "Interactions between thyroid disorders and kidney disease," Indian Journal of Endocrinology and Metabolism 2012; 16 (2): 204–213.
5. Chonchol M, Lippi G, Salvagno G, *et al*. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clin J Am Soc Nephrol 2008; 3(5):1296- 1300.
6. Meuwese CL, Dekker FW, Lindholm B, et al. Baseline levels and trimestral variation of triiodothyronine and thyroxin and their association with mortality in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2012;7:131–138.
7. Iglesias P, Díez JJ, "Thyroid dysfunction and kidney disease," European Journal of Endocrinology 2009; 160(4): 503–515.
8. Ozen KP, Asci G, Gungor O, *et al*. Nutritional state alters the association between free triiodothyronine levels and mortality in hemodialysis patients. Am J Nephrol.2011; 33:305–312.
9. Wiederkehr MR, Kalogiros J, Krapf R. Correction of metabolic acidosis improves thyroid and growth hormone axes in hemodialysis patients. Nephrol Dial Transplant 2004; 19:1190.
10.Zoccali C, Tripepi G, Cutrupi S, *et al*. Low triiodothyronine: a new facet of inflammation in end- stage renal disease. J Am Soc Nephrol.2005; 16:2789.
11. Basu G, Mohapatra A. "Interactions between thyroid disorders and kidney disease," Indian Journal of Endocrinology and Metabolism 2012; 16 (2): 204–213.
12. Duntas L, Wolf CF, Keck FS, Rosenthal J. Thyrotropin-releasing hormone: pharmacokinetic and pharmacodynamic properties in chronic renal failure. Clin Nephrol 1992; 38:214.
13. Wheatley T, Clark PM, Clark JD, *et al*. Abnormalities of thyrotrophin (TSH) evening rise and pulsatile release in hemodialysis patients: evidence for hypothalamic-pituitary changes in chronic renal failure. ClinEndocrinol (Oxf) 1989; 31:39.
14.Palmer BF, Henrich WL. Thyroid function in chronic kidney disease.http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?19/17/19741/abstract/20. Last literature review version 19.3: Sep 30, 2011.
15. Rodrigues MC, Santos GM, da Silva CA, Baxter JD, Webb P, Lomri N, Neves FA, Ribeiro RC &Simeoni LA. Thyroid hormone transport is disturbed in erythrocytes from patients with chronic renal failure on hemodialysis. Renal Failure 2004; 26: 461–466.
16. Meuwese CL, Dekker FW, Lindholm B, *et al*. Baseline levels and trimestral variation of triiodothyronine and thyroxine and their association with mortality in maintenance hemodialysis patients. Clin J Am Soc Nephrol 2012; 7:131.
17. Carrero JJ, Qureshi AR, Axelsson J, *et al*. Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. J Intern Med. 2007; 262:690–701.
18. Rhee CM, Alexander EK, Bhan I, *et al*. Hypothyroidism and mortality among dialysis patients. Clin J Am Soc Nephrol. 2013; 8:593–601.
19. Zoccali C, Benedetto F, Mallamaci F, *et al.* Low triiodothyronine and cardiomyopathy in patients with end-stage renal disease. J Hypertension 2006; 24:2039–2046.
20. Meuwese CL, Carrero JJ, Cabezas-Rodriguez I, *et al.*Nonthyroidal illness: a risk factor for coronary calcification and arterial stiffness in patients undergoing peritoneal dialysis? J Intern Med. 2013; 274:584– 593.

21. Tatar E, Kircelli F, Asci G, *et al.*Associations of triiodothyronine levels with carotid atherosclerosis and arterial stiffness in hemodialysis patients. Clin J Am Soc Nephrol. 2011; 6:2240–2246.
22. Medri G, Carella C, Padmanabhan V, *et al*. Pituitary glycoprotein hormones in chronic renal failure: evidence for an uncontrolled alpha-subunit release. J Endocrinol Invest.1993; 16:169.
23. Zoccali C, Mallamaci F. Thyroid Function and Clinical Outcomes in Kidney Failure.Clin J Am Soc Nephrol.2012; 7: 12–14.
24. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA *et al*. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014; 63(5):713-35.
25. Nicholas AB, Nicki RC, Brian RW, John AA, endocrine disease. Strachan MW, Walker BR. Davidson's Principles& Practice of Medicine. Churchill Livingstone, 20th Edition: 746- 753.
26. Stylianos F, Konstantinos S, Elias T*et al*. Low T3 syndrome and long-term mortality in chronic hemodialysis patients. World J Nephrol. 2015; 4(3): 415–422.Published online 2015 Jul 6. doi: 10.5527/wjn.v4.i3.415.
27. SerhatAytug. Euthyroid Sick Syndrome. Medscape http://emedicine.medscape.com/article/118651- overview
28. Leslie J. DeGroot. The non thyroidal illness syndrome. Thyroid Disease Manager. http://www.thyroidmanager.org/chapter/the-non-thyroidal-illness-syndrome/Last Updated: February 1, 2015
29. Dan L. Longo, Dennis L. Kasper, J. Larry Jameson, hypertensive vascular disease. Theodore A. Kotchen. Harrison's principles of internal medicine. Inc./USA: McGraw-Hill Companies, 18th Edition: 2047.
30. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33(Suppl. 1): S62–S69
31. Arif S M. Evaluation of Thyroid Function in Patients with Chronic Kidney Disease. IRAQI J MED SCI, 2011; 9 (2)
32. Vanhorebeek I, Langouche L, Van den Berghe G: Endocrine aspects of acute and prolonged critical illness. Nat ClinPract Endo-crinolMetab.2006; 2:20–31.
33. Amato AA, Santos GM, NevesFde A: Thyroid hormone action in chronic kidney disease. CurrOpinEndocrinol Diabetes Obes.2008; 15:459– 465.
34. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int. 2005;67(3):1047-52.
35. Wilson GR, Curry RW Jr Subclinical thyroid disease. Am Fam Physician. 2005;72(8):1517-24.
36. Saroj K, Rajendra KC, Sharad G, Madhab L, Nirmal B. Thyroid dysfunction and dyslipidemia in chronic kidney disease patients. BMC Endocrine Disorders 2015; 15:65
37. Shantha GPS, Kumar AA, Bhise V, Khanna R, Sivagnanam K, Subramanian KK. Prevalence of subclinical hypothyroidism in patients with end-stage renal disease and the role of serum albumin: a cross-sectional study from South India.Cardiorenal Med. 2011; 1(4):255- 60.
38. Paudel K. Prevalence and clinical characteristics of hypothyroidism in a population undergoing maintenance hemodialysis. J ClinDiagn Res. 2014;8(4):MC01-4.
39. Monthir MS. Thyroid Function Tests of Type 2 Diabetic Patients in Baghdad Governorate (El- Mahmoodiya District). Medical Journal of Babylon 2014; 11 (1)
40. Papazafiropoulou A. Prevalence of thyroid dysfunction among Greek Type 2 diabetic patients attending an outpatient clinic. Journal of Clinical Medicine Research. 2010;2(2):75–78.
41. Akbar DH, Ahmed MM, Al-Mughales J. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics. *ActaDiabetologica.*2006;43(1):14–18.
42. Radaideh ARM, Nusier MK, Amari FL, et al. Thyroid dysfunction in patients with type 2 DM in Jordan. Saudi medical Journal. 2004;25(8):1046–1050.
43. AL-WazzanHT, AlaaD, RafaaA, MedhetK. Prevalence and associated factors of thyroid dysfunction among type 2 diabetic patients, Kuwait. Bull Allex. Med. 2012;46(2).
44. Malyszko J, Malyszko JS, Pawlak K &Mysliwiec M. Thyroid function, endothelium, and inflammation in hemodialyzed patients: possible relations? Journal of Renal Nutrition 2007, 17: 30–37.