

## Evaluation of Thyroid Function in Patients with Chronic Kidney Disease

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### Abstract

- Background** Thyroid function has been extensively evaluated in patients with chronic kidney disease, however the results are variable.
- Objective** The study was designed to investigate the thyroid dysfunction in uremic patients clinically and biochemically.
- Methods** The study was conducted in the department of medicine and dialysis unit in AL-Kadhimiya Teaching Hospital in Baghdad. Three groups were taken sixteen patients with end stage renal disease undergoing regular hemodialysis, 22 patients with chronic renal failure treated conservatively and 21 healthy volunteers with no previous history of thyroid disease and their renal function were normal (control group), serum TT3, TT4 and TSH were estimated in all patients and control group by RIA Kits. The results were tabulated and statistically analyzed using Chisquare and t-test.
- Results** Fifty nine persons included in this study divided into three groups (regular hemodialysis 16, conservative treatment 22 and the control group were 21). Goiter was demonstrated in 12.5% in hemodialysis group, 4.54% of the conservatively treated group. Uremic patients kept on conservative treatment or on regular hemodialysis showed significant reduction of TT3 and TT4 in comparison to the control group, however the level of TSH didn't show significant alterations, and there were no significant deference in TT3 and TT4 between the patients on conservative management and those maintained on regular hemodialysis.
- Conclusions** Low TT3 and TT4 are often observed in clinically euthyroid patients with chronic renal failure. These abnormalities do not appear to change significantly after the institution of regular dialysis, on other hand TSH values in clinically euothyroid patients with chronic renal failure were within the normal range, this normal TSH may indicate functional euthyroid status.
- Key words** Hemodialysis, Chronic renal disease, Triiodothyronin (T3), Thyroxin (T4), Thyroid stimulating hormone (TSH)

### Introduction

The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. It is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology, all levels of the hypothalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion, epidemiologic data suggests that predialysis patients with chronic kidney disease have an increased risk of hypothyroidism; many cases are sub clinical<sup>(1,2)</sup>.

Thyroid function has been extensively evaluated in patients with chronic kidney disease, however the result are variable, an increased incidence of goiter in those patients has been reported in studies conducted in China and Turkey, while other centers such as United States, Canada, Great Britain and Australia found the reverse<sup>(3-5)</sup>.

Primary hyperthyroidism is extremely rare, while the prevalence of hypothyroidism is increased in patients with chronic renal failure<sup>(6-9)</sup>.

Some manifestations of hypothyroidism such as pallor, hypothermia and asthenia may also occur in uremia, the exclusion of diagnosis of hypothyroidism on clinical grounds may be extremely difficult, it's basically based on biochemical tests<sup>(10)</sup>.

Most studies of thyroid hormones in clinically euthyroid patients with varying grades of chronic renal failure showed significant decrease in TT3, TT4 and FT3 levels compared with control<sup>(11-14)</sup>. A low T3 and T4 syndrome is evident when glomerular filtration rate (GFR) is reduced below  $30 \pm 16$  ml/min<sup>(15)</sup>. Usually there is more distinct suppression of T3 than of T4<sup>(16)</sup>. The concentrations of reverse T3 (rT3), the inactive metabolite of T4 in plasma are usually low but normal or even elevated values have been reported by some authors<sup>(16,17)</sup>. Serum T3 in transplanted patients seems to be higher than control group found in some series<sup>(18)</sup>.

Thyroid binding globulin (TBG) concentrations are usually normal in hemodialysis patients and low or normal in patients underwent continuous ambulatory peritoneal dialysis<sup>(19,20)</sup>. TBG levels increased significantly after renal transplantation<sup>(21)</sup>.

Studies of thyroid hormone kinetics revealed normal production rates of thyroid hormone, metabolic clearance rates of the hormone may or may not be increased in patients with end stage renal disease<sup>(22-25)</sup>. Peripheral deiodination of T4 to T3 is impaired<sup>(26)</sup>, this finding is consistent with the more pronounced decrease of T3 than of T4 in progressive renal failure, and instead there is preferential diversion to inactive metabolites<sup>(25)</sup>.

In contrast to other non – thyroidal illness, rT3 production and metabolic clearance rate are normal, and there is increase extra vascular binding of the hormone, resulting in low normal values<sup>(27)</sup>. A lot of the studies confirmed that pituitary-thyroid axis is abnormal in uremic patients depending on the observation of the normal thyroid-stimulating hormone concentration despite low TT3 and TT4<sup>(28)</sup>, and an abnormal response of thyroid stimulating hormone after administration of

exogenous thyrotrophin releasing hormone<sup>(29-31)</sup>.

The changes in the temporal organization TSH release in patient with uremia<sup>(32,33)</sup>, in spite of this there is a study which suggested maintenance of pituitary thyroid axis<sup>(34)</sup>.

## Methods

The study was conducted in the department of medicine and dialysis unit in Al-Kadhimiya Teaching Hospital in Baghdad. Thirty-eight patients with no previous history of thyroid dysfunction and with varying grades of chronic renal failure were included in this study.

Twenty-two patients were on conservative treatment. Remaining sixteen patients who also had severed renal failure were on regular hemodialysis treatment (RDT). Twenty healthy volunteers with normal renal function and no previous history of thyroid dysfunction were included in this study as a control group.

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

We emphasized on the presence of the following points in the history:

- A.** A family history of goiter or altered thyroid function.
- B.** A personal and family history of other organ-specific autoimmune diseases particularly of insulin-dependent diabetes, pernicious anemia, vitiligo, and myasthenia gravis.
- C.** History of intake of iodine-containing medications, such as amiodarone, lithium carbonate.
- D.** History of thyroid surgery or radioactive iodine intake.

While physical examination focused on the presence of:

1. Goiter±bruit.
2. Eye signs (exophthalmos, lid retraction..... etc).
3. Pretibial myxedema.
4. 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 triiodothyronine (TT3) and serum total thyroxin (TT4), serum thyrotrophin (TSH), and were performed by (T3 [1251] RIA kit REF: RK-6CTI), (T4 [1251] RIA kit REF: RK-5 CTI), (Turbo TSH [1251] IRMA kit REF: RK-ICTI) respectively; these systems provide direct quantitative in vitro administration of L-3,5,3- triiodothyronine (T3), thyroxin (T4) and (TSH) human thyroid stimulating hormone in human serum. Patients who were on regular hemodialysis, sample of blood were taken before starting hemodialysis sessions to avoid artificial results caused by heparin.

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 and the sex of the patients and the control group and duration of renal failure, type of dialysis and associated diseases for the patients, and result of basic laboratory investigations which include hemoglobin level, packed cell volume, blood urea, serum creatinin were integrated in this study

Results of clinical and hormonal assessment of thyroid dysfunction obtained in patients with chronic renal failure were compared with those of the control group by statistical analysis using Chi-square test and t-test,  $p$  value < 0.005 considered significant

## Results

The total population included (59) patients, (16) On regular haemodialysis and (22) on conservative treatment involving peritoneal dialysis and (21) healthy volunteers as control group.

There were (38) men and (21) women, the mean age was (40) years (range 21-65 years).

All those on haemodialysis were hypertensive and one has diabetes mellitus while those on conservative treatment (27.25%) were diabetes and about (77.27%) were hypertensive. Age, sex distribution and other parameters such as: associated diseases (hypertension and diabetes mellitus) and duration of renal failure for the patients and control groups are displayed in table 1.

The result of basic laboratory investigations for the patients and control groups are shown in table 2, both groups of patients showed anemia with more or less similar levels of PCV in contrast with those from the control group who have PCV level within normal range which obviously caused by uremia, on the other hand there was mild improvement in renal function tests among H.D group in comparison with the conservatively treated group.

Regarding clinical assessment of thyroid dysfunction for the patients and the control group (Table 3):

- A. No clinical evidence of possible thyroid dysfunction was detected in about (81.25%) of the hemodialysis group, (81.82%) of the conservative treated group and (85.72%) of the control group.
- B. The presence of goiter was demonstrated in (12.5%) of the hemodialysis group, (4.54%) of the conservative treated group and it was not demonstrated in the control group.
- C. Family history of insulin dependent diabetes mellitus was seen in (6.25%) of the hemodialysis group, (9.09%) of the conservatively treated group and (9.52%) of the control group.
- D. A family history of goiter or altered thyroid function was found in (4.54%) of the conservatively treated group and (4.76%) of the control group and no such history was noticed among the hemodialysis group.

All patients on conservative treatment and on regular hemodialysis showed significant reduction in their TT3 and TT4 in comparison with those in control subject (Tables 4 and 5). However TSH level did not show significant alterations (Table 6).

There were no significant differences in TT3 and TT4 between the patients on conservative management and those on hemodialysis, it was found that (68.75%) and (62.25%) of the H.D. patients have TT3 and TT4 levels below normal range respectively, while (54.55%) and

(72.72%) of the conservatively treated group have TT3 and TT4 levels below normal range respectively as shown in Table 4 and Table 5. The mean values of TT3, TT4 and TSH were illustrated in Table 6.

**Table 1. The demographic features of uremic and control groups**

Parameters		Hemodialysis group No. 16	Conservative group No. 22	Control group No. 21
Age range (years)		21-60	24-65	26-50
Age mean		36.2	42.6	39.5
Sex	Male	9 (56.25%)	12 (54.5%)	17 (80.95%)
	Female	7 (43.75%)	10 (45.5%)	4 (19.05%)
Hypertension	Yes	16 (100%)	17 (77.2%)	2 (9.5%)
	No	0	5 (22.72%)	19 (90.5%)
Diabetes Mellitus	Yes	0	6 (27.27%)	0
	No	16 (100%)	16 (72.72%)	21(100%)
D.O.U range		(1-3.5) years	(0.34-3) years	0
D.O.U mean		2.6 years	1.2 years	0

D.O.U = Duration of uremia,

**Table 2. The results of the laboratory investigations for the patients and control groups**

Investigations		HD patients	Patients on conservative treatment	Control groups	p value 1	p value 2	Normal values
PCV	Male	31.4±2.1	29.6±2.4	47±3.6	< 0.05	< 0.05	40-54
	Female	30.6±2.9	31.7±2.7	41.4±2.9	< 0.05	< 0.05	37-47
Blood urea mmol/L		31.2±5.7	38.6±6.1	3.5±2.3	< 0.05	< 0.05	2.5-6
Serum creatinine µmmol/L		467±86	531±93	86±30	< 0.05	< 0.05	55-120

PCV = Packed cell volume, HD = Hemodialysis

**Table 3. The patients and control groups distributed according to the presence of clinical evidence of possible thyroid dysfunction by history taking and physical examination**

Groups	Hemodialysis group	Conservatively treated group	Control group
A	0	1 (4.54)	1 (4.76)
B	1 (6.25)	2 (9.09)	2 (9.52)
C	0	0	0
D	0	0	0
E	2 (12.5)	1 (4.54)	0
F	0	0	0
G	0	0	0
H	0	0	0
Total	3 (18.75)	4 (18.18)	3 (14.28)

A = Family history of goiter or altered thyroid function, B =A personal or family history of other organ specific autoimmune disease, C = History of intake of iodine- containing medications, D = History of thyroid surgery or radioactive iodine intake, E = Goiter± bruit, F = Eye signs, G = peritibial myxedema, H = delayed reflexes

**Table 4. Number and percentage of uremic patients and control groups distributed according to the (TT3) level**

TT3 level (nmol/L)	Hemodialysis group	Conservatively treated group	Control group
TT3 above normal (> 3.3)	0	0	0
TT3 upper normal (1-2.9)	0	0	2 (9.5%)
TT3 mid normal (1.7-2.49)	0	1 (4.55%)	18 (85.75%)*
TT3 lower normal (1-1.69)	5 (31.25%)*	1 (4.55%)	1 (4.75%)
TT3 below normal (<1)	11 (68.75%)	12 (54.55%)	0

\*= statistically significant *p* value < 0.05 using chi- square test

**Table 5. Number and percentage of the patients and control group according to the (TT4) level**

TT4 level (nmol/L)	Hemodialysis group	Conservatively treated group	Control group
TT4 above normal (0-150)	0	0	0
TT4 upper normal (125-155)	0	0	1 (4.75%)
TT4 mid normal (95-124.9)	0	1 (4.54%)	19 (90.5%)*
TT4 lower normal (65-94.9)	6 (37.75%)	5 (22.72%)	1 (4.75%)
TT4 below normal (<65)	10 (62.25%)	16 (72.72%)*	0

\*= statistically significant *p* value < 0.05 using chi- square test

**Table 6. TT3, TT4 and TSH mean values for the patients and control groups**

Hormones (nmol/L)	Hemodialysis patients	Conservatively treated group	Control group	<i>p</i> value 1	<i>p</i> value 2	Normal values
TT3	0.69± 0.26	0.78±0.21	2.1±0.25	< 0.05	< 0.05	1.0-3.3
TT4	48±13	40±11	110±22	< 0.05	< 0.05	65-155
TSH	2.55±0.37	2.23±0.40	2.30±0.45	> 0.05	> 0.05	0.3-3.75

### Discussion

There is no significant difference between uremic patients, whether they were kept on hemodialysis or conservative treatment compared with control group in regard to the presence of possible thyroid dysfunction depending on clinical criteria employed in this study apart from the presence of goiter in 12.5% of the hemodialysis group and 4.54% of the conservatively treated group as compared to the absence of such findings among the control group.

These results comply with those found in United States, Canada, Great Britain and Austria which found no significant increase in the incidence of goiter among uremic patients in comparison with general populations, but contradict with the results obtained in republic

of China and Turkey which showed significant increase in the incidence of goiter among the uremic patients <sup>(3-5)</sup>, this deference in results might be attributed to the geographical variation in the incidence of thyroid dysfunction, method used in detection of goiter and the size of sample under study.

There is significant reduction in TT3 and TT4 levels in patients with uremia regardless the mode of therapy in comparison with those of control group , this findings was similar to most of the results of investigators who have studied thyroid hormones level in clinically euthyroid patients with varying grades of chronic renal failure <sup>(11-14)</sup> this reduction in thyroid hormones may be due to the effect of chronic renal failure on the thyroid hormones which include altered peripheral metabolism

like impairment of peripheral deiodination of T4 which is the main source of T3 resulting in low TT3, possible lowering of thyroxin-binding globulin and possible decrease in the excretion of thyroxin binding to thyroid binding proteins both lead to low TT4 ,on other hand the result were different from those of Lim et al<sup>(26)</sup>, Ramirez et al<sup>(34)</sup>

In this study it was found that TSH levels didn't show significant alterations between the uremic patients and the control group and they were within the normal range. This result was similar to the most of studies that focused on thyroid function in end stage renal disease<sup>(11-14)</sup>. The normal TSH level observed in this study may reflect the biochemical euthyroid state of the patients which was also noticed by clinical assessment in this study or maybe due to multiple defect in all levels of the hypothalamic-pituitary-thyroidal peripheral axis in uremic patients which were reported in many previous studies abroad<sup>(4,28,29,30, 31,32, 33,35)</sup>.

It is found that significant deference in TT3 and TT4 between the patients on conservative management and those on hemodialysis these findings are similar to the study done by Pagliacci et al<sup>(19)</sup> and differ from Verger et al<sup>(36)</sup> who noticed that slight or no decrease of thyroid hormone in patients with peritoneal dialysis in contrast to hemodialysed patients, this variation with current study might be due to the different definition of conservative therapy (in this study conservative therapy refers to dietary and pharmacological treatment plus peritoneal dialysis as required) while that of the studies done abroad, conservative therapy comprises mainly continuous ambulatory peritoneal dialysis plus the dietary and pharmacological intervention.

In conclusion the abnormalities in thyroid function tests, including low TT3 and TT4 values are often observed in clinically euthyroid patients with chronic renal failure, these abnormalities do not appear to change significantly after the institution of regular dialysis.

On the other hand TSH values in clinically euthyroid patients with chronic renal failure were within the normal range, this normal TSH may indicate functional euthyroid status.

Its recommend that further studies concentrating on improving clinical and biochemical criteria to diagnose thyroid dysfunction in uremic patients are needed.

It is also important to answer the question of what is the effect of thyroxin replacement in uremic patients and diagnosed as to have hypothyroidism.

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