



# STUDY OF THYROID DISTURBANCE IN DIABETIC AND NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS

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## ABSTRACT

**Objective:** study the prevalence of thyroid disturbance in diabetic chronic kidney disease (CKD) patients and non-diabetic CKD patients.

**Background:** CKD has been known to affect the pituitary-thyroid axis and the peripheral metabolism of thyroid hormones. Hyperthyroidism and hypothyroidism have been associated with insulin resistance which has been reported to be the major cause of impaired glucose metabolism in type 2 diabetes mellitus (T2DM).

**Methods:** This study included (120) CKD patients aged from 25 years to 70 years from Menofia university hospitals during the period from May 2015 to October 2015. They were classified into two groups: (I) (64 patients) (Diabetic group), (II) (56 patients) (Non-diabetic group). Each group was subdivided into 2 subgroups (A,B) according to creatinine clearance (CrCl): (A) (CrCl>45ml/min), (B) (CrCl<45ml/min). Members of the study were subjected to thorough history taking, complete physical examination and to kidney function testing (serum creatinine (Scr), blood urea nitrogen (BUN)), hemoglobin A1c (HbA1c), thyroid function tests (TSH, free T3, free T4), thyroglobulin, serum albumin (SA).

**Results:** The mean age in diabetic patients (group I) was 53.7 years while in non-diabetic patients (group II) was 46 years. The mean TSH for subgroup IA was 5.4  $\mu$ U/ml while subgroup IB was 1.4  $\mu$ U/ml and for subgroup IIA was 1.6  $\mu$ U/ml while for subgroup IIB was 2.1  $\mu$ U/ml. There was highly significant difference between subgroup IA and IB (p value=<0.001) and between subgroup IA and IIA (p value=<0.001). There was no significant difference between subgroup IIA and IIB (p value=0.658) and between subgroup IB and IIB (p value=0.467).

**Conclusion:** This study shows that thyroid disturbance is more common in diabetic CKD patients than non-diabetic CKD patients and that hypothyroidism is more common in diabetic patients with early CKD stages than late CKD stages.

## Indexing terms/Keywords

Thyroid disturbance, chronic kidney disease (CKD), diabetic nephropathy

## Academic Discipline And Sub-Disciplines

Endocrinology, Nephrology.

## 1. INTRODUCTION

Chronic kidney disease (CKD) has been known to affect the pituitary-thyroid axis and the peripheral metabolism of thyroid hormones. Low triiodothyronine (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).

Thyroid hormones influence renal development, kidney structure, renal hemodynamics, glomerular filtration rate (GFR), the function of many transport systems along the nephrons, and sodium and water homeostasis. These effects of thyroid hormone are in part due to direct renal actions and in part are mediated by cardiovascular and systemic hemodynamic effects that influence kidney function. As a consequence, both hypothyroidism and hyperthyroidism associate with clinically important alternations in kidney function and have relevance to its assessment. Disorders of thyroid function have also been linked to development of immune-mediated glomerular injury, and alternations in thyroid hormones and thyroid hormone testing in patients with kidney disease (2).

Hyperthyroidism and hypothyroidism have been associated with insulin resistance which has been reported to be the major cause of impaired glucose metabolism in type 2 diabetes mellitus (T2DM) (3).

Diseases of the kidney are a common finding in people with diabetes mellitus (DM). A variety of forms of kidney disease can be seen, including diabetic nephropathy, ischemic damage related to vascular disease and hypertension, as well as other renal diseases that are unrelated to DM (4).

## 2. SUBJECTS AND METHODS

Our study included 120 patients aged from 25 years to 70 years from Menoufia University Hospitals (all were chronic kidney disease patients).

The patients were classified into two groups: Group I: This group included 64 diabetic patients. Group II: This group included 56 non-diabetic. Each group was subdivided into two subgroups according to their creatinine clearance (CrCl): Subgroup IA: This subgroup included 32 diabetic patients with CrCl> 45 ml/min/1.73m<sup>2</sup>. Subgroup IB: This subgroup included 32 diabetic patients with CrCl< 45 ml/min/1.73m<sup>2</sup>. Subgroup IIA: This subgroup included 24 non-diabetic patients



with  $\text{CrCl} > 45 \text{ ml/min/1.73m}^2$ . Subgroup IIB: This subgroup included 32 non-diabetic patients with  $\text{CrCl} < 45 \text{ ml/min/1.73m}^2$ .

## 2.1. Inclusion Criteria

Patients who had clinical diagnosis and laboratory findings of chronic kidney disease for more than three months evidenced by increased serum creatinine above normal level and/or decreased eGFR (estimated by MDRD equation).

## 2.2. Exclusion Criteria

ESRD patients on regular HD.

## 2.3. All Studied Patients Were Subjected To

### 2.3.1. Evaluation of Patients

Thorough history was taken with special emphasis on symptoms of hypothyroidism and its duration and symptoms of hyperthyroidism and its duration. Complete physical examination with special emphasis on signs of hypothyroidism and its duration and signs of hyperthyroidism and its duration.

### 2.3.2. Laboratory Investigations

All groups were subjected to renal function tests (serum creatinine (Scr), blood urea nitrogen (BUN)), creatinine clearance (CrCl), hemoglobin A1c (HbA1c), serum thyroid function tests (TSH, free T3 and free T4), serum thyroglobulin level (Tg), serum Albumin (SA).

Thyroid profile was measured directly in the serum samples by the DS-EIA-THYROID-TSH kit which is intended for quantitative determination of TSH, free T3, free T4 concentrations in human serum by a microplate enzyme immunoassay. Enzyme immunoassay was also used for the quantitative determination of Tg in human serum.

## 2.4. Statistical Methodology

Statistical presentation and analysis of the present study was conducted with SPSS V.20. Data was expressed into two phases:

### 2.4.1. Descriptive

Mean value and Standard Deviation [SD]: for quantitative data, frequency and percentage for qualitative data

### 2.4.2. Analytic

- **T test** : for comparison of two independent quantitative variables normally distributed.
- **U test (Mann whittney test)**: for comparison of two independent quantitative variables not normally distributed.
- **X<sup>2</sup> (Chi 2)**: for comparison between two or more independent qualitative variables normally distributed.
- **Fisher exact test** : for comparison between two or more independent qualitative variables not normally distributed.
- **Person Correlation Coefficient [r]**: for comparison between two dependent quantitative not normally distributed variable.
- Accuracy: the ratio of the true positive and true negative on all patients.
- ❖ P value > 0.05 was considered statistically non significant.
- ❖ P value < 0.05 was considered statistically significant.
- ❖ P value < 0.001 was considered statistically highly significant.

### 3. RESULTS:

In this work, 120 persons were included from Menofia university hospitals in the period from May 2015 to October 2015.

**Table 1: Demographic characteristics of the studied groups.**

	Diabetics		Non diabetics		$\chi^2$	P value
	N(64)	%	N(56)	%		
<i>Age(years)</i>					3.4	0.001 HS
Mean $\pm$ SD	53.7 $\pm$ 7.4		46.7 $\pm$ 14.6			
<i>Sex</i>					18.8	<0.001 HS
Male	48	75	20	35.7		
Female	16	25	36	64.3		
<i>Smoking</i>					17.1	<0.001 HS
Non smoker	32	50	48	85.7		
Smoker	32	50	8	14.3		

$\chi^2$ : Chi square test

P value:

NS= nonsignificant (P-value > 0.05), S = significant (P-value  $\leq$  0.05), HS= highly significant (P-value  $\leq$  0.001).

Age of the studied groups (see Table 1): The mean age in diabetic patients (group I) was 53.7 years while in non-diabetic patients (group II) was 46 years. These results show that there was highly significant difference between the two studied groups (P value=0.001). Sex of the studied groups: diabetic patients (group I) included 48 males (75%) and 16 females (25%), non-diabetic patients (group II) included 20 males (35.7%) and 36 females (64.3%). These results show that there was highly significant difference between the two studied groups (P value=<0.001). Smoking among the studied groups: diabetic patients (group I) included 32 non-smoker (50%) and 32 smoker (50%), non-diabetic patients (group II) included 48 non-smoker (85.7%) and 8 smoker (14.3%). These results show that there was highly significant difference between the two studied groups (P value=<0.001).

**Table 2: Laboratory data of the studied groups:**

	Diabetics N(64)	Non diabetics N(56)	U test	P value
CrCl (ml/min/1.73m <sup>2</sup> )	37.7 $\pm$ 23.6	42.3 $\pm$ 25.4	1.027	0.306 NS
HbA1c (%)	7.2 $\pm$ 1.9	5.2 $\pm$ 0.6	7.6*	<0.001 HS
SA (g/dl)	3.4 $\pm$ 0.4	3.6 $\pm$ 0.3	2.6*	0.009 S
ACR (mcg/mg)	2311.1 $\pm$ 172.1	1200.3 $\pm$ 939.8	2.3	0.024 S
Scr (mg/dl)	3.4 $\pm$ 2.3	2.6 $\pm$ 1.8	1.99	0.049 S
BUN (mg/dl)	41.4 $\pm$ 16.8	36 $\pm$ 21.2	1.5	0.125 NS
Ca (mg/dl)	8.2 $\pm$ 0.5	8.4 $\pm$ 0.8	1.2*	0.227 NS
Po <sub>4</sub> (mg/dl)	4.6 $\pm$ 0.6	4.2 $\pm$ 0.6	3.2*	0.002 S

\*t test U test: Mann whitney test CrCl: creatinine clearance HbA1c: hemoglobin A1c SA: serum albumin  
ACR: albumin/creatinine ratio Scr: serum creatinine BUN: blood urea nitrogen Ca: calcium PO<sub>4</sub>: phosphorus

CrCl of the studied groups (see Table 2): the mean Cr Cl for the diabetic patients (group I) was 37.7 ml/min/1.73m<sup>2</sup> while for the non-diabetic patients (group II) was 42.3 ml/min/1.73m<sup>2</sup>. These results shows that there was no significant difference between the two studied groups (P value=0.306). HbA1c of the studied groups: the mean HbA1c for the diabetic patients (group I) was 7.2 % while for the non-diabetic patients (group II) was 5.2 %. These results shows that there was highly significant difference between the two studied groups (P value=<0.001).

SA of the studied groups (see Table 2): the mean serum albumin for the diabetic patients (group I) was 3.4 g/dl while for the non diabetic patients (group II) was 3.6 g/dl. These results shows that there was significant difference between the two studied groups (P value=0.009). ACR of the studied groups: the mean ACR for the diabetic patients (group I) was 2311.1 mcg/mg while for the non diabetic patients (group II) was 1200.3 mcg/mg. These results show that there was significant difference between the two studied groups (P value=0.024).

Scr of the studied groups (see Table 2): the mean Scr for the diabetic patients (group I) was 3.4mg/dl while for the non diabetic patients (group II) was 2.6 mg/dl. These results show that there was significant difference between the two



studied groups (P value=0.049). BUN of the studied groups: the mean BUN for the diabetic patients (group I) was 41.4 mg/dl while for the non-diabetic patients (group II) was 36 mg/dl. These results show that there was no significant difference between the two studied groups (P value=0.125).

Ca of the studied groups (see Table 2): the mean Ca for the diabetic patients (group I) was 8.2 mg/dl while for the non-diabetic patients (group II) was 8.4 mg/dl. These results show that there was no significant difference between the two studied groups (P value=0.227). PO<sub>4</sub> of the studied groups: the mean PO<sub>4</sub> for the diabetic patients (group I) was 4.6 mg/dl while for the non-diabetic patients (group II) was 4.2 mg/dl. These results show that there was significant difference between the two studied groups (P value=0.002).

**Table 3: Laboratory data of the studied subgroups:**

	Subgroup IA N(32)2	Subgroup IB N(32)4	Subgroup IIA N(24)1	Subgroup IIB N(32)3	K test	P value	posthocLSD
CrCl (ml/min/ 1.73 m2)	59.6±8.2	15.8±8.3	67.8±14.2	23.1±10.6	183.3	<0.001	p <sup>a</sup> :<0.001 p <sup>b</sup> :<0.001 p <sup>c</sup> :0.004 p <sup>d</sup> :0.005
HbA1c %	7.7±2.2	6.7±1.3	5.5±0.7	5.01±0.4	23.9*	<0.001	p <sup>a</sup> :0.004 p <sup>b</sup> :0.251 p <sup>c</sup> :<0.001 p <sup>d</sup> :<0.001
SA (g/dl)	3.4±0.5	3.4±0.3	3.5±0.2	3.6±0.4	2.9	0.04	p <sup>a</sup> :0.892 p <sup>b</sup> :0.211 p <sup>c</sup> :0.26 p <sup>d</sup> :0.016
ACR (mcg/mg)	1706.9 ± 759.9	2915.3 ± 35.3	140.6 ± 34.1	1995.1 ± 267.4	5.4	0.002	p <sup>a</sup> :0.06 p <sup>b</sup> :0.008 p <sup>c</sup> :0.025 p <sup>d</sup> :0.153
Scr (mg/dl)	1.5±0.3	5.2±1.9	1.2±0.2	3.6±1.8	55.2	<0.001	p <sup>a</sup> :<0.001 p <sup>b</sup> :<0.001 p <sup>c</sup> :0.522 p <sup>d</sup> :<0.001
BUN (mg/dl)	8.52±8.9	54.2±12.3	22.3±8.2	46.3 ± 22.2	31	<0.001	p <sup>a</sup> :<0.001 p <sup>b</sup> :<0.001 p <sup>c</sup> :0.116 p <sup>d</sup> :0.028
Ca (mg/dl)	8.3±0.6	8.2±0.4	8.9±0.1	7.9±0.9	13.9	<0.001	p <sup>a</sup> :<0.001 p <sup>b</sup> :<0.001 p <sup>c</sup> :<0.001 p <sup>d</sup> :0.087
PH (mg/dl)	4.2±0.6	4.9±0.5	3.9±0.3	4.4±0.6	20.9	<0.001	p <sup>a</sup> :<0.001 p <sup>b</sup> :<0.001 p <sup>c</sup> :0.037 p <sup>d</sup> :<0.001

p<sup>a</sup>: Subgroup IA and Subgroup IB.

p<sup>b</sup>: Subgroup IIA and Subgroup IIB.





p<sup>c</sup>: Subgroup IA and Subgroup IIA.

p<sup>d</sup>: Subgroup IB and Subgroup IIB.

K test: Fisher exact test

CrCl of the studied subgroups (see Table 3): the mean CrCl for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 59.6 ml/min/1.73m<sup>2</sup> while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 15.8 ml/min/1.73m<sup>2</sup> and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 67.8 ml/min/1.73m<sup>2</sup> while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 23.1 ml/min/1.73m<sup>2</sup>. These results show that: there was highly significant difference between subgroup IA and IB (p value=<0.001) and between subgroup IIA and IIB (p value=<0.001) while there was significant difference between subgroup IA and IIA (p value=0.004) and between subgroup IB and IIB (p value=0.005).

HbA1c of the studied subgroups (see Table 3): the mean HbA1c for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 7.7 % while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 6.7 % and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 5.5 % while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 5.01 %. These results show that: there was significant difference between subgroup IA and IB (p value=0.004) while there was no significant difference between subgroup IIA and IIB (p value=0.251) and there was highly significant difference between subgroup IA and IIA (p value=<0.001) and between subgroup IB and IIB (p value=<0.001).

SA of the studied subgroups (see Table 3): the mean SA for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 3.4 g/dl and for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was also 3.4 g/dl and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 3.5 g/dl while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 3.6 g/dl. These results show that: there was no significant difference between subgroup IA and IB (p value=0.892), between subgroup IIA and IIB (p value=0.211) and between subgroup IA and IIA (p value=0.26) while there was significant difference between subgroup IB and IIB (p value=0.016).

ACR of the studied subgroups (see Table 3): the mean ACR for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 1706.9 mcg/mg while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 2915.3 mcg/mg and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 140.6 mcg/mg while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 1995.1 mcg/mg. These results show that: there was no significant difference between subgroup IA and IB (p value=0.06) and between subgroup IB and IIB (p value=0.153) while there was significant difference between subgroup IIA and IIB (p value=0.008) and between subgroup IA and IIA (p value=0.025).

Scr of the studied subgroups (see Table 3): the mean Scr for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 1.5 mg/dl while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 5.2 mg/dl and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 1.2 mg/dl while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 3.6 mg/dl. These results show that: there was highly significant difference between subgroup IA and IB (p value=<0.001), between subgroup IIA and IIB (p value=<0.001) and between subgroup IB and IIB (p value=<0.001) while there was no significant difference between subgroup IA and IIA (p value=0.522).

BUN of the studied subgroups (see Table 3): the mean BUN for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 8.52 mg/dl while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 54.2 mg/dl and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 22.3 mg/dl while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 46.3 mg/dl. These results show that: there was highly significant difference between subgroup IA and IB (p value=<0.001) and between subgroup IIA and IIB (p value=<0.001). There was significant difference between subgroup IB and IIB (p value=0.028) while there was no significant difference between subgroup IA and IIA (p value=0.116).

Ca of the studied subgroups (see Table 3): the mean Ca for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 8.3 mg/dl while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 8.2 mg/dl and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 8.9 mg/dl while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 7.9 mg/dl. These results show that: There was highly significant difference between subgroup IA and IB (p value=<0.001), between subgroup IIA and IIB (p value=<0.001) and between subgroup IA and IIA (p value=<0.001) while there was no significant difference between subgroup IB and IIB (p value=0.087).

PO<sub>4</sub> of the studied subgroups (see Table 3): the mean PO<sub>4</sub> for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 4.2 mg/dl while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 4.9 mg/dl and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 3.9 mg/dl while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 4.4 mg/dl. These results show that: there was highly significant difference between subgroup IA and IB (p value=<0.001), between subgroup IIA and IIB (p value=<0.001) and between subgroup IB and IIB (p value=<0.001) and there was significant difference between subgroup IA and IIA (p value=0.037).



**Table 4: Thyroid profile among the studied subgroups.**

	Subgroup IA N=32	subgroup IB N=32	subgroup IIA N=24	subgroup IIB N=32	K test	P value	Posthoc LSD
TSH (mIU/ml)	5.4±3.6	1.4±1.1	1.6±1.5	2.1±1.3	8.3	<0.001	p <sup>a</sup> :<0.001 p <sup>b</sup> :0.658 p <sup>c</sup> :<0.001 p <sup>d</sup> :0.467
Free T3 (pg/ml)	2.7±1.8	3.7±1.9	3.6±1.3	3.2±1.2	2.4	0.07	p <sup>a</sup> :0.015 p <sup>b</sup> :0.335 p <sup>c</sup> :0.047 p <sup>d</sup> :0.18
Free T4 (pmol/L)	13.5±8.5	17.1±8.9	16.5±6.7	16.4±4.9	1.5	0.228	p <sup>a</sup> :0.056 p <sup>b</sup> :0.958 p <sup>c</sup> :0.14 p <sup>d</sup> :0.697
Tg (ng/ml)	11.5±9.4	10.6±7.4±18.9	20.2±19.5	23.8±18.4	6.5	<0.001	p <sup>a</sup> :0.804 p <sup>b</sup> :0.347 p <sup>c</sup> :0.026 p <sup>d</sup> :<0.001

TSH: thyroid stimulating hormone T3: triiodothyronine T4: tetraiodothyronine Tg: thyroglobulin

As regard thyroid profile among the studied subgroups (see Table 4): the mean TSH for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 5.4 µIU/ml while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 1.4 µIU/ml and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 1.6 µIU/ml while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 2.1 µIU/ml. These results show that: there was highly significant difference between subgroup IA and IB (p value=<0.001) and between subgroup IA and IIA (p value=<0.001) while there was no significant difference between subgroup IIA and IIB (p value=0.658) and between subgroup IB and IIB (p value=0.467).

Free T3 of the studied subgroups (see Table 4): the mean free T3 for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 2.7 pg/ml while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 3.7 pg/ml and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 3.6 pg/ml while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 3.2 pg/ml. These results show that: There was significant difference between subgroup IA and IB (p value=0.015) and between subgroup IA and IIA (p value=0.047) while there was no significant difference between subgroup IIA and IIB (p value=0.658) and between subgroup IB and IIB (p value=0.18).

Free T4 of the studied subgroups (see Table 4): the mean free T4 for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 13.5 pmol/L while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 17.1 pmol/L and the mean free T4 for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 16.5 pmol/L while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 16.4 pmol/L. These results show that: there was no significant difference between subgroup IA and IB (p value=0.056), between subgroup IIA and IIB (p value=0.958), between subgroup IA and IIA (p value=0.14) and between subgroup IB and IIB (p value=0.697).

Tg of the studied subgroups (see Table 4): the mean Tg level for the diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IA) was 11.5 ng/ml while for diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IB) was 10.6 ng/ml and for the non-diabetic patients with GFR >45 ml/min/1.73m<sup>2</sup> (subgroup IIA) was 20.2 ng/ml while for non-diabetic patients with GFR<45 ml/min/1.73m<sup>2</sup> (subgroup IIB) was 23.8 ng/ml. These results show that: there was no significant difference between subgroup IA and IB (p value=0.804) and between subgroup IIA and IIB (p value=0.347) while there was significant difference between subgroup IA and IIA (p value=0.026) and highly significant difference between subgroup IB and IIB (p value=<0.001).

#### 4. DISCUSSION



Thyroid hormones regulate growth, development, differentiation and metabolism of virtually all tissues of vertebrates. The kidney and cardiovascular system are some of the most important targets of the thyroid hormones (5).

Kidney and thyroid function are interrelated through several mechanisms. Thus, thyroid hormones are necessary for the maintenance of electrolyte and water homeostasis (directly by affecting the glomerular /tubular kidney function and the structure of the kidney itself and indirectly by affecting the cardiovascular system and the renal blood flow) (2).

The kidney normally plays an important role in the metabolism, degradation and excretion of thyroid hormones. CKD affects thyroid function in many ways, including low circulating thyroid hormone levels, altered peripheral hormone metabolism, insufficient binding to carrier proteins, reduced tissue thyroid hormone content and altered iodine storage in the thyroid gland (6).

On the other hand, DM is an important health problem affecting major populations worldwide. The influence of endocrine and non-endocrine organs other than the pancreas on DM documented. Occasionally, other endocrine disorders such as abnormal thyroid hormone levels are found in DM (7).

In one study population consisted of 200 subjects divided into two groups: diabetics and non-diabetics. The level of TSH was significantly decreased whereas the levels of T4 and free T4 were significantly increased in diabetic patients compared to control subjects. However, the T3 and free T3 levels did not differ significantly between groups (8).

In another study by Taksali et al. they found that 31% of the diabetic group had hypothyroidism while 14% of the non-diabetic group had hypothyroidism. On the other hand hyperthyroidism was more in the non-diabetic group (10% in diabetics, 22% in non-diabetics) (9).

In spite of the high incidence of thyroid disturbance in diabetes mellitus and also in CKD, very limited studies searched for the correlation of the three disorders.

In one recent study by Bajaj et al. on 62 CKD patients, they found that 25.8% of the patients had subclinical hypothyroidism and 4.8% of the patients had overt hypothyroidism. They found no significant difference between diabetics and non-diabetics as regard thyroid function (10).

At *Menoufia University* hospitals in 2015 we tested thyroid profile in CKD patients. The aim of this work was to study the prevalence of thyroid disturbance in diabetic CKD patients and non-diabetic CKD patients.

In this study, as regard age, the current study agrees with Bajaj et al. where the mean age of the diabetic group was significantly more than the non-diabetic group (10).

Pasupathi et al. and Stojceva-Taneva et al. also found the same results (8),(11). This may be due to the increased incidence of diabetes with age and the presence of non-diabetes causes of CKD in group II, as chronic glomerulonephritis, autoimmune causes and polycystic kidney disease, which is more common in younger age (12).

As regard the sex of the studied groups, this study agrees with a study by Graham et al included 74 diabetic patients 54 patients were males and 20 patients were females (13). Reasons for this sex difference may include differences in lifestyle and the testosterone deficiency that is common in men with diabetes, leading to a more pronounced deficit of neurosteroids (14).

There was highly significant difference between the two studied groups as regard HbA1c. This was also agreed with Pasupathi et al. who found that the mean HbA1c in the diabetic group was 11.3% while in the non-diabetic group 3.2% with highly significant difference between the two studied groups (8). It is a fact that HbA1c increases significantly in diabetic patients especially uncontrolled patients.

As regard SA Pasupathi et al. found that the mean SA for the diabetic group was 3.3 g/dl and for the non-diabetic group was 4.1 g/dl with significant difference between the two groups which was also matched with Lorenzo et al. and these results agree with the results of this study. However, Bajaj et al. found no significant difference between the two studied CKD groups (8),(15),(10).

As regard ACR, there was significant difference between the two studied groups. This was matched with the common finding of increased albuminuria in diabetic patients due to increased passage of albumin through the glomerular filtration barrier. This requires ultra-structural changes rather than alterations in glomerular pressure or filtration rate alone (16).

This result was matched with Pasupathi et al. and Stojceva-Taneva et al. who found highly significant difference between the two groups as regard proteinuria (8),(11).

There was significant difference between the two studied groups as regard Scr. This may be due to increased mean age of the diabetic group and the comorbidities associated with diabetes causing CKD as hypertension. However, this was not matched with Bajaj et al. who found no significant difference between the two studied groups as regard creatinine (10).

As regard BUN, current study results were matched with Bajaj et al. who found no significant difference between the two studied groups (10).

When we analyzed the laboratory data of the studied subgroups we found that, as regard CrCl, there was highly significant difference between subgroup IA and IB and between subgroup IIA and IIB. These results were logic as the subgroups are made according to the CrCl.





As regard HbA1c, there was significant difference between subgroup IA and IB. This is accepted due to the fact that insulin dose decrease and glycemic control become better with the decline of GFR in diabetic patients (17),(18). However, in 2015 Joly et al. found that HbA1c was higher in patients with lower eGFR in their study on 986 adult diabetic CKD patients (19).

There was no significant difference between subgroup IIA and IIB as these patients are non diabetic. There was highly significant difference between subgroup IA and IIA and between subgroup IB and IIB and this is logic as group I (A,B) are diabetic patients and group II (A,B) are non diabetic patients.

As regard SA there was no significant difference between subgroup IA and IB and between subgroup IIA and IIB. These results show that there is no correlation between GFR and SA. This is agreed with Menon et al. who found the same result in their study (20).

There was no significant difference between subgroup IA and IIA, but there was significant difference between subgroup IB and IIB. This may be due to the old age of the diabetic group (21). Pasupathi et al. found that the mean serum albumin for the diabetic group was 3.3 g/dl and for the non diabetic group was 4.1 g/dl with significant difference between the two groups which was also matched with Lorenzo et al. However, Bajaj et al. found no significant difference between the two studied CKD groups (8),(15),(10).

As regard ACR, there was no significant difference between subgroup IA and IB, but there was significant difference between subgroup IIA and IIB. Hermans et al. found no significant difference in ACR with decline of GFR in CKD patients (22). However, several studies have documented relationship between proteinuria and end-stage renal disease. Imai et al. reported that the rate of decrease of eGFR was more than two times higher in participants with proteinuria than in those without it (23). Iseki et al. also reported that they identified a strong, graded relationship between ESRD and positive dipstick urinalysis for proteinuria (24). In addition, macroalbuminuria was a better risk marker than low eGFR or erythrocyturia to identify individuals at risk for accelerated GFR loss in population screening with 4-year follow-up (25).

There was significant difference between subgroup IA and IIA, but there was no significant difference between subgroup IB and IIB. This is due to increased albuminuria in diabetic patients which is improved after declining of GFR toward ESRD (26).

As regard serum creatinine and BUN, there was highly significant difference between subgroup IA and IB and between subgroup IIA and IIB. This was because the subgroups are made according to CrCl.

As regard thyroid profile, this study showed that there was highly significant difference between the two diabetic subgroups. However, there was no significant difference between subgroup IIA and IIB.

Rai et al. found that TSH was significantly higher in diabetic group with normal kidney than the diabetic nephropathy group, but there was no correlation between TSH and serum creatinine (7).

This improvement in serum TSH in diabetic group with deterioration of GFR may be due to improved diabetes control with decreased GFR.

However, Rhee et al. found that for every 10 ml/min/1.73 m<sup>2</sup> lower eGFR, there was an 18% higher risk of hypothyroidism and this was not matched with the current study results (27).

As regard free T3 and free T4, free T3 was decreased in diabetics than non-diabetics (significantly between subgroups IA and IIA), but free T4 changes were statistically non-significant.

A study by Islam et al., showed that the levels of FT3 was significantly lower in type 2 diabetics when compared with the controls. FT4 and TSH did not show any statistically significant difference between type 2 diabetics and controls but this study wasn't on CKD patients (28).

Another study by Swamy et al., showed that the serum T4 level was low and TSH was high in type 2 diabetics when compared with controls and this difference was statistically significant. T3 was also low in type 2 diabetics when compared with controls but this difference was not statistically significant (29).

Another explanation of thyroid disturbance in diabetic patients may be due to Tg level changes in diabetic patients. Tg is used by the thyroid gland to produce the thyroid hormones (T4 and T3) (30).

When we statistically analysed the thyroglobulin results, we found that there was no significant difference between subgroup IA and IB and between subgroup IIA and IIB. On the other hand, there was significant difference between subgroup IA and IIA and there was highly significant difference between subgroup IB and IIB.

In contrast to our study, Nakamura et al. found that there was no correlation between thyroglobulin and HbA1c or fasting blood sugar, but their study didn't include non diabetic patients (31).

## 5. CONCLUSION

Thyroid disturbance is common among CKD patients especially diabetic ones. Subclinical hypothyroidism and overt hypothyroidism are the most common thyroid abnormalities among CKD patients. Patients with CKD should have thyroid profile regularly to diagnose and treat any thyroid disturbance.





However, the restraint of this study is smaller sample size and further larger patient studies should be performed to assess the prevalence of thyroid disturbance among diabetic CKD patients.

## 1.6. REFERENCES

1. Mohamedali M, Maddika S, Vyas A, Iyer V, Cheriya P. Thyroid disorders and chronic kidney disease. *International J Nephrology*. 2014; ID 520281: 6 pages.
2. Mariani L and Berns J. The renal manifestations of thyroid disease. *American Society of Nephrology J*. 2012; 23(1): 22-26.
3. Wang C. The relationship between type 2 Diabetes mellitus and related thyroid diseases. *J Diabetes Research*. 2013; ID 390534: 9 pages.
4. McFarlane P, Gilbert R, MacCallum L, Senior P. Chronic kidney disease in diabetes. *Canadian J Diabetes*. 2013; 37(1): 129-136.
5. Miulescu R, Neamtu M, Margina D, Poiana C, Paun D. Associations between thyroid dysfunction and chronic kidney disease. *Rom J Diabetes NutrMetab Dis*. 2014; 21(1): 37-42.
6. Rajeev G, Rayappa W, Vijayalakshmi R, Swathi M, Kumar S. Evaluation of thyroid hormone levels in chronic kidney disease patients. *Saudi J Kidney Dis and transplantation*. 2015; 26(1): 90-93.
7. Rai S, Ashok J, Prajna K, et al. Thyroid function in type 2 diabetes mellitus and in diabetic nephropathy. *J Clin Diagn Res*. 2013; 7(8): 1583–1585.
8. Pasupathi P, Bakthavathsalam G, Saravanan G, Sundaramoorthi R. Screening for Thyroid Dysfunction in the Diabetic/Non-Diabetic Population. *Thyroid Science*. 2008; 3(8): 1-6.
9. Taksali R, Bindu S and Mulay S. Evaluation of Thyroid Dysfunction in Type II Diabetes Mellitus: A Case Control Study. *IJCMAAS*. 2013; 1(1): 16-20.
10. Bajaj S, Gupta A, Gupta P, Srivastava A, Purwar N. Prevalence of hypothyroidism in diabetic and non-diabetic chronic kidney disease and effect of treatment on GFR. *Nephrol Dial Transplant*. 2015; 30(3): 503-504.
11. Stojceva-Taneva O, Selim G, Stojkovski L, Ivanovski N. Hypertension and progression of nephropathy in diabetic and non-diabetic chronic kidney disease patients. *Hippokratia*. 2007; 11(2): 72–76.
12. Banaga A, Mohammed E, Siddig R, et al. Causes of end stage renal failure among haemodialysis patients in Khartoum State/Sudan. *BMC Res Notes*. 2015; 8:502-508.
13. Graham U, Magee G, Hunter S, Atkinson A. Diabetic nephropathy and chronic kidney disease at a busy diabetes clinic: A study of Outpatient Care and suggestions for improved care pathways at a subspecialty specialist diabetic renal clinic. *Ulster Med J*. 2010; 79(2): 57-61.
14. Kamenov Z, Parapunova R and Georgieva R. Earlier development of diabetic neuropathy in men than in women with type 2 diabetes mellitus. *Gend Med*. 2010; 7(6): 600-615.
15. Lorenzo V, Saracho R, Zamora J, Rufino M, Torres A. Similar renal decline in diabetic and non-diabetic patients with comparable levels of albuminuria. *Nephrol Dial Transplant*. 2010; 25: 835–841.
16. Satchell S and Tooke J. What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium? *Diabetologia*. 2008; 51(5): 714–725.
17. Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G. Decreased insulin requirement in relation to GFR in nephropathic Type 1 and insulin-treated Type 2 diabetic patients. *Diabet Med*. 2003; 20(8): 642-5.
18. Kulozik F and Hasslacher C. Insulin requirements in patients with diabetes and declining kidney function: differences between insulin analogues and human insulin? *Ther Adv Endocrinol Metab*. 2013; 4(4): 113–121.
19. Joly D, Choukroun G, Combe C, et al. Glycemic control according to glomerular filtration rate in patients with type 2 diabetes and overt nephropathy: a prospective observational study. *Diabetes Res Clin Pract*. 2015; 108(1): 120-7.
20. Menon V, Wang X, Greene T, et al. Relationship between c-reactive protein, albumin, and cardiovascular disease in patients with chronic kidney disease. *American Journal of Kidney Diseases*. 2003; 42(1): 44-52.
21. Gomi I, Fukushima H, Shiraki M, et al. Relationship between serum albumin level and aging in community-dwelling self-supported elderly population. *J NutrSciVitaminol*. 2007; 53: 37-42.
22. Hermans M, Henry R, Dekker J, et al. Estimated Glomerular Filtration Rate and Urinary Albumin Excretion Are Independently Associated with Greater Arterial Stiffness: The Hoorn Study. *J Am Soc Nephrol*. 2007; 18: 1942–1952.
23. Imai E, Horio M, Yamagata K, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. *Hypertens Res*. 2008; 31: 433–441.



24. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int.* 2003; 63: 1468–1474.
25. Halbesma N, Kuiken D, Brantsma A, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *J Am Soc Nephrol.* 2006; 17: 2582–2590.
26. Olivero J, Frommer J and Gonzalez J. Medical nephrectomy: The last resort for intractable complications of the nephrotic syndrome. *Am J Kidney Dis.* 1993; 21: 260-263.
27. Rhee C, Kalantar-Zadeh K, Streja E, et al. The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. *Nephrol Dial Transplant.* 2014; 0: 1–6.
28. Islam S, Yesmine S, Khan A, Alam N. A comparative study of thyroid hormone levels in diabetic and nondiabetic patients. *South East Asian J Trop Med Public Health.* 2008; 39(5): 913–916.
29. Swamy R, Kumar N, Srinivas K, et al. Evaluation of hypothyroidism as a complication of type 2 diabetes mellitus. *Biomedical Research.* 2012; 23(2): 170–72.
30. Venturi S, Donati F, Venturi A, Venturi M. Environmental iodine deficiency: A challenge to the evolution of terrestrial life? *Thyroid.* 2000; 10 (8): 727–9.
31. Nakamura S, Sakata S, Kojima N, Komaki T, Matsuda M, Miura K. Serum thyroglobulin concentration in patients with diabetes mellitus. *Endocrinol Jpn.* 1987; 34(4): 473-8.

