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The Correlation between Thyroid Hormone Levels and the Kidney Disease Progression Risk in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Thyroid hormone (TH) influences renal tubular function as well as the renin-angiotensin system.
Objective: The goal of this research was to evaluate the link between TH levels and the risk of renal disease development in patients with type 2 diabetes mellitus (T2DM).
Subjects and methods: This trail was carried out on 80 T2DM patients aged from 18 to 70 years old, both sexes, 20 normal healthy volunteers as controls age- and sex-matched. All patients were subjected to history taking, complete clinical examination, routine laboratory, and specific investigations (Renal function tests, estimated glomerular filtration rate (eGFR), albumin/creatinine ratio, lipid profile, HBA1c, and thyroid function tests [Thyroid-stimulating hormone (TSH), free Tri-iodothyronine (FT3) and free thyroxine (FT4) levels in serum].
Results: According to TSH, at a cut-off value of 1.015, the area under the curve was 0.950, the sensitivity was 100%, the specificity was 80%, the PPV was 95.24%, and the NPV was 100%. Regarding FT3, at a cut-off value of 1.95, the area under the curve was 0.684, the sensitivity was 95%, the specificity was 78.8%, the PPV was 52.78% and the NPV was 98.44%. According to FT4, at a cut-off value of 0.75, the area under the curve was 0.699, the sensitivity was 100%, the specificity was 82.5%, the PPV was 58.82%, and the NPV was 100%.
Conclusions: Albumin/creatinine ratio, eGFR, HBA1c, TSH, and FT4 were significantly associated with the kidney disease progression risk in patients with T2DM.
Keywords: TSH, Kidney disease, Progression risk, T2DM.

INTRODUCTION

Hyperglycemia and abnormal protein, carbohydrate, and lipid metabolism are hallmarks of DM, a metabolic disease. It's a prevalent disorder. Hyperglucagonemia, pancreatic B cell dysfunction, and increased renal glucose reabsorption are the main causes of diabetes mellitus [1, 2].

With an estimated global incidence of 2.8% in 2000 and a projected rise to 4.4% in 2030, diabetes mellitus is quickly emerging as one of the most important health concerns on a global basis [3].

DM is linked to a high incidence of morbidity as a finding of a variety of complications, including , nephropathy, neuropathy, retinopathy, and cardiovascular disease [4]. Diabetic nephropathy, a serious microvascular complication of T2DM, is a major contributor to CKD. The interplay of hemodynamic and metabolic variables starts it [5].

The two endocrine illnesses that are most commonly seen in clinical practice are thyroid problems and DM. It has been demonstrated that DM and thyroid disorders are interdependent, and there has been a long history of reports of associations among the two conditions [6, 7]. DM has a variable impact on thyroid function tests, whereas THs have a role in controlling the metabolism of carbohydrates and pancreatic function.

The thyroid gland is one of the most important organs in the human body. It is in charge of most of the physiological functions of the body [8]. Thyroid disorders are prevalent in numerous populations, with varying prevalence rates. Hypothyroidism was identified in 4.6% of the 17,353 subjects who participated in the National Health and Nutrition Examination Survey study, which represented the USA population. Hyperthyroidism was identified in 1.3% of the subjects [9]. According to the most research, thyroid illness is more common in women than in men and in diabetes patients than in non-diabetic people. Furthermore, as people age, thyroid dysfunction becomes more common [8-10]. Hemodynamic and cardiovascular alterations associated with TH impair renal blood flow, renal tubular function, and the renin-angiotensin system [10]. On the other hand, the kidney is an organ that is in charge of the metabolism and excretion of TSH, and it is also an organ that is the target of the activities of several iodothyronine [11].

The hypothalamus-pituitary-thyroid axis is significantly affected by CKD and acute kidney injury. The worsening of kidney function is frequently associated with hormonal derangements at the hypothalamic-pituitary axis. Recent research indicates that these hormonal disorders may contribute to the development of CKD [12].

The glomerular and tubular functions, as well as the homeostasis of electrolytes and water, are significantly altered by thyroid dysfunction. There is small number of studies that have examined the potential relationship among urine albumin creatinine ratio (UACR) and thyroid status and eGFR among a relative number of diabetic mellitus participants, particularly in euthyroid diabetic patients, despite the fact that several studies have suggested the association of thyroid disorders and CKD or diabetic kidney disease (DKD) with conflicting results The glomerular and tubular functions, as well as the homeostasis of electrolytes and water, are significantly altered by thyroid dysfunction. Although, several studies have suggested the association of thyroid disorders with CKD or DKD with conflicting results, there are few

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studies that have looked at the potential relationship between thyroid status and eGFR and UACR among a relative number of participants with diabetes mellitus, especially in euthyroid diabetic patients [13-15].

However, it is unclear if normal TH levels and DKD are related in T2DM patients [16]. The purpose of this investigation was to investigate the relationship among TH levels and the risk of kidney disease progression in patients with T2DM.

PATIENTS AND METHODS

This study was carried out on 80 T2DM patients aged from 18 to 70 years old, both sexes, 20 normal healthy volunteers as controls with matched age and sex.

Exclusion criteria: Patients, with a history of autoimmune diseases, such as systemic lupus, obstructive uropathy, corticosteroid therapy, pregnancy, and type 1 diabetes mellitus.

Patients were separated to two groups: Group 1 (control group): (n=20) normal healthy volunteers, and group 2 (Patients' group): (n=80) patients with T2DM.

All patients were subjected to history taking, complete clinical examination, Routine laboratory investigations [Complete blood count (CBC), liver function tests (Alanine aminotransferase (ALT), serum albumin, prothrombin time (PT & INR) aspartate aminotransaminase (AST) and total and indirect bilirubin (Serum urea, creatinine, Sodium, potassium levels (Na & k)], specific investigations [Renal function tests. (urea and creatinine), eGFR, albumin / creatinine ratio, lipid profile (cholesterol and triglycerides), glycated haemoglobin (HBA1C), and thyroid function: Thyroglobin stimulated hormones (TSH), free Tri-iodothyronine (FT3) and free thyroxine (FT4) levels in serum].

Blood sampling and processing: After a fast of 8-10 hours, a 10 ml venous blood sample was collected in plain vacutainer tubes in accordance with the quality control and safety procedure for sample collection. EDTA was supplemented with 2 ml for CBC. An additional 2 ml was collected in EDTA-treated tubes and utilized for the determination of HbA1c percentage on a DCA 2000 analyzer. Using fine centrifugation at 3000 rpm for 15 minutes, serum was separated from the other vacutainer for routine and special lab use.

Specific laboratory investigations, thyroid profile assessment principle: Serum TSH was measured using ELISA kit supplied by ATLAS company, UK, catalogue No 8.12.02.0.0096. Test principle: The kit used a double-antibody sandwich ELISA to assay TSH. Serum FT3 was measured using ELISA kit supplied by ATLAS company, UK, catalogue No 8.12.04.0.0096. Test principle: The kit used a double-antibody sandwich ELISA to assay FT3.

Serum FT4 ELISA kit supplied by ATLAS company, UK, catalogue No 8.12.03.0.0096. Test principle: The kit used a double-antibody sandwich ELISA to assay FT4.

Albumin creatinine ratio: Morning midstream urine sample, albumin tested by salfosalsilic acid test by spectrophotometer and creatinine by INDIKO (United group company).

Ethical approval: The patient or their family gave written approval and were informed. The trial was approved by the Faculty of Medicine's Ethical Committee at Tanta University in Egypt. The Helsinki Declaration was followed throughout the course of the trial.

Statistical analysis

The statistical study was carried out using SPSS version 28.0. The Shapiro-Wilks test and histograms were used to evaluate the data distribution's normality. Presented as mean ± SD, the quantitative parametric data were analyzed using the unpaired student t-test. The median and IQR were used to represent quantitative non-parametric data, which were analyzed using the Mann Whitney test. Qualitative variables were analyzed using the X^2-test or Fisher's exact test, and were shown as frequency and percentage (%) as applicable. The correlation among two quantitative variables in a single group was detected using the symbols. In order to account for variables, regression analysis was implemented. Multivariate analysis involved the examination of two or more variables. The most complex multivariate analysis consisted of a dependent variable and numerous independent variables. ROC curve analysis was used to assess each test's overall diagnostic performance. A perfect test is said to be a curve that runs from the lower left corner to the upper left corner and then to the upper right corner. The AUC evaluates the overall performance of the test; an area at or close to 100% indicated the best performance, while an AUC greater than 50% indicated satisfactory performance. Sensitivity, also known as the true positive rate, is the probability of a positive test—that is, if the test is indeed positive. The probability of a negative test, if it is indeed negative, is known as specificity (or true negative rate). The proportion of true positive outcomes among all positive results is known as the PPV. The NPV is the proportion of actual negative outcomes to all negative outcomes. Any two-tailed P value $\leq$ 0.05 was considered statistically significant.

RESULTS

There were significant increase in group 2 compared to group 1 regarding INR, serum creatinine, blood urea, albumin/creatinine ratio, lipid profile (Cholesterol, and triglycerides), HBA1c, TSH, FT4 ($P< 0.05$), and significant reduction in group 2 compared to group 1 regarding Hb, serum albumin, eGFR, and FT3. While, there were non-significant differences among both groups regarding baseline data (Oldness, and gender), platelets, TLC, ALT, AST, total bilirubin, indirect bilirubin, Na level and K level (Table 1).

Table (1): Baseline data, laboratory investigation, lipid profile, and thyroid hormone of the studied participants (n = 100)

		Group 1 (n=20)	Group 2 (n=80)	P value
Baseline data				
Age (years)		49.2 ± 12.29	48.38 ± 13.56	0.805
Gender	**Male**	11 (55%)	43 (53.8%)	0.920
	Female	9 (45%)	37 (46.2%)	
Laboratory investigation				
Hb (g/dL)		12.11 ± 1.10	10.79 ± 1.12	**<0.001****
Platelets (10^3/µL)		233.5 ± 57.99	265.94 ± 65.68	0.128
TLC (10^3/ µL)		6.85 ± 1.14	7.12 ± 1.32	0.593
ALT (U/L)		28 (14-90)	30 (21-116)	0.221
AST (U/L)		27 (18-48)	31 (16-90)	0.051
Total bilirubin (mg/dL)		0.57 (0.2-9)	0.5 (0.5-13)	0.879
Indirect bilirubin (mg/dL)		0.3 (0.11-4)	0.3 (0.2-4.3)	0.675
PT (Seconds)		11.89 ± 0.61	12.94 ± 1.37	**<0.001****
INR		1.08 ± 0.06	1.13 ± 0.12	**0.017***
Serum albumin (g/dL)		4.03 ± 0.27	3.75 ± 0.32	**<0.001****
Serum creatinine (mg/dL)		0.695 ± 0.16	1.97 ± 0.48	**<0.001****
Blood urea (mg/dL)		33.55 ± 7.04	95.79 ± 22.99	**<0.001****
Sodium level (mmol/L)		137.6 ± 1.96	138.3 ± 3.45	0.236
Potassium level (mmol/L)		4.03 ± 0.42	4.11 ± 0.49	0.508
Albumin/creatinine ratio (mg Alb/g creat)		19.3 ± 4.4	363.34 ± 90.10	**<0.001****
eGFR (mL/min/1.73m2)		160.45 ±38.98	58.88 ± 12.35	**<0.001****
Lipid profile				
Cholesterol (mg/dL)		110.25 ±25.05	198.41 ± 48.78	**<0.001****
Triglycerides (mg/dL)		127.4 ± 24.23	211.06 ± 51.99	**<0.001****
HBA1C (%)		4.67 ± 0.35	8.62 ± 1.25	**<0.001****
Thyroid hormone				
TSH (µIU/mL)		1.92 ± 0.46	6.5 ± 1.51	**<0.001****
FT3 (pg/mL)		2.81 ± 0.63	2.44 ± 0.61	**0.019***
FT4 (ng/mL)		1.2 ± 0.23	1.04 ± 0.24	**0.04***

Median and range: Nonparametric test. Hb: hemoglobin, TLC: total leucocytic count ALT: Alanine aminotransferase, AST: Aspartate transaminase, PT: Prothrombin time, INR: International normalization ratio, eGFR: estimated glomerular filtration rate, TSH: thyroid stimulating hormone, FT3: Free Tri-iodothyronine, FT4: Free thyroxine, *: significant as P value < 0.05.

TSH was negatively correlated with hemoglobin, serum albumin, eGFR, FT3, and FT4. Also, TSH was positively correlated with blood urea, serum creatinine, albumin/creatinine ratio, cholesterol, triglycerides, and HBA1c. While, the TSH was not correlated with age, gender, TLC, platelets, AST, ALT, total bilirubin, indirect bilirubin, PT, INR, Na level, and K level. FT3, and FT4 were negatively correlated with blood urea, serum creatinine, albumin/creatinine ratio, triglycerides, and TSH. Also, FT3, and FT4 were positively correlated with serum albumin, eGFR, and FT4. While, FT3 was not correlated with age, gender, hemoglobin, TLC, platelets, AST, ALT, total bilirubin, indirect bilirubin, PT, INR, Na level, k level, and cholesterol (Table 2).

Table (2): Correlations between TSH, FT3, and FT4 and other parameters

Variables	TSH		FT3		FT4	
	r	p-value	R	p-value	R	p-value
Age	-0.124	0.218	0.072	0.476	0.129	0.202
Gender	-0.013	0.896	-0162	0.107	-0.049	0.627
Hb	**-0.44**	**0.001****	0.178	0.077	**0.285**	**0.004***
Platelets	0.113	0.262	-0.156	0.120	-0.061	0.545
TLC	0.118	0.241	0.025	0.805	-0.059	0.559
ALT	0.065	0.518	-0.147	0.143	0.051	0.613
AST	0.024	0.811	-0.067	0.507	0.003	0.980
Total bilirubin	0.107	0.289	0.013	0.894	-0.048	0.634
Indirect bilirubin	0.116	0.249	0.011	0.911	-0.063	0.536
PT	0.145	0.150	-0.066	0.512	-0.03	0.765
INR	0.054	0.595	0.029	0.774	-0.012	0.904
Serum albumin	**-0.779**	**0.001****	**0.502**	**0.001****	**0.735**	**0.001****
Blood urea	**0.772**	**0.001****	**-0.432**	**0.001****	**-0.613**	**0.001****
Serum creatinine	**0.916**	**0.001****	**-0.458**	**0.001****	**-0.664**	**0.001****
Sodium level	0.127	0.207	-0.038	0.704	-0.062	0.540
Potassium level	0.205	0.041*	-0.163	0.106	-0.118	0.242
Albumin/creatinine ratio	**0.903**	**0.001****	**-0.419**	**0.001****	**-0.588**	**0.001****
eGFR	**-0.752**	**0.001****	**0.357**	**0.001****	**0.397**	**0.001****
Cholesterol	**0.405**	**0.001****	-0.174	0.083	**-0.216**	**0.031***
Triglycerides	**0.414**	**0.001****	**-0.355**	**0.001****	**-0.255**	**0.001****
HBA1C	**0.700**	**0.001****	**-0.359**	**0.001****	**-0.368**	**0.001****
TSH	---	---	**-0.488**	**0.001****	**-0.742**	**0.001****
FT3	**-0.488**	**0.001****	---	---	**0.455**	**0.001****
FT4	**-0.742**	**0.001****	**0.455**	**0.001****	---	---

r: correlation coefficient, TSH: thyroid stimulating hormone, FT3: Free Tri-iodothyronine, FT4: Free thyroxine, Hb: hemoglobin, TLC: total leucocytic count ALT: Alanine aminotransferase, AST: Aspartate transaminase, PT: Prothrombin time, INR: International normalization ratio, eGFR: estimated glomerular filtration rate, *: significant as P value < 0.05.

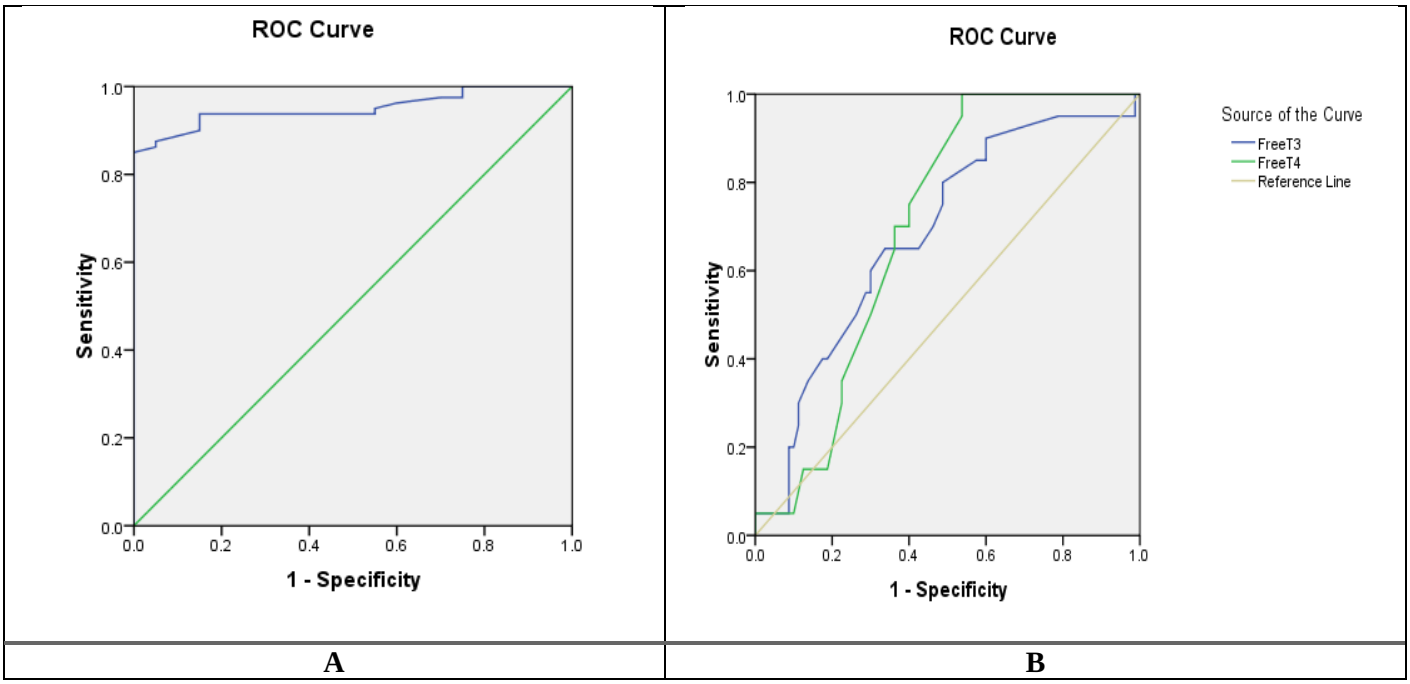
The linear regression analysis revealed that albumin/creatinine ratio, eGFR, HBA1c, FT4 and TSH were significantly associated with the kidney disease progression risk in patients with T2DM (P< 0.05) (Table 3).

Table (3): Regression analysis for predictor factors affecting thyroid hormone levels and the kidney disease progression risk in patients with T2DM among the studied cases

	Standardized Coefficients		t	Sig.	95% Confidence Interval	
	Beta	Std error			Lower Bound	Upper Bound
Age	0.001	0.001	0.240	0.811	-0.002	0.003
Gender	-0.013	0.031	-0.414	0.680	-0.073	0.048
Hb	-0.011	0.014	-0.816	0.417	-0.038	0.016
Albumin/creatinine ratio	0.002	0.001	8.528	**0.001****	0.002	0.003
eGFR	0.001	0.001	-2.000	**0.048***	-0.002	0.001
HbA1C	0.060	0.013	4.729	**0.001****	0.035	0.085
TSH	-0.033	0.016	-2.038	**0.044***	-0.065	0.001
FT3	0.031	0.027	1.144	0.256	-0.023	0.084
FT4	0.371	0.076	4.902	**0.001****	0.221	0.521

Hb: hemoglobin, TLC: total leucocytic count, eGFR: estimated glomerular filtration rate, TSH: thyroid stimulating hormone, FT3: Free Tri-iodothyronine, FT4: Free thyroxine *: significant as P value < 0.05.

To discriminate the kidney disease progression risk in patients with T2DM from the control group, according to TSH: At a cut-off value of 1.015, the AUC was 0.950, the sensitivity was 100%, the specificity was 80%, the PPV was 95.24%, and the NPV was 100%. Regarding FT3: At a cut-off value of 1.95, the AUC was 0.684, the sensitivity was 95%, the specificity was 78.8%, the PPV was 52.78% and the NPV was 98.44%. According to FT4: At a cut-off value of 0.75; the AUC was 0.699, the sensitivity was 100%, the specificity was 82.5%, the PPV was 58.82%, and the NPV was 100% (Figure 1).



A B

Figure (1): (A) ROC curve for TSH, (B) FT3, and FT4 to discriminate the kidney disease progression risk in patients with T2DM from the control group.

DISCUSSION

An important reason of CKD is diabetic nephropathy, a significant microvascular complication of T2DM. It is the consequence of the interactions among metabolic and hemodynamic factors [8]. About 20% to 40% of diabetic individuals develop DKD, and 40% also develop ESRD [8]. Elevated UACR levels and reduced eGFR are the two main markers of diabetic renal function. Blood sugar, insulin resistance, and cell metabolism are all regulated by THs. Compared to healthy people, patients with diabetes have a greater prevalence of impaired thyroid function (by around 2.2–17% increase) [17].

In the current trail, T2DM patients group exhibited a significantly lower hemoglobin level (mean 10.79 ± 1.12) than the control group (12.11 ± 1.10), with a p-value of less than 0.001. This is in agreement with **Barbieri and associates** [18] who found that reduced hemoglobin, hematocrit, and RBCs have been seen in anemia patients. This can be linked to normocytic normochromic anemia, a feature of anemia of chronic disease (ACD). ACD is a light-to-moderate anemia that reduces the lifespan of RBCs from the normal 120 days to about 80 days. The primary cause of the insufficient bone marrow response is reduced secretion of erythropoietin (EPO), and an inadequate bone marrow response to EPO [19]. Additionally, anemia is a prevalent comorbidity of diabetes, and it is detectable during the initial stages of blood impairment, as per **Jain *et al.*** [20]. Additionally, it has the potential to exacerbate the genesis and progression of microvascular and macrovascular complications.

In the current investigation, there wasn't statistically significant difference among the two groups in terms of PT and WBCs. There wasn't statistically significant difference among the groups in terms of liver enzymes, total, and indirect bilirubin. The PT findings were statistically significant among the groups (p-value < 0.001). The control group exhibited a lower PT value, with a mean of 11.89 ± 0.61, compared to the T2DM patients' group, which had a mean of 12.94 ± 1.37. The findings were statistically significant among the groups in terms of INR (p-value =0.017). The control group exhibited a lower INR with a mean of (1.08 ± 0.06) compared to the T2DM patients' group, which had a mean of (1.13 ± 0.12). This is in accordance with **Mohammed** [21] who demonstrated that diabetic patients exhibited significantly elevated values of APTT, PT, and INR.

In the present trail, there was a statistically significant results among groups as regards serum albumin (p-value <0.001). The control group showed higher serum albumin with a mean of 4.03 ± 0.27 than the T2DM patients' group with a mean of 3.75 ± 0.32. Our findings are in harmony with **Rehman *et al.*** [22] that showing Serum albumin was significantly reduced in both type 1 and T2DM compared to control group in this trial.

In the current trial, there was a statistically significant results among groups as regards serum creatinine (p-value < 0.001). The control group showed lower serum creatinine with a mean of 0.695 ± 0.21 than the T2DM patients' group with a mean of1.97 ± 0.54. There was a statistically significant results among groups as regards blood urea (p-value < 0.001). The control group showed lower blood urea with a mean of 33.55 ± 7.04 than the T2DM patients' group with a mean of 95.79 ± 44.03. This is in agreement with **Azeez *et al.*** [23] there trial found that blood glucose concentration, urea concentrations and plasma creatinine were noticed to be greater in T2DM subjects [24]. But, contrary to our findings, **Khatiwada *et al.*** [25]

reported that fasting blood glucose (mg/dl) level did not show significant relation with the CKD progression. Adequate glycemic control with hypoglycemics medications may be an appropriate explanation for this difference from our findings.

In the current trial, there was non-statistically significant difference among groups as regards Na level (p-value =0.236). The control group showed a mean of 137.6 ± 1.96 and T2DM patients' group with a mean of 138.3 ± 3.45. There was non-statistically significant difference among groups as regards K level (p-value =0.508). The control group showed a mean K value of 4.03 ± 0.42 and T2DM patients' group with a mean of 4.11 ± 0.49. There was a statistically significant results among groups as regards albumin/creatinine ratio (p-value < 0.001). The control group showed lower albumin/creatinine ratio with a mean of 19.3 ± 4.4 than T2DM patients' group with a mean of 363.34 ± 98.31. And also proved by **Abdelwahid *et al.*** [26] who showed significant increase of ACR in diabetic patients than control group.

In the current trial, there was a statistically significant results among groups as regards eGFR (p-value < 0.001). The control group showed higher eGFR with a mean of 160.45 ± 65.12 than the T2DM patients' group with a mean of 58.88 ± 23.69. This is in agreement with **Subramanyam *et al.*** [27] who reported that HbA1c values increased with decreasing eGFR, indicating that poor glycemic control correlated with increasing incidence of renal damage.

In the current trial regarding cholesterol: There was a statistically significant results among groups as regards cholesterol (p-value < 0.001). The control group showed lower cholesterol with a mean of 110.25 ± 25.05 than the T2DM patients' group with a mean of 198.41 ± 85.82. Triglycerides, there was a statistically significant results among groups as regards triglycerides (p-value < 0.001). The control group showed lower triglycerides with a mean of 127.4 ± 24.23 than the T2DM patients' group with a mean of 211.06 ± 80.34. This is in agreement with **Phadak *et al.*** [28] who demonstrated that levels of FBS, HbA1c, total cholesterol and TGs significantly increased in T2DM cases as compared to controls.

In the current trial, there was a statistically significant results among groups as regards HBA1c (p-value < 0.001). The control group showed lower HBA1c with a mean of 4.67 ± 0.35 than the T2DM patients' group with a mean of 8.62 ± 1.25. This is in line with **Field and Pinnelli** [29] who found a highly significant association between FBG and HbA1c in our study, which is consistent with other research.

In the current research, there was a statistically significant results among groups as regards TSH (p-value < 0.001). The control group showed lower TSH with a mean of 1.92 ± 0.84 than T2DM patients' group with a mean of 6.5 ± 2.36. This is in agreement with **Rong *et al.*** [30] that showing positive linear relationship among T2DM risk and TSH.

FT4 in the present trial showed a statistically significant results among groups as regards FT4 (p-value =0.04). The control group showed higher FT4 with a mean of 1.2 ± 0.23 than the T2DM patients' group with a mean of 1.04 ± 0.33. This is in agreement with **Bharat *et al.*** [31] that showed serum T4 level is reduced significantly in DM cases when compared to control (p-value < 0.01).

FT3 in the present trail, there were statistically significant results among groups as regards FT3 (p-value =0.019). The control group showed a higher FT3 with a mean of 2.81 ± 0.63 than the T2DM patients' group with a mean of 2.44 ± 0.62. Uncontrolled diabetes was associated with low plasma T3 levels and high levels of glycosylated hemoglobin (12%). Conversely, when diabetes was under control and glycosylated hemoglobin was low (about 6%), plasma T3 levels increased thrice. These levels were even greater than comparable values in euthyroid individuals [32]. This is in agreement with **Rong *et al.*** [30] that showed negative linear relationship among both FT3 and FT4 level at T2DM risk. However this was in contrast with **Bharat *et al.*** [31] who showed non-significant change in trial cases when compared to controls.

Regarding to our findings, large number of diabetic patients showed significant increase risk of subclinical hypothyroidism. This is proved by **Yang *et al.*** [33] that found the DKD group had a greater frequency of subclinical hypothyroidism. This is in contrast with **Diez and Lglesias** [34] who showed a significant increase in the risk of hyperthyroidism in diabetic group mainly the female gender.

In the present study, TSH was negatively correlated with eGFR, FT3, and FT4 and positively correlated with albumin/creatinine ratio. F3 and FT4 were negatively correlated with serum creatinine, albumin/creatinine ratio and TSH and positively correlated with, eGFR. This is consistent with **Yang *et al.*** [33] who demonstrated that FT3 and FT4 had a positive correlation with eGFR and a negative correlation with ACR and SCr. On the other hand, TSH had a positive correlation with ACR and a negative correlation with eGFR. And also, in contrast with **Chen *et al.*** [35] who showed FT4 negatively correlated with eGFR.

Also, the linear regression analysis revealed that albumin/creatinine ratio, eGFR, HBA1c, TSH, and FT4 were substantially linked to the risk of renal disease development in T2DM patients.

We suggested that future trails should involve a greater number of patients and a longer duration in order to more accurately define the incidence of DN and thyroid dysfunction in T2DM. It is imperative that specialists and practicing clinicians are aware of the high prevalence of thyroid dysfunction and microvascular complications in T2DM, and it is mandatory to screen for DN and thyroid function in these patients. Additionally, it is important to maintain good control of all risk factors of DM in order to reduce its complications.

LIMITATIONS

It was a single-center study, and the results may differ elsewhere, a relatively small sample size, and it was an observational trial, which demonstrated lower evidence results.

CONCLUSION

From our results, we concluded that albumin/creatinine ratio, eGFR, HBA1C, TSH, and FT4 were significantly associated with the kidney disease progression risk in patients with T2DM.

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