JOURNAL OF TECHNIQUES

Journal homepage*: http://journal.mtu.edu.iq*

The Renal and Liver Complications Development among Patients with Type 2 Diabetes Mellitus in Kirkuk City

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Article Info.	Abstract
	Diabetes is a chronic metabolic malady that has raised levels of blood glucose, which in last, it will cause severe harms to the heart, blood vessels, eyes, kidneys, and nerves. In this article trials to investigate the development of the renal and liver disorders among patients with T2DM in a population of Kirkuk city. The hospital-based cases- control study was conducted for patients with T2DM patients that attended the diabetic clinics in Kirkuk during the period from March 2021– to August 2021 and were screened for serum conc. of liver function tests (Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP)), renal function tests (Creatinine and Urea) especially with (family history of diabetes, & hypertension. Patients recruited for this study, showed serum urea and creatinine significantly more than that in control, $p < .001$, while for renal glomerular filtration rates significantly lower than that in control group, $p < 001$. Their kidney disease stage frequencies were significantly different in diabetic patients than in control $P < 0.001$. Stage (II) was the most frequently stage within the T2DM group ($n = 58, 58\%$), while stage (I) was the most frequently observed category within the control group ($n = 28, 56\%$). The mean of AST for T2DM (30.63 ± 6.08) was significantly more than that in the control (25.13 ± 4.32). T2DM reveal significant differences in the mean value (32.51 ± 8.96) of ALT which was more than the control (20.59 ± 4.38). The estimation of GFR as soon as possible with testing of urea and creatinine confirms the diagnosis of renal disease and staging of the renal disease. The liver enzymes illustrate in T2DM a significant correlation in comparison to the control group.

1. Introduction

Diabetes Mellitus (DM) is a chronic health condition that has many facets and advanced metabolic malady raised by a series of genetic and environmental factors [1]. The need for continued knowledge of diabetes self-management and help in reducing the risk of acute complications and long-lasting repercussions is critical. To improve diabetes outcomes, there is substantial evidence to support a variety of therapies that play a role in it [2]. Traditionally, complications of diabetes have been split into macrovascular consequences (for example, cardiovascular disease (CVD) and microvascular consequences (for example, influencing the kidneys, retina, and nervous system) [3].Diabetic nephropathy (DN) an important health problem. Influencing more than fifty percent of diabetes complaints, it's the main reason for the last phase of renal disease, which makes renal dialysis or transplantation necessary, and is significantly associated with elevated morbidity and death rate of the cardiovascular [4]. One of the most distinguished hazard factors for the evolution of the chronic renal disease is T2DM; where about thirty percent to fifty percent of patients reach the last phase of renal disease universally are diabetic. Although previously diabetic nephropathy (DN) was classically considered a metabolic illness, novel proofs propose that the pathogenesis of the disease is significantly influenced by the response of the immune system [5]. A remarkable cause of the liver disease was found to be diabetes which can be assessed by estimation of enzymes, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) [6], where hyperglycemic complaints were found to have a broad range of liver diseases, including the abnormal enzymes of the liver to the intense failure of the liver [7].

Nomenclature & Symbols			
ALT	alanine transaminase	CVD	cardiovascular disease
min	minimum	AST	aspartate transaminase
S.Cr	serum creatinine	DN	diabetic nephropathy
ALP	alkaline phosphatase	℃	Degrees Centigrade
DM	Diabetes Mellitus	k	kappa
max	maximum	α	alpha
ml/min/1.73m2	Milliliter per minute per 1.73 meter square	FH	family history
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration	HT	hypertension
eGFR	Estimated *glomerular filtration rate*	ROC	Receiver operating characteristic curve
P	probability value	T2DM	type 2 diabetes Miletus
FBS	fasting blood sugar	DKD	Kidney disease of diabetic
U/L	international unit per liter	mg /dl	milligram per deciliter
GFR	Glomerular filtration rate	SPSS	statistical package of social sciences

2. Materials and Methods

2.1. Chemicals

This study was carried out in the registered attendances of the Diabetic Consultation Clinics of Kirkuk during the period from March 2021– to August 2021. A total of 150 subjects were screened for liver function tests (Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP)), renal function tests (Creatinine and Urea), and glucose concentration according to manufactured instructions of COBAS (C311) kits and instrument, The COBAS C311 automatically calculated the conc. of each sample.

2.2. Study design

The study involved one hundred patients (70 women and 23 men) and 50 healthy individuals. Complete information including (family history of diabetes, hypertension, for all patients was recorded. Approximately five ml of venous blood was collected from each subject. The blood samples were centrifuged for 5 min at 3000 rpm, and sera were separated and stored in another plane tube at about (-20℃) until assayed, which did not exceed a week. With avoiding repetitive freezing and thawing of serum samples.

2.3. The GFR study and renal disease staging

Glomerular filtration rate (GFR): according to the equation of The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is: $eGFR = 141 \times min(SCr/k,1)^a \times max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018 \text{ if Female}] \times [1.159 \text{ if Black}]$[8]. And Kidney disease stages determination criteria [(Stage 1 a normal eGFR greater than or equal to 90 mL/min/1.73m^2), (Stagee2 slightly decreased eGFR between 60–89 mL/min/1.73m^2), (Stage 3 mild–moderate or severe decrease in eGFR between 45–59mL/min/1.73m^2 or between 30–44 mL/min/1.73m^2), (Stage 4 severe decrease in eGFR between 15–29 mL/min/1.73m^2), (Stage 5 kidney failure as eGFR decreases to less than 15 mL/min/1.73m^2 or dialysis is started)] [9].

2.4. Statistical analyses

Statistical Package for Social Sciences version (SPSS) version 26 was used for data analysis, and the data are expressed as means ± standard deviation. Differences between study groups were evaluated by one-way analysis of variance (ANOVA) (Fisher's exact probability test) and the chi-square test were used to analyze the association. P-values less than 0.05 were considered statistically significant. Receiver operating characteristic curve (ROC) analysis was used to find out the best parameter.

3. Results

Results in Table 1 showed that a significant link was found between the family history of diabetes millets disease and the study groups p<0.05. For FH of DM, The most frequently observed category within the control group was (-ve) family history (n = 38, 76%). While (+ve) FH was the most frequently observed category within the T2DM group (n = 69, 69%).
In the same Table, there is a significant difference was found in the family history of hypertension in the study groups. Negative family history of hypertension was the most frequently observed category within both the T2DM (n = 63, 63%) and control groups (n = 32, 64%).

Table 1 distribution of family history of diabetes and hypertension in study groups

Groups	Risk factors					
	FH DM		Total	FH HT		Total
	yes	no		yes	no	
T2DM	69	31	100 (67.7%)	37	63	100 (66.7%)
Control	12	38	50 (32.3%)	18	32	50 (33.3%)
Total	81 (54.0%)	69 (46.0%)	150	55 (36.7%)	95 (63.3%)	150
Chi-squared	27.174			0.014		
DF	1			1		
Significance level	P ≤ 0.000			P = 0.9050		

Results obtained from Table 2 represented the distribution of urea for group T2DM was significantly different from the distribution of urea for the control, p < .001. The mean rank for group T2DM was 88.16 and the mean rank for group control was 50.18.

While the distribution according to creatinine illustrates significant differences in which the mean for T2DM (1.03± 0.23 mg /dl) was higher than the mean for control (0.68± 0.16 mg /dl), p < .001. The mean rank for group T2DM was 95.07 and the mean rank for group control was 34.18.

Data illustrated in the same Table and Fig. 1 the distribution of study groups according to renal glomerular filtration rates showed the mean for T2DM (68.30± 23.34 mL/min/1.73m^2) was significantly lower than the mean for control (110.6± 28.8 mL/min/1.73m^2), p < .001. The mean rank for group T2DM was 53.08 and the mean rank for group control was 116.51.

The mean of fasting serum glucose (FSG) was different significantly between the T2DM and control group, p <.001, For T2DM the mean is 168.16± 32.69 mg /dl, which was more than that in control, 95.00± 13.07 mg /dl..

Table 2 Descriptive statistics and two-tailed Mann-Whitney U test results of kidney function tests in the study groups

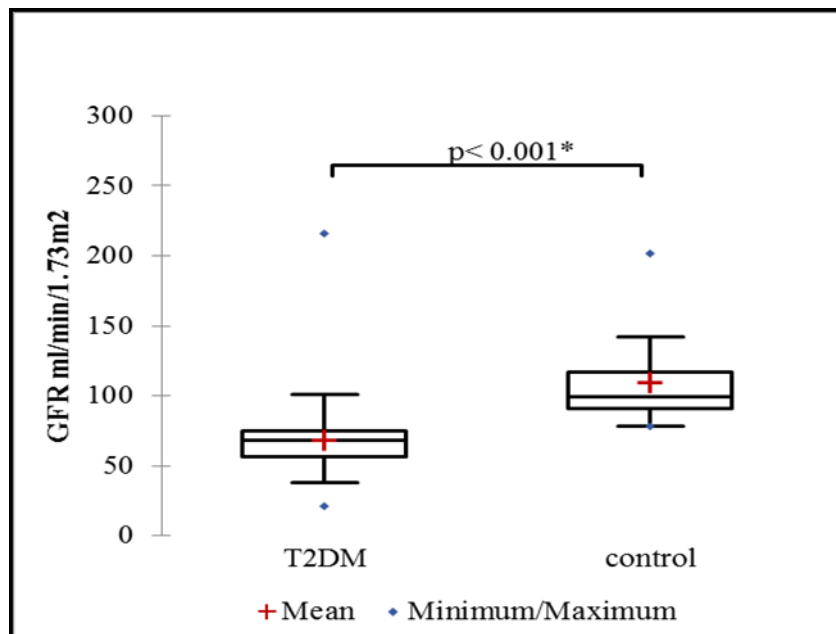| Test Variable	T2DM		control		two-tailed Mann-Whitney *U* test	
	Mean± SD	Mean rank	Mean± SD	Mean rank	U	p
Urea (mg /dl)	42.34± 12.81	88.16	32.06± 5.62	50.18	3766	**< .001**
Cr (mg /dl)	1.03± 0.23	95.07	0.68± 0.16	34.18	4466	**< .001**
GFR mL/min/1.73m^2	68.30± 23.34	53.08	110.6± 28.8	116.51	305	**< .001**
FSG (mg /dl)	168.16± 32.69	SE = 3.27	95.00± 13.07	SE= 1.85	……..	**< 0.001**

Fig 1. Ranks of GFR by the group

Their kidney disease stages in Table 3 show a significant difference between the diabetic patients and the control (P< 0.001). Stage (II) was the most frequent stage within the T2DM group (*n* = 58, 58%), while stage (I) was the most frequently observed category within the control group (*n* = 28, 56%).

Table 3 Frequencies and percentages of the stage of kidney disease within T2DM and control groups depending on eGFR

Stage	T2DM	control	P- value
0	3 (3%)	15 (30%)	
I	9 (9%)	28 (56%)	
II	58 (58%)	7 (14%)	< .001
III	28 (28%)	0 (0%)	
IV	2 (2%)	0 (0%)	
Total	100 (100%)	50 (100%)	

T2DM: type 2 diabetes mellitus, P: probability value, %: percentage

Data illustrated in Table 4 and Fig. 2 show that the mean for T2DM (30.63± 6.08 U/L) is significantly more than the mean for control (25.13± 4.32 U/L) according to AST the distribution of AST, p < .001. The mean rank for the T2DM group was 87.67 and the mean rank for the control group was 48.68.

The T2DM ALT reveal significant differences in the mean value (32.51± 8.96 U/L) that was more than the mean for control (20.59± 4.38 U/L), p < .001. The mean rank for the T2DM group was 93.19 and the mean rank for the control group was 40.12.

With regard, the distribution of ALP for group T2DM showed non-significantly differences from the distribution of ALP for the control category, p = .023. The mean rank for the T2DM group was 69.81 and the mean rank for the control group was 86.87. The mean for T2DM (92.77± 22.70 U/L) was lower than the mean for control (99.22± 14.6 U/L)

Table 4 Descriptive statistics and two-tailed Mann-Whitney U test results of liver function tests in the study groups

Variable	control		T2DM		two-tailed Mann-Whitney U test	
	Mean rank	Mean± SD	Mean rank	Mean± SD	U	p
AST (U/L)	48.68	25.13± 4.32	87.67	30.63± 6.08	3741	< .001
ALT (U/L)	40.12	20.59± 4.38	93.19	32.51± 8.96	4269	< .001
ALP (U/L)	86.87	99.22± 14.6	69.81	92.77± 22.70	1931.5	.023

AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, P: probability value, SD: standard deviation, T2DM: type 2 diabetes mellitus, U: two-tailed Mann-Whitney U test
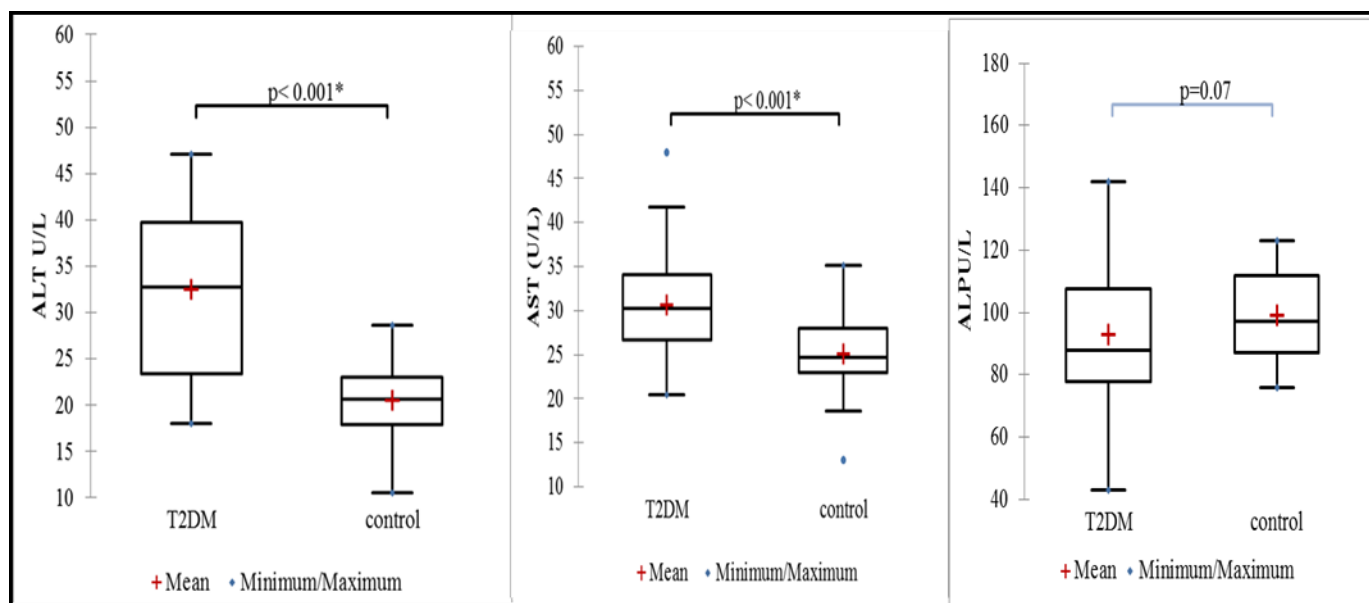

Fig 2. Descriptive statistics of the liver function tests in the study groups

4. Discussion

Diabetes mellitus Type 2 (T2DM) represents adults for a large majority of all diabetes identify, and its incidence has been steadily rising over the last few decades. This study tries to determine if there is the development of complications, such as renal or liver disorders among the patient of T2DM in a population of Kirkuk city.

The study's most noteworthy finding is that a synergistic effect of a parent's FH of DM and a sibling's FH of DM on the link with metabolic syndrome and the constituent of elevated blood glucose were detected. Individuals with DM in their parents and siblings had a greater rate of metabolic syndrome than those without DM in their family. Several theories could account for our findings, like Chiu et al, who mentions that the metabolic syndrome was correlated significantly with a family history (FH) of DM, in any case of whether there was a parental or sibling FH [10].

Kyrou et al also conducted that Type 2diabetes Mellitus history of the family is identified as a decisive not modularly T2DM hazard agent, constituting with ease investigated marker of the underlying hereditary readiness of T2DM. Several researches with European cohorts indicate that T2DM family history is a separate foreteller factor of T2DM in both women and men [11].

Furthermore, among the studies included by Zeru et al, the variable family history study reflects having family history DM disease will increase the risk of type-2 DM with the odds ratio of 6.14 (95% CI: 2.8, 13.46) [12].

Family history of hypertension in current research show, there is a significant difference was found among the family history of hypertension in the study groups. Negative family history of HT was the most frequently observed category within both the T2DM and control groups. These in contrast with the directory from varied settings propose that elevated blood pressure family history and diabetes are potentially and harmonically associated with physiological markers of vascular diseases. For instance, Qiu et al, reported that type 2 diabetes family history was correlated with raised plasma levels of significant biological parameters of the disease [13].

Kidney disease of diabetes (DKD) is a severe health condition that complicates many diabetics' lives and is a leading cause of the last phase of renal disease. The existence of diabetic renal illness is well directly connected to the development of cardiovascular events, which has a substantial influence on survival. In the current study, we found that approximately most of the patients with T2DM visiting the diabetic centers had diabetic nephropathy, according to the distribution of urea, creatinine and glomerular filtration rate (GFR) for group T2DM was significantly different from control. The mean for T2DM was larger than the mean for control in both urea and creatinine; while in revers with GFR the mean for T2DM (68.30± 23.34) was significantly lower than the mean for control. As it shows the development of kidney disease in diabetic patients and helps in the classification of it into stages from nephropathy to the end stage of renal failure with confirmatory tests of urea and creatinine that prove the diagnosis of kidney diseases.

Our finding is consistent with Radcliffe et al that mention several clinical characteristics have been described that are associated with a high risk of evolving diabetic renal illness involving a rate of eGFR decline, concomitant microvascular complications, and positive family history [14], but were inconsistent with Luis-Lima et al, who demonstrated that when comparing estimated and measured GFR, it was discovered that the calculated GFR had a 30 percent inaccuracy. Furthermore, in individuals with a GFR of less than 60 mL/min, the inaccuracy is significantly larger. Furthermore, twenty-five percent of hyperfiltration patients have the missed diagnosis and thirty percent of patients with diabetic nephropathy are not right staged in the chronic renal diabetes stage [15].

There was a significant correlation in the assessment of the enzymes marker of the liver AST and ALT with diabetic patients of type 2 in our study, in which were the mean values of ALT and AST were significantly higher in type 2 diabetes participants than in the control group ($P < 0.001$). That is in agreement with other researchers like Shibabaw et al, which have also found the mean values of liver enzymes AST and ALT elevated significantly in Diabetes mellitus Type 2 patients in contrast to the group of controls [16].

Findings in our research likewise were in line with a study conducted in Iraq and India by Sunitha et al and Judi et al, in which the high levels of liver enzymes AST and ALT were associated with type2 diabetes statistically [17, 18].

A study by Kawaguchi et al. documented that the characteristics of insulin resistance were examined in connection to chronic liver disease. According to the findings, hepatogenous diabetes is characterized by increased insulin resistance, which is frequently linked to longstanding liver disease [19].

5. Conclusion

Patients with T2DM in this study had a significant correlation with a positive family history of diabetes mellitus. Estimation of GFR as soon as possible with testing of urea and creatinine confirms the diagnosis of renal disease and staging of the renal disease to aid in treatment. The results of patients with diabetes type 2 tests of liver enzymes illustrate a significant correlation in comparison to the control group.

Acknowledgement

Ethical Approval

Ethical approval for this study was granted from the ethical committee of the Iraqi Ministry of Health (no. 12961).

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