ASSOCIATION BETWEEN SERUM TRIGLYCERIDE LEVEL AND CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES MELLITUS

Taha O. Mahwy [a], Karokh Fazil Hamahussien [b], and Delman Al-Attar [c]

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ABSTRACT

Background

Diabetes mellitus type 2 is a long-term metabolic disorder that is characterized by high blood sugar, insulin resistance, and a relative lack of insulin. Diabetic kidney disease which is known as diabetic nephropathy is the chronic loss of kidney function occurring in those with diabetes mellitus and is the single strongest predictor of mortality in patients with diabetes. However, in spite of the achievement of recommended targets for blood glucose and blood pressure, the residual risk for diabetic nephropathy remains high among patients with type 2 diabetes. Hypertriglyceridemia may be one of the factors responsible for this high residual risk. Recent studies demonstrated that intra-renal accumulation of lipids may contribute to glomerular injury.

Objectives

This study aimed to find an association between hypertriglyceridemia and chronic kidney disease in type 2 diabetes mellitus patients.

Patients and Methods

In this cross-sectional study 241 patients evaluated with documented type 2 diabetes mellitus to find any relation between hypertriglyceridemia and chronic kidney disease in type 2 diabetes mellitus. Data collected from 300 patients with type 2 diabetes mellitus, 161 males and 139 females. Of these 59 cases were excluded, 35 males and 24s female patients because of incomplete data was available, with mean age was 54.24 years. laboratory test for measuring fasting (total cholesterol, HDL, LDL, triglyceride, urinary albumin, and urinary creatinine) done using COBAS INTEGRA 400 PLUS (Roche), then ACR measured two samples was obtained.

Results

In our study 139 patients had high serum triglyceride level, the other 102 patients had normal serum triglyceride level. 154 patients had normal urine ACR, (n=77, 50.0%) had high triglyceride level, (n=77, 50.0%) had normal triglyceride level, 57 patients had microalbuminuria, (n=42, 73.7%) had high triglyceride level, (n=15, 26.3%) had normal triglyceride level, 30 patients had macroalbuminuria, (n=20, 66.7%) had high triglyceride level , (n=10, 33.3%) had normal triglyceride level, p-value was significant, ($p<0.005$) .

Conclusion

In the current study we found that hypertriglyceridemia is an independent risk factor for CKD. Furthermore, hypertension, hypercholesterolemia, high HbA1c and duration of diabetes were also identified as risk factors for CKD.

Keywords: *Hypertriglyceridemia, Chronic kidney disease, Diabetes mellitus type 2.*

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[a] Department of Medicine, College of Medicine, University of Sulaimani, Kurdistan Region, Iraq.
[b] Kurdistan Board Candidate of Internal Medicine/ Kurdistan Region/ Iraq.
Correspondence: hamakarokh@gmail.com
[c] Faruk Medical City, Kurdistan Region, Iraq.

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INTRODUCTION

Type 2 diabetes mellitus is a long-term metabolic disorder that is characterized by high blood sugar, insulin resistance, and a relative lack of insulin [1]. People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries [2].

Long-term complications from high blood sugar include heart disease, strokes, diabetic retinopathy and nephropathy which can result in blindness, kidney failure, and poor blood flow in the limbs which may lead to amputations [3]. Diabetic kidney disease which is known as diabetic nephropathy is the chronic loss of kidney function occurring in those with diabetes mellitus and is the single strongest predictor of mortality in patients with diabetes [4]. Kidney disease attributed to diabetes is a major but under-recognized contributor to the global burden of the disease. Between 1990 and 2012, the number of deaths attributed to DKD rose by 94% [5]. This dramatic rise is one of the highest observed for all reported chronic diseases [6].

Diagnosis is based on the measurement of abnormal levels of urinary albumin in a diabetic patients [7] The incidence of diabetic nephropathy is higher in people with diabetes that have one or more of the following conditions [8] 1) poor control of blood glucose, 2) Uncontrolled high blood pressure, 3) Past or current cigarette use 4) A family history of diabetic nephropathy. However, in spite of the achievement of recommended targets for blood glucose and blood pressure, the residual risk for diabetic nephropathy remains high among patients with type 2 diabetes [9, 10]. Diabetic dyslipidemia-high triglycerides (TGs) and/or low HDL-cholesterol (HDL-C) levels-may be one of the factors responsible for this high residual risk [10]. recent studies demonstrated that intra-renal accumulation of lipids may contribute to glomerular injury [11–12].

PATIENTS AND METHOD

In this cross-sectional study 241 patient with documented type 2 diabetes mellitus evaluated to find any relation between hypertriglyceridemia and chronic kidney disease in type 2 diabetes mellitus. 300 cases were taken, 161 males and 139 females. Of these 59 cases were excluded, 35 males and 24 females patients because of incomplete data was available,with mean age was 54.24 years. The data was taken from patient between 1/7/2018 to 1/4/2019 in endocrine center of Sulaimani and Faruk medical city. The exclusion criteria were those patients with type 1 diabetes and those with renal replacement therapy.

Patient age, sex and period of diabetes mellitus were obtained and we categorized patients into three groups less than 40 years, 40-65 years, more than 65 years. Height and weight were measured then, BMI calculated. We obtained information about smoking status, alcoholic, chronic medical illness, use of antihypertensive, lipid-lowering and antidiabetic medication both oral and insulin. Laboratory test for measuring fasting (total cholesterol, HDL, LDL, triglyceride, urinary albumin, and urinary creatinine) done using COBAS INTEGRA 400 PLUS (Roche). then ACR measured. Two samples were obtained. HbA1c, blood urea, and creatinine was measured then eGFR was calculated by using MDRD study equation. Then we categorized the patients according to HbA1c into two groups those with HbA1c less than 7(good control) and those with HbA1c 7 or more (bad control) because according to American diabetes association for microvascular disease prevention, the HbA1c goal in non-pregnant adult, in general, is less than 7 [13].

Data were entered into Microsoft excel sheet in which cleaning of data and coding of the variables done there; then transferred into SPSS program (version22) (Statistical Package of Social Sciences), here two approaches were used for the analysis. Descriptive approach: for the calculation of frequencies, percentages, means and standard deviations, and constructing tables and diagrams.

Analytical approach: to find associations between variables and finding P-Values, here the Chi-square test, T-test, ANOVA table, and Fisher's exact test were used; a P-Value ≤ 0.05 regarded as statistically significant, while a P-Value of 0.001 regarded as statistically highly significant.

Normal triglyceride level defined as a TG < 150 mg/dl (1.7 mmol/l) normal cholesterol level defined as a TC<200mg/dl, LDL cholesterol defined as a LDL<130 mg/dl, HDL cholesterol defined as a HDL>40mg/dl [14]. The definition of CKD developed by Kidney Disease Outcomes Quality Initiative (KDOQI) [15]was: Kidney damage present at least 3 months, as defined by structural or functional abnormalities (most often

based on increased albuminuria, e.g., urinary albumin-creatinine ratio [UACR] ≥30 mg/g); and/or

Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 present at least 3 months.

Within this framework, KDOQI then classified CKD into five stages, as follows:

Stage 1: Kidney damage with GFR ≥90 mL/min/1.73 m^2.

Stage 2: Kidney damage with GFR 60-89 mL/min/1.73 m^2.

Stage 3: GFR 30-59 mL/min/1.73 m^2.

Stage 4: GFR 15-29 mL/min/1.73 m^2.

Stage 5: GFR <15 mL/min/1.73 m^2 or kidney failure treated by dialysis or transplantation.

Urinary albumin excretion is defined as: Normal< 3 0 (µg/mg creatinine), Microalbuminuria 30–299 (µg/mg creatinine), Macro (clinical)-albuminuria 300 (µg/mg creatinine)

Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have abnormal urinary albumin excretion. [16]

The BMI is defined as the body mass divided by the square of the body height and is universally expressed in units of kg/m2, resulting from mass in kilograms and height in meters. The WHO regards a BMI of less than 18.5 as underweight and may indicate malnutrition, an eating disorder, or other health problems, while a BMI equal to or greater than 25 is considered overweight and above 30 is considered obese [17]. These ranges of BMI values are valid only as statistical categories.

Category	BMI (kg/m2)		BMI Prime	
	from	to	from	to
Very severely underweight		15		0.60
Severely underweight	15	16	0.60	0.64
Underweight	16	18.5	0.64	0.74
Normal (healthy weight)	18.5	25	0.74	1.0
Overweight	25	30	1.0	1.2
Obese Class I (Moderately obese)	30	35	1.2	1.4
Obese Class II (Severely obese)	35	40	1.4	1.6
Obese Class III (Very severely obese)	40	45	1.6	1.8
Obese Class IV (Morbidly Obese)	45	50	1.8	2
Obese Class V (Super Obese)	50	60	2	2.4
Obese Class VI (Hyper Obese)	60		2.4	

RESULTS

Of the total number of patients (241 patients), there was male predominance which was present 52.3% of the patients, also most of the participants' age was between 40-56 years which was forming 84.2% and most of the patients were overweight 48.1%. (Table 1).

Table 2 the 137 (56.8%) of patients had a history of hypertension and 118 (49%) patients were using ACEI or ARB.

Table 3 the majority of patients (75.9%) in this study had poor glycemic control (HbAIC was equal to or more than 7).

Of the total number of patients, 57.7% of them had high serum triglyceride level and 42.3% had normal serum triglyceride levels. Table 4.

Among the study participants, 222(92.1%) patients had normal serum creatinine and blood urea but only 154(63.9%) patients had normal urine ACR the other 87(36.1%) patients had abnormal urine ACR(23.7% had microalbuminuria and 12.4% had macro albuminuria). (Table 5).

Table (6 and 7) the relation of variables with urine ACR. it shows a statistically significant relationship between hypertension, HbA1C and urine ACR (p-value <0.003) also there was a significant relation between

urine ACR and diabetic duration, total cholesterol, and LDL cholesterol. But no significant relation between urine ACR and HDL cholesterol (p<0.997).

Table 8 the association between serum triglyceride level and urine ACR. Which was showing statistically significant relation (p<0.005), 154 patients had normal urine ACR, (50%) of them had high serum triglyceride level but 57 patients had microalbuminuria, (73.7%) of them had hypertriglyceridemia and 30 patients had macroalbuminuria, (66.7%) of them had hypertriglyceridemia.

Table 9, the association between serum triglyceride level and stages of chronic kidney disease according to eGFR, which was showing no statistically significant relation (p<0.282). 169 patients had stage 1 CKD, (54.4%)of them had a high triglyceride level. 56 patients had stage 2 CKD, (62.5%) of them had a high triglyceride level. 14 patients had stage 3 CKD, (71.4%) of them had a high triglyceride level. 2 patients had stage 4 CKD, (100%) had a high triglyceride level.

Table 10 showing the association between serum triglyceride and diabetes mellitus duration with urine ACR. When we classified the patient according to the period of diabetes that they had also shown a statistically significant relation between serum triglyceride level and urine ACR (p<0.001). It shows that those that had a longer period of diabetes and high serum triglyceride level had a high percentage of abnormal urine ACR.

Table 1. Frequency and percentage of the variables.

Variables	Frequency	Percentage
Gender		
Male	126	52.3
Female	115	47.7
Age groups		
Less than 40 year	12	5
40-65 year	203	84.2
More than 65 year	26	10.8
BMI		
Normal	34	14.1
Overweight	116	48.1
Obese	91	37.8
Smoking history		
No Smoker	159	66
Current Smoker	56	23.2
Ex-Smoker	26	10.8
Alcohol history		
Yes	30	12.4
No	211	87.6
Total	241	100

Age: Mean 54.24 Year, age Std. Deviation 9.4. Minimum32, Maximum84

Table 2. Frequency and percentage of the variables.

Variables	Frequency	Percentage
Systolic BP		
Normal	44	18.3
High	197	81.7
Diastolic BP		
Normal	139	57.7
High	102	42.3
Hypertension history		
Yes	137	56.8
No	104	43.2
IHD history		
Yes	26	10.8
No	215	89.2
ACEI or ARB		
Yes	118	49
No	123	51
Total	241	100

Table 3. Frequency and percentage of the variables.

Variables	Frequency	Percentage
FBS		
Normal	13	5.4
High	228	94.6
HbA1C		
Less than 7	58	24.1
Equal and more than 7	183	75.9
DM duration		
Less than 5 year	70	29
5-10 year	105	43.6
More than 10 year	66	27.4
DM treatment		
Oral hypoglycemic agent	189	78.4
Insulin	8	3.3
Combination	44	18.3

Table 4. Frequency and percentage of the variables.

Lipid Profile	Frequency	Percentage %
Total S. Cholesterol		
High	44	18.3
Normal	197	81.7
S. TG		
High	139	57.7
Normal	102	42.3
HDLC		
Abnormal	119	49.4
Normal	122	50.6
LDLC		
Abnormal	49	20.3
Normal	192	79.7
Total	241	100

Table 5. Frequency and percentage of the variables.

Variables	Frequency	Percentage %
S. Creatinine		
Normal	222	92.1
High	19	7.9
Bl. Urea		
Normal	222	92.1
High	19	7.9
eGFR stages		
Stage 1	169	70.2
Stage 2	56	23.2
Stage 3	14	5.8
Stage 4	2	0.8
Urine ACR		
Normal	154	63.9
Micro	57	23.7
Macro	30	12.4
Lipid-lowering agent		
Yes	179	74.3
No	62	25.7
Total	241	100

Table 6. Association between variables and urine ACR.

Variables	Urine ACR			Total	P-Value
	Normal No. (%)	Micro No. (%)	Macro No. (%)		
Age groups					
<40 year	11 (91.7)	0 (0.0)	1 (8.3)	12 (100)	0.137
40-65 year	126 (62.1)	29 (24.1)	28 (13.8)	203 (100)	
>65 year	17 (65.4)	8 (30.8)	1 (3.8)	26 (100)	
Gender					
Male	80 (63.5)	27 (21.4)	19 (15.1)	126 (100)	0.363
Female	74 (64.3)	30 (26.1)	11 (9.6)	115 (100)	
DM duration					
<5 year	54 (77.1)	12 (17.2)	4 (5.7)	70 (100)	0.008
5-10 year	66 (62.9)	28 (26.7)	11 (10.4)	105 (100)	
>10 year	34 (51.5)	17 (25.8)	15 (22.7)	66 (100)	
HbA1C					
<7	48 (82.8)	7 (12.1)	3 (5.1)	58 (100)	0.003
≥ 7	106(57.9)	50(27.3)	27(14.8)	183(100)	
Hypertension hx.					
Yes	75 (54.7)	40 (29.2)	22 (16.1)	137 (100)	0.003
No	79 (76.0)	17 (16.3)	8 (7.7)	104 (100)	
Total	154 (63.9)	57 (23.7)	30 (12.4)	241 (100)	

Table 7. Association between variables and urine ACR.

Variables	Urine ACR			Total	P-Value
	Normal No. (%)	Micro No. (%)	Macro No. (%)		
S. Cholesterol					
Normal	133 (67.5)	44 (22.3)	20 (10.2)	197 (100)	0.023
High	21 (47.7)	13 (29.6)	10 (22.7)	44 (100)	
HDLC					
Normal	78 (63.9)	29 (23.8)	15 (12.3)	122 (100)	0.997
Abnormal	76 (63.9)	28 (23.5)	15 (12.6)	119 (100)	
LDLC					
Normal	128 (66.7)	45 (23.4)	19 (9.9)	192 (100)	0.048
Abnormal	26 (53.1)	12 (24.5)	11 (22.4)	49 (100)	
Total	154 (63.9)	57 (23.7)	30 (12.4)	241 (100)	

Table 8. Tthe association between serum triglyceride level and urine ACR).

		S.TG Groups		Total	P-Value
		High TG	Normal TG		
URINE ACR	**Normal**	77	77	154	0.005
		50.0%	50.0%	100.0%	
	Micro	42	15	57	
		73.7%	26.3%	100.0%	
	Macro	20	10	30	
		66.7%	33.3%	100.0%	
Total		139	102	241	
		57.7%	42.3%	100.0%	

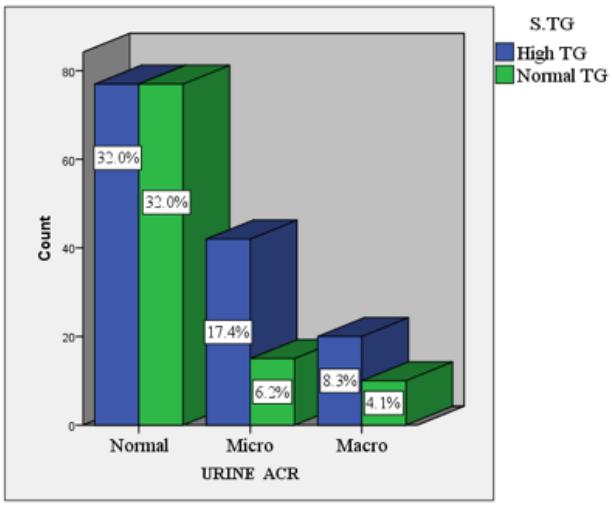

Figure 1. Association between serum triglyceride level and urine ACR).

Table 9. Association between serum triglyceride level and stages of chronic kidney disease according to eGFR),

		S.TG Groups		Total	P-Value
		High TG	Normal TG		
eGFR Stages	Stage 1	92	77	169	0.282
		54.4%	45.6%	100.0%	
	Stage 2	35	21	56	
		62.5%	37.5%	100.0%	
	Stage 3	10	4	14	
		71.4%	28.6%	100.0%	
	Stage 4	2	0	2	
		100.0%	0.0%	100.0%	
Total		139	102	241	
		57.7%	42.3%	100.0%	

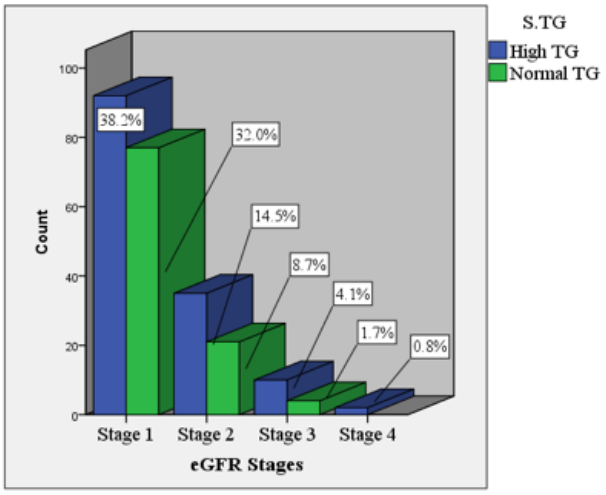

Figure 1. Association between serum triglyceride level and stages of chronic kidney disease according to eGFR).

Table 10. The association between serum triglyceride and diabetes mellitus duration with urine ACR.

S.TG Groups and DM duration			URINE ACR			Total	P-Value
			Normal	Micro	Macro		
High TG	Duration of DM	5-10 year	33	18	5	56	0.001
			58.9%	32.1%	8.9%	100.0%	
		5 year	29	9	2	40	
			72.5%	22.5%	5.0%	100.0%	
		>10 year	15	15	13	43	
			34.9%	34.9%	30.2%	100.0%	
	Total		77	42	20	139	
			55.4%	30.2%	14.4%	100.0%	
Normal TG	Duration of DM	5-10 year	33	10	6	49	0.46
			67.3%	20.4%	12.2%	100.0%	
		< 5 year	25	3	2	30	
			83.3%	10.0%	6.7%	100.0%	
		>10 year	19	2	2	23	
			82.6%	8.7%	8.7%	100.0%	
	Total		77	15	10	102	
			75.5%	14.7%	9.8%	100.0%	

DISCUSSION

In the current study, we found a positive relationship between serum triglyceride level and CKD which is measured by urinary ACR, the p-value was significant ($p<0.005$). We found that CKD prevalence more in those patients with high serum triglyceride level which is support the previous study that is done in Thailand [18] and Taiwan [19], also when we classify the patient according to period of diabetes mellitus we found that CKD prevalence more in those patient with high serum triglyceride level p-value was significant ($p<0.001$). Recent studies demonstrated that intra-renal accumulation of lipids may contribute to glomerular injury [11–12]. Also, there is some evidence suggest that hypertriglyceridemia can induce renal microvascular endothelial damage via different mechanisms [20].

Also, another study that was done in Italy showing the same result which was high triglyceride level was an independent risk factor for the development and progression of CKD [21]. The same result also was observed in the Japanese population, one study which was done in the japan showing high TG-HDL constitute a significant risk factor of CKD [22]. Moreover, one study which was done in Korea about the effect of Omega-3 fatty acid supplementation on diabetic nephropathy progression in diabetic patients with hypertriglyceridemia showing that O3FA supplementation in diabetic patients with hypertriglyceridemia ameliorated urine ACR and preserved GFR, The pathway of beneficial effects of O3FA in kidney has been studied in animal experiments which was improvement of dyslipidemia and attenuation of inflammation [23]. But when we measured CKD by eGFR we didn't found statistically significant relation ($p<0.282$), in this study we diagnosed CKD by urine ACR because it is more sensitive in detecting early stage of CKD [24, 25], and eGFR equations less accurate in patients with GFR values near or above 60 ml/min [26, 27].

In our study, the frequency of patients with hypertriglyceridemia was higher than the study which is done in Thailand (57.7% versus 51%) [18]. Also, the prevalence of CKD was higher in our study than that study which is done in Thailand (36.1% versus 26.9%) [18]. In this study we found positive association between hypertension and CKD, statistically there was significant association ($p<0.003$), we found that CKD prevalence more in those patients with hypertension which is support the previous study that is done in Thailand [18] and Taiwan [19], this is because of chronic

high blood pressure causes damages to kidney tissue; this includes the small blood vessels, glomeruli, kidney tubules, and interstitial tissues. The tissue hardens and thickens which is known as nephrosclerosis.[28]

The narrowing of the blood vessels means less blood is going to the tissue and so less oxygen is reaching the tissue resulting in tissue death (ischemia)[29]. In our study we found that there is positive relationship between serum cholesterol and CKD , statistically there was significant association ($p<0.023$), the prevalence of CKD was higher in those patients with hypercholesterolemia , the same result was found in study which is done in Taiwan [19], also in our study we found that there is positive relationship between LDL-C and CKD statistically there was significant association ($p<0.048$) , it means that CKD more in those patient with high LDL-C, but we didn't find any statistically significant association between HDL-C and CKD ($p<0.997$) in contrast to the previous study which was done in Italy showing that low HDL-C was independent risk factor for the development and progression of CKD[21]. We didn't find any significant relationship between age group and CKD in our study so age appears not to be a risk factor for CKD ($p<0.137$)in our study in reverse of study which is done in Thailand [18] and Taiwan [19] which is showing that age is a risk factor for CKD. Also in our study, we found a statistically significant relationship between period of diabetes mellitus and CKD ($p<0.008$) it means that the prevalence of CKD is more in those that they have diabetes mellitus for longer period. In our study also we found that there is a positive relationship between HbA1c and CKD statistically there was a significant relationship ($p<0.004$) It means that high HbA1c is one of the risk factors for CKD.

In this study we had some limitations and strengths, the limitations of our study was this study was a cross-sectional study it was difficult to establish causality so for establishing the relationship between the risk factor and the development of CKD we should have prospective follow-up study, another limitation was small sample size. One of the strengths of our study is that we obtained two samples of urine ACR which is mandatory to confirm CKD. In conclusion, our study found that hypertriglyceridemia is an independent risk factor for CKD in type 2 diabetic patients. Furthermore, hypertension, hypercholesterolemia, high HbA1c and period of diabetes were also identified as a risk factor for CKD. Our result support screen for hypertriglyceridemia and manage it if present to decrease the prevalence of CKD in type 2 diabetic patients, also for screening and managing other risk factor in a way to decrease the prevalence of CKD in type 2 diabetic patients.

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