RESEARCH ARTICLE

Association of high serum triglycerides and triglycerides/ HDL ratio with raised HbA1c, creatinine, microalbuminuria and development of diabetic kidney disease and diabetic renal failure. Mathematical and statistical regression models of 10,370 diabetic patients

Kamran Mahmood Ahmed Aziz*

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Renal disorders and chronic kidney disease (CKD) in diabetics, or the diabetic kidney disease (DKD), renal failure and end stage renal disease (ESRD) still remains most important complications of diabetes with high prevalence. Apart from hyperglycemia, causes and risk factors must be analyzed to reduce the economic burden. Current research was conducted to study the triglycerides and triglycerides to HDL-C ratio (TG/HDL) and their involvement in the development of proteinuria/nephropathy, raising creatinine levels (CKD/DKD). 10,370 Diabetic Patients were recruited in the study for more than 12 years, from 2005 until 2017. 6201 (59.8% were males and 4169 (40.2%) females. 3940 (38%) subjects demonstrated nephropathy while 1348 (13%) demonstrated DKD/CKD. HbA1c was significantly correlated with triglycerides and TG/HDL ratio and microalbumin ($p<0.0001$, 0.021 and <0.0001, respectively). Triglycerides and TG/HDL were also highly correlated with creatinine and micoalbumin ($p=0.006$, $p=0.002$, $p<0.0001$ and $p<0.0001$ respectively). Levels of HbA1c, triglycerides, TG/HDL and creatinine were elevated among the patients with nephropathy (p-values: 0.001, 0.001, 0.004, <0.0001, respectively). Similarly, Levels of HbA1c, triglycerides, TG/HDL and microalbuminuria were elevated among the patients with DKD (p-values: 0.03, 0.018, 0.009, <0.0001 respectively). Regression models were also developed to demonstrate the effect of dyslipidemia or elevated serum triglycerides in raising the serum creatinine and urine microalbumin levels and development of DKD; all regression models were significant ($p<0.0001$). For diagnostic statistics, Receiver Operating Curve (ROC) was constructed. The ROC for triglycerides and nephropathy demonstrated area under the curve (AUC) 0.559 (95% CI 0.530 to 0. 588; p-value<0.0001). By this observation and data analysis, for the detection of the development of nephropathy, a triglyceride cutoff point of 138 mg/dl with 65% sensitivity and 55% specificity was observed. Similarly, ROC for detection of DKD, a triglyceride cutoff point of 153 mg/dl with 60% sensitivity and 61% specificity was found (AUC 0.581; 95% CI 0.522 to 0.640; p-value<0.0001). Study findings concluded and recommended that all diabetic patients should be screened for the dyslipidemia and nephropathy to prevent DKD and ESRD.

Key Words: Microvascular disease, triglycerides, cardiovascular, diabetes, microalbuminuria

INTRODUCTION

Diabetes mellitus is major cause of microvascular disease, including neuropathy, retinopathy, nephropathy. The landmark trial, DCCT (diabetes control and complication trial) has demonstrated that reductions in HbA1c levels will reduce the risk of microvascular and macrovascular complications [1-3]. Elevated levels of HbA1c or uncontrolled diabetes is usually associated with increased levels of serum triglycerides [4,5]. Additionally, it was found that dyslipidemia in the diabetic state is also associated with renal disease [6].

Chronic involvement of kidney in diabetes, also called chronic kidney disease (CKD) and now better termed, the diabetic kidney disease (DKD), leads to microalbuminuria and gross proteinuria and ultimately to end stage renal disease (ESRD). Atherosclerotic cardiovascular disease (ASCVD) is one of the major leading causes of morbidity and mortality among diabetic patients, which usually coexist with DKD [7].

Hyperglycemia and hypertension are the main risk factors for the development and progression of DKD [8]. However, it has been observed that in spite of the achievement of recommended targets and goals for glycemic control and blood pressure, the residual risk for diabetic nephropathy remains high among type-2 diabetic patients [9,10]. Hence, in other words, diabetic dyslipidemia still remains one of the major risks for the DKD or ESRD, apart from hypertension [11,12]. Hence, cardiovascular complications, such as hypertension (HTN) or ischemic heart disease (IHD) are also associated with kidney disorders in diabetes, as both of them share a common risk of dyslipidemia. Several epidemiological studies have found an association between lipids diabetic kidney disease and other diabetes related disorders [13-23]. Triglycerides and triglyceride to HDL-C ratio (TG/HDL), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were studies as well. HDL-C is considered good cholesterol, and have also cardiovascular protective effect; however, elevated levels of other lipids are considered harmful and are considered risk factors for cardiovascular and renal system. This effect is augmented when the patient is diabetic [24-28].

TG/HDL ratio can be considered an excellent tool and strategy for estimating risk of atherosclerosis among diabetes patients. Furthermore, DKD/CKD is also associated with atherosclerosis [29,30]. Hence, association of lipids, especially triglycerides, with the development of renal impairment must be studied.

Under this background and literature review, our main objective was to study involvement of serum lipids (triglycerides and TG/HDL ratio) in the development of diabetic renal disease or disorders. Until date there are no studies which have demonstrated direct association and involvement of triglycerides with raised serum HbA1c, creatinine, and microalbuminuria with consequent development of DKD. Furthermore, studies are lacking for the statistical regression models which can predict renal impairment by the given triglyceride or triglyceride to HDL-C ratio (TG/HDL). These were the objectives of the current research, to study how these risk factors can contribute to the development of DKD under the influence of

Diabetology Clinic, Aseer Diabetes Center of Aseer Central Hospital, Ministry of Health, Abha, Saudi Arabia

Correspondence: Aziz KMA, Diabetology Clinic, Aseer Diabetes Center, Aseer Central Hospital, Ministry of Health, P.O. Box 34, Abha, Saudi Arabia, Tel: 00966-568361040; E-mail: drkamran9999@yahoo.com

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dyslipidemia. It was our aim also to develop statistical regression models for triglyceride and triglyceride to HDL-C ratio to demonstrate the effect of dyslipidemia or elevated serum triglycerides in raising the serum creatinine and urine microalbumin levels and development of DKD.

METHODS

This is a prospective cross sectional analytical and cohort study, conducted at the diabetology clinic of Aseer Diabetes Center of Aseer Central Hospital, Ministry of Health, Saudi Arabia. Study duration was more than 12 years, from August 2005 until September 2017. The study recruited 10,370 diabetic patients (after exclusion criteria) who, were followed up in this clinic. Study included both type-1 and type-2 diabetic patients. Children (less than 13 years of age), patients with severe liver or hepatic disorders, patients demonstrating urinary tract infection, known cases of nephrotic syndrome before the onset of diabetes, patients with end stage renal disease (ESRD) or dialysis and pregnant women were excluded from the study.

Patients demonstrating levels of serum creatinine>1.5 were defined as chronic renal/kidney disease (CRD/CKD) and these diabetic subjects were also considered “diabetic kidney disease” (DKD). Furthermore, patients demonstrating microalbuminuria or gross proteinuria were labeled as “nephropathy”.

Laboratory methods

All samples were collected in fasting state of 12 hours, early in the morning. Serum triglyceride (mg/dl) was measured by an enzymatic procedure; the sample is incubated with lipoprotein lipase (LPL) enzyme reagent that converts triglycerides to free glycerol and fatty acids. These are further oxidized to dihyhroxyacetone phosphate and hydrogen peroxide (H_2O_2) which is again converted to quinoneimine, absorbance of which is directly proportional to the total amount of glycerol. Absorbance is measured by bichromatic (510,700 nm) endpoint technique.

HDL-C (mg/dl) was measured directly in plasma by Automated High Density Lipoprotein (AHDL) method by the Dimension® clinical chemistry system and analyzer (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A), in vitro diagnostic test intended for quantitative determination of HDL-C. Triglycerides and HDL ration was measured as TG/HDL.

Serum creatinine (mg/dl) was quantitatively measured by CREA methodology by Dimension® clinical chemistry system and device (Siemens Healthcare Diagnostics Inc. Newark, DE 19714, USA). The technique for the measurement of creatinine in plasma and urine involved picrate which, in the presence of a strong base NaOH, chemically reacts with creatinine to form a red chromophore. The rate of increasing absorbance at 510nm due to the formation of this chromophore is directly proportional to the creatinine concentration in the sample of blood or urine and which, is measured using by a bichromatic (510,600 nm) rate methodology. Hence, creatinine in the plasma was determined quantitatively [31-33].

HbA1c was measured by A1c Flex® Reagent by the Dimension® clinical chemistry system, in vitro diagnostic assay for the quantitative determination of both percent hemoglobin A1c and total hemoglobin, based on a turbidimetric inhibition immunoassay (TINIA) principle, and the measurement of total hemoglobin is based on a modification of the alkaline hematin reaction, an NGSP certified methodology (Siemens healthcare diagnostics Inc. Newark, DE 19714, USA). The percentage of total hemoglobin that is glycated was calculated and reported as %HbA1c (in g/dL), and final result has been standardized to the results obtained in DCCT.

For the detection of nephropathy and presence of albumin or protein in urine, fasting urine samples were examined for the presence of microalbuminuria, macroalbuminuria or proteinuria. All urine samples were first examined for the presence of gross proteinuria by QuikCheck™ urinalysis reagent strips (ACON biotech, Co., Ltd.) to rule out macroalbumin in urine. This technique is based on the phenomenon of pH indicators which releases hydrogen ions to the protein. Samples which demonstrated macroalbuminuria (in mg/dl) or gross proteinuria by the color indicator of the reagent strips (ranging from 1+ to 4+) were defined/ labeled as “nephropathy”. Samples with negative albumin were further examined for the presence of microalbumin in urine by MALB method used by Dimension® clinical chemistry system and device, in vitro diagnostic test for quantitative measurement of albumin (mg/L) in human urine by particle-enhanced turbidimetric inhibition immunoassay (PETINIA) methodology (Siemens Healthcare Diagnostics Inc. Newark, DE 19714, USA). Samples demonstrating microalbuminuria (albumin excretion in urine in the range of 30-300 mg/L) were also labeled and defined as nephropathy.

All laboratory sample requests were entered in a computer software and results retrieved by Natcom Hospital Information System (NATCOM HIS; National Computer System Co. Ltd [34].

Statistical methods

Patients' data were analyzed by IBM® SPSS® statistics, version 20, for Microsoft Windows. All statistical tests were applied according to the available standard medical statistical methods. Data were summarized as percentages with mean ± SD and 95% CI for the variables.

Independent t-test was used to test the significance between the groups of variables. For Pearson's correlation analysis and regression model development, all standard statistical assumptions were taken into account that variables must show linear relationship.

Predictive regression models were used to develop relationship of triglycerides (and TG/HDL ratio) and other variables (creatinine, microalbumin), and it was then estimated by mathematical linear equations to confirm that how serum lipids contribute to the development of high or increased levels of serum creatinine, urine microalbumin and development of DKD. To maximize the likelihood ratio, ROC curve was used for the estimation of sensitivity and specificity for triglycerides with detection of cutoff points for diagnosing DKD. Statistical power of 90% was built for detection of significance and p-values (two-sided) of less than 0.05 were considered significant.

Patient consent

This study was reviewed and approved by the research committee of Aseer Diabetes Center, and all methodologies on subjects reported in current study were in accordance with the Helsinki Declaration of 1975 (revised in 2008).

RESULTS

Demographic data for the patients is presented in Table-1. Nephropathy was observed in 38% of patients, while 13% demonstrated DKD/CKD. Descriptive statistics for variables are shown in table-2. Table-3 shows correlations between variables. It can be observed that correlations are significant for triglycerides and TG/HDL. Highest correlations were observed between TG/HDL with creatinine and microalbumin (0.298 and 0.394 respectively; p-values<0.0001 for both).

Table-4 shows significant t-test among group of variables (HbA1c, triglycerides, TG/HDL and creatinine). Hence, it is evident from the table-4 that levels of HbA1c, triglycerides, TG/HDL and serum creatinine were elevated among the patients with nephropathy, with significant p-values. Similarly, table-5 demonstrates significant differences of variables (HbA1c, triglycerides, TG/HDL and urine microalbumin) among the groups with and without DKD. It is evident that the levels of these variables are elevated among the patients with DKD.

Table-6 demonstrates the significant correlation and regression models between different variables. The regression models were significantly associated, with p-values <0.000 for all variables. This data prove that triglycerides and TG/HDL significantly contributes to the elevated levels

of serum creatinine and urine microalbumin and ultimately development of DKD.

Table 1: Demographic data of diabetic patients.

Parameters	Description with N (%); Totals=10,370	
Gender	Male	Female
	6201 (59.8%)	4169 (40.2%)
Type of Diabetes	Type-1	Type-2
	1451 (14%)	8919 (86%)
Nephropathy	Positive	Negative
	3940 (38%)	6430 (62%)
Diabetic Kidney Disease (DKD/CRD/CKD) status	Positive	Negative
	1348 (13%)	9022 (87%)

Table 2: Descriptive statistics for the variables with mean ± SD.

Variables	Mean ± SD
Age (years)	54 ± 14.4
Diabetes duration (years)	16 ± 9.7
Serum creatinine (mg/dl)	0.958 ± 0.681
HbA1c %(g/dl)	7.9 ± 1.48
Triglycerides (mg/dl)	157 ± 95.7
TG/HDL	4.32 ± 3.5
Microalbumin in urine (mg/L)	78.3 ± 107.3

For diagnostic statistics, and to confirm the regression models, and significant association of triglycerides with the development of nephropathy and DKD, Receiver Operating Curve (ROC) were constructed. The ROC for triglycerides and nephropathy demonstrated area under the curve (AUC) 0.559 (95% CI 0.530 to 0. 588; p-value <0.0001). By this observation and data analysis, for the detection of the development of nephropathy, a triglyceride cutoff point of 138 mg/dl with 65% sensitivity and 55% specificity was observed. Similarly, ROC for detection of DKD, a triglyceride cutoff point of 153 mg/dl with 60% sensitivity and 61% specificity was found (AUC 0.581; 95% CI 0.522 to 0.640; p-value <0.0001). These results are shown in table-7 and graphically in figures-1 and 2.

Table 3: Correlations of variables.

Variables	Pearson Correlation (r)	p-value
HbA1c and triglycerides	0.205	<0.0001
HbA1c and TG/HDL	0.103	0.021
Triglycerides and serum creatinine	0.269	0.006
TG/HDL and serum creatinine	0.298	0.002
Triglyceride and microalbumin	0.312	<0.0001
TG/HDL and microalbumin	0.394	<0.0001
HbA1c and microalbumin	0.212	<0.0001
Microalbumin and serum creatinine	0.273	<0.0001

DISCUSSION

Diabetic dyslipidemia is associated with microvascular and macrovascular complications of diabetes, as has been shown in the studies conducted past few decades [35,36]. Regarding guidelines for diabetic patients provided by American Diabetes Association (ADA) and National Cholesterol Education Program (NCEP), a target for LDL-C is <100 mg/dl, for triglycerides is <150 mg/dl; HDL-C>40 mg/dl is considered protective.

[37,38]. Generally, under these guidelines, a normal value of TG/HDL would be <3.75 (150 mg/dl/40 mg/dl).

Table 4: Significant statistical tests between groups of variables (with and without nephropathy) with mean ± SD and p-values.

Variables and indicators	Patients Variable Values With or Without Nephropathy		
	Mean ± 95% CI		P-values
	With Nephropathy	Without Nephropathy	
HbA1c % (g/dl)	8.2 ± 1.5	7.65 ± 1.46	0.001
	7.97 to 8.26	7.53 to 7.77	
	With Nephropathy	Without Nephropathy	
Triglyceride (mg/dl)	166.8 ± 105.5	149.4 ± 92.2	0.001
	159 to 175	144 to 156	
	With Nephropathy	Without Nephropathy	
TG/HDL Ratio	4.62 ± 3.77	4.08 ± 3.26	0.004
	4.32 to 4.93	3.85 to 4.31	
	With Nephropathy	Without Nephropathy	
Creatinine (mg/L)	1.15 ± 0.99	0.825 ± 0.25	<0.0001
	1.1 to 1.23	0.80 to 0.84	

Table 5: Significant statistical tests between groups (with and without DKD) of variables with mean ± SD and p-values.

Variables and indicators	Patients Variable Values With or Without DKD		
	Mean ± 95% CI		P-values
	With DKD	Without DKD	
HbA1c % (g/dl)	9.3 ± 2.2	7.8 ± 1.48	0.03
	9.1 to 10.2	7.75 to 7.94	
	With DKD	Without DKD	
Triglycerides (mg/dl)	179 ± 97	155 ± 91	0.018
	159 to 196	151 to 160	
	With DKD	Without DKD	
TG/HDL Ratio	5.18 ± 3.39	4.25 ± 2.9	0.009
	4.51 to 5.84	4.1 to 4.4	
	With DKD	Without DKD	<0.0001
Urine microalbumin (mg/L)	183 ± 128	64.2 ± 113	
	146 to 221	56.5 to 71.8	

One of the important and interesting finding demonstrated by recent research studies is the intra-renal accumulation of lipids which ultimately contribute to the glomerular injury via inflammatory pathways involving oxidative stress, pro-inflammatory cytokine and growth factor release [39-45]. Specifically, de novo triglycerides association with diabetes renal complication (DKD) has been observed also [46,47]. Conversely, and as demonstrated by studies, high levels of HDL-C is protective to the cardiovascular and renal systems [48].

High TG/HDL ratio in diabetic state is a significant risk factor for arterial stiffness and carotid atherosclerosis. Hence, atherosclerosis (due to high Triglycerides or TG/HDL) may contribute to the development of DKD [17]. Hence, clinical efforts should be done to reduce triglycerides and to elevate HDL-C to reduce diabetic related complications contributed by dyslipidemia [49-55].

Current study was designed and conducted to observe significant association of triglycerides and TG/HDL ratio with elevated levels of serum creatinine, and microalbuminuria and ultimately development of DKD or diabetic renal disease. Also elevated levels of HbA1c was observed among the patients who demonstrated creatinine > 1.5 mg/dl (DKD) and nephropathy (p=0.001; table-4). This signifies the importance of glycemic control [2]. Our data has demonstrated that 38% of the patients with diabetes developed nephropathy; while 13% demonstrated DKD. This is an alarming figure for the health care policy makers. Both triglycerides and TG/HDL were highly correlated with HbA1c (p <0.0001 and p=0.021, respectively; table-3); HbA1c was also significantly

correlated with microalbuminuria (p<0.0001). This signifies that elevated blood glucose elevates TG and ultimately both contribute to the development of DKD. Hence, to control elevated blood glucose should be the primary target. Diabetologist and physicians should make all efforts to reduce HbA1c to the standard goals in order to avoid further diabetes complications and to follow best available guidelines [56-58]. Furthermore, it was observed that both creatinine and urine microalbumin were significantly correlated (r=0.273; p <0.0001). Hence, microalbuminuria (nephropathy) and rising serum creatinine (CKD/DKD) were associated significantly, leading to Diabetic renal disease or renal failure.

Table 6: Correlation and regression models for the different variables.

Data and Variables	Pearson's Correlation (r)	P-Value for Pearson's Correlation	Regression Analysis				
			R^2	F-Statistic	ANOVA Model P-Value	T-Statistic	P-Value
Triglycerides and serum creatinine	0.269	0.006	0.072	7.59	0.006	23.3	<0.0001
TG/HDL and serum creatinine	0.298	0.002	0.088	9.4	0.002	30.9	<0.0001
Triglycerides and urine microalbumin	0.312	<0.0001	0.097	16.1	<0.0001	5.56	<0.0001
TG/HDL and urine microalbumin	0.394	<0.0001	0.155	17.56	<0.0001	7.03	<0.0001
Mathematical / Statistical Regression models and equations							
Triglycerides and serum creatinine		Serum creatinine = 0.884+[0.001 × serum triglycerides]					
TG/HDL and serum creatinine		Serum creatinine = 0.906+[0.016 × TG/HDL]					
Triglycerides microalbuminuria		Microalbuminuria = 17+[0.075 × serum triglycerides]					
TG/HDL and urine microalbumin		Microalbuminuria = 15+[2.9 × TG/HDL]					

Table 7: Results of ROC with AUC, 95% CI, p-values and triglyceride cutoff points.

Test variables	Area under the curve (AUC)	Standard error	95% CI	P-Value	Coordinate triglyceride cutoff points for the detection/ diagnosis of nephropathy and DKD
Triglycerides and nephropathy status	0.559	0.015	0.530 to 0. 588	<0.0001	138 mg/dl (65% sensitivity and 55% specificity)
Triglycerides and DKD status	0.581	0.03	0.522 to 0.640	0.005	153 mg/dl (60% sensitivity and 61% specificity)

Excretion of albumin (or microalbumin) in the urine is an early marker of renal dysfunction or damage in diabetes, causing proteinuria or nephropathy, which may lead to stage renal disease (ESRD) with high incidence (up to 40-50%).

Persistence albumin excretion in urine in the range 30-299 mg/24 h (termed microalbuminuria, and first defined in 1985) is the earliest indicator and marker of incipient diabetic nephropathy and early renal damage in type-1 and type-2 diabetic subjects. Traditionally, the term "diabetic nephropathy" was previously defined as chronic kidney disease (CKD) resulting due to chronic exposure of hyperglycemia in diabetes. However, recently the Diabetes and Chronic Kidney Disease work group of the National Kidney Foundation (NKF) and Kidney Disease Outcomes Quality Initiative (KDOQI) suggested that a diagnosis of CKD presumed to be caused by diabetes should be referred to as “diabetic kidney disease (DKD)” and the term diabetic nephropathy” should be reserved for kidney disease caused by diabetes with histopathological injury demonstrated or proven by renal biopsy. CVD risk is increased to double in diabetic patients with microalbuminuria than those without microalbuminuria. There is inverse relation between microalbumin and GFR. Hence, as albumin excretion in urine increases, GFR decreases and also CVD risk increases progressively. Studies have demonstrated that microalbuminuria ≥ 300 mg/24 h (also called macroalbuminuria) may progress to ESRD if adequate interventions are not taken [11,59-67].

Our statistical analysis have shown significant correlation among triglycerides, serum creatinine and urine microalbumin (p=0.006 and p<0.0001, respectively; table-3). Similarly TG/HDL ratio was also associated and significantly correlated with serum creatinine and urine microalbumin (p <0.0001 for both; table-3). This implies involvement of lipids (especially triglycerides) in raising creatinine and urine microalbuminuria. It was interested to note that, highest correlations were found between TG/HDL ratio with microalbumin (r=0.394; table-3), indicating increasing proteinuria when triglycerides are elevated and HDL decreases (protective cholesterol).

While comparing variables for the development of nephropathy or proteinuria (i.e., with or without nephropathy), it was observed that HbA1c was significantly higher among the patients who demonstrated nephropathy (8.2 ± 1.5; 95% CI 7.97 to 8.26 and 7.65 ± 1.46; 95% CI 7.53 to 7.77 respectively; p=0.001). Similarly, the group demonstrating nephropathy showed higher levels of Triglycerides (166.8 ± 105.5; 95% CI 159 to 175 and 149.4 ± 92.2 144 to 156 respectively; p=0.001), and raised TG/HDL ratio (4.62 ± 3.77; 95% CI 4.32 to 4.93 and 4.08 ± 3.26 95% CI 3.85 to 4.31 respectively; p=0.004). Our data has also proved that creatinine levels were also higher among the groups demonstrated nephropathy (1.15 ± 0.99; 95% CI 1.1 to 1.23 and 0.825 ± 0.25; 95% CI 0.80 to 0.84 respectively; p<0.0001). All these evidence indicate involvement of higher levels of triglycerides (and low HDL) in the

development of nephropathy (proteinuria) and chronic renal failure or diabetic kidney disease (CKD/DKD) by increasing serum creatinine.

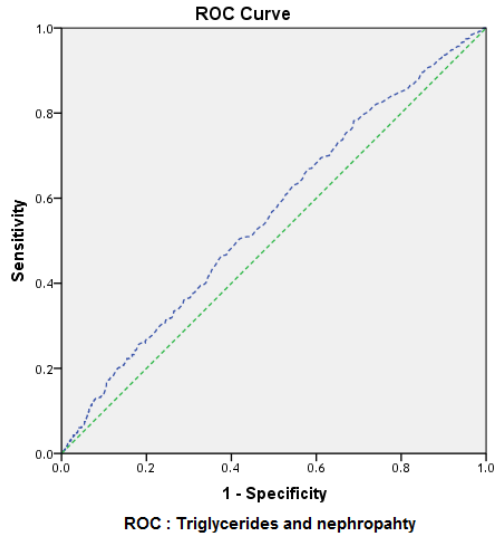

Figure 1: ROC for triglycerides and nephropathy.

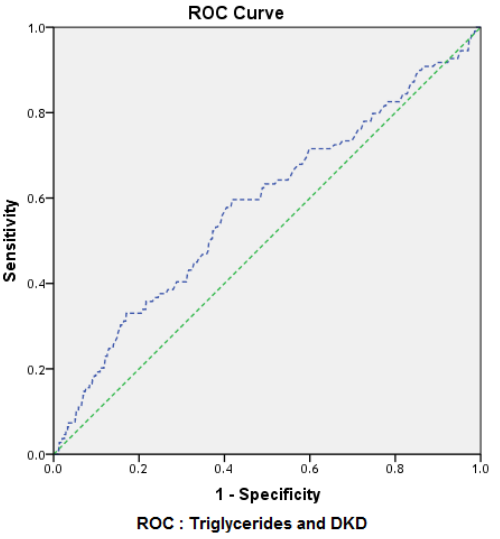

Figure 2: ROC for triglycerides and DKD.

When variables were compared with the group of patients with or without DKD, it was observed that HbA1c was higher among the patients with DKD with significant difference (9.3 ± 2.2; 95% CI 9.1 to 10.2 and 7.8 ± 1.48; 95% CI 7.75 to 7.94 respectively; p=0.03). This again demonstrates the significance of good glycemic control. Serum triglyceride levels were higher among the patients with DKD (179 ± 97; 95% CI 159 to 196 and 155 ± 91; 95% CI 151 to 160; p=0.018). Similarly, TG/HDL ratio was higher among DKD patients with significant difference (5.18 ± 3.39; 95% CI 4.51 to 5.84; and 4.25 ± 2.9; 95% CI 4.1 to 4.4 respectively; p=0.009). It was also observed that urine microalbumin levels were also significantly higher among the DKD group (183 ± 128; 95% CI 146 to 221 and 64.2 ± 113; 95% CI 56.5 to 71.8 respectively; p <0.0001). These findings are consistent with previous studies, as mentioned above. However, previous research studies did not analyzed the cohort data in such a manner analyzed in the current study. Similarly, regression models were not developed which shows correlation between triglycerides (or TG/HDL ratio) and serum creatinine with development of proteinuria (nephropathy) and diabetic kidney disease. This was achieved in the current study which has demonstrated that how rising triglyceride levels can contribute to the development of DKD/CKD in diabetic subjects.

Table-6 demonstrates the mathematical regression models and equations. The mathematical equation for triglycerides and serum creatinine is: serum creatinine=0.884 + [0.001 × serum triglycerides]. Hence, if Triglycerides are 200 mg/dl, for example, then serum creatinine will be approximately 0.18 mg/dl. However, if triglyceride levels are up to 270, for example, then the predicted serum creatinine would be 1.154 mg/dl. Chronic exposure of tryglycerides with levels of 400 mg/dl will increase the serum creatinine to 1.284 (~1.3). Chronically, this dramatic increase in serum creatinine will lead to DKD. Similarly, and according to this experimental observation, chronic elevations of triglycerides will increase microalbuminuria or proteinuria excretion via kidney. For example, by the given mathematical equation in table-6, if the triglyceride levels are within the normal range, or less than 150 mg/dl, the microalbuminuria levels will be 28 mg/L. However, chronic elevation of triglycerides with the level of 250, for example, will lead to more albumin excretion from the kidney with the levels reaching 35.75 mg/L.

Regarding TG/HDL ratio, and according to the guidelines, a ratio less than 3.75 is considered normal. According to the data analysis of the current study (table-6), a TG/HDL ratio of 4, for example, will give the value of serum creatinine of 1.04 mg/dl. However, and for example, if HDL-C is low with the value of 35 mg/dl, and triglycerides are high with the levels of 300 mg/dl, then the TG/HDL ratio will be 8.57; this will increase the serum creatinine up to levels of 1.2 mg/dl. Similarly, regarding albumin secretion and TG/HDL ratio, it can be observed from the table-6 that, if TG/HDL ratio is 3.75, the according to the hypothesized mathematical equation, microalbuminuria levels will be up to 25.9 mg/L. However, if this ratio is 8.75, then microalbumin excretion from the kidney will be up to 40.3 mg/L. Hence, elevated triglycerides of TG/HDL ratio will lead to the elevation of serum creatinine, urine micoalbumin, and ultimately to DKD.

To confirm the finding of the current study, and to find the cutoff levels for triglycerides which may lead to the nephropathy and DKD, receiver operating curve (ROC) was used. According to the table-7, it can be observed that the area under the curve (AUC) for relation of triglycerides with the development of nephropathy was 0.559 (95% CI 0.530 to 0. 588; p <0.0001) with triglyceride cutoff point value 138 mg/dl (65% sensitivity and 55% specificity).Similarly, area under the curve (AUC) for relation of triglycerides with the development of DKD (or CKD) was 0.581 (95% CI 0.522 to 0.640; p=0.005) with triglyceride cutoff point value 153 mg/dl (60% sensitivity and 61% specificity). Figures 1 and 2 demonstrate these results graphically.

The diabetologist must screen every patient for the dyslipidemia and microalbuminuria; early treatment is recommended, to prevent development and progression of diabetes related complications.

Three classes of medications are available in the market and appropriate for the management of major triglyceride elevations: fibric acid derivatives (gemfibrozil (Lopid) and fenofibrate (Lipanthyl), niacin, and omega-3 fatty acids. Furthermore, high doses statins (simvastatin, atorvastatin, rosuvastatin) also effective to lower triglycerides by 50%. Niacin (vitamin B-3) decreases triglyceride levels by at least 40% and can raise HDL cholesterol levels by 40% or more. However, it is associated with some side effects such as chemical hepatitis and worsening of glycemic control and increasing the insulin resistance. Omega-3 fatty acids (with a dose of 4 g/day). The triglyceride-lowering effects of fish oils are entirely dependent on the omega-3 content. HDL-C levels can effectively be raised by regular exercise/activity or daily regular walk [68-84].

To prevent nephropathy (and development of microalbuminuria), it is recommended that diabetic hypertensive patients should be treated with ACE inhibitors or ARBs, usually in combination with a diuretic. Target blood pressure for diabetics and those with DKD/CKD stages 1-4 should be <130/80 mmHg [11].

CONCLUSIONS AND RECOMMENDATIONS

Diabetic nephropathy, DKD and ESRD are renal complications of diabetes. As demonstrated by the current study, triglycerides and TG/HDL ratio were significantly associated with the development of nephropathy and DKD. Hence, with the glycemic control, it is advisable to target diabetic dyslipidemia or hypertriglyceridemia to prevent renal complications. Early detection of blood pressure, microalbuminuria screening and lipid profile analysis is recommended at tertiary care diabetes centers.s

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