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Original Article

Significance of glycated LDL in different stages of diabetic nephropathy

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ABSTRACT

Aim: The aim of this study was to investigate the role of elevated glycated LDL (low-density lipoprotein) in the progression of diabetic kidney disease among type 2 diabetes (T2D) subjects.
Materials and methods: This case-control observational study is a part of Saudi Diabetes Kidney Disease (SAUDI-DKD) study conducted during the period from April 2014 to June 2015. This study cohort is divided into two groups; the first group was T2D patients without diabetic nephropathy (DN) (n = 24) and the second group was T2D with DN (n = 45). Serum glycated LDL levels were determined by ELISA. Pearson's correlation analysis was performed, and the diagnostic accuracy was assessed using the area under the ROC curve.
Results: There was a threefold increase of serum glycated LDL level among diabetic subjects when compared with non-diabetic subjects and this level progressively increased with the progression of DN. The glycated LDL was found to have a significant diagnostic accuracy with AUC of 0.685 and 0.775 for cases with microalbuminuria and macroalbuminuria respectively.
Conclusion: The glycated LDL could play a significant role in predicting diabetic patients who are susceptible to develop DN among T2D patients.

1. Introduction

Diabetes mellitus is one of the most common chronic diseases associated with high morbidity and mortality, wherein about 424.9 million adults globally had diabetes in 2017 and this is expected to rise to 628.6 million by 2045 [1]. Diabetic nephropathy (DN) is considered to be one of the most common complications which affect approximately 30% of the global population with diabetes. It is also the leading cause of end-stage renal disease in many populations and is associated with high mortality and increased medical care cost [2–4]. The patients with diabetes suffering from diabetic kidney disease are more frequently subjected to hospitalization with or without any cardiovascular events [5]. The incidence of diabetic kidney disease has not shown any decrease in the last 20 years despite improvements in diabetes management and better glucose control [6]. There is enough scientific evidence that proves the role of screening and early intervention in delaying the disease progression for DN [7].

DN is characterized by a progressive increase in albuminuria and glomerular damage as a result of glomerular sclerosis that may resemble atherosclerosis where the lipids may play an important role. The increased level of glucose in patients with diabetes will glycate different proteins, one of which is the β-lipoprotein molecule in low-density lipoprotein (LDL) cholesterol that would affect the chemical and physical structure of LDL and increase its atherogenicity effect [8]. The glycation of LDL molecule promotes oxidation of the apolipoprotein core. This eventually allows glycol oxidized LDL to exaggerate cellular responses and enhance macrophage infiltration and produce excessive extracellular matrix production in the glomeruli that may lead to the development of glomerulosclerosis [9,10].

Scientific literature proves the correlation between glycated LDL and urinary albumin excretion which in turn supports the hypothesis that an elevation of glycated LDL represents an

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atherogenic risk factor and may contribute to glomerulosclerosis as observed in patients with diabetes kidney disease [11,12]. Although glycated LDL may help in identifying subjects with diabetes who are at a high risk of developing microvascular complications, more studies on glycation of lipoproteins are needed to explore the importance of this mechanism in microvascular complications and its role in glomerulosclerosis, which is the clear indicator of DN [8]. However, studies on younger patients with chronic kidney disease (CKD) shows no association between glycated LDL and CKD stages, suggesting the necessity of larger studies to elucidate its role in kidney disease [13].

In this study, we investigate the role of elevated glycated LDL in causing DN and its progression in persons with type 2 diabetes (T2D) using a cohort from Arab ethnicity known to have diabetes epidemic.

2. Materials and methods

2.1. Study sample and design

This is a matched case-control study using the Saudi Diabetes Kidney Disease (SAUDI-DKD) cohort attended University Diabetes Center at King Saud University during the period from 1 April 2014 till 18 June 2015. The selected cohort for this study was divided into two groups; the first group consists of 24 patients with T2D without DN and the second group consisted of 26 T2D patients with microalbuminuria and 19 patients with macroalbuminuria. Out of these cohort, 24 diabetic subjects without DN and another 26 diabetic patients with microalbuminuria and 19 diabetic patients with macroalbuminuria were randomly selected. All the patients recruited for these three groups were older than 30 years of age regardless of their gender. To come up with normal value for glycated LDL 20 normal subjects without diabetes used as a third matching group were recruited separately from the same ethnicity of normal companions found during the survey. All the selected healthy normal subjects had normal lipid parameters. Pregnant women, patients with non-diabetic kidney disease and patients with blood disorders or anemia were excluded from the three study groups.

This study was reviewed and approved by the institutional review board at the College of Medicine, King Saud University. Informed consent was obtained from each subject and the study was conducted in accordance with declarations of Helsinki and followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting recommendation guidelines [14].

2.2. Data collection

Clinical data including age, gender, body mass index (BMI) and duration of diabetes were collected from the hospital charts. Both systolic and diastolic blood pressure (SBP and DBP) was measured by trained nurses in a sitting position using mercury sphygmomanometer. After an overnight fast of 10 h, venous blood samples were collected using EDTA and plain tubes and fresh 10 cc urine sample was obtained in plain sterile bijou tube. Serum and urine samples were stored at −20 °C and were transported to the central laboratory at the Strategic Center for Diabetes Research.

2.3. Patients' classification

Subjects without diabetes were subjected to 75 gm glucose load to perform 2 h oral glucose tolerance test (OGTT). The American Diabetes Association (ADA) criteria of fasting <100 mg/dl and 2 h post prandial < 140 mg/dl was used to identify normal subjects [15]. For patients with T2D, ADA criteria were used to define those cases who were managed with either oral hypoglycemic agents and/or insulin.

The diabetic kidney disease cohort was classified according to the estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (ACR) values, wherein the non-nephropathic subjects had eGFR >60 ml/min/1.73 m^2 and ACR <30 mg/g, microalbuminuria subjects with ACR between 30 and 299 mg/g, whilst the macroalbuminuria subjects had ACR ≥ 300 mg/g. The urinary ACR was calculated from the urinary albumin to creatinine ratio.

The renal function tests, lipid profile parameters, Apo A1 and Apo B as well as urinary parameters, were performed using Rx Daytona clinical chemistry analyzer by Randox (UK). Hemoglobin A1c (HbA1c) was assessed based on a latex agglutination inhibition assay with the same chemistry analyzer. Serum glycated LDL level was analyzed using commercially available kit (Mybiosource) based on enzyme linked immunosorbent assay (ELISA). Intra- and inter-assay precisions of coefficient of variation (CV %) of glycated LDL assay was <8% and <10% respectively.

2.4. Data analysis

Data were analyzed using SPSS version 21.0, IBM, Chicago, Illinois, USA. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentages. Student *t*-test and ANOVA was used to compare groups. eGFR was calculated by http://www.davita.com/gfr-calculator and ACR by http://www.pace-med-apps.com/ualbcalc.htm. Correlation analysis was carried out using Pearson correlation. Receiver operating characteristic (ROC) curve analysis was carried out for microalbumiuria, macroalbuminuria and both groups for diagnostic accuracy. Box plot was drawn for glycated LDL according to albumin excretion and eGFR. A p value ≤ 0.05 was used as a level of significance.

3. Results

In this study, the glycated LDL normal value for this ethnic group was calculated by using 20 normal subjects without diabetes who were matched for age, gender, BMI and who had normal lipid and renal function with no history of hyperlipidemia. The mean LDL for this cohort was 128.0 ± 26.5 mg/dl and the concentration of glycated LDL was 0.17 ± 0.05 mg/dl. When calculating the percentage of glycated LDL to total LDL it was found to be 0.13%.

Table 1 demonstrates the demographic and clinical characteristics of the selected cohort with diabetes with or without DN. It has been shown that both groups matched the same except for SBP, fasting blood sugar (FBS), HbA1c and eGFR which was significantly different among DN subjects as expected.

In this study, glycated LDL concentration and its percentage were significantly higher among patients with micro or macroalbuminuria when compared with patients without nephropathy. The glycated LDL to HbA1c ratio was also significantly higher among nephropathic patients even though both these groups did not show any significant difference for Apo A1 and Apo B.

When the different stages of DN namely microalbuminuria and macroalbuminuria were observed, there was a significant increase of glycated LDL concentration and percentage among patients with macroalbuminuria but no significant difference was observed in the ratio of glycated LDL to HbA1c. Moreover, as expected, there was a significant increase in urea and urinary ACR (UACR) going from normal diabetic to microalbuminuria and then macroalbuminuria cases, but both Apo A1 and Apo B concentration did not show any significant difference when compared between nephropathic and non-nephropathic subjects.

Table 1
Demographic and clinical characteristics of T2D and different stages of DN (n = 69 total subjects).

Patient characteristics	T2D without DN n = 24	T2D with DN n = 45	p value	Microalbuminuria n = 26	Macroalbuminuria n = 19	p value
Age (y)	55.1 ± 5.4	55.4 ± 7.1	0.859	54.6 ± 6.9	56.4 ± 7.5	0.679
Gender (M/F)	8/16	22/23	0.214	10/16	12/7	0.102
Duration of diabetes (y)	18.0 ± 5.4	19.6 ± 6.1	0.280	20.6 ± 6.4	18.2 ± 5.4	0.221
BMI (kg/m^2)	32.0 ± 4.4	33.0 ± 6.0	0.483	34.9 ± 5.6	30.4 ± 5.8	0.019
SBP (mmHg)	127.8 ± 15.9	144.5 ± 19.4	<0.001	137.5 ± 16.4	154.2 ± 19.3	<0.001
DBP (mmHg)	73.0 ± 8.8	74.5 ± 10.0	0.547	73.8 ± 10.2	75.5 ± 9.8	0.695
Total cholesterol (mg/dl)	184.9 ± 32.9	203.7 ± 64.6	0.186	206.5 ± 68.6	199.8 ± 59.9	0.389
Triglyceride (mg/dl)	162.2 ± 68.7	207.7 ± 115.9	0.083	187.4 ± 85.5	235.5 ± 146.0	0.066
HDL cholesterol (mg/dl)	45.9 ± 11.5	45.2 ± 10.3	0.800	46.1 ± 9.6	44.1 ± 11.3	0.793
LDL cholesterol (mg/dl)	136.4 ± 37.7	149.1 ± 68.0	0.400	157.1 ± 73.1	138.2 ± 60.6	0.407
FBS (mg/dl)	160.3 ± 61.3	221.8 ± 82.9	0.002	229.9 ± 79.4	210.8 ± 88.3	0.007
HbA1C (%)	9.5 ± 1.7	10.6 ± 2.05	0.045	10.2 ± 1.8	11.1 ± 2.2	0.043
Glycated LDL (mg/dl)	0.55 ± 0.23	0.86 ± 0.38	0.001	0.82 ± 0.31	0.90 ± 0.47	0.004
Glycated LDL (%)	0.42 ± 0.18	0.67 ± 0.42	0.011	0.60 ± 0.36	0.75 ± 0.48	0.018
Glycated LDL (%)/HbA1C (%)	0.04 ± 0.02	0.06 ± 0.04	0.031	0.06 ± 0.03	0.07 ± 0.04	0.084
Urea (mg/dl)	32.3 ± 10.1	47.8 ± 29.2	0.015	36.5 ± 15.7	63.2 ± 36.1	<0.001
Creatinine (mg/dl)	1.3 ± 1.1	1.6 ± 0.68	0.330	1.3 ± 0.28	1.9 ± 0.92	0.068
UACR (mg/g)	9.3 ± 7.9	482.8 ± 878.8	0.011	112.3 ± 78.0	989.7 ± 1187.5	<0.001
eGFR (ml/min/1.73m^2)	61.4 ± 12.0	49.9 ± 12.2	0.001	53.7 ± 10.2	44.1 ± 13.0	<0.001
APO A1 (mg/dl)	146.7 ± 20.4	154.9 ± 28.6	0.251	158.1 ± 27.6	150.5 ± 30.2	0.331
APO B (mg/dl)	107.1 ± 18.3	97.6 ± 41.3	0.289	91.6 ± 39.1	105.7 ± 43.9	0.238

BMI (body mass index), SBP (systolic blood pressure), DBP (diastolic blood pressure), HDL (high density lipoprotein) cholesterol, LDL (low density lipoprotein) cholesterol, FBS (fasting blood sugar), UACR (urinary albumin creatinine ratio), eGFR (estimated glomerular filtration rate), T2D (type 2 diabetes), DN (diabetic nephropathy). Values are given as mean ± SD. $p \leq 0.05$ is statistically significant. Normal value of glycated LDL in healthy subjects is 0.17 ± 0.05 mg/dl.

Pearson's correlation analysis for glycated LDL concentration have shown a significant positive correlation with SBP, UACR, urea, Apo A1 and HbA1c.This study also demonstrated that age, BMI, waist circumference and DBP has no effect on the level of glycated LDL. At the same time total cholesterol, triglyceride, high density lipoprotein (HDL) and LDL concentration has non-significant positive correlation. In contrary FBS, eGFR and APO B had negative non-significant correlation (Table 2).

Fig. 1 A is the box plot value for glycated LDL concentration in different study groups where it showed significant increase among subjects with diabetes when compared with subjects without diabetes. The glycated LDL concentration showed a significant increase among subjects with microalbuminuria but not with macroalbuminuric patients when compared with patients with diabetes without nephropathy. When correlating glycated LDL with eGFR values, it was the lowest among subjects with eGFR ≥60 ml/min/1.73 m^2. Glycated LDL increased significantly in subjects who had eGFR between 45 and 59 ml/min/1.73 m^2 but not among subjects with eGFR either between 44 and 30 ml/min/1.73m^{2}or less than 29 ml/min/1.73 m^2 as shown in Fig. 1 B.

When ROC curve was used to evaluate the diagnostic value for glycated LDL in predicting DN in patients with microalbuminuria and macroalbuminuria, the area under the curve (AUC) values were 0.685 ± 0.58 and 0.755 ± 0.61 respectively which had a significant diagnostic value with $p < 0.05$. The AUC was lower when both groups were added with a significant value, as shown in Fig. 2.

Table 2
Pearson correlation analysis of glycated LDL concentration with clinical and biochemical parameter.

Parameter	Glycated LDL (mg/dl) (r)	p value
Age (y)	0.022	0.860
BMI (kg/m^2)	0.032	0.802
Waist circumference (cm)	0.026	0.841
SBP (mmHg)	0.309	0.013
DBP (mmHg)	0.065	0.609
HbA1C (%)	0.283	0.024
FBS (mg/dl)	−0.011	0.932
Total cholesterol (mg/dl)	0.149	0.239
Triglyceride (mg/dl)	0.047	0.711
HDL cholesterol (mg/dl)	0.184	0.146
LDL cholesterol (mg/dl)	0.028	0.823
Diabetes duration (y)	0.031	0.808
UACR (mg/g)	0.480	0.001
Urea (mg/dl)	0.252	0.045
Creatinine (mg/dl)	0.115	0.366
eGFR (ml/min/1.73m^2)	−0.209	0.104
APO A1 (mg/dl)	0.475	0.001
APO B (mg/dl)	−0.013	0.918

$p \leq 0.05$ is statistically significant.

4. Discussion

It is very clear from this study that there was a threefold increase in glycated LDL among patients with diabetes when compared with the subjects without diabetes, which is also the observation from other such studies [16]. This increased level of glycated LDL among patients with diabetes have also been reported among Arabs irrespective of their hyperlipidemia state [17]. The mean glycated LDL concentration progressively increased with UACR, correlating with the degree of hyperglycemia represented by elevated HbA1c. Both glycated LDL and albumin excretion are influenced by hyperglycemia so it will be difficult to separate those two factors when testing for glomerular structural change [11]. The glycated LDL concentration and its percentage in patients with macroalbuminuria were almost double of that observed in patients with diabetes without proteinuria. This observation is similar to what has earlier been found in Caucasian and Chinese ethnicities [11,18]. This could be explained by the fact that glycated LDL exaggerates cellular response and increases macrophage infiltration which may lead to glomerulosclerosis.

A positive correlation between glycated LDL and SBP was observed in this study. This could be a result of sclerotic changes that affects the vessel elasticity which may increase the systolic part of blood pressure. Additionally, a culture porcine aortic endothelial cells exposed *invivo* to glycated LDL increased superoxide release by fivefold when compare to non-glycated LDL which would support our findings in this study [16].

This study has demonstrated a positive correlation between UACR and glycated LDL similar to what has earlier been reported by

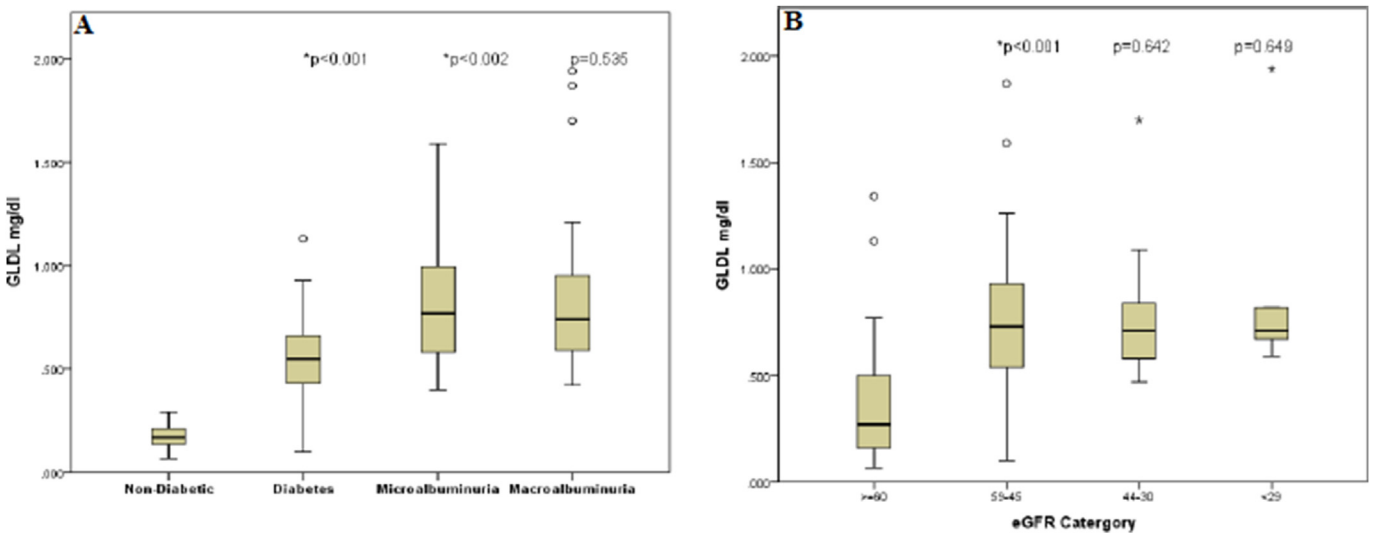
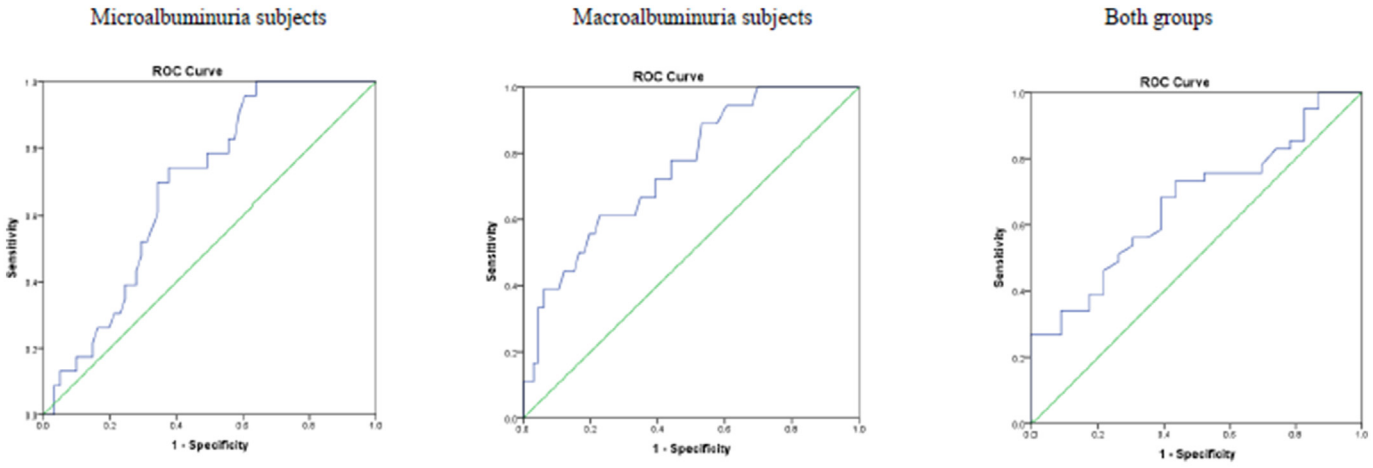


Fig. 1. Box plot values for glycated LDL (GLDL) concentration classified according to albumin excretion and eGFR values.



	Area under the Curve(AUC)	Std Error	95% confidence Interval		P value
			Lower Bound	Upper Bound	
Microalbuminuria subjects	0.685	0.58	0.572	0.799	0.009
Macroalbuminuria subjects	0.755	0.61	0.635	0.875	0.001
Both groups	0.668	0.68	0.534	0.801	0.027

Fig. 2. The area under the ROC curve values for glycated LDL in subject with microalbuminuria, macroalbuminuria and both groups.

Cohen et al. and can also be an indicator for renal function deterioration among patients with diabetes [11]. Such findings are consistent with the hypothesis that glycated LDL is an atherogenic factor which would exaggerate urinary albumin excretion. In this study, we have also found that the mean glycated LDL concentration in patients with macroalbumiuria and microalbuminuria was significantly higher than normoalbuminuric subjects. This may indicate that glycated LDL correlates with albumin excretion and that glycated LDL increase may antecede DN.

Glycated LDL also correlated positively with HbA1c as expected but with a stronger correlation with Apo A1 and is similar to what had earlier been found among Kuwaitis subjects with diabetes [17]. On the contrary, we have found that glycated LDL correlated negatively with Apo B although it was non-significant which could be the reflection of glycation of Apo B in the glycated LDL molecule as more glycation reduces Apo B concentration.

In this study, glycated LDL had a good diagnostic accuracy for both microalbuminuria and macroalbuminuria. The diagnostic value for glycated LDL needs further evaluation through conducting prospective studies since abnormal levels of glycated LDL may proceed kidney injury especially when it has been found that glycated LDL induces adverse cellular response including foam cell formation, cell proliferation and matrix overproduction that may end by glomerulosclerosis.

The limitation of this study includes its cross-sectional design, which limits assessing temporal relation and causality. The primary strength of this study is it being a study involving different stages of DN with a very accurate case definition. The secondary strength

point is it being one of the early studies which investigated the role of glycated LDL in DN. The involvement of subjects without diabetes in this study has helped in setting normal values for glycated LDL in this ethnicity.

5. Conclusion

We could thereby conclude from this study that hyperglycemia observed among patients with diabetes would increase LDL glycation markedly and that the concentration of glycated LDL will be even higher in patients with microangiopathy. Glycated LDL is known to promote atherogenicity and could play an important role in diabetic kidney disease even during the early stages of DN. Glycated LDL concentration had a good diagnostic value in detecting both microalbuminuria and macroalbuminuria. Our findings in this study indicate a real need for large prospective studies that would evaluate glycated LDL value in screening for DN, especially microalbuminuria and macroalbuminuria.

Authors' contribution

All authors substantially contributed to: (1) conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

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Compliance with ethical standards

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board at College of Medicine, King Saud University (IRB approval number: E-13-1010) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all the study subjects.

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