ORIGINAL ARTICLE

Targeting LDL Dyslipidemia for Controlling Progression of Nephropathy in Diabetic Population: A Cross Sectional Analytical Study

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ABSTRACT

Objectives: The purpose of the current study was to find out the correlation and cause effect relationship between LDL cholesterol and nephropathy in diabetic population.
Design: Retrospective cross sectional analytical study.
Patients and Methods: A total of 883 adult diabetic patients were selected for this study. Serum LDL cholesterol, creatinine, urine macroalbumin and microalbumin were measured by standardized laboratory methodology. LDL>100mg/dl was labeled as dyslipidemia and presence of microalbuminria or macroalbuminuria was defined as nephropathy.
Results: Out of 883 patients, 630 patients (71.3%) showed dyslipidemia while 253 patients (28.7%) were found to have nephropathy. Subjects with dyslipidemia (LDL>100) showed slightly higher serum creatinine levels with mean 1.022±0.74 mg/dl as compared to those without dyslipidemia with mean creatinine 1.004±0.63 mg/dl. However subjects labeled with nephropathy demonstrated marked elevated serum LDL cholesterol with mean 125.7±44.8 mg/dl as compared to those without nephropathy where LDL mean was 114±39 mg/dl. Spearman's correlation for cause effect relationship between serum LDL and nephropathy was highly significant ($p < 0.001$).
Conclusion: The observed data indicate that higher LDL levels are associated with raised creatinine levels, development and progression of nephropathy. Controlling LDL dyslipidemia is one of the effective strategies towards diabetes management to prevent diabetic nephropathy.

Key words: Diabetes, Dyslipidemia, LDL-Cholesterol, Microalbuminuria, Nephropathy.

INTRODUCTION

Diabetic nephropathy still remains one of the leading causes of end stage renal disease (ESRD) worldwide, requiring renal replacement therapy.[1-2] Preventing or delaying the progression of nephropathy is therefore important. According to current available medical literature, where baseline albumin excretion rate (AER) and chronic hyperglycemia are well defined risk factors,[3] hyperlipidemia also contribute to progression of diabetic kidney disease and nephropathy[4] and 60% of patients with chronic renal disease (CRD) show dyslipidemia.[5-6] Interestingly, studies have shown common etiological factors and pathobiologic mechanisms which are involved both in kidney damage and atherosclerosis.[7] Therefore it can be stated that the risk factors are similar for two separate diseases. With the advancement of nephropathy, risk of other diabetic complications also rises. Typically risk of cardiovascular disease (CVD) increases dramatically with the progression of renal disease. In other words, targeting therapy to limit or control progression of nephropathy may also limit cardiovascular complications, and vise versa.

Furthermore, microalbuminuria and macroalbuminuria are predictors of future proteinuria, progressive decline in renal function and diabetic kidney diseased leading to ESRD requiring dialysis or renal transplantation, accelerated atherosclerosis, and ultimately premature death from coronary artery disease (CAD).[8-10] Patients with type-2 diabetes mellitus are at increased for the development of cardiovascular morbidity and mortality compared with non diabetic subjects. This risk rises even further when diabetic subjects demonstrate proteinuria, irrespective of quantity.[11-16] Hence detecting nephropathy at maicroalbumin stage is of crucial importance to prevent further progression of nephropathy. However, poor glycemic control, smoking and hypertension also remain the risk factor for the development of nephropathy and other diabetes related complications.[17]

Current available literature also shows that small dense LDL (low density lipoproteins) particles are known to be highly atherogenic, linked with insulin resistance, and cause cardiovascular disease via atherosclerosis.[18-20] Oxidized LDL (oxLDL) cause endothelial injury,

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atherosclerosis and play significant role in tissue ischemia.[21] Furthermore, in vitro studies on rats, oxidized LDL particles induce ischemia and, stress, and damage in cultured renal tubular cells.[22] Research finding in a cross-sectional study, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), has also demonstrated significant relation of LDL with that of albumin excretion (AER) and nephropathy.[23] Hypercholesterolemia and LDL dyslipidemia are hence triggers for the development and progression of nephropathy in diabetic subjects. LDL dyslipidemia directly affect the kidney by enhancing albumin excretion and further development of advanced nephropathy. The natural history of diabetic nephropathy initially demonstrates only microalbuminuria, undetectable by routine laboratory urine analysis, which may progress to macroalbuminuria, and finally to heavy proteinuria. Once proteinuria develops, glomerular filtration rate (GFR) declines, eventually leading to ESRD over several years. This highlights the importance of microalbumin detection in urine samples by specialized laboratory methodology.

In most of the busy clinical settings, only the management of hyperglycemia is focused initially, leaving behind the predictors for the development of dyslipidemia and nephropathy. Early detection of elevated LDL levels, microalbuminuria and macroalbuminuria and their specific treatments are of crucial importance in the diabetes management. Given this background, objective of the current study was to find out association and cause effect relationship between LDL cholesterol and nephropathy in diabetic population, which so far has not been studied.

PATIENTS AND METHODS

The present study is a retrospective cross sectional analytical study. For this, data of adult 883 known diabetic patients were collected on follow up visits to diabetology clinic of Aseer Diabetes Center of Aseer Central Hospital, from august 2008 till September 2011. Children (less than 13 years) and pregnant diabetic subjects were excluded from the study. Similarly patients demonstrating presence of proteinuria due to infection or known cases of chronic kidney disease, nephrotic syndrome or gross proteinuria / albuminuria prior to the diagnosis of diabetes were also excluded from the study.

All laboratory measurements were done in fasting state of not less than 12 hours. LDL (mg/dl) was measured directly in plasma by Automated Low Density Lipoprotein (ALDL) method for the Dimension® clinical chemistry system and analyzer (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A), an in vitro diagnostic test intended for quantitative determination of low density lipoprotein cholesterol (LDL-C). Similarly serum creatinine (mg/dl) was measured quantitatively by CREA method by Dimension® clinical chemistry system (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A). LDL > 100 mg/dl was labeled as dyslipidemia. Criteria for nephropathy were determined by presence of microalbuminuria, macroalbuminuria or proteinuria in the urine samples. For this, Quik Check™ urinalysis reagent strips (ACON biotech, Co., Ltd) were used in first morning urine samples in fasting state. Patients exhibiting macroalbuminuria or proteinuria by the color change were labeled nephropathy. Those with negative albuminuria or proteinuria with reagent strips, were again screened for the presence of microalbuminuria (mg/L) on fresh early morning urine samples by MALB method used on Dimension® clinical chemistry system, in vitro diagnostic test for quantitative measurement of albumin in human urine by particle-enhanced turbidimetric inhibition immunoassay (PETINIA) methodology (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A). Presence of microalbumin in urine was again labeled as nephropathy. All data for categorical and continuous variables were entered and analyzed using computer statistical package SPSS version 12 for Windows (SPSS Inc., USA).

RESULTS

Out of 883 patients, 562 (63.6%) were males and 321 (36.4%) females; 76 subjects were type-1 (8.6%) and 807 (91.4%) were type-2. Overall mean age was 56.5±14.8 years with mean duration of diabetes 13.8±9 years. Six hundred thirty patients (71.3%) showed dyslipidemia (LDL >100 mg/dl) while over all 253 patients (28.7%) were found to have nephropathy. Patient's demographic characteristics with dyslipidemia and nephropathy status are shown in Table-1.

Subjects with dyslipidemia (LDL>100 mg/dl) showed serum creatinine levels with mean 1.022 mg/dl as compared to those without dyslipidemia with mean creatinine 1.004 mg/dl. However subjects labeled with nephropathy demonstrated marked elevated serum LDL cholesterol with mean 125.7 mg/dl as compared to those without nephropathy where LDL mean was 114 mg/dl. Additionally, subjects demonstrating nephropathy showed higher levels of creatinine with mean 1.347 mg/dl, comparing those without nephropathy with mean 0.897 mg/dl. These results are presented in table-2. The relationship between the LDL and the development and progression of nephropathy is shown graphically by box plot in figure-1. Spearman's correlation for cause effect relationship between serum LDL and nephropathy was highly significant at the level of $p < 0.001$.

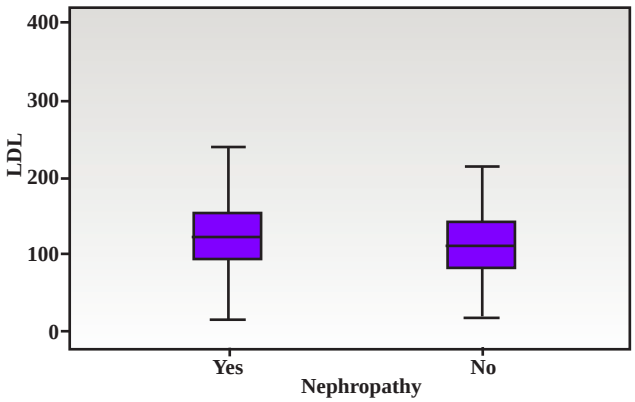
Table-1: Demographic Characteristics of Diabetic Patients

Parameters	Description with n(%)	
Gender	Male 562 (63.6%)	Female 321 (36.4%)
Type of Diabetes	Type-1 76 (8.6%)	Type-2 807 (91.4%)
Dyslipidemia status	LDL <100mg/dl 253 (28.7%)	LDL > 100mg/dl 630 (71.3%)
Nephropathy status	No Nephropathy 630 (71.3%)	Nephropathy 253 (28.7%)

Table-2: Variables of interest with standard deviations and confidence intervals

Variable	Mean ± SD (95%CI)
Age	56.5±14.8 years
Duration of Diabetes	13.8±9 years
Serum Creatinine (mg/dl) for LDL > 100	1.02±0.74 (0.963 to 1.080)
Serum Creatinine (mg/dl) for LDL < 100	1.00±0.63 (0.926 to 1.082)
LDL cholesterol (mg/dl) with Nephropathy	125.7±44.8 (120.2 to 131.19)
LDL cholesterol (mg/dl) without Nephropathy	114±39 (110.95 to 117.10)
Serum Creatinine (mg/dl) with Nephropathy	1.34±1.13 (1.208 to 1.486)
Serum Creatinine (mg/dl) without Nephropathy	0.89±0.35 (95% CI 0.851 to 0.907)
Spearman correlation for cause effect relationship between LDL and Nephropathy	p value < 0.001

Figure 1: Box Plot: LDL levels in mg/dl versus nephropathy development with microalbuminuria or macroalbuminuria



DISCUSSION

According to the statistical results of the current study, it can be concluded that LDL dyslipidemia is one of the major risk factors for the development of nephropathy. Creatinine is a well defined marker of kidney function. In this study, the levels of creatinine have been also measured for the diabetic patients with LDL >100mg/dl and results have shown that they were slightly higher with mean of 1.022 mg/dl as compared to those with LDL<100mg/dl and with mean 1.004 mg/dl. Thus creatinine levels begin to rise as LDL dyslipidemia appears. Furthermore, creatinine levels were even higher among the patients with established nephropathy with mean 1.347 mg/dl as compared to those without nephropathy, mean serum creatinine 0.897 mg/dl. Most importantly, among the patients with nephropathy, LDL-cholesterol levels were found to be much higher, with mean 125.7 mg/dl, comparing with those without nephropathy, with mean LDL 114 mg/dl. It is evident from these findings that LDL-cholesterol is a major factor and commonly encountered when serum creatinine levels rise and those with established nephropathy and positive urine samples for the presence of microalbumin or macroalbumin. It was the main objective of the current study to find out cause effect relationship between LDL-cholesterol and nephropathy. This association was found to be highly significant at the level of p-value of <0.001. In this study, most of the patients were referred from the peripheral health care centers to the diabetes center for annual follow up and were not on any therapy for lowering lipids or LDL-cholesterol. This indicates that diabetic patients must be started anti-lipid therapy at primary care levels if lipids or LDL cholesterol levels are higher than the goals. Recent available literature documents LDL goal to be less than 100mg/dl and less than 70mg/dl with overt coronary artery disease (CAD) or cardiovascular disease (CVD). Use of statin therapy is recommended if LDL remains above 100mg/dl after the diet and exercise have failed to reduce LDL, especially those with multiple risk factors (e.g., obesity, hypertension, smoking, or family history of CVD.[24-27] Nonetheless, measurement of macroalbumin or microalbumin is an integral part of diabetes management for detection of early diabetic nephropathy. 20-40% of diabetic patients develop diabetic nephropathy, which in turn is a major risk for triggering chronic renal disease (CRD) and end stage renal disease (ESRD) in diabetic population. In the present study, all patients were therefore screened for the established nephropathy, that is presence of macroalbuminuria or microalbuminuria in urine samples, and if found positive, were labeled as nephropathy and plotted against serum LDL levels. Persistent microalbuminuria (albuminuria ranging 30-299 mg/24hour) is a typical feature of early stages of nephropathy in type-1 diabetes, is a marker for the development of nephropathy in type-2 diabetes, and indicator for increased CVD risk.[24,28-29] According to current research studies, patients who progress from microalbuminuria to macroalbuminuria usually progress to ESRD. However

if treatment is initiated at early stages by ACE-inhibitors or ARBs, progression may be slowed. Aggressive blood pressure control of <130/80 mmHg is also one of the strategies to limit albumin excretion in urine and limiting nephropathy.[24,30-32] Like other risk factors, LDL cholesterol also has direct effect on the development and progression of nephropathy in diabetic population,[22-23,33-34] and is involved in increasing the albumin excretion rate by the kidneys.[35] Having said this, the cause effect relationship of LDL and nephropathy in this study has demonstrated that there is a strong relationship between these two pathologies, i.e., LDL dyslipidemia and nephropathy. LDL is among the major risk factors leading to diabetic nephropathy and is also associated with elevated mean creatinine levels. Currently there is much evidence available on the intense oxidative stress due to lipids in diabetes and metabolic syndrome.[36-37] Elevated serum lipids (lipotoxicity) will cause oxidative stress (lipid peroxidation stress) to all tissues, including renal inflammation, and hence leading to multiple diabetic complications. ESRD is a serious heath problem with high morbidity and mortality. However it can be delayed or prevented by targeting the risk factors. Renal function can effectively be monitored by measuring serum creatinine levels periodically, and at least annually without CRD, and every six months with CRD or nephropathy. Early nephropathy can be detected by the presence of microalbumin or macroalbumin in early morning urine samples. Routine urine analysis strips cannot detect the presence of microalbuminuria, which must be detected by specialized and advanced laboratory methodology. These and as well as fasting lipid profile should also be requested while managing diabetes in outpatient diabetology clinics. LDL cholesterol is now identified as the primary target of lipid lowering therapy. Hence early screening for LDL dyslipidemia and its treatment by lipid lowering drugs or statins should be considered in newly diagnosed diabetic patient, apart from management of hyperglycemia. Close monitoring of creatinine levels with that of microalbumin in urine is one of the standard methodology for monitoring renal function in diabetic population. The tertiary care diabetes center should be equipped with facilities such as detection of microalbumin in urine and LDL dyslipidemia.

CONCLUSION

According to the current study findings, LDL dyslipidemia is one of the major risk factor for the development and progression of nephropathy. Therefore early screening and treatment with statins is recommended for elevated LDL levels to prevent diabetic nephropathy development and its progression.

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