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DYSLIPIDEMIA IN PATIENTS OF DIABETIC NEPHROPATHY WITH OVERT PROTEINURIA

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Summary

Background and Aims: *Diabetic nephropathy (DN) is one of the leading causes of end stage renal disease (ESRD). Dyslipidaemia is common in both dialysis and non-dialysis populations. Dyslipidaemia is also one of factors for progression of chronic kidney disease (CKD). Besides Dyslipidaemia is also responsible for premature atherosclerosis which increases cardiovascular morbidity in CKD patients .This study is aimed at to show patterns of Dyslipidaemia in overt diabetic nephropathy pts admitted in Nephrology Department of Chittagong Medical College.*

Materials and Methods: *It is a cross-sectional case-control study. Sixty six diabetic patients with mean age 49.5± 11years with serum creatinine >1.5mg% and urinary total protein (UTP) >500mg/day were enrolled as cases and thirty three diabetic patients with mean age 43.5± 8.9 years with serum creatinine < 1.5 mg% and UTP < 500mg/day were included as controls.*

Results: *Majority (92.4%) of patients in case group had Dyslipidaemia compared to 23.3% of the patients in control group (p <0.001).The level of serum total cholesterol, triglyceride and LDL cholesterol were significantly higher in case group than those in control group (227.0 ± 76.2 vs. 176.3 ± 23.4 mg/dl, p < 0.001; 230.1 ± 80.0 vs. 134.8 ± 40.4, p < 0.001 and 132.6 ± 73.6 vs. 99.7 ±23.6, p = 0.001). The serum HDL was almost comparison of similar in both groups (49.1 ± 8.1 vs. 47.7 ± 12.4) (p = 0.509). Presence of raised triglyceride was 41-fold (95% CI = 9.52 – 177.39) higher in diabetic patients with nephropathy than that in diabetic patients without nephropathy (p < 0.001).*

Conclusion: *Serum triglyceride was observed to be independently associated with the development of diabetic nephropathy. Lipid-lowering therapy is, therefore, essential to control dyslipidaemia in order to reduce the incidence of diabetic nephropathy along with the prevention of early atherosclerotic cardiac diseases.*

Kew words

Diabetic Nephropathy; overt proteinuria; dyslipidaemia

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Introduction

Diabetic nephropathy is the leading cause of chronic kidney disease and is more prevalent among African Americans, Asians, and Native Americans than Caucasians[1]. Overt diabetic nephropathy has been classically defined by the presence of proteinuria > 0.5 g/24 h. Between 20% and 40% of patients with diabetes ultimately develop nephropathy[2]. If untreated, 80% of people who have type 1 diabetes and microalbuminuria will progress to overt nephropathy, whereas only 20-40% of those with type 2 diabetes over a period 15 years will progress[3].

Chronic kidney disease(CKD) results in profound lipid disorders, which stem largely from impaired maturation of high-density lipoprotein (HDL) and impaired clearence of triglyceride-rich lipoprotein and their atherogenic remnants. Hence plasma concentration of triglyceride-rich lipoprotein are elevated in CRF. Impaired maturation of HDL in CKD is primarily due to downregulation of lecithin-cholesterol acyltransferase (LCAT) and, to a lesser extent, increased plasma cholesteryl ester transfer protein (CETP). Together, these abnormalities may contribute to the risk of arteriosclerotic cardiovascular disease and may adversely affect progression of renal disease and energy metabolism in CKD[4]. Experimental studies have demonstrated that lipids may induce glomerular and tubulointerstitial injury, and that lipid-lowering treatments ameliorate renal injury[5].

The concentration of total cholesterol, VLDL, LDL cholesterol, and triglycerides rises with increasing albumin excretion rate in patients with type 1 diabetes[6]. Similarly, in the nondiabetic population, those with microalbuminuria have similar lipid abnormalities demonstrated a strong correlation between triglyceride-rich apoB-containing lipoproteins and the rate of progression in nondiabetic patients with chronic kidney disease[7,8]. Therefore, the treatment of Dyslipidaemia in patients with diabetic nephropathy is of utmost significance not only for cardiovascular protection but also to help preserve their renal function. So, suspicion and detection of Dyslipidaemia not only reduce cardiovascular mortality and also halt progression of CKD to end stage renal disease(ESRD) which is as like as death sentence in low and middle economy countries like Bangladesh. The aim of our study is to find out specific pattern of lipid abnormality in overt DN in hospitalized CKD patients.

Materials and methods

The present study was a cross-sectional case-control study. The study was conducted in the Department of Nephrology and Department of Medicine of Chittagong Medical College (CMC) Hospital in collaboration with the Department of Biochemistry, CMC between 1 July, 2007 to 30 June, 2008.

The study populations were divided into case and control. Diabetic patients with serum creatinine > 1.5 mg/dl and or 24 hours urine protein > 500 mg were considered as case.Diabetic patients with serum creatinine 1.5 mg/dl and or 24 hours urine protein 500 mg were selected as control. Most of the controls were receiving injection Insulin and Angiotensin converting enzyme(ACE) inhibitors. Adult diabetic patients with age >18 years and with/without nephropathy were included. CKD patients due to causes other than diabetic nephropathy and Acute kidney injury(AKI) over top of CKD patients were excluded. A total of 96 diabetic patients – 66 cases and 30 controls (meeting the above enrollment criteria) were consecutively (purposively) included in the study. Informed Written consent was obtained from each participant. The study was approved by the Ethical Committee of CMC. The demographic characteristics like age, sex and relevant investigations like total cholesterol, HDL, LDL and triglyceride were recorded in a structured case record form.

Operational definitions[9]

Serum total cholesterol > 200 mg/dl was termed as raised total cholesterol.

Serum LDL > 130 mg/dl was defined as raised LDL.

Serum triglyceride > 150 mg/dl was considered as raised triglyceride.

Serum HDL < 40 mg/dl was termed as low HDL.

If serum total cholesterol, LDL and triglyceride were found raised and/or serum HDL < 40 mg/dl, the case was considered dyslipidemic.

Data were collected by interview of the patients, clinical examination and laboratory investigations .

Serum Cholesterol and Tryglyceride were estimated by CHOD-PAP-Method and GPO-PAP-Method respectively using auto-analyzer (photometer 5010) in Biochemistry lab, CMC. Serum HDL Cholesterol was measured using auto-analyzer (Stanbio Laboratory, Boerne, Texas, photometer 5010) in Biochemistry lab, CMC.Utilization of the above mentioned assay values and the Friedewald equation provide for the calculation of an acceptable value for LDL cholesterol. According to Friedewald et al, LDL can be calculated with a few restrictions, as follows: LDL = Total Cholesterol – HDL – TG/5.The results were shown in mg/dl.

Data were processed using software SPSS version 11.5.The test statistics used to analyze the data were descriptive statistics, Chi-square (x^2) test and Student's t-test. The categorical data were compared between groups using Chi-square (x^2) test, while the quantitative data were compared between groups using Student's t-test. For all analytical tests, the level of significance was set at 0.05 and $p < 0.05$ was considered significant.

Results

The age range in both cases and control were 18-70 years. The mean age was somewhat higher in cases than that in controls . Male patients were predominant in the both groups. The groups were identical with respect to sex ($p = 0.668$). (Table I)

Table I : Age and sex distribution between case and control groups (n = 96)

Criteria	Group #		
	Case	Control (n = 66)	p-value (n = 30)
Age(years)			
<40	9(13.6)	10(33.3)	
40 – 50	22(33.3)	11(36.7)	
50 – 60	22(33.3)	9(30.0)	
60	13(19.7)	00	
Mean ± SD	49.5 ± 11.0	43.5 ± 8.9	0.010
SEX			
Male	41(62.1)	20(66.7)	.668
Female	25 (37.9)	10((33.3)	

Figures in the parenthesis denote corresponding percentage

Table II compares the lipid profile between case and control groups. The level of serum total cholesterol, triglyceride and LDL cholesterol were significantly higher in case group than those in control group .The serum HDL was almost similar in both groups

Table II : Comparison of mean lipid profile between case and control groups

Investigations	Group #		
	Case (n = 66)	Control (n = 30)	p-value
Total cholesterol (TC) (mg/dl)	227.0 ± 76.2	176.3 ± 23.4	< 0.001
Triglyceride (TG) (mg/dl)	230.1 ± 80.0	134.8 ± 40.4	< 0.001
LDL cholesterol (mg/dl)	132.6 ± 73.6	99.7 ± 23.6	0.001
HDL cholesterol (mg/dl)	47.7 ± 12.4	49.1 ± 8.1	0.509

Data were presented as mean ± SD.

Table III demonstrates that both case and control groups were almost identical with respect to HDL cholesterol . The Table shows that case group had significantly raised LDL cholesterol , Tryglyceride and total cholesterol as opposed to control group .

Table III : Comparison of pattern of lipoprotein between case and control groups

Lipoprotein	Case (n = 66)	Group # Control (n = 30)	p-value
Low HDL (< 40 mg/dl)			
Yes	16(24.2)	4(13.3)	0.222
No	50(75.8)	26(86.7)	
Raised LDL (> 130 mg/dl)			
Yes	25(37.9)	4(13.3)	0.015
No	41(62.1)	26(86.7)	
Raised Tg* (> 150 mg/dl)			
Yes	59(89.4)	4(13.3)	< 0.001
No	7(10.6)	26(86.7)	
High total cholesterol (> 200 mg/dl)			
Yes	33(50.0)	4(13.3)	0.001
No	33(50.0)	26(86.7)	
Dyslipidaemia			
Yes	61(92.4)	7(23.3)	< 0.001
No	5(7.6)	23(76.7)	

Figures in the parentheses indicate corresponding percentage.
* Tg: Tryglyceride

Table IV demonstrates the binary logistic regression analysis of Odds Ratios for lipid profile status of the patients likely to be associated with diabetic nephropathy. The variables that were significant associated with diabetic nephropathy in univariate analyses were all entered into the model directly. Of the 4 variables, triglyceride was found to be the independent predictors of diabetic nephropathy ($p < 0.001$). Presence of raised triglyceride was 41-fold higher in diabetic patients with nephropathy than that in diabetic patients without nephropathy ($p < 0.001$).

Table IV : Independent predictors of diabetic nephropathy

Variables of interest	Univariate analysis (p-value)	Multivariate analysis Odds Ratio (95% CI of OR)	p-value
Age	0.010	0.96(0.891 – 1.025)	0.209
Total cholesterol (TC) (mg/dl)	< 0.001	0.43(0.024 – 7.59)	0.563
Triglyceride (TG) (mg/dl)	< 0.001	41.10(9.52 – 177.39)	< 0.001
LDL cholesterol (mg/dl)	0.001	3.00(0.19 – 47.62)	0.435

Discussion

Diabetic nephropathy is one of the leading causes of kidney disease in patients of ESRDand affects ~ 40% of type 1 and type 2 diabetic patients. It increases the risk of death mainly from cardiovascular causes . Diabetic nephropathy is more prevalent among African Americans, Asians and Native Americans than Caucasians[1].

The basis for the prevention of diabetic nephropathy is the treatment of its known risk factors : hypertension, hyperglycemia, smoking and dyslipidemia. These are also risk factors for cardiovascular disease and should be vigorously treated. In this study one of the risk factors Dyslipidaemia has been explored.

We found significantly higher mean age in case group compared to control group (49.5 ± 11.0 vs. 43.5 ± 8.9, $p = 0.010$). This is because the study was a cross-sectional one and the study-population was collected over a period of 6 months. At that time average age of control group was lower than that of case group. The groups were almost identical with respect to sex ($p = 0.668$) with a male predominance in either groups.

In the present study, the mean total cholesterol, triglyceride and LDL cholesterol were significantly higher in diabetic nephropathy patients than those in diabetic patients without nephropathy ($p < 0.001$, $p < 0.001$ and $p = 0.001$ respectively). HDL cholesterol was not found to be significantly different between the groups ($p = 0.509$). Majority (92.4%) of patients in diabetic nephropathy group had dyslipidemia as opposed to only 23.3% in the only diabetic group ($p < 0.001$). Iwalokun and his colleagues (2007) observed a significant ($p < 0.05$) difference between case and control group, in terms total cholesterol (182.7 ± 12.2 vs. 173.8 ± 7.4 mg/dL), LDL-C (117.2 ± 14.1 vs. 107.6 ± 6.8 mg/dL), HDL-C (38.1 ± 4.7 vs. 42.2 ± 5.3 mg/dL) and triglycerides (137.1 ± 11.3 vs. 120.4 ± 7.5 mg/dL).

Raised LDL cholesterol (>130 mg/dl), raised total cholesterol (> 200 mg/dl) and raised triglyceride (>150 mg/dl) were significantly common in diabetic nephropathy group compared to only diabetic group ($p < 0.001$). Majority (92.4%) of patients in diabetic nephropathy group had dyslipidemia compared to 23.3% in diabetic patients without nephropathy ($p < 0.001$) which is consistent with the study by[10]. The possible explanation of 5 cases not developing dyslipidemia and 7 controls developing dyslipidemia is as follows: There might have some protective factors (genetic influence) which prevent some of the DN patients from developing dyslipidemia, while causes other than DN might have influenced the development of dyslipidemia (familial hyperlipidemia in Fredrickson's classification)

Studied plasma triglycerides, total cholesterol, HDL cholesterol and apolipoproteins in 170 diabetic patients (both type1 and type 2) and 46 age-matched healthy normal subjects[11]. Significantly increased triglycerides, low HDL cholesterol and normal cholesterol levels were found in both groups of diabetics compared to normal subjects. In Bangladesh found an increase in serum triglycerides but a decrease in HDL cholesterol in untreated newly diagnosed diabetics compared with controls[12]. Serum total cholesterol levels were similar in diabetics and control subjects. These two studies selected newly diagnosed diabetic patients who did not develop nephropathy. On the contrary, the present study worked with diabetic patients of stage 3 and stage 4 nephropathy. Therefore, both the serum triglycerides and total cholesterol levels were higher in this study.

A large cross-sectional study of 330 Italian patients with diabetes (both type 1 and type 2) has been undertaken by to investigate the prevalence of hyperlipidemia. Overall 5% of diabetic patients had type IIa hyperlipidemia, 2% had type IIb and 17% had type IV hyperlipidemia as defined by Fredrickson classification[13]. This study supports the findings of the present study.

In univariate analysis age and all the components of lipid, except HDL, demonstrated their significant presence in diabetic nephropathy group than those in only diabetic group. As these variables were entered directly into the binary logistic regression model, only triglyceride was found to be the independent predictor of diabetic nephropathy ($p < 0.001$). Presence of raised triglyceride was more than 40-fold (95% CI = 9.52 – 177.39) higher in diabetic patients with nephropathy than that in diabetic patients without nephropathy ($p < 0.001$). In a similar study carried out a univariate analyses and found that age, triglycerides, total cholesterol, HDL and LDL cholesterol all were associated with diabetic nephropathy[14]. As binary logistic regression analysis was performed with the stages of diabetic nephropathy as the dependent variables, the nephropathy status persisted to be predictive of all the variables as in univariate analysis.

In our study, triglyceride component of serum lipid was found independent predictor of diabetic nephropathy. The difference may be due to small number and cross sectional type of our study.

The present study had certain limitations like i) other confounding variables for progression of nephropathy were not excluded , ii) Number of Controls should be at least equal to the number of cases. But most of the control subjects were reluctant to voluntarily participate in the study , iii) LDL measurement was done using Friedewald formula instead of direct measurement.

Conclusion

Dyslipidemia in diabetic patients has been clearly demonstrated to be an important risk factor for diabetic nephropathy. Diabetic lipid disorders are characterized by hypertriglyceridaemia, increased LDL and raised total cholesterol. However, only serum triglyceride was observed to be independently associated with the development of diabetic nephropathy. If it can be proved in large population study , only Triglycerides estimation and its lowering therapy may be essential to prevent progression of CKD to ESRD.

Disclosure

All the authors declared no competing interestes

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