ORIGINAL ARTICLE

Prevalence of dyslipidemia among adult diabetic patients with overt diabetic nephropathy in Anambra state South-East Nigeria

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Abstract

Background: Dyslipidemia has been identified as a risk factor for the development and progression of diabetic renal disease.

Objective: This study was done to determine the prevalence of dyslipidemia among diabetic patients with overt nephropathy.

Materials and Methods: A total of 72 diabetic patients with overt diabetic nephropathy and 36 age- and sex-matched normoalbuminuric diabetic patients were studied. Their fasting lipid profile, fasting blood sugar, and renal function tests were evaluated.

Results: Total serum cholesterol and serum triglycerides were significantly higher in patients with overt diabetic nephropathy compared to the controls; 66.7% and 62.5% versus 36.1% and 30.6%, respectively (P = 0.003 and 0.002, respectively).

Conclusions: Diabetic patients with overt diabetic nephropathy have significant dyslipidemia and aggressive lipid lowering in these patients may retard their progression to end-stage renal disease.

Key words: Diabetes mellitus, diabetic nephropathy, dyslipidemia, prevalence

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Introduction

Diabetic nephropathy (DN) is a common complication of diabetes mellitus (DM). It is also a common cause of end-stage renal disease (ESRD) worldwide and is prevalent in our environment.[1-3] With the increasing epidemic of diabetes mellitus and its far reaching complications worldwide, the implication in a developing country like Nigeria is that of identification of risk factors that accelerate the onset of chronic complications like DN and institution of measures to retard its progression to ESRD. Dyslipidemia using World Health Organization (WHO) criteria [serum triglyceride- 150-400 mg/dL (1.7-4.5 mmol/L), total cholesterol (TC) > 200 mg/dL (>5.2 mmol/L), low-density lipoprotein (LDL)-cholesterol (LDL-C) > 135 mg/dL (>3.5 mmol/L), high-density lipoprotein (HDL)-cholesterol (HDL-C) < 35 mg/dL (<0.9 mmol/L) in men or <40 mg/dL (<1.0 mmol/L) in women, and a ratio of total cholesterol to HDL-cholesterol > 5] has been identified as a risk factor in the development of micro- and macrovascular complications in diabetic patients including DN.[4] Lipids induce renal injury by various pathophysiological mechanisms but data on the role of dyslipidemia in increasing the susceptibility to nephropathy or ESRD in DM patients are sparse and inconclusive. Moorhead *et al.* in 1982 hypothesized that hyperlipidemia promotes progression of chronic renal

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disease after the initiating event has damaged the glomerular capillary wall, thereby allowing increased passage of lipids and lipoproteins into the renal mesangium.[5]

Details of the mechanism by which lipids cause or exacerbate glomerular injury are incompletely understood. In the human glomeruli, both mesangial and epithelial cells take up lipoproteins via specific receptors.[6] Mesangial cells express scavenger receptors, which are involved in the preferential uptake of modified glycosylated and oxidized LDL. Accumulation of modified LDL in the mesangium has been noted to favor their uptake by infiltrated glomerular monocytes, leading to activation of these cells into macrophages.[7] This preferential phagocytosis of modified LDL-C by monocytes has been reported to play a pivotal role in the formation of mesangial foam cells.[8] Second, accumulated modified lipoproteins within the mesangium stimulate mesangial cell secretion of various chemotactic factors and adhesion molecules (eg, macrophage colony stimulating factor, intracellular adhesion molecule-1), enhancing the renal recruitment of macrophages. These factors result in monocyte infiltration, which is reported to play a key role in the pathogenesis of glomerulosclerosis and tubular fibrosis, particularly in DN.[8] These intra-mesangial recruited macrophages may, in turn, further oxidize LDL creating a vicious self-perpetuating cycle resulting in progressive renal injury. Third, activated macrophages in the renal mesangium stimulate the release of reactive oxygen species and expression of prosclerotic and proliferative cytokines such as transforming growth factor B1 (TGFB-1) and platelet-derived growth factor-AB (PDGF-AB). These cytokines stimulate the production of extracellular matrix proteins, thereby promoting mesangial expansion as described in DN. in vitro studies have demonstrated that LDL and oxidized LDL stimulate *TGF-B1* gene expression in human glomerular, mesangial, and epithelial cells. Therefore, TGF-B1 appears to be an important mediator of lipid-induced mesangial matrix expansion as well as play a key role in the pathogenesis of DN.[7,9] Finally, the uptake of modified LDL by mesangial macrophages has been reported to stimulate eicosanoid synthesis including thromboxanes and leukotrienes, leading to potentially deleterious alterations in intra-glomerular hemodynamics.[6]

The damaging effect of hyperlipidemia on the kidneys extends beyond the glomerulus. In the tubulointerstitium, animal studies have demonstrated that hyperlipidemia is associated with significant interstitial macrophage infiltration and increase in *TGF-B1* gene expression in the interstitial cells suggesting a cytokine-mediated role of lipids in the development or aggravation of tubulointerstitial lesions.[10] Also, in overt DN, it has been proposed from experimental *in vivo* studies that the tubular uptake and metabolism of the lipid component of filtered lipoproteins lead to local expression of chemokines and cytokines and promote interstitial inflammation.[11] These findings in animal models, however, is cautiously extrapolated to humans because contrasting results have been observed in humans.[11]

Globally, statistics on the prevalence of dyslipidemia on a subpopulation of diabetic patients with overt nephropathy is scanty and, locally, it is even more so in Nigeria. Against this background, our study sought to determine the role of dyslipidemia as a risk factor for DN by determining the prevalence of dyslipidemia in Nigerian adult diabetic subjects with overt DN. It is hoped that the outcome of this study will draw attention to the need for aggressive management of dyslipidemia in DN patients.

Materials and Methods

A total of 342 diabetic patients that presented consecutively at the medical outpatient, diabetic, renal clinics, and admitted into the medical wards of the Nnamdi Azikiwe University Teaching Hospital Nnewi (NAUTH), were recruited for this study and screened for diabetic nephropathy. A total of 320 eligible and consenting patients were screened and 72 satisfied the inclusion criteria for DN and were studied. Inclusion criteria were all known adult diabetic patients of both sexes, including newly presenting diabetic patients with overt proteinuria. Overt proteinuria was defined as albumin/creatinine ratio of >300 mg albumin per gram of creatinine on a spot urine sample.

Thirty-six diabetic patients with normoalbuminuria drawn from the total sample population by simple random sampling were studied as controls. They were age- and sex-matched with the subjects with overt DN. Normoalbuminuria was defined as urine albumin/creatinine ratio of <30 mg albumin per gram of creatinine on a spot urine sample.

Diabetes mellitus was diagnosed and grouped into Type 1 or Type 2 using the WHO criteria.[12] Hypertension was defined as blood pressure ≥140/90 mmHg.[13] Urine samples were collected in clean urine containers for estimating the urine albumin/creatinine ratio. This was done as a spot urine collection, and about 20 ml of urine was collected and the samples were stored in the refrigerator at 4°C and later transported to the Chemical Pathology laboratory for analysis. Fasting blood samples were collected after a 14-h overnight fast for estimation of fasting blood sugar, total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol. Blood samples for packed cell volume, electrolytes, urea, and creatinine were also collected. The kit used for the urine albumin/creatinine was from RANDOX Laboratories LTD, Diamond Road, Crumlin Co, Antrim UK, BT 294QY. Appropriate colorimetric kits for all four subsets of lipids were used and purchased from Biosystems S. A., Costa Brava, 30, Barcelona (Spain). Samples were assayed at the Chemical pathology laboratory of NAUTH Nnewi. Estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine value assayed using the

Modification of diet in renal disease (MDRD)[14] abbreviated equation as follows:

$186 \times S\,(Cr)^{-1.154} \times Age^{-0.203} \times 0.742$ (if female) $\times$ 1.210 (if black).

The lipid assays were done using already standardized and well established methodology.[15] Measurement of total cholesterol was by cholesterol oxidase/peroxidase reaction, HDL-C was assayed using phosphotungstic acid in the presence of magnesium chloride to precipitate out very low-density lipoprotein (VLDL) and LDL-C. After centrifugation, the supernatant containing HDL was assayed for HDL-C. TG was assayed using enzymatic colorimetric method after hydrolysis of the triglycerides. LDL-C was calculated by indirect method using Friedewald *et al*.[16] equation, summarized as follows: LDL-C = (TC-HDL-C)-(TG/2.2) all concentrations given in mmol/L.

Dyslipidemia was taken as serum triglyceride 150-400 mg/dL (1.7-4.5 mmol/L), total cholesterol >200 mg/dL (>5.2 mmol/L), LDL-cholesterol >135 mg/dL (>3.5 mmol/L), HDL-C < 35 mg/dL (<0.9 mmol/L) in men or <40 mg/dL (<1.0 mmol/L) in women.[4]

Data entry and analysis were done using SPSS statistical software version 13. Results are presented as frequency tables, mean ±SD, and means were compared using Students *t test*, while Chi-square was used to test for association and $P \leq 0.05$ was considered significant.

Result

A total of 320 eligible and consenting diabetic patients were screened over a period of 12 months. Among those screened, 27 (8.4%) were Type 1 DM patients, while 293 (91.6%) were Type 2. Of these, 72 had overt diabetic nephropathy. The prevalence of DN in this study was 22.5%. The mean age of the study group (DN present) was 55 ± 12 years compared to 52 ± 13 years in the control group. The peak age of occurrence of DN was in the age group of 40-49 years (27; 37% closely followed by the age group of 50-59 years (15; 20.8%). More females (51.4%) than males (48.6%) had DN and the sex distribution was also similar in the controls, with 55.6% females and 44.4% males. The difference in the age and gender distribution of the study and control subjects was not statistically significant ($P = 0.35$).

[Table 1] shows the lipid profile of subjects with and without DN. Mean TG of 1.98 mmol/L in subjects with DN was significantly higher than 1.63 mmol/L in the controls ($P = 0.004$). Mean TC was 5.05 mmol/L in DN patients compared to 4.57 mmol/L in the controls, and this difference was statistically significant ($P = 0.04$). Mean LDL-C and HDL-C in subjects and controls were similar. Mean LDL-C was 3.28 mmol/L in DN patients and 3.02 mmol/L in controls ($P = 0.33$), mean HDL-C was 0.95 mmol/L for the DN group and 0.86 mmol/L for the control group ($P = 0.45$).

Table 1: Lipid profile of subjects with and without DN

Serum lipid (mmol/l)		Diabetic nephropathy		*t* and *P* values
		Present	Absent	
Triglyceride	Mean	1.98	1.63	$t = 2.73$
(TG)	SD	0.78	0.46	$P = 0.004$
Total cholesterol	Mean	5.05	4.57	$t = 1.99$
(TC)	SD	1.17	1.18	$P = 0.049$
LDL	Mean	3.28	3.02	$t = 0.99$
	SD	1.71	1.29	$P = 0.33$
HDL	Mean	0.95	0.86	$t = 0.75$
	SD	0.55	0.68	$P = 0.45$

Table 2: Frequency distribution of dyslipidemia in diabetics with and without DN

Serum lipid		Diabetic nephropathy		Total (%)	X^2 and *P* values
		Present (%)	Absent (%)		
Triglyceride	Dyslipidemia	48 (66.7)	13 (36.1)	61 (56.5)	$X^2 = 9.12$
	Normal	24 (33.3)	23 (63.9)	47 (43.5)	$P = 0.003$
Total cholesterol	Dyslipidemia	45 (62.5)	11 (30.6)	56 (51.9)	$X^2 = 9.81$
	Normal	27 (37.5)	25 (69.4)	52 (48.1)	$P = 0.002$
LDL	Dyslipidemia	33 (45.8)	14 (38.9)	47 (43.5)	$X^2 = 0.47$
	Normal	39 (54.2)	22 (61.1)	61 (56.5)	$P = 0.49$
HDL	Dyslipidemia	42 (58.3)	25 (69.4)	67 (62.0)	$X^2 = 1.26$
	Normal	30 (41.7)	11 (30.6)	41 (38.0)	$P = 0.26$

[Table 2] compares the frequency distribution of dyslipidemia in the study and control subjects. Dyslipidemia was more prevalent in the diabetics with overt nephropathy. Elevated TC and hypertriglyceridemia were significantly more prevalent in DN subjects compared to subjects without DN ($P = 0.003$ and $P = 0.002$, respectively). Although LDL-C was more elevated in those with DN (45.8%), compared with controls (38.9%), this difference was not statistically significant ($P = 0.49$). Lower levels of serum HDL-C was more prevalent in the controls (69.4%) than the DN group (58.3%), but this difference was not significant too ($P = 0.26$).

The mean eGFR of those with DN was 39.72 ± 10.30 ml/min/1.73 m^2, while that of the control subjects was 67.18 ± 20.25 ml/min/1.73 m^2; this difference was statistically significant ($P = 0.0001$). A majority (80.9%) of patients with DN were either in stages 3 or 4 of chronic kidney disease, while 86.1% of the control patients were in stage 2 or 3 chronic kidney disease. None of the control subjects were in stages 4 or 5 chronic kidney disease.

The mean albumin creatinine ratio for those with diabetic nephropathy was 388.99 ± 54.87 and 19.95 ± 5.97 for those without diabetic nephropathy ($P = 0.0001$).

Discussion

Previous studies have shown conclusively that lipid abnormalities in patients with diabetes mellitus is a major problem and associated with increased risk of cardiovascular disease.[15] The most common pattern of dyslipidemia in such patients consists of elevated levels of serum triglyceride (TG) and low levels of HDL-C. The result of our study, apart from agreeing with earlier reports that dyslipidemia is prevalent in diabetic patients, also shows that dyslipidemia is more severe among diabetic patients with DN than diabetic patients without DN. Using the WHO[4] cut-off values for hypercholesterolemia, 66.7% of the study population with overt DN had hypertriglyceridemia, 62.5% had hypercholesterolemia, 45.8% had elevated LDL-C, and 58.3% had decreased HDL-C. These values were by far higher than those observed in the control group, with the exception of HDL-C. Among the control group, 36.1% had hypertriglyceridemia, 30.6% had hypercholesterolemia, 38.9% had elevated LDL-C, and 69.4% had decreased HDL-C.

The pattern of dyslipidemia observed in our study was similar to reports from Saudi Arabia,[17,18] where the incidence of dyslipidemia was noted to be in the range of 25-60% among diabetic patients. There was also some similarity with results of Lipid Research Clinic Prevalent studies, where lipids and lipoprotein abnormality rates were approximately 25% and 50% for TG and total cholesterol, respectively.[19] Studies from Nigeria have reported similar findings, where hypercholesterolemia was present in 43.5% and hypertriglyceridemia in 34.8% of patients with Type 2 DM.[2]

The combination of hypercholesterolemia and hypertriglyceridemia found in DN patients in this study is similar to that reported in the Saudi Arabian study,[17,18] where significantly higher levels of TG and TC were noted among patients with DN. This also agrees with reports from the Diabetes Control and Complications Trial/Diabetes Interventions and Complications Study (DCCT/EDIC)[20,21] cohort group study, where the lipid profile relating to albumin excretion rate (AER) is elevated TG, TC, and LDL-C. The severe dyslipidemia noted in patients with DN is similar to that shown by earlier researchers who reported significantly higher plasma concentrations of TG, VLDL, LDL, and lower levels of HDL-C in incipient and overt macroalbuminuric compared to normoalbuminuric diabetic patients.[22,23] It has been suggested that these findings may be related to reduced metabolic processes and impaired excretion of metabolic waste products worsened by poor glycemic control, insulin resistance, and poor control of hypertension observed in their study population.[22,23] The progression of DN seems to be linked with serum lipids and is thought to be independent of glycemic and blood pressure control.[24]

The nature of the lipid interaction was also noted to be different at various stages of renal disease. DN progression in normoalbuminuric patients was linked to the LDL-C; in microalbuminuric subjects, it was linked to the TG content of VLDL and IDL particles; and in macroalbuminuric patients, progression to ESRD was associated with LDL size but not with triglyceride-linked indexes. This observation is consistent with the findings of Coonrod *et al*.[25]who reported that TG and cholesterol had different effects on the progression of nephropathy, depending on the duration of diabetes. The results of this study, however, did not and could not assess causal relationship because it was not a prospective study.

Conclusions

This study showed clearly that lipoprotein abnormalities are highly prevalent in adult Nigerian diabetic patients with normoalbuminuria and macroalbuminuria and more so in diabetics with macroalbuminuria. Aggressive management of dyslipidemia in diabetic subjects, especially those with overt nephropathy, may retard their progression to ESRD. For those with normoalbuminuria, it may prevent progression to overt DN.

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