Atherogenic Dyslipidemia in Diabetic Nephropathy

Katore Sarika D[1*], Mahajan Bhushan H.[2], Fating Prasanna M.[3], Muddeshwar Manohar G.[4], Pramanik Sanjay[5]

{[1]Junior Medical Officer, [2]Assistant Professor, [3]Junior Resident, Professor and Head}

Department of Biochemistry, Government Medical College, Nagpur, Maharashtra, INDIA.

*Corresponding Address:

sarikakatore@gmail.com

Research Article

Abstract: **Background:** Dyslipidemia plays an important role in progression of kidney disease in patients of diabetes mellitus and leads to cardiovascular complications. The present study aimed to asses atherogenic lipid profile in patients of diabetes mellitus and diabetic nephropathy. **Aim:** To evaluate atherogenic lipid profile in patients of diabetes mellitus and diabetic nephropathy. **Settings and Designs:** This cross sectional study was undertaken in the Department of Biochemistry and kidney Unit, Department of Medicine and Department of Nephrology of Government Medical College and super speciality hospital Nagpur, Maharashtra. **Material and Method** : Total cholesterol (TC), Triglycerides(TG), High density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), atherogenic ratio i.e. TC/HDL, LDL/HDL, was assessed in diabetes mellitus (n=50), diabetic nephropathy (n=50) and healthy individuals (n=50).Mean of biochemical parameter were compared by performing repeated measures one way ANOVA(F-test) and Post hoc multiple comparison of mean of three groups by Bonferroni t-test. **Results:** Values of total cholesterol, triglyceride ,LDL-C and TC/HDL, LDL/HDL were significantly higher in diabetes mellitus with diabetic nephropathy and diabetes mellitus without diabetic nephropathy but values of HDL-C ($p<0.001$) were significantly lower in diabetes mellitus with diabetic nephropathy and diabetes mellitus without diabetic nephropathy as compared to controls. **Conclusion:** Atherogenic dyslipidemia was more pronounced in diabetic nephropathy as compared to diabetes mellitus**.**

Keywords*:* DM (diabetes mellitus), Atherogenic Dyslipidemia, cardiovascular disease, diabetic nephropathy, Atherogenic ratio.

Introduction

The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defect in insulin secretion, insulin action or both [1]. The global prevalence of diabetes mellitus is expected to increase up to 5.4% by the year 2025[2]. According to the International Diabetes Federation (IDF), prevalence of diabetes in India is expected to increase from 61.3 million people in 2011 to 101.2 million by 2030. Diabetes leads to various complications such as coronary artery disease, peripheral vascular disease, stroke, neuropathy, diabetic nephropathy, retinopathy and diabetic foot. Diabetic nephropathy is characterized by a progressive rise in urine albumin excretion, increasing blood pressure, leading to declining glomelar filtration and eventually end stage renal disease (ESRD)[3]. Diabetes mellitus leads to dyslipidemia and this dyslipidemia is more in presence of diabetic nephropathy. Lipid abnormalities associated with diabetic mellitus and Diabetic nephropathy include high plasma levels of TG, VLDL-C, IDL-C, LDL-C and low concentrations of HDL-C[4]. In the case of poor glycaemic control in diabetic nephropathy, total cholesterol is increased due to an accumulation of LDL – C[5]. Dyslipidemia plays an important role in the progression of kidney disease in patients with diabetes mellitus. The changes in lipoproteins specifically triglyceride rich lipoproteins cause damage to kidney. Lipids cause renal injury by oxidative stress. Hence, the present study aimed to assess the atherogenic dyslipidemia in patients with diabetic nephropathy diabetes mellitus in comparison with healthy controls.

Material and Methods

Subjects: The present study has been carried out in Govt. medical college and hospital, Nagpur, India Jaunary 2011 to July 2012. The study protocol was approved by the Institutional Ethical Committee. Informed written consent was obtained from all the study subjects enrolled in the study. Study sample was consisted of total of 150 individuals; 50 diagnosed cases of diabetes mellitus with diabetic nephropathy irrespective of type I and type II diabetes (Cases) in the age group of 30-70 years and 50 patients of diabetes mellitus of either sex, admitted in kidney unit of medicine department in the institute and Nehrology department in GMC and super speciality hospital, Nagpur and 50 age and sex matched controls were also selected for study.

Exclusion criteria: Patients with gestational diabetes, Individual with urinary tract infection, Patients with provisional diabetes or impaired glucose tolerance, Patients having any mental disorder, Individuals having any past medical history of various vascular complications before the diagnosis of diabetes mellitus such as ischemic heart disease, cerebral and peripheral vascular diseases, congestive heart failure and renal

failure and Those who did not consent to participate in the study.

Sample collection: Five ml of venous blood samples were collected from the subjects in plain bottles after an overnight fast of 12 hours. The samples were allowed to stand for half an hour. The serum was separated and serum lipid profile was estimated on the same day.

Laboratory analysis: Estimation of serum cholesterol was done with the kit based on cholesterol oxidase peroxidase (End Point) [Accurex Biomedical private limited, Thane, India. Kit][6]. Triglyceride estimation was done with the kit based on Glycerol 3 phosphate oxidase peroxidase (End Point) [Accurex Biomedical private limited, Thane, India. Kit] [7]. HDL-C estimation was done with the kit based on precipitation method of [Accurex Biomedical private limited, Thane, India. Kit] [8]. The estimation was done on TRANSASIA ERBA CHEM-5 plus Semi-Automatic Analyzer [Erba Diagnostic Mannheim GmbH, Germany]. LDL-C and VLDL-C was calculated by Friedewald's formula [9].

Statistical analysis: Statistical data was recorded on Microsoft Excel programme. Data was analysed by using statistical software STATA version 10.0 All continuous variables were presented as mean ± standard deviation. Categorical variables are expressed expressed as percentages. Lipid parameters in three group were compared by performing repeated measures one way ANOVA (F-test). Post hoc multiple comparison of mean of three groups by Bonferroni t-test.

Results

Demographic profile were depicted in table 1 patients of diabetic nephropathy with mean age 56.02 ± 6.92 years consisted of 34 males with and 16 females and patients of diabetes mellitus with with mean age 50.44 ± 9.46 of years consisted of 33 males and 17 females whereas mean age of controls 50.08 ± 8.42 years consisted of 33 males and 17 female (Table 1)

Table 1: Age and Gender Distribution of study group

	Controls	Diabetic nephropathy patients'	Diabetes mellitus patients
Age	50.08±8.42	56.02.08±6.92	50.44±9.46
Male	33	34	33
Female	17	18	17

Table 2 shows mean and standard deviation of lipid profile and atherogenic ratios among three groups. Mean of serum total cholesterol, triglycerides, low density lipoproteins, very low density lipoprotein were significantly higher (p<0.001) in diabetic nephropathy and diabetes mellitus patients as compared to controls whereas mean of high density lipoprotein was significant low (p<0.001) in diabetic nephropathy and diabetes mellitus patients as compared to controls. There was significant difference in lipid parameters and atherogenic ratio of diabetic nephropathy as compared to diabetes mellitus.

Table 2: Mean and standard deviation for serum Lipid Profile in controls, case of Diabetes Mellitus without diabetic Nephropathy and Cases of Diabets Mellitus With Diabetic Nephropathy

Variable	Control (Mean± SD)	Diabetes mellitus without diabetic nephropathy (Mean± SD)	Diabetes Mellitus with diabetic nephropathy (Mean± SD)
TG (mg%)	115.58 ± 30.6	147.7 ± 53.10[b]	187.18 ± 43.22[a,b]
TC (mg%)	143.3 ± 30.51	190.64 ±48.59[b]	230.4 ± 43.98[a,b]
HDL-C (mg%)	42.56 ± 9.01	35 ±11.81[b]	28.16 ± 10.47[b,c]
LDL-C (mg%)	77.66 ± 29.29	126.07 ±49.60[b]	164.55 ± 45.07[a,b]
VLDL-C (mg%)	23.11 ± 6.01	29.29 ±10.79[b]	37.44 ± 8.64[a,b]
LDL-C/HDL-C	1.93 ± 0.94	4.51 ±3.10[b]	8.15 ± 4.17[a,b]
TC/HDL-C	3.50 ± 1.07	6.55 ±3.76[b]	9.52 ± 4.64[a,b]

a=p<0.001 when compared with DM; b=p<0.001 when compared with controls; c =p<0.01 when compared with DM

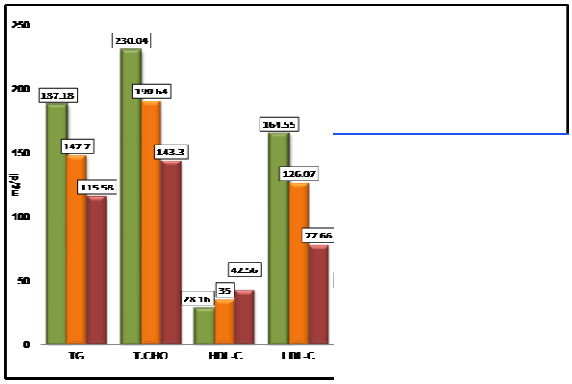

Figure 1: Lipid profile in diabetes mellitus with nephropathy, diabetes mellitus without nephropathy and in control group

Discussion

Lipoprotein abnormalities are more common in diabetic nephropathy patients and contributes to coronary heart diseases in diabetic nephropathy patients[10]. In our study we found higher mean level of total cholesterol, TG, VLDL, LDL, LDL/HDL ratio and TG/HDL ratio and decreased HDL levels in diabetes patients with and without nephropathy when compared to controls. Our study very well correlates with Ejuoghanran OS *et al* [11], Dwivedi J *et al* [12], Eghan BA [13], Patel ML *et al* [14]. In our study the probable cause of dyslipidemia in patients of DM without nephropathy and DM with nephropathy may be insulin resistance [15]-[17]. The characteristic diabetic dyslipidemia associated with

insulin resistance include hypertriglyceridemia and high levels of VLDL and low levels of HDL cholesterol and apolipoprotein (apo) A-I [18],[19]. A high concentration of triglyceride-rich VLDL particles inhibits insulin binding to its receptor and affects Insulin action [20].Insulin has effect on the activity of adipose tissue lipoprotein lipase (LPL), as shown by both in vitro and in vivo studies [21].Thus, diminished LPL activity in insulin resistant individuals may reduce VLDL catabolism and increased hepatic VLDL triglyceride secretion and hepatic apoB-100 production and secretion and increased flux of free fatty acids to the liver, which further accentuate hypertriglyceridemia [22]. The increase in LDL-C in case of DM with or without diabetic nephropathy with poor glycaemic control is due to glycation of LDL and oxidative modification of LDL. Oxidized modified lipoproteins are the direct mediators of glomerular injury which progresses to diabetic nephropathy. Insulin has profound effects on HDL metabolism, and low levels of HDL cholesterol and apoA-I and a high ratio of total cholesterol to HDL cholesterol are strongly related to insulin resistance and are unique to patients with NIDDM [15]-[17]. According to **Deckert** hypothesis, microalbuminuria plays an important role in vascular damage[23].Lipoprotein lipase attaches to surface endothelium is decreased by generalised endothelial cell damage thereby causing hepatic lipase in diabetic subjects with microalbuminuria. Microalbuminuric patients had lower LPL mass than normoalbuminuric patients and LPL mass was inversely correlates with TG and positively correlates with HDL. LPL enzyme plays important role in dyslipidemia in diabetic nephropathy [24]. First, urinary protein loss stimulates an increased LDL synthesis by the liver. It is likely that proteinuria with the resultant hypoalbuminemia leads to an upregulation of 3-hydroxy-3-methylglutaryl CoA reductase with a consequent hypercholesterolemia[25]. Lipoproteins are taken up by specific receptors in mesangial and epithelial cells of glomeruli. Mesangial cells express scavenger receptors which uptakes the modified glycosylated and oxidized LDL. Accumulation of modified LDL in the mesangium itself causes its own uptake by infiltrated glomerular monocytes which are activated and gets converted into macrophages. Phagocytosis of modified LDL-C by monocytes plays an important role in the formation of mesangial foam cells. Accumulated modified lipoproteins within the mesangium stimulate secretion of various chemotactic factors and adhesion molecules such as macrophage colony stimulating factor and intracellular adhesion molecule-1. These factors result in monocyte infiltration which plays an important role in the pathogenesis of glomerulosclerosis and tubular fibrosis in diabetic nephropathy. These intramesangial macrophages further oxidize LDL resulting in progressive renal injury. An activated macrophages in the renal mesangium stimulate the release of reactive oxygen species and expression of cytokines such as transforming growth factor β1 and platelet derived growth factor-AB which stimulate the production of extracellular matrix proteins and promoting mesangial expansion as described in diabetic nephropathy. LDL-C and oxidized LDL-C stimulate transforming growth factor-β1 gene expression in human glomerular, mesangial and epithelial cells. Therefore, transforming growth factor -β1 appears to be an important mediator of lipid induced mesangial matrix expansion as well as play an important role in the pathogenesis of diabetic nephropathy. The uptake of modified LDL by mesangial macrophages also stimulate the eicosanoid synthesis such as thromboxanes and leukotrienes leading to potentially harmful effect in intraglomerular hemodynamics [26]-[29]. In the patients of diabetic nephropathy, there is elevated levels of serum triglyceride (TG) and low levels of HDL-C. The increase in LDL-C in case of poorly controlled glycaemic control is due to glycation of LDL and oxidative modification of LDL. Oxidized modified lipoproteins are the direct mediators of glomerular injury which progresses to diabetic nephropathy.

Conclusion

Diabetic dyslipidemia is more pronounced in diabetic nephropathy as compared to diabetes mellitus patients. Lipid ratios are better indicators of atherogenic risk in patients with diabetic nephropathy as compared to lipids alone. Monitoring of lipid status with better management may delay diabetic nephropathy as well as delays the risk of CVD in diabetic nephropathy patients.

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