ISSN 2250-3153

Dyslipidemia and Oxidative Stress in Maintenance Hemodialysis Patient- An Emerging Threat to Patient

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***Abstract*- Background:** Lipid abnormalities and enhanced oxidative stress in CRF patients on hemodialysis accelerates the process of atherosclerosis resulting in cardiovascular complications. So the aim of this study to investigate the alterations in the serum lipid status in CRF patients on long term hemodialysis and determination of oxidative stress to know the risk of development of cardiovascular complications in these patients.

Methods: This cross sectional comparative study was carried out to determine the pattern of lipid profile and oxidative stress in patients on maintenance hemodialysis (MHD). After taking informed consent total 110 subjects were enrolled for the study in the Department of Medicine, CSM Medical University, Lucknow. Out of which 60 patient of CRF on MHD were taken as a case group, (42 male 70% and 18 female 50%), mean duration of hemodialysis was 4.5±2.05years with frequency of three session/week and each session for four hours. 50 healthy volunteers seeking treatment for other minor problem were taken as a controls (31 male 62% and 19 female 38%).

Results: Mean value of HDL cholesterol is significantly decreased in CRF patients when compared to controls. Serum LDL-C, VLDL-C were also increased in dialysis subjects in comparison to normal healthy controls (p value 0.05 &0.001). TC/HDL-C and LDL-C/HDL-C ratio were significantly increased (p value<0.001). S.MDA was significantly increased and SOD was significantly decreased in cases when compare to controls. These changes were more pronounced in hemodialysis patients when compare to controls. We also did the correlation between lipid and oxidative stress parameters, in which S.MDA was positively correlated with all the lipid parameters except HDL-C and SOD was negatively correlated with all the lipid parameters except HDL-C.

Conclusion: This study supports that patients on MHD show abnormalities of lipid metabolism like hypertriglyceridemia, increased total cholesterol and low HDL-C and increased oxidative stress which could contribute to accelerated atherosclerosis and cardiovascular disease that might be responsible for increase in morbidity and mortality.

***Index Terms*-** Dyslipidemia, Oxidative stress, Maintenance Hemodialysis, Malondialdehyde, Superoxide Dismutase

I. INTRODUCTION

Chromic renal failure (CRF) is the state which results from a permanent and usually progressive reduction is renal function, in a sufficient degree to have adverse consequences on other system.[1] The incidence and prevalence of chronic kidney disease (CKD) are increasing worldwide. According to the 1998 – 2004 National Health and Nutritional Survey (NHANES), the prevalence of CKD in the US population is 15.3%.[2] In the developing countries, the awareness and burden of CRF on society has been highlightened during last decade. In India incidence of CRF is not well documented because of lack of national registry and data regarding its incidence. It has been estimated that the prevalence of CRF in India may be up to 870 people/million population.[3]

A patient with CRF leads to many complications over a period of time. The most common include cardiovascular, cerebrovascular and peripheral vascular disease. The incidence of cardiovascular disease is high in patients on hemodialysis (HD).[4] Approximately 50% of patients with end stage renal disease (ESRD) die from cardiovascular events, which indicate that cardiovascular mortality is 30 times higher in dialysis patients.[5] The kidney dialysis outcome quality initiative (KDOQI) guide lines state that patients on MHD with fasting triglycerides (TG) > 5.56 mmol/L, Low-density lipoprotein (LDL) > 2.59 mmol/L and non-HDL cholesterol > 3.36 mmol/L should be considered for treatment to reduce the cardiovascular complication in these patients.[6] Death due to cardiovascular complication in these patients are 4–20 fold higher in CRF patients than any other cause in general population.[7] These complications are due to many metabolic and endocrinal disturbances among which dyslipidemia is one of the constant feature of CRF. Lipid abnormality can be detected as early as renal function beings to decline (GFR<50 ml/min) but the type and severity vary among different patients.[8,9]

CRF patients on hemodialysis are also subjected to enhanced oxidative stress due to reduced antioxidant system and increased pro-oxidant activity[10]. During this process polyunsaturated fatty acid, present in cell membrane are oxidized in vivo to form aldehydes of variable chain length like malondialdehyde (MDA). This lipid per-oxidation product can structurally alter DNA, RNA, body protein and other biomolecules[11]. Lipid abnormalities and enhanced oxidative stress in CRF patients on hemodialysis accelerates the process of atherosclerosis resulting in cardiovascular complications. Keeping in view the mortality associated with CVD in patients on Hemodialysis, this study was carried out to investigate the alterations in the serum lipid status in CRF patients on long term hemodialysis and to determine the oxidative stress to know the risk of development of cardiovascular complications in these patients.

II. METHODS

A hospital based cross sectional comparative study was conducted in Nephrology Unit, Department of Medicine CSM Medical University (Erstwhile KGMC), Lucknow India from August 2010 to July 2011. 60 cases of CRF were selected from dialysis unit & Nephrology OPD and fifty controls group with age, sex matched normal healthy adults without any major illness were enrolled in the study after informed consent and this study was approved by Institutional ethics committee of CSMMU, Lucknow, UP.

A total number of 110 subjects were participated in the study, Out of which 60 clinically diagnosed cases of chronic renal failure > 20 years of age were included in the study. All 60 CRF cases were kept on maintenance hemodialysis for 3-4 hours three times /week receiving dialysis from 6 month to 5 years.

Patients with diabetes mellitus, familial hyperlipoproteinemia and who were on hypolipidemic drugs were excluded from the study after taking detailed history and examination. About 5 ml of venous blood were drawn under aseptic precautions, in a sterile bulb from selected subject after a period of overnight fasting; serum was separated by centrifugation and used for analysis. Serum lipid profile which includes triglycerides (TG), total cholesterol (TC), high density cholesterol (HDL-C) were measured by enzymatic method and serum low density cholesterol (LDL-C) and very low density cholesterol (VLDL-C) were calculated by using Friedwald formula (LDL-C=TC (HDL-C + TG/2.2).[12] In the analysis of serum malondialdehyde (MDA) by thiobarbituric acid method and superoxide dismutase (SOD) by marklund method were used. Lipid profile was analyzed by using ERBA kits in microlab semi analyzer of MERK Company, all the reagents used in the estimation were of analytical grade.

Data analysis was done using statistical software SPSS-16 version. Comparison of mean was done using student t-test and comparison of proportion by chi-square test. The levels of statistical significance were taken as $p< 0.05$. Pearson correlation coefficient used to correlate lipid profile and oxidative stress parameters.

III. RESULT

110 individual were recruited in this study 60 CKD (Male: Female ratio 42(70%): 18(30%) and 50 controls (Male: female ratio 31(62%):19(38%). Chronic glomerulonephritis (50%) was the leading cause of CKD, followed by interstitial nephritis (22%), chronic pyelonephritis (6%) and polycystic kidney disease (2%). Mean age group of patient was 45.6±12.6 (33-65) versus 48.5±11.5 (35-65) in control. Mean hemoglobin in patients versus controls was (9.5±14.5 & 12.5±2.05) respectively. Mean blood urea and serum creatinine was (120±42.2 versus 14.2±3.2) and (7.8±3.4 versus 0.6±0.2) respectively. Mean serum calcium and phosphorus was (8.3±0.50 versus 9.5±0.48 and 5.73±1.8 versus 3.2±0.40). In CKD group mean duration of dialysis was 4.5±2.05years and frequency of dialysis was three times per week for four hours. (Table-1)

Comparative analysis of serum lipid profile between controls and cases shows mean value of TC, TG, LDL-C, VLDL-C, TC/HDL-C and LDL/HDL-C values are increased in cases when compared to controls (p value < 0.001) except HDL-C (p value < 0.05). (Table-2)

Serum MDA level when compared between hemodialysis patients and controls showed significant increased level of MDA ($p < 0.001$) in hemodialysis group. Comparative analysis of serum SOD levels between controls and cases shows mean values of SOD are decreased in hemodialysis patients when compared to controls ($p < 0.001$). (Table-3)

There is a statistically significant correlation between lipid profile and oxidative stress as shown in Table-4.

Table -1 Basic Demographic and Clinical Characteristics of the study groups

Demographic and clinical Characteristics	**Patient (n=60) (Mean±SD)**	**controlee (n=50) (Mean±SD)**
1. Age (years)	45.6±12.6 (33-65)	48.5±11.5(35-65)
2. Gender		
Male	42 (70%)	31 (62%)
Female	18 (30%)	19 (38%)
3. Hemoglobin (g/dl)	9.5±1.45	12.5±2.05
4. Blood Urea (mg/dl)	120±42.2	14.2±3.2
5. Serum creatinine (mg/dl)	7.8±3.4	0.6±0.2
6. Serum calcium (mg/dl)	8.3±0.50	9.5±0.48
7. Serum phosphorus (mg/dl)	5.73±1.8	3.2±0.40
8. Hemodialysis duration (yrs)	4.5±2.05	0
9. Hemodialysis frequency	3-4 hrs/day 3times in week	0

Table – 2 Comparison of serum lipid profile between controls and cases

	Particulars	TC mg/dl	TG mg/dl	HDL-C mg/dl	LDL/C mg/dl	VLDL-C mg/dl	TC/HDL–C	LDL/HDL–C
Controls n=50	mean ± SN	182.1± 22.3	115.0± 30.2	44.3 ± 5.0	115.4 ± 23.4	23.0 ± 6.1	4.2 ± 0.69	2.64 ± 0.64
Cases n=60	mean ± SN	205.7± 24	219.28± 37.82	36.1±5.3	125.4 ± 20.4	43.8 ± 7.7	5.8 ± 1.0	3.55 ± 0.85
Controls V/S Cases	t values	5.29	15.75	8.27	2.38	15.53	9.88	6.14
	p value	<0.001	<0.001	< 0.001	< 0.05	< 0.001	< 0.001	< 0.001

Table -3: Comparison of serum MDA & SOD between controls and hemodialysis patients

Group	Hemodialysis patients	Controls
Number	60	50
Serum MDA nmol/ml	6.5±1.0	3.0±0.5
Serum SOD U/ml	3.6±1.20	9.5±2.2
p value	<0.05	<0.001

Unpaired t-test; p<0.05 significant, p<0.001-highly significant

Table-4: Correlation between lipid profile and oxidative stress parameters

		TC mg/dl	TG mg/dl	HDL-C mg/dl	HDL-C mg/dl	VLDL-C mg/dl	Serum MDA nmol/ml	Serum SOD U/ml
Serum MDA nmol/ml	**r value**	0.292	0.336	-0.682	0.216	0.556	1	-0.707
	p value	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001
Serum SOD U/ml	**r value**	-0.372	-0.381	0.512	0.185	-0.668	-0.706	1
	p value	<0.001	<0.001	<0.001	<0.05	<0.001	<0.001	

r value; Pearson correlation coefficient
p value; >0.05 significant

IV. DISCUSSION

Our study shows peak incidence of CKD in age group of between the third and fourth decades. In developed countries the prevalence of CKD increases with advancing age and the peak incidence is found in 7th and 8th decades.[13] The reason for disparity in peak age range among CKD patients from developed countries and our society population may be related to genetic, sociocultural factors, access to diagnostic tools, therapeutic modalities and the pattern of disease causing CKD.[14,15]

Disorder of lipoprotein metabolism, imbalance between generation of free radicals and antioxidant defense system during uremia and dialysis are important mechanism of atherogenesis in CRF. The mean value of triglyceride is significantly increased in cases when compared to controls. This result is accordance with studies done by SM Alam et al,[16] Bharat Shah et al,[17] P Lee et al,[18] and Z.A. Massy.[19] Hypertriglyceridemia is a common feature of CRF. Presence of insulin resistance in renal failure activate hormone sensitive lipase causing increased free fatty acid which stimulates the production of apoB-100 containing lipoproteins like VLDL leading to hyper triglyceridemia. Several authors also suggested that hyper triglyceridemia in CRF may be due to defective metabolism of TG rich lipoprotein lipase (LPL) and hepatic lipase.[20,21,22]

The mean value of total cholesterol is significantly increased in cases when compared to controls. This is in accordance with the study of MM Avram et al,[23] P.O. Attman etal[24] and Mayumi Tsumura et al.[25] Many studies have reported variable result. A study done by B.S. Das et al[26] observed decreased level of total cholesterol in CRF patients. The reason for this decrease may be due to reduced food intake. CRF is associated with hypercholesterolemia which is due to associated proteinurea and renal insufficiency perse. Proteinurea leads to alteration in gene expression for HMG-COA reductase resulting in increased activity of HMG–COA reductase leading to hyper-cholesterolemia.[26]

Mean value of HDL-C is significantly decreased in CRF patients when compared to controls. Studies conducted by Z.A Massey et al,[19] B.S. Das et al,[26] and Tetsuo Shoji et al,[27] have

also observed the same results. The reason for decreased concentration of HDL in CRF in not fully understood. It may be due to decreased activities of LPL, hepatic triglyceride lipase (HTGL), lecithin cholesterol acyltransferase (LCAT) and increased concentration of cholesterol esters transfer protein (CETP) and decreased apo lipoprotein concentration.[20,21]

MDA is a lipid peroxidation product which is formed during oxidation process of Polyunsaturated Fatty Acid (PUFA) by reactive oxygen species. MDA is the sensitive marker of lipid peroxidation. MDA level is significantly elevated in hemodialysis patients when compared to conservatively managed patients. This is in accordance with study of C.M Loughrey et al [28], A. Marjani [29] and Talia Weinstein et al[30]. Although hemodialysis leads to improvement of several biochemical parameters like creatinine, urea levels and plasma lipid patterns, but it can cause harmful atherogenic effects. The increase in lipid peroxidation resulting from hemodialysis could be provoked by bio incompatibility of dialysis membrane. When cells come in contact with the dialyzer membrane leads to sensitization of cell membrane components leading to compliment activation which cause formation of other reactive oxygen species which will initiate peroxidation of PUFA.[31,32]

SOD functions as a scavenger of superoxide radical in the body. Mean value of SOD is significantly decreased in hemodialysis (p value < 0.05) patients when compared to conservatively managed patients. This is in accordance with the study of A. Marjani [29], M Sasikala et al[31] and M. Nouri et al[32]. Mechanisms involved in decreased serum SOD activity in CRF patients may be due to increased production of ROS such as H_2O_2 which is known to suppress SOD activity. Decreased SOD activity among hemodialyzed patients could be due to decreased levels of Cu^{++} and Zn^{++} as they are cofactors of cytoplasmic SOD. Increased lipid peroxidation causes consumption of antioxidant enzymes, particularly in hemodialysis patients, may be also one of the reasons for decreased SOD levels.[33]

V. CONCLUSION

The result of this study indicate that patient undergoing maintenance hemodialysis show important abnormalities of lipid metabolism such as hypertriglyceridemia, elevated level of total cholesterol, low HDL-C and oxidative stress which could contribute to accelerate the atherosclerosis and cardiovascular disease and may increase the morbidity and mortality in this group. As a first step of controlling hyperlipidemia, body weight normalization, dietary modification, regular exercise and education about diet should be applied. It may also be useful to supplement the diet with polyunsaturated fatty acid from fish oil in order to reduce triglycerides. Statin can be used safely in CKD patients with careful monitoring.

ACKNOWLEDGMENT

We Acknowledge Prof. MK Mitra, Department of Medicine, for his suggestion and constant source of inspiration.

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