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Original Article

Internal Medicine Section

A Comparative Study of Lipid Profile and Cardiovascular Risk Biomarkers Among Chronic Haemodialysis Patients and Healthy Individuals

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ABSTRACT

Introduction: Lipid abnormalities and increase in inflammatory markers are common among patients with End Stage Renal Disease (ESRD) and it tends to persist/worsen even after initiating Intermittent Haemodialysis (IHD). The cardiovascular mortality and morbidity remains significantly high in this population.

Aim: The present study was carried out to assess the pattern of lipid abnormality in our population and to find its association with inflammatory markers.

Materials and Methods: It was a cross-sectional, observational study on ESRD patients undergoing Haemodialysis (HD) in comparison with age and sex matched healthy individuals in a tertiary care hospital. About 40 adult male and female patients aged >18 years, undergoing chronic HD for more than 6 months were enrolled in Group A. Patients who were alcoholics, tobacco consumers and those on steroids and hypolipidemic drugs were excluded. Group B consisted of healthy, age and sex matched controls. Serum lipid profile, lipoprotein A, apolipoprotein A1, apolipoprotein B and apo B/A1 ratio, serum uric acid, homocysteine, hs-CRP and testosterone levels were estimated among patients undergoing intermittent HD and healthy individuals. Chi-square/Fisher's-exact test was used for comparing ratios. A p-value of <0.05 was considered statistically significant.

Results: The mean Total Cholesterol (TC), Low Density Lipoprotein (LDL) and Non-HDL High Density Lipoprotein cholesterol was significantly lower in HD patients as compared to control group with all the three parameters attaining statistical significance (p<0.005). The mean lipoprotein A level was significantly higher (p=0.037), while Apo A1 was found to be significantly lower (p=0.001) in patients receiving HD. Inflammatory markers like uric acid was high (p<0.005) and serum testotsterone level in male HD patient was significantly low (p<0.005).

Conclusion: The mean values of traditional serum lipid profile remained lower in HD patients than the control group. The abnormalities in lipoprotein A and apolipoproteins were more pronounced in patients undergoing HD. The mean level of testosterone also was found to be lower in male patients receiving HD. Hence, estimation of lipoprotein A, apolipoproteins and inflammatory markers may serve as a potential tool in cardiovascular risk stratification.

Keywords: Inflammatory markers, High sensitivity C-reactive protein, High density lipoprotein

INTRODUCTION

Cardiovascular Disease (CVD) is the most common reported cause of death even though the Haemodialysis (HD) patients have an affinity toward better survival. There are various factors involved in etio-pathogenesis of CVD in chronic kidney disease, which include oxidative stress, endothelial dysfunction, vascular inflammation, worsening HD and dyslipidemia [1-5]. As a primary step of plaque formation the monocyte adhesion and macrophage differentiation in to foam cells happen [6,7]. This above process is further worsened by uraemic dyslipidemia which is characterized by reduction in Apo A containing lipoproteins in HDL and increased concentration of either intact or partially metabolized triglyceride rich Apo B in Very Low-Density Lipoprotein (VLDL), Intermediate-Density Lipoprotein (IDL), and LDL [8,9].

Hyperhomocysteinemia is the main non-traditional risk factor thought to affect the development of CVD in CKD. Several clinical studies have shown elevated homocysteine levels in the HD patient group and that hyperhomocysteinemia increases cardiovascular mortality [10,11].

Inflammation [a rise in High-Sensitivity C-Reactive Protein (hs-CRP)] has also been shown to be correlated with cardiovascular events [12]. The hs-CRP has been found to be a more sensitive marker for inflammation when compared to CRP.

Testosterone deficiency is known to have an adverse effect on several key cardiovascular risk factors which include central obesity, insulin resistance, hyperglycaemia, dyslipidemia, inflammation and hypertension [13]. Evidence shows that the degree of atherosclerosis as assessed by the degree of Carotid Intimal Media Thickness (CIMT) is inversely associated with testosterone levels [14,15]. In our study, we wished to compare these cardiovascular risk biomarkers in patients undergoing HD and healthy individuals.

MATERIAL AND METHODS

This cross-sectional, comparative study was done at Mahatma Gandhi Medical College and Research Institute Puducherry, India, on 80 subjects. It included both males and females in the age group of 30-60 years. The mean and Standard Deviation (SD) of Lipoprotein A in HD patients was taken as 61.98±36.36 mg/

dl from the review of literature and the same for normal healthy individual was 31±27.42mg/dl. With α = 0.01 and a power of 90%, the minimum sample size was calculated as 33 for each arm. Hence, the sample size was rounded to 40 for cases and 40 for controls.

Group A (Cases) included 40 patients with established ESRD undergoing chronic HD for more than 6 months at the Institute. All patients were undergoing three sessions of HD in a week with each lasting for 4 hours using bicarbonate buffer with a blood flow of 250ml/min and dialysate flow of 500ml/min, with 1.6m^2 surface area hollow fiber polysulfone membrane dialyser. All these patients were randomly selected.

Group B (Controls) included 40 apparently healthy age and sex matched male and female volunteers with normal renal function who were employees of SBV University, Puducherry, India and individuals who attended health check-ups.

This study was done in conformity with the Declaration of Helsinki and it was approved by Institutional Human Ethics Committee of Mahatma Gandhi Medical College and Research Institute, Puducherry, India.

All the participants were interviewed and a full medical, substance abuse and occupational history were taken by the principal investigator. Patients in Group A were interviewed and examined in the dialysis unit of the institute prior to the commencement of dialysis session. The duration of maintenance HD, presence of any co-morbidities, dietary history and current medication history was taken from participants of Group A.

Participants of Group B were interviewed and examined in General Medicine outpatient department after obtaining a valid consent. Participants in this group had a normal urine routine, Blood Urea Nitrogen (BUN), serum creatinine and the estimated Glomerular Filtration Rate (GFR) by Modification of Diet in Renal Disease (MDRD) formula was normal. Further, they were subjected for ultrasonography to rule out structural abnormalities.

The blood samples were analyzed for apolipoprotein A1, B and lipoprotein A, by fully automated Nephelometry BN II (Siemens Dade Behring BN II Nephelometer GMI SKU≠: 8100-30-1002). TC was estimated by Cholesterol Oxidase-Peroxidase (CHOD POD) method [16,17], HDL by enzyme selective protection method, LDL by homogenous enzymatic colorimetric assay and TG by enzymatic colorimetric method (GPO) [18]. Testosterone was estimated by fully automated bi-directionally interfaced chemi luminescent immune assay, homocysteine by competitive chemi luminescent immune assay and uric acid by uricase/peroxidase method.

STATISTICAL ANALYSIS

The SPSS, version 19.0 software tool was used for the data processing. All the values were expressed as mean±SD unless otherwise indicated. The differences in the mean values between the groups were analyzed by using the independent Student's t-test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 40 subjects were enrolled in both the groups. There were 33 males and 07 females in Group A as compared to 32 males and 08 females in Group B. The average age of subjects in Group A was 48.30±10.95 years as compared to 48.18±9.732 years in Group B. The BMI in Group A was 20.76±4.249 as compared to 24.33±4.465 in Group B [Table/Fig-1].

There was a significant difference in Body Mass Index (BMI) (p=0.001), Blood Urea Nitrogen (BUN) (p=0.001), Serum Creatinine (p=0.001), Systolic Blood Pressure (SBP) (p=0.001) and Diastolic Blood Pressure (DBP) (p=0.001) among Group A and Group B [Table/Fig-1].

Parameters	Group A - Cases	Group B Controls	p-value
Total Number (N)	40	40	
Sex; Male Female	 33 07	 32 08	0.775
Age	48.30±10.95	48.18±9.732	0.957
BMI	20.76±4.249	24.33±4.465	0.001
Addictions	Nil	Nil	
Systolic Blood Pressure (SBP) mmHg	156.25±22.152	121.38±7.970	0.001
Diastolic Blood Pressure (DBP) mmHg	93.75±13.90	75.06±5.768	0.001
Blood Urea Nitrogen (BUN) mg/dl	53.75±17.75	12.12±3.33	0.001
Serum Creatinine mg/dl	10.07±2.774	0.79±0.134	0.001

[Table/Fig-1]: Baseline characters.

In the present study, the mean TC, LDL and Non-HDL among Group A were 131.45±33.878mg/dl, 71.42±21.98mg/dl and 99.78±29.473mg/dl which was significantly lower (p<0.005) when compared to Group B whose levels were 167.25±32.306mg/dl, 102.5±28.807mg/dl and 131.94±30.601mg/dl, respectively [Table/Fig-2].

In the present study, the mean HDL, TG and VLDL among Group A and Group B was 31.82±9.735mg/dl vs 35.48±7.43mg/dl (p=0.063), 120.65±72.09 mg/dl vs 137.48±62.418mg/dl (p=0.268) and 24.02±14.42mg/dl vs 26.98±12.384mg/dl (p=0.328) respectively which did not achieve statistical significance [Table/Fig-2].

The mean TC/HDL and LDL/HDL ratio was 4.34±1.135 and 2.35±0.675 which was significantly lower among Group A as compared to Group B with a value of 4.99±1.172 (p=0.013) and 3.03±0. 905 (p<0.005) which was statistically significant [Table/Fig-2]. In our study, the mean lipoprotein A level in Group A was 38.16±32.753mg/dl as compared to 24.91±21.478mg/dl in Group B which was significantly higher (p=0.037) [Table/Fig-3].

The mean value of cardioprotective apolipoprotein A1 level in Group A was 98.02±20.310mg/dl as compared to 111.92±15.034mg/dl in Group B which was significantly lower (p<0.001) [Table/Fig-3].

The mean atherogenic apolipoprotein-B was found to be 68.38±20.799mg/dl in Group A as compared to 89.18±20.489 mg/dl in Group B which was found to be significantly lower (p<0.005) [Table/Fig-3].

We also observed that the mean levels of ApoB/A1 ratio among Group A was 0.72±0.224 mg/dl as compared to 0.87±0.307 mg/dl in Group B which was significantly lower (p=0.013) [Table/Fig-3].

Parameters	Group A-Cases	Group B-Controls	p-value
Total Cholesterol (mg/dl)	131.45±33.878	167.25±32.306	<0.005*
Triglycerides (mg/dl)	120.65±72.097	137.48±62.418	0.268
HDL (mg/dl)	31.82±9.735	35.48±7.435	0.063
LDL (mg/dl)	71.42±21.987	102.50±28.807	<0.005*
VLDL (mg/dl)	24.02±14.429	26.98±12.384	0.328
Non-HDL (mg/dl)	99.78±29.473	131.94±30.601	<0.005*
TC/HDL ratio	4.34±1.135	4.99±1.172	0.013*
LDL/HDL ratio	2.35±0.675	3.03±0. 905	<0.005*

[Table/Fig-2]: Serum lipid profile.

Parameters	Group A-Cases	Group B-Controls	p-value
Lipoprotein-A (mg/dl)	38.16±32.753	24.81±21.478	0.037*
Apolipoprotein-A1 (mg/dl)	98.02±20.310	111.92±15.034	0.001*
Apolipoprotein-B (mg/dl)	68.38±20.799	89.18±20.489	<0.005*
Apo B/A1 ratio	0.72±0.224	0.87±0.307	0.013*

[Table/Fig-3]: Serum apolipoprotein levels.

The mean value of serum testosterone was found to be 212.97±155.197 ng/dl in Group A as compared to 331.53±187.279 ng/dl in Group B which was found to be significantly lower (p<0.005) [Table/Fig-4]. After age and sex adjustment of serum testosterone, 15 (45.45%) participants in Group A and 01(3.125%) participant in Group B had low testosterone levels. Whereas 18 (54.54%) participants in Group A had normal levels of serum testosterone as compared to 31 (96.87%) in Group B which was statistically significant (p=0.002) [Table/Fig-5]. The mean HsCRP level in Group A was 4.12±3.342mg/dl as compared to 4.16±3.619 among Group B which was not found to be statistically significant (p=0.966) [Table/Fig-4].

When hs-CRP level was compared with that of serum testosterone level in Group A, 5 (33.3%) participants had hs-CRP of 1-3mg/dl carrying intermediate risk and 10 (66.6%) participants had a value of >3mg/dl carrying a high risk among patients with low testosterone levels. Among patients with normal testosterone levels, 8 (44.4%), 3 (16.6%) and 7 (38.8%) participants had HsCRP levels of <1, 1-3 and >3mg/dl [Table/Fig-6].

Of the 40 patients in Group A, 26 (65%) had serum homocysteine levels of <30µmol/L as compared to 31(77.5%) in Group B. Only 14(35%) patients in Group A had serum homocysteine levels of >30µmol/L as compared to 09 (22.5%) in Group B. The values did not vary significantly (p=0.216) [Table/Fig-5].

The mean serum uric acid level among Group A was 7.25±1.386 mg/dl as compared to Group B with 4.61±1.278mg/dl which was found to be statistically significant (p<0.005) [Table/Fig-4]. Of 40 patients in Group A, 17(42.5%) had serum uric acid level of >7mg/dl as compared to only 02(5%) among Group B which was found to be statistically significant (p<0.0001) [Table/Fig-5].

Parameters	Group A-Cases	Group B-Controls	p-value
hs-CRP (mg/dl)	4.12±3.342	4.16±3.619	0.966
Homocysteine (µmol/L)	25.57±13.712	22.10±11.279	0.231
Uric Acid (mg/dl)	7.25±1.386	4.61±1.278	<0.005*
Testosterone (mg/dl)	212.97±155.197	331.53±187.279	<0.005*

[Table/Fig-4]: Serum levels of hs-CRP, homocysteine, uric acid and testosterone.

hs-CRP	<1 mg/dl	1-3mg/dl	>3mg/dl
Cases (n=40)	09 (22.5%)	09 (22.5%)	22 (55%)
Controls (n=40)	12 (30%)	10 (25%)	18 (45%)
Homocysteine	**<30µmol/L**	**>30µmol/L**	
Cases (n=40)	26 (65%)	14 (35%)	
Controls (n=40)	31 (77.5%)	09 (22.5)	
Serum Uric acid	**<7.0mg/dl**	**>7.0mg/dl**	
Cases (n=40)	23 (57.5%)	17 (42.5%)	
Controls (n=40)	38 (95%)	02 (5%)	
Serum Testosterone	**Low**	**Normal**	
Cases (n=33)	15 (45.45%)	18 (54.54%)	
Controls (n=32)	01 (3.125%)	31 (96.87%)	

[Table/Fig-5]: Normal and abnormal levels of hs-CRP, homocysteine, uric acid and testosterone in both the groups.

hs-CRP	Serum Testosterone (Group A)	
	Low	Normal
<1	-	8 (44.4%)
1-3	5 (33.3%)	3 (16.6%)
>3	10 (66.6%)	7 (38.8%)
Total	15	18

[Table/Fig-6]: Association of serum testosterone with hs-CRP levels in Group A.

DISCUSSION

In the present study, out of 40 patients in Group A, 15 (37.5%) Patients had malnutrition (BMI<18.5Kg/m^2). In a study conducted by Maheshwari N et al., [19] the BMI among patients undergoing HD was 19.83±4.05 as compared to 22.21±3.8 among control group with 48% of patients undergoing HD having malnutrition. This observation suggests a higher prevalence of malnutrition among our patients as compared to the western counterparts.

Diabetes mellitus and hypertension were found in 36 and 35 patients respectively in group a, while none of participants in group b had any co-morbidities like diabetes mellitus, hypertension, coronary artery disease, peripheral vascular disease and cerebrovascular disease.

Maheshwari N et al., observed that there was no statistically significant difference in TC, TG and LDL cholesterol among patients receiving HD and control group [19]. A similar observation was noticed by Dipika Baria et al., where the TC and LDL levels did not vary significantly. Our study is peculiar in this regards that the TC, LDL and Non-HDL levels were lower among Group A (Cases) as compared to Group B which is suggestive of higher prevalence of malnutrition [20].

The level of HDL cholesterol was lower in Group A as compared to Group B. A low level of HDL cholesterol was observed in various previous studies [19-21]. Similarly, the level of TG and VLDL was also lower in Group A as compared to Group B. Our study is in contradiction with various other studies where they observed an elevated levels of TGs among HD patients [19,20,22].

The mean TC/HDL and LDL/HDL ratio was found to be lower in Group A as compared to Group B. This observation is again in contradiction with findings of Jamal Q Abumwais et al., where these ratios were found to be higher among dialysis patients when compared to healthy controls [23].

Our study revealed low levels of TC, TG, HDL, VLDL, Non-HDL, TC/HDL ratio and LDL/HDL ratio among patients undergoing HD when compared to controls. Malnutrition probably is the reason explaining the above findings.

ESRD also is characterized by an elevated level of pro-atherogenic and pro-thrombogenic effects of elevated lipoprotein A. In the present study, the mean lipoprotein A level was significantly higher in Group A when compared to Group B. Schwaiger et al., observed an elevated level of serum lipoprotein A and an unaltered TC, HDL, LDL and TG levels [24]. Our study is in conformity with that of Koch et al., and Neela Mannangi et al., [21,22].

Uraemic dyslipidemia is characterized by a low level of apolipoprotein-A1, a similar finding was noted in our study where the mean apo A1 was lesser in Group A as compared to Group B. AM Rao et al., in their study involving CKD patients at different stages also noted a lower value of apolipoprotein A in ESRD which was found to be statistically significant when compared to control group [25].

The level of pro atherogenic apolipoprotein-B was found to be low in Group A. This finding is in contradiction with observations of AM Rao et al., where they found a significantly higher level of Apo B among ESRD patients as compared to controls [25].

The above observations reflect that ESRD patients have significantly lower levels of cardioprotective apo A1, while the atherogenic apo B levels tend to remain low.

The principal abnormality detected in our population with ESRD undergoing HD was a low levels of HDL cholesterol, low levels of apolipoprotein A1 and higher levels of lipoprotein A. The traditional total cholesterol, Triglycerides, LDL, VLDL and Non-HDL tends to be significantly lower in ESRD patients when compared to controls reflecting-

1. That the traditional Serum Lipid profile has limited role in assessing lipid abnormalities in ESRD patients.

2. Statins have limited/no role in correcting lipid abnormalities in ESRD patients [26].

3. Higher prevalence of malnutrition probably leading to the above situation.

As the serum testosterone concentration decline with age, the reference range should be age-specific, hence considering 2.5th percentile of total testosterone to be 348ng/dl in a sample of young men as per Bhasin et al., and value of less than 184ng/dl for elderly men as per Yeap et al., the results were analyzed [27,28]. The mean serum testosterone level in male HD patients was significantly lower when compared to healthy controls.

Juan Jesus Carrero et al., in their study observed that low serum testosterone was inversely correlating with all cause and CVD related mortality, they also observed that only 23% of their patients had truly normal testosterone levels [29]. Bello AK et al., in their study found that the mean serum testosterone was 234.1±146.1ng/dl, a higher serum testosterone level was associated with significantly low unadjusted risk of death as compared to those with low serum testosterone levels [30]. F Albaaj et al., concluded that more than half of their male renal failure patients had biochemical hypogonadism, which was considered to be a potentially reversible risk factor for osteoporosis and sexual dysfunction [31].

When hs-CRP was compared with serum testosterone levels, 10 (66.6%) of patients in Group A had hs-CRP level of >3mg/dl as compared to 7 (38.8%) in Group B. A similar observation of low testosterone with a high CRP was observed by Jaun Jesus Carrero et al., [29]. The above observations suggest that low testosterone levels are associated with significant inflammation which may accelerate endothelial dysfunction and increase the risk of cardiovascular events in HD patients.

In the present study, the mean homocysteine levels did not vary significantly between the groups. N Nand et al., in their study on CKD patients found that there was a significant elevation in serum Homocysteine levels among CKD patients (94.4%) as compared to healthy controls [32]. Though folic acid, vitamin B12 and Vitamin B6 supplementation significantly reduced homocysteine, there was no significant difference on the total number of all-cause mortality and deaths due to CVD, as observed in HOPE-2 and other trials [33,34], none of these trials enrolled HD patients.

The mean serum uric acid level was significantly higher in Group A as compared to Group B. In the LIFE trial, the losartan group was associated with regression of LVH and a lower incidence of Coronary events and stroke in those patients with low serum uric acid levels ($p<0.001$) [35].

Madero et al., on subset analysis of MDRD trial found that higher uric acid level was associated with higher all-cause and cardiovascular related mortality [36].

Walead latif et al., in their study found a mean serum uric acid level of 6.97mg/dl, where they included patients undergoing HD which is in contradiction to the MDRD and LIFE trial which was focused on CKD patients not receiving HD [35]. It was observed in their study that there was no upward trend in mortality risk even when patients had a uric acid level of >8.2 mg/dl, concluding that a relative normal values of uric acid was associated with higher risk of death from all-causes and CVD. They suggested a cardioprotective role of uric acid in patients undergoing HD.

The above paradoxical phenomenon represents example of the so called “Reverse Epidemiology” in the dialysis population. The conventional risk factors of CVD and mortality in the general population like BMI, serum cholesterol, blood pressure and uric acid level are found to relate to outcome in an opposite direction in haemodialysis patients [36].

The concept of Reverse epidemiology is likely explained by Protein-Energy Malnutrition (PEM), inflammation or the combination are more common in dialysis patients than in the general population and many such elements of Malnutrition Inflammation and Atherosclerosis (MIA) syndrome such as low BMI, hypocholesterolaemia, hypocreatininemia, hypouricaemia and a lower Blood pressure are known risk factors of poor outcome in dialysis patients [37].

LIMITATION

The smaller sample size and a single centric study was the limitation of this study.

CONCLUSION

The present study population displays a peculiar abnormality where the traditional lipid profile tends to remain normal, indicating their limited values. All patients undergoing haemodialysis need to be assessed for lipoprotein A and apolipoproteins. Hypogonadism in male HD patients showed a higher level of inflammation. Testosterone replacement to be considered on an individual basis in symptomatic patients. Frequent reassessment of the patients on replacement therapy should be done.

Our observation does not favor use of statins in HD patients. A good nutrition support aiming at increasing HDL cholesterol, regular physical activity, smoking cessation and maintaining healthy weight for height remains important in HD patients.

CONFLICT OF INTEREST

Authors have no conflict of interest.

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