Coronary risk factors in maintenance hemodialysis patients: Who is the culprit – hemodialysis or chronic renal failure?

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Abstract

Objective: Dyslipidemia, common in uremic patients subjected to maintenance hemodialysis (HD), represents an independent risk factor for atherosclerosis; but the association between long-term HD and uremic dyslipidemia is not crystal clear. The present study was aimed to ascertain any association. Materials and Methods: The effects of chronic renal failure (CRF) and HD duration on serum lipids, lipoproteins and homocysteine (HC) were studied in 84 patients suffering from CRF subjected to maintenance HD and were compared with 68 healthy, age-, sex- and race-matched control cohorts. Results: Increase in serum free cholesterol (FC), triglycerides, very low-density lipoprotein cholesterol and HC levels, and decrease in esterified cholesterol (EC), EC/FC ratio, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol levels were highly significant (P < 0.001) in pre-dialysis patients compared to controls. Further disturbances were observed (P < 0.05) by repeated HD, resulting in further significant increase in FC, and decrease in EC/FC ratio and HDL-C levels after 40 dialysis schedules. Conclusion: Levels of HDL-C, plasma FC, and ratio of EC/FC appeared to be clearly altered by HD duration, submitting patients to a greater risk of atherosclerosis due to maintenance HD.

Key words: Atherosclerosis, cholesterol, hemodialysis, uremia

Introduction

Atherosclerosis is recognized as the major cause of cardiovascular disease (CVD) in hemodialysis (HD), and it is responsible for 40–50% of deaths in this population.[1] It has been suggested that dialysis itself can accelerate atherosclerosis, while many patients enter dialysis with atherosclerosis, which can lead to a high risk of early mortality during the first years of dialysis.[2]

Dyslipidemia, often observed in patients with chronic renal failure (CRF), results in abnormal concentrations and composition of plasma lipoproteins. The prominent features of uremic dyslipidemia are an increase in plasma triglycerides (TGs) and a reduction in high-density lipoprotein cholesterol (HDL-C).[3-4] Hypertriglyceridemia is also considered as an independent risk factor for CVD[6] and is explained in CRF by a defective catabolism of triglyceride-rich lipoproteins by the lipolytic enzymes.[7,8]

However, the effects of long-term HD on lipolytic activities are still lying in gray zone. Some studies have reported that lipid and lipoprotein compositions do not appear to be influenced by dialysis duration and no relationship exists between plasma TG levels and dialysis duration,[9-11] whereas others have found correlation between hypertriglyceridemia, cholesterol, lecithin-cholesterol acyltransferase (LCAT) activity and HD duration.[12-13]

Homocysteine (HC) is another predisposing factor of atherothrombosis through endothelial dysfunction, enhancement of inflammation, and thrombophilic profile.[16] Serum levels of HC are increased in patients on HD and predisposes them to CVD.[17] HC also induces glomerular injury and sclerosis.[18]
Based on these observations, a longitudinal study was carried out with the principal objective of evaluating the effects of HD duration on plasma lipids, lipoproteins and HC levels in patients with CRF.

**Materials and Methods**

The present study was carried out in the dialysis unit of a medical college and was approved by the institutional ethical committee. The study included patients suffering from CRF, subjected to maintenance HD for the first time, and age-, sex- and race-matched healthy controls with no present or past history of hematological or renal disease. A written, informed consent was obtained from all the study participants. Patients with acute or chronic infection were excluded from the study.

Patients were dialyzed twice to thrice a week, depending on the need, for 3–4 hours in each schedule, with volumetric dialyzer machines using bicarbonate or acetate buffer based dialyze with blood flow of 250 ml/min and dlyizate flow of 500 ml/min, using 1.6 m² surface area hollow fiber polysulfone membrane dialyzers. Patients were continuously monitored by measuring blood urea (BU) and creatinine levels. For measuring blood biochemical parameters, three blood samples of 10 ml each were withdrawn from the patients: first sample before dialysis (pre-dialysis sample), second sample after first dialysis and third after 40th dialysis (post-dialysis 1 and post-dialysis 40, respectively). Pre-dialysis samples were taken before the administration of heparin, while post-dialysis samples were taken 24–36 hours after the completion of dialysis, when the effect of heparin was abolished. Only one blood sample of 10 ml was withdrawn from controls to estimate baseline values.

Total serum cholesterol (TC) and esterified cholesterol (EC) were estimated by Zlatki’s method as modified by Zak, while free cholesterol (FC) and serum TGs were estimated by enzymatic GPO/PAP method of McGown et al. HDL-C levels were measured by the method of Burstein et al. Low-density lipoprotein cholesterol was estimated (LDL-C) by the method of Stokes et al. and very low-density lipoprotein cholesterol (VLDL-C) by the method given by Lowenstein and Neusy. Plasma HC was assessed by the fluorescence polarization immunoassay (Abbott IMX Instruments, Chicago, IL, USA) method. All values were expressed as mean ± standard deviation (SD), and student’s t-test and chi-square test were used for statistical analysis.

**Results**

The present study included 84 individuals (60 males and 24 females) suffering from CRF and 68 age-, sex- and race-matched, healthy controls (48 males, 20 females). Of the 84 patients, 42 patients had hypertension (HT) induced renal failure, 16 patients had diabetes mellitus (DM), 20 patients had both HT and DM, while six patients had systemic lupus erythematosus (SLE) as the cause of end-stage renal disease (ESRD). All the patients had pre-dialysis reduced glomerular filtration rate (GFR) values, raised BU and raised serum creatinine (SC) levels [Table 1].

The TC was significantly lower in pre-dialysis patients than in controls (P < 0.05), but no further significant change was observed on repeated HD. Serum FC was significantly higher (P < 0.001), while EC was significantly lower (P < 0.001) in pre-dialysis patients than in controls, and further significant change was observed in serum FC (P < 0.05) on repeated HD after 40th dialysis. This resulted in a highly significant decrease of EC/FC ratio in pre-dialysis patients as compared to the control group (P < 0.001), which was further decreased significantly after 40 repeated schedules of HD (P < 0.05 after 40 dialysis schedules as compared to pre-dialysis values). The same pattern was followed by HDL-C, i.e., it was significantly lower in pre-dialysis patients (P < 0.001) and by repeated HD (P < 0.05). The serum TGs, VLDL-C, LDL-C, and HC levels were significantly different in pre-dialysis patients than in the control group (P < 0.001), but no further changes were observed in the values of these biochemical parameters by maintenance HD [Table 2].

BU and SC levels showed a significant fall after first dialysis as compared to pre-dialysis values [Table 3].

**Discussion**

CVD is the main cause of mortality in CRF patients on HD. This cardiovascular mortality in CRF patients is presumed to be mainly due to serum lipid disturbances, increased level of HC and increased oxidation stress. If this pattern of lipid abnormalities is characteristic of CRF and if HD further aggravates it, is not clear. The present study demonstrates the changes in FC, EC/FC ratio and HDL-C levels as an effect of maintenance HD in CRF patients.

Lowering of TC was evident in pre-dialysis group and further maintenance HD was of no help to bring it to normal, and...
Table 2: Values of different biochemical parameters in blood samples of controls and patients at different stages of dialysis

| Parameter | Controls | Patients | Pre-dialysis | Post-dialysis 1 | Post-dialysis 40 |
|-----------|----------|----------|--------------|-----------------|-----------------|
| TC (mg/dl)| 170.5 ± 21.1 | 156.6 ± 21.2 | 159.4 ± 20.9 | 160.9 ± 14.3 |
| FC (mg/dl)| 59.7 ± 27.8 | 81.9 ± 26.8 | 86.2 ± 26.6 | 92.1 ± 23.3 |
| EC (mg/dl)| 110.8 ± 15.2 | 74.7 ± 24.7 | 73.2 ± 29.5 | 68.8 ± 17.8 |
| HDL-C     | 45.5 ± 4.6 | 27.6 ± 6.1 | 26.6 ± 5.5 | 20.3 ± 6.3 |
| VLDL-C    | 29.8 ± 2.5 | 44.8 ± 10.8 | 45.8 ± 11.1 | 45.6 ± 8.2 |
| TGs       | 149.1 ± 12.7 | 224.3 ± 54.0 | 229.3 ± 55.5 | 231.8 ± 41.5 |
| EC/FC ratio| 1.85  | 0.91 | 0.84 | 0.74 |

Values in mean ± SD, TC: Total serum cholesterol, FC: Free cholesterol, EC: Estenified cholesterol, TGs: Triglycerides, HDL-C: High-density lipoprotein cholesterol, VLDL-C: Very low-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL: Homocysteine. *Significant (% P < 0.05) and **highly significant (% P < 0.001) difference between pre-dialysis and control values, =Significant (% P < 0.05) difference between post-dialysis and pre-dialysis values

Table 3: Change in blood urea (BU) and serum creatinine (SC) values before and after dialysis

| Parameter | Pre-dialysis | Post-dialysis 1 | Post-dialysis 40 |
|-----------|--------------|-----------------|-----------------|
| Blood urea (mg/dl)| 153.8 ± 53.9 | 132.1 ± 22.6 | 117.6 ± 20.9 |
| Serum creatinine (mg/dl)| 12.4 ± 3.5 | 10.1 ± 3.1 | 8.9 ± 2.9 |

Values in mean ± SD. *Significant (% P < 0.05) difference between post-dialysis (1) and pre-dialysis values, =Significant (% P < 0.05) difference between post-dialysis (40) and post-dialysis (1) values

the results are consistent with those of earlier studies. Hypcholesterolemia, as observed in CRF patients before starting HD, could be due to the decreased rate of esterification of cholesterol, as a result of decreased LCAT activity. Accordingly, a major portion of TC in pre-dialysis patients was contributed by FC, resulting in lowering of EC/FC ratio in pre-dialysis. Although single dialysis had no significant effect on it, maintenance HD further increased the FC and lowered the EC and thus the EC/FC ratio.

It has been reported in earlier studies that LCAT activity does not improve significantly after a follow-up of single dialysis. As we followed up the patients for 40 dialysis schedules in the present study, we were able to confirm without doubt that LCAT activity does not improve even after repeated HD in patients on maintenance HD, as is evident by non-improvement in the level of EC (EC levels rather decreased in patients on maintenance HD). This decrease in LCAT activity, as explained in previous studies, could be due to decrease in enzyme mass or reduced Apo A1 (an activator of LCAT) synthesis in uremic hemodialyzed patients.

Hypertriglyceridemia, as observed in pre-dialysis patients compared to normal subjects, was also in accordance with earlier reported studies. No significant change in the level of TGs was observed on maintenance HD. In CRF patients, post-heparin plasma lipoprotein lipase activity and hepatic lipase activity have been reported to be reduced, while the apo CII/apo CIII ratio is decreased. A possible disturbance in the activity of both enzymes, accompanied by an increase in apo CIII in VLDL, results in a prolonged half-life of the VLDL particles, which may explain the observed hypertriglyceridemia in these patients.

However, the effects of long-term HD on lipolytic activity are not crystal clear. Some studies have found positive correlation between hypothyroidism, plasma cholesterol levels and HD duration, while others have reported a negative correlation. In the present study, we observed a negative correlation between levels of TGs and duration of HD and confirm that long-term HD treatment has no effect on the levels of TGs.

The other prominent feature of uremic dyslipidemia is reduction in HDL-C. Consistent with the earlier studies, serum HDL-C was significantly lowered in pre-dialysis patients as compared to controls, and this showed further highly significant decrease on maintenance HD.

The reduction in serum HDL-C levels could be because of enhanced TG levels, as there is an inverse correlation between TGs and HDL-C levels. Hypertriglyceridemia stimulates the TG enrichment and cholesterol depletion of HDL-C particles, thus causing a conformational change of HDL-C particles and reduction in HDL-C levels. Moreover, there occurs a positive correlation between LCAT activity and HDL-C levels; so, in uremic patients where LCAT activity is reduced, there is decreased conversion of HDL₃ to HDL₂ and consequently, decreased levels of HDL-C.

VLDL-C was significantly higher, while LDL-C was significantly lower in pre-dialysis patients compared to controls; with repeated HD, there was no further alteration in the levels of LDL-C and VLDL-C. Again, the results are consistent with those of the earlier reported studies.

Serum HC levels were also high in pre-dialysis patients compared to the control group, and there was no effect of maintenance HD on the levels of HC. Numerous studies have shown that mild to moderate elevation of plasma HC concentration occurs in 5–7% of the general population and in 85–90% of uremic patients. Increased HC concentration in the plasma of uremic patients is one of the non-traditional atherosclerosis risk factors, acting synergistically with the traditional risk factors for CVD.

The results of the present study differed from that of the authors who found that lipid and lipoprotein compositions...
did not appear to be influenced by dialysis duration in CRF patients.[1,2] Ifudu et al. did not find any change in TG and cholesterol concentrations with increased HD duration in patients hemodialyzed for 10–24 years.[9] However, the increase in TG and cholesterol concentrations positively correlated with the HD duration in the study of Sohbt et al.[13] Moreover, Paragh et al. showed that plasma TGs positively correlated with HD duration in patients hemodialyzed for 8–181 weeks.[13] In the present study; HDL-C, plasma FC, and ratio of EC to FC appeared to be clearly altered by HD duration. The evaluative lipid profile seemed to be more atherogenic, thus contributing to high cardiovascular risk.

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**How to cite this article:** Gupta K, Mahajan R. Coronary risk factors in maintenance hemodialysis patients: Who is the culprit - hemodialysis or chronic renal failure?. Int J App Basic Med Res 2011;1:11-4.

Source of Support: Nil. Conflict of Interest: None declared.