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Serum paraoxonase activity, high-sensitivity C-reactive protein, and lipoprotein disturbances in end-stage renal disease patients on long-term hemodialysis

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tHcy

BACKGROUND: Hemodialysis patients are at high risk for atherosclerotic events. Enhanced oxidant stress, dyslipidemia, and inflammation may have a major role in this risk. In this work, we assessed lipoprotein status, total homocysteine, high-sensitivity C-reactive protein (hs-CRP), and paraoxonase activity in hemodialysis patients to determine the correlations among these parameters and to compare these values with those measured in normal control subjects.

METHODS: We enrolled 109 end-stage renal disease patients on long-term hemodialysis and 100 age- and gender-matched healthy subjects. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol levels were evaluated using colorimetric methods. Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. Serum levels of hs-CRP, apolipoproteins (Apo) AI, B, E, and lipoprotein(a) were measured by nephelometry. Lipoprotein particle (Lp) A-I and LpA-I:A-II were determined by immunoelectrophoresis. Total homocysteine levels were evaluated by the fluorescence polarization immunoassay method. Paraoxonase activity was determined using the paraoxon-like substrate.

RESULTS: Compared with controls, hemodialysis patients had more frequent atherogenic dyslipidemia, hyperhomocysteinemia, and elevated hs-CRP levels. These latter findings inversely correlate with ApoA-I and LpA-I:A-II and positively with ApoB, lipoprotein(a), and ApoB/ApoA-I ratio. Homocysteine levels correlated positively with age. Paraoxonase activity was decreased in hemodialysis patients, especially in elderly patients. This enzyme activity positively correlated with LpA-I:A-II, and inversely with hs-CRP, LDL-cholesterol, and ApoE levels.

CONCLUSION: The present study demonstrated an abnormal lipoprotein profile associated with increased hs-CRP and decreased paraoxonase activity in hemodialysis patients. Hence, inflammation, dyslipidemia, and increased oxidant stress linked to uremia may be contributors to increased cardiovascular risk in this population.

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Cardiovascular diseases are the most common cause of death in chronic hemodialysis patients.[1] Atherosclerosis development can be mediated by several mechanisms simultaneously. Dyslipidemia with both quantitative and, especially, qualitative aspects characteristic of chronic renal failure are among the major causes of this pathology. Recently, inflammation and oxidative stress that appear in uremia have been associated with carotid atherosclerosis.[2] C-reactive protein (CRP), an inflammatory protein, is a marker of overall and cardiovascular death in the general population and in dialysis patients.[3] Increased concentration of blood CRP precedes monocyte appearance in the arterial intima,[4] mediates low-density lipoprotein (LDL) uptake by monocytes/macrophages,[5] and leads to activation of expression of adhesion molecules and chemokines.[6,7] In contrast, experimental studies suggest that homocysteine can enhance lipoprotein oxidation, reduce glutathione peroxidase activity, and increase affinity of lipoprotein(a) [Lp(a)] for plasmin-modified fibrin.[8,9]

Oxidative stress and inflammation may be linked in patients with end-stage renal disease (ESRD). It has been suggested that inflammation and duration of dialysis are the most important determinants of oxidative stress in hemodialysis patients.[10] Handelman and colleagues[11] found an association between F2-isoprostanes and CRP levels in these patients. A significant positive correlation was also found between acute-phase proteins and markers of oxidative stress in ESRD patients.[12] A tentative association exists between increased oxidative stress and inflammation, which are both common features of ESRD. This may contribute to endothelial dysfunction and an increased risk of coronary heart disease.[13] Serum paraoxonases (PON) are able to decrease the risk of coronary artery disease by destroying proinflammatory molecules involved in the initiation and progression of atherosclerotic lesions.[14] PONs (aryldialkylphosphatase, EC 3.1.8.1) are a series of serum esterase enzymes synthesized in the liver. PON1 is characterized by its ability to hydrolyze the organophosphate substrate paraoxon, which is the toxic metabolite of the insecticide parathion. It belongs to the family of serum paraoxonases, consisting of PON1, PON2, and PON3. PON1 and PON3 are secreted from the liver into the blood circulation, where they are associated with high-density lipoprotein (HDL) particles.[15]

Rosenblat and colleagues[16] have recently described the role of PON1 hydrolytic activity to be in mediating inhibition of LDL oxidation and stimulation of cholesterol efflux from macrophages. The authors also reported that apolipoprotein (Apo) A-I in HDL stimulates PON1 lactonase activity.[16] Furthermore, Mackness and colleagues[17] demonstrated that PON1 could prevent accumulation of lipoperoxides in LDL.[17]

In the present study, we investigated lipoprotein status, high-sensitivity CRP (hs-CRP), total homocysteine (tHcy), and PON activity in ESRD patients on long-term hemodialysis treatment and compared these findings with those in healthy controls. We have also tested for possible correlations between PON activity, hs-CRP, tHcy, and lipoprotein profile.

Table 1 Main clinical characteristics in end-stage renal disease patients enrolled in this study

Parameters	Hemodialysis patients
Age (y), mean ± SD	44.92 ± 14.4
Gender (male/female), n	62/47
Dialysis	
Length of treatment (y), mean ± SD	9.44 ± 4.42
Duration of session	4 h/3 sessions/wk
Membrane	Polysulfone
Solution	Bicarbonate
Hemoglobin (g/dL), mean ± SD	10 ± 6.96
Albumin (g/dL), mean ± SD	40.26 ± 4.16
Blood pressure (mmHg), mean ± SD	
Systolic	122.11 ± 20.78
Diastolic	75.64 ± 18.65
Hypertension (%)	20
Anemia (%)	3
Obesity (%)	8
Angina pectoris (%)	9
Myocardial infraction (%)	6

Methods

Study subjects

Two-hundred and seventy-six ESRD patients on long-term hemodialysis treatment were initially examined for participation in this study. Exclusion criteria included diabetes, antioxidant and/or hypolipemic medication, and clinical signs of infectious diseases. One-hundred and nine ESRD patients were finally enrolled in this study. Clinical data were obtained for all patients. All patients were given calcium. Sixteen percent were given various vitamin D supplements and 20% were receiving antihypertensive drugs. The main clinical characteristics are summarized in Table 1. One-hundred healthy subjects matched for age and gender served as controls. Mean age of controls was 46.83 ± 11.79 years. Patients gave informed consent, and the study was approved by the local ethics committee.

Laboratory tests

Blood samples were collected after 12 hours (overnight) fasting prior to initiating a scheduled hemodialysis session.