Age and time on dialysis are major associations with carotid plaques in non-diabetic HD patients

**ABSTRACT**

**Introduction:** Accelerated atherosclerosis is a well-recognized characteristic of end stage renal disease (ESRD), as one of the leading factors associated with the high cardiovascular morbidity and mortality in this patient population. Several studies have been done correlating the presence of atherosclerotic carotid plaques with nutritional status and inflammation in this setting. Nevertheless, traditional risk factors like hypertension, smoking and dyslipidemia must always be taken into account in the context of the specific ethnic, geographic and cultural aspects of a given renal population. **Aim:** The present study was designed to describe the prevalence of advanced atherosclerosis, as detected by the presence of carotid plaques, and its correlation with epidemiological data, traditional and non-traditional risk factors in non-diabetic hemodialysis (HD) patients. **Methods:** Thirty-nine patients on a regular HD program were evaluated (mean age: 47.0±12.8 years, 20 men, mean time on dialysis: 5.2±2.9 years). Atherosclerosis was assessed by carotid Doppler and inflammation by serum C reactive protein (CRP). Data on nutritional status, biochemical parameters, and arterial pressure (AP) were also analyzed. **Results:** Carotid plaque was a prevalent finding, observed in 64.1% of the patients. The age (50.8±10.6 years) and time on dialysis (6 [1-15] years) were significantly higher in the group of patients with plaques, compared to the group of patients without plaques (41.3±14.5 and 4 [1-11], respectively, P<0.05). There was no statistical difference between the groups regarding CRP, nutritional status, biochemical parameters, and mean pre and post HD arterial, diastolic and systolic pressure. Carotid plaques were associated with age higher than 38 (OR.: 28.29; 95% CI.: 2.68-712.8; p<0.001), and time on dialysis higher than 4 years (OR.: 5.5; 95% CI.: 1.02-33.37; p<0.05). In addition, 70% of patients with post HD diastolic AP lower than 90 mmHg presented carotid plaques. **Conclusions:** The age and time on dialysis were the major factors associated with the presence of carotid plaques in non-diabetic HD population studied. In addition, the data on arterial pressure support the search for advanced atherosclerosis in patients presenting low levels of post HD diastolic arterial pressure. carotid plaques, arterial pressure. None of the markers of inflammation or nutritional status was associated with these atherosclerotic lesions.

**Keywords:** hemodialysis, atherosclerosis, carotid plaques, arterial pressure.

**INTRODUCTION**

Cardiovascular disease (CVD) is the main cause of morbidity and mortality in hemodialysis (HD) patients, and one of the features is accelerated atherosclerosis\(^1\-^3\). It has been well demonstrated that the state of inflammation, frequently observed in renal patients, is an important cause of both protein-energy malnutrition, oxidative stress, and an increased incidence of atherosclerosis in this population\(^4\-^6\). In addition, traditional risk factors like smoking, dyslipidemia and systemic hypertension are present and play an important role in atherogenesis, as they do in the general population\(^7\). Thus, both traditional and non-traditional factors combine to turn atherogenesis into an accelerated process in dialysis patients.

A given population on hemodialysis is part of the general population from a world region in which factors like race, diet, prevalence of hypertension, dyslipidemia, smoking and others, may dispose characteristic traditional risk factors for cardiovascular disease in that region. In Europe, the incidence of death from ischemic heart disease is 3 to 4
times greater in Northern compared to Southern Europe, and in both areas the prevalence of myocardial infarction in the renal population is about 18 times, relative to the local general population\textsuperscript{5}. The importance of traditional risk factors was also evidenced in the study by Malatino and a group from south Italy, in which smoking and hypertension were the factors more strongly associated with carotid atherosclerotic lesions in a group of patients on HD and PD\textsuperscript{6}.

Carotid plaque is an important sign of atherosclerosis, greater incidence of atherosclerosis in coronary circulation n, increased carotid intima-media thickness (CIMT) and age are the most predictive factors of the occurrence of carotid atherosclerotic plaques, followed by hypertension and smoking\textsuperscript{11}. Hojs\textsuperscript{12} compared CIMT and the prevalence of plaques in the common carotid and internal carotid arteries in 28 randomly selected HD patients with normal controls. The CIMT values of the common carotid and internal carotid arteries were higher in HD patients than in controls, with more HD patients having plaques.

The present study attempted to investigate the associations between the presence of carotid plaques, with traditional risk factors such as systemic hypertension, dyslipidemia, smoking, and epidemiological data from a group of hemodialyzed non-diabetic patients. The non-traditional risk factors such as nutritional parameters, and inflammation were equally investigated respective to the presence of plaques. Diabetic patients were excluded in order to remove a well-known cause of generalized vascular disease.

**Patients and Methods**

**Study Population**

Thirty-nine HD patients were randomly selected to investigate carotid atherosclerosis by ultrasonography, and major cardiovascular risk factors. These patients were submitted to nutritional evaluation, and serum levels of C-reactive protein (CRP), as the indicator of inflammatory status. As inclusion criteria, all the patients had been on HD for at least six months, and the age ranged from 18 years to 75 years old. Patients with diabetes mellitus, severe cardiac disease, acute infection, immune disease and those using catheter for dialysis access were excluded. The patients never changed their modality of treatment (peritoneal dialysis to HD, or vice-versa). Patients taking anti-hypertensive drugs (calcium channel blockers; ACE-inhibitors; beta blockers) were not excluded.

The study was approved by the Ethics Committee for Human Research of the Universidade Federal do Rio de Janeiro.

**Definitions and Measurements**

Carotid B-Mode Ultrasonography: Ultrasonography of the common carotid arteries was performed by a single physician (M. Turano). The procedures were done bilaterally in all 39 patients, using an Echo-Color Doppler instrument (CX 800 APOGE) with a 7.5MHz high-resolution probe. The patients were investigated in the non-dialysis day, in the supine position with the head slightly turned from the sonographer. Carotid plaques were identified as echogenic prominences towards the arterial lumen, associated with a filling defect in the flow map of the Color Doppler. The plaques were screened from the common, internal and external, carotid arteries. Plaque occurrence was assigned for their presence or absence, and the degree of atherosclerosis was defined as the number of plaques found.

Arterial Pressure (AP): Pre- and post-HD measurements were depicted as the mean of recording measurements from 3 days of HD in one week. The mean pre- and post-HD AP were obtained for each patient and considered for overall statistical assessment. The presence of plaques was associated with levels of systolic and diastolic AP, above or below 140 mmHg and 90 mmHg. The results were shown as the prevalence of plaques in each range of AP.

Smoking: Smoking habit was defined as positive when practiced anytime in life.

Nutritional Status: Anthropometric measurements (AM) were performed by the same trained dietician, immediately after the end of the midweek HD session. AM used were: body mass index (BMI), triceps skinfold (TSF), and midarm circumference (MAC). TSF was measured with a Lange Skinfold Caliper (Cambridge Scientific) the average of three measurements was taken as the final result. BMI was calculated as body weight (kg)/height (m)\textsuperscript{2}. Dry weight (weight after HD session) was used.

Laboratory Measurements: After an overnight fast, blood was drawn just before the midweek dialysis session to determine the concentration of total cholesterol, urea, creatinine, albumin, CRP, calcium, phosphate and hemoglobin, by routine procedures. Urea was also determined after the same midweek session to calculate KT/V, according to formula of Daurgidas. C-reactive protein was measured by immunoturbidimetry and all values higher than 6 mg/L were considered abnormal.

**Statistical Analysis**

Data were expressed as mean SD, median [max-min], or percentage, as convenient. Student’s t – test was used to test the difference between the means and the Mann-Whitney U-test for non-parametric data. The Chi-square


test was used to perform association tests. When the group members were inappropriately small, Fisher’s test was used instead. ROC analysis was performed for best sensitivity and specificity when convenient. Statistical significance was accepted as p < 0.05.

**RESULTS**

Carotid plaques were observed in 64.1% of the patients. In this group, 36% presented one plaque, 24% two plaques, 28% three plaques and 12% with four plaques. The analysis of both groups, with and without carotid plaque, showed that the age and time on dialysis were significantly higher in the group with plaques, compared to the group without plaques. KT/V and URR, two indexes of dialysis adequacy, were not significantly different between the groups. There were no significant differences on weight gain, BMI, triceps skinfold, muscle arm circumference, serum albumin, cholesterol, phosphorus, calcium, CRP, and mean pre and post hemodialysis arterial, diastolic and systolic pressure.

A significant association was observed between atherosclerotic plaques and age ≥ 38 years (OR.: 28.29; 95% CI.: 2.68-712.8; p < 0.01), and patients on HD for more or equal period of 4 years (OR.: 5.5; 95% CI.: 1.02-33.37; p < 0.05). The values of 38 for age and 4 years for time on HD were taken as cutoff points derived from ROC curve analysis. Regarding the smoking habit, among the patients considered smokers (n = 21), 16 presented carotid plaques, and among those with plaques (n = 25), 16 were smokers. However, these data did not achieve statistical significance.

The most relevant finding was the prevalence of plaques in the patients with post-HD diastolic AP less than 90 mmHg, which was 70%.

**DISCUSSION**

Patients on HD are at high risk of atherosclerosis, which is more frequent when compared to the general population. In addition to the well known traditional risk factors, uremia-specific factors appear to enhance dramatically the progression of the pathological processes involved on atherogenesis. Krasniak et al. evaluating factors involved on atherosclerosis in 73 hemodialysis patients, found atherosclerotic plaques in the carotid arteries in 72% of these patients. Similarly, Stolic et al. found atherosclerosis in 68% of HD patients between the age of fifty and seventy years. In the present study, we found carotid plaques in 64.1% of the patients, which is in agreement with the studies just mentioned, and reveal that the prevalence of atherosclerotic disease is high and seems to be comparable in different areas of the world.

Inflammation causes muscle and visceral protein catabolism, and the amino acids are used either to supply energy or as substrates for the production of cytokines. Consequently, inflammation decreases albumin concentration, usually used as an index of malnutrition, and hypoalbuminemia is associated with increased risk of mortality in HD patients. The uremic state per se and factors associated with the dialysate procedure, such as bioincompatibility and non-sterile dialysate, may contribute to inflammation. Our study, however, could not observe any difference of nutritional parameters investigated. Also, serum albumin and C-reactive protein were not statistically different between the groups. It is noteworthy that the mean levels of pre HD serum albumin were above 3.5 g/dL in the groups with and without plaques, whereas mean levels of C-reactive protein were well above 6 mg/L in both groups. These results reveal that in the HD population studied the groups with and without plaques comprised comparable numbers of patients with systemic inflammation.

The levels of serum cholesterol were not significantly different between both groups. However, It was not possible to determine whether the group with atherosclerotic plaques presented hypercholesterolemia some time in their life. Nevertheless, in a previous study by Cheung et al., serum total cholesterol was not associated with atherosclerotic cardiovascular disease. Other parameters such as mean levels of serum calcium and phosphorus were not statistically different either. Additionally, there was no association between carotid plaques and smoking, although we may have overestimated the habit since the positive data took into account individuals who had smoked at some moment of life, no matter the duration and the amount of cigarettes consumed.

Although malnutrition is correlated with mortality, obesity (BMI > 30 kg/m²) could be associated with increased prevalence of atherosclerotic conditions and long-term risk of cardiovascular death in HD patients. BMI and body composition are strong predictors of death and the protective effect on mortality provided by high BMI is limited to those patients with normal or high muscle mass and not high body fat. The present study did not show any difference of BMI and the weight gain when individuals with and without plaques were compared. However, since these data are derived from a cross-sectional study, they cannot indicate an effect of these parameters on the slow development of the atherogenic process.

In the present study, carotid plaques were correlated with age and time on dialysis. Increased risk for atherosclerotic plaque was associated with age higher
than 38 years, and time on HD higher than 4 years. Stolic et al.\textsuperscript{14} investigated the frequency of atherosclerosis and risk factors in HD patients. In that study, the duration of dialysis and age were also significant factors for atherosclerosis and, in agreement with our study, no statistically difference was found in the frequency of atherosclerosis and smoking. Prati et al.\textsuperscript{11} evaluated the determinants of plaque occurrence and found association between age and atherosclerotic plaque. Zumrutad\i et al., in a prospective study, assessed the determinants of the progression of carotid artery intima-media thickness for 1 year in HD patients without significant comorbidities. They concluded that in addition to age and male gender, non-specific inflammation might have a possible role in the progression of atherosclerosis.

Hypertension plays an important role in the development of CVD\textsuperscript{22}. Generally, in HD patients, while there is an elevation of systolic AP, diastolic AP seems to decrease, and the resultant effect is high pulse pressure, which induces a deleterious effect on the cardiovascular system\textsuperscript{23}. Hypertension contributes to the development of atherosclerosis in the carotid arteries\textsuperscript{24}. Malatino et al\textsuperscript{9} performed B-mode ultrasound examination on the internal carotids of 119 HD patients, 106 of whom had some degree of carotid atherosclerosis. Systolic AP, serum cholesterol and cigarette smoking predicted the degree of carotid stenosis, whereas pulse pressure, age and smoking history predicted the number of plaques. On the other hand, relative hypotension is a potent marker of mortality in dialysis patients. Hypotension may reflect the severity of disease, ischemic heart disease and/or cardiomyopathy, and the intensity of therapy used to treat the disease\textsuperscript{25}. Our present study showed that the prev AP less than 87 mmHg was 70% compared with 20% in those with diastolic post-HD AP ≥ 87 mmHg. Previous report has shown association between mortality and low pre- or post-dialysis diastolic AP\textsuperscript{26}. Similarly, Iseki et al.\textsuperscript{5} found an inverse correlation between death rate and diastolic AP. The crude death rate was 40% when the diastolic AP < 70 mmHg, 35% at 70 to 79 mmHg, 25% at 80 to 89 mmHg, 25% at 90 to 99 mmHg, and 13% at >100 mmHg. In that study, the causes for the relationship between death rate and AP in hemodialysis patients were not determined, but the authors suspected that atherosclerotic disease was the main reason. The fact that vessels with advanced disease might be unresponsive to the vasoconstrictive response to the decreased blood volume after HD remains to be better elucidated.

In conclusion, the present study showed that carotid atherosclerotic plaques observed are highly prevalent in patients on hemodialysis. The results confirmed data from previous studies, in which age and time on dialysis are strongly associated with the development of atherosclerosis in renal patients. Therefore, atherosclerosis is progressive and affects patients the longer they live. Other factors such as inflammation and malnutrition, as well as traditional risk factors such as cholesterol levels and hypertension were not associated with the atherosclerotic lesions in this group of patients. It is noteworthy that near normal to low post-hemodialysis diastolic arterial pressure might be associated with the presence of carotid plaques, suggesting that careful monitoring of arterial pressure is of great importance in detecting the presence of advanced atherosclerotic disease.

REFERENCES


