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RELATIONSIP BETWEEN CAROTID AND CARDIAC ULTRASONOGRAPHIC CHANGES AND RISK FACTORS IN HEMODIALYSIS PATIENTS

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Abstract. Cardiovascular disease is the leading cause of mortality in hemodialysis patients. Carotid and cardiac ultrasonographic abnormalities are the rule in these patients. The aim of this study is to evaluate the interrelation between these changes and cardiovascular risk factors in our patients. In 54 stable chronic hemodialysis patients current demographic and biochemical parameters were recorded. Ultrasonographic measurement of intima-media thickness, diastolic diameter of common carotid artery, evaluation of carotid atherosclerotic plaques and transthoracic ecocardiography with evaluation of left ventricular mass index and valvular calcifications were performed, and correlated with cardiovascular risk factors. We found a high frequency of ultrasonographic abnormalities. Remarkably, nontraditional cardiovascular risk factors such as malnutrition, anemia and calcium-phosphate imbalance seem more important than traditional risk factors such as age, gender, smoking, diabetes mellitus, arterial hypertension or obesity for these ultrasonographic changes in hemodialysis patients.
Keywords: cardiovascular risk, hemodialysis, ultrasonography

Introduction

Carotid and cardiac ultrasonograpy are easily performed, noninvasive, safe, reproductible, and accurate. Increased intima-media thickness (IMT) and diastolic diameter of common carotid artery (DCCA) are non-invasive markers of damage of vascular wall, easily evaluated by ultrasonography. Increased IMT is an early marker of atherosclerosis, while increased DCCA is a marker of arteriosclerosis and both are strong predictors of cardiovascular events and mortality in general population. Echocardiographic abnormalities are associated with development of cardiac failure and death [1]. Abnormalities of left ventricular (LV) size, shape, or function are present in 70-80 % of dialysis patients. Causes of these echocardiographic abnormalities are highly diverse and include age, coronary artery disease, gender, hypertension (HT), anemia, the uremic internal milieu, hyperparathyroidism, large interdialytic fluid gains, and the presence of arteriovenous fistulae and grafts [2].

Poor cardiovascular prognosis in hemodialysis (HD) patients is determined both by traditional risk factors, present in the general population, such as age, gender, race, family history of cardiovascular disease, diabetes, dyslipidemia, arterial hypertension, obesity, smoking and by the so called nontraditional risk factors, such as anaemia, malnutrition, inflammation, calcium-phosphate imbalance, oxidative stress, hyperhomocysteinemia, hyperfibrinogenemia, hyperhidration and increase in renin-angiotensin-aldosterone system activity [3].

The aim of this study is to evaluate the interrelation between ultrasonographic changes such as increased IMT, atheromatous (ATS) plaques, increased DCCA and left ventricle mass (LVM), valvular calcifications, systolic and diastolic dysfunction and traditional risk factors such as age, gender, smoking, diabetes mellitus, arterial hypertension or

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obesity as well as specific uremia risk factors like anaemia, malnutrition, inflammation and calcium-phosphate imbalance in HD patients.

Patients and methods

The study was performed in 2008 and included 54 stable chronic HD patients (mean age 60.2±10.2 years, 26 females, 28 males), randomly selected, treated with hemodialysis for an average of 46±55 months (range 3–251 months) in Nefromed Dialysis Center, Cluj-Napoca, Romania. The dialysis prescription was thrice weekly 4 hours, standard bicarbonate dialysis with polysulfone dialyser.

The demographical and biochemical parameters were those currently determined in the dialysis center: age, gender, time on dialysis expressed in months, smoking status, body mass index (BMI), Charlson comorbidity index, presence of diabetes mellitus, number of antihypertensive drugs, erythropoietin dose per body weight per week. Biochemical determinations comprised creatinine, hemoglobin, ferritin, albumin, C-reactive protein (CRP), Ca, P, PTH, total cholesterol, HDL, LDL, VLDL cholesterol and triglycerides.

The performed examinations were carotid ultrasonography and transthoracic echocardiography. Ultrasonographic examinations were carried out one hour after dialysis on Agilent Sonos 4500 by a cardiologist unaware of the patients' clinical details.

Carotid ultrasonography. IMT was measured in the left common carotid artery, 2 cm before bifurcation. CCA diameter was evaluated at the same level during end-diastole. The presence or the absence of atheromatous ATS plaques was also evaluated.

Transthoracic echocardiography measured the thickness of interventricular septum (IVS), left ventricular posterior wall (LVPW), LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), LV end-diastolic volume (LVEDV) and LV end- systolic volume (LVESV), left ventricular mass index (LVMi), evaluation of systolic function, diastolic function and valvular calcifications. Echocardiographic measurements of IVS, LVPW, LVEDD and LVESD were done in M-Mode. The left ventricle mass was calculated using Devereux formula: LVM = 0.8x[1.04x(IVS + LVPW + LVEDD)^3- LVEDD ^{3}]+0.6 g and was indexed at the corporal surface area to obtain LVMi.

To assess the systolic function we calculated the ejection fraction (EF) of LV using Simpson method: EF(%) = (LVEDV - LVESV / LVEDV) x100. The diastolic function was determined by evaluating the anterograd mitral flow, the pulmonary venous flow and tissue Doppler at the level of lateral mitral annulus.

To assess blood pressure (BP) we calculated the media of 12 predialysis values from the month before evaluation.

Statistical analysis was performed with Sigma Stat software version 11. Data was expressed as mean ± standard deviation. Student *t*-test and Mann-Whitney test were used to make comparisons between groups of patients with and without ATS plaques, valvular calcifications, systolic dysfunction and diastolic dysfunction and between patients with IMT>0.8 mm versus those with IMT<0.8 mm with regard to continuous variables and the Chi square test for dicotomical variables. Univariate linear regressions were performed to assess associations between IMT, DCCA and LVMi as dependent variables and risk factors as independent variables. A p-value <0.05 was considered to be statistically significant.

Results

The demographic and biochemical parameters of the patients are presented in Table I.

Parameter	Values
Cholesterol (mg/dl)	171.9 ± 51.4
Triglycerides (mg/dl)	155.3 ± 81.3
HDL-cholesterol (mg/dl)	43.8 ± 12.2
LDL-cholesterol (mg/dl)	90.1 ± 43
VLDL-cholesterol (mg/dl)	30.8 ± 16.1
Hemoglobin (g/dl)	11.4 ± 1.4
Ferritin (ng/ml)	504.3 ± 347.8
rHuEpo (UI/bw/wk)	79.8 ± 51.1
Albumin (g/l)	3.9 ± 0.4
C-reactive protein (mg/dl)	1.5 ± 1.9
Ca (mg/dl)	8.6 ± 0.6
P (mg/dl)	5.7 ± 1.8
Ca x P	49.4 ± 17.5
PTH (pg/ml)	443.1 ± 571.2 (8-3071)
Kt/V	1.36 ± 0.15
BMI (kg/m^2)	27.2 ± 6.5
Mean arterial pressure (mmHg)	95.4 ± 9.3

Table I. Characteristics of the cohort

The results show a high frequency of ultrasonographic abnormalities: 14 (26%) patients had IMT>0.8 mm, 20 (37%) patients had DCCA>9 mm, 17 (32%) had increased LVMi, 36 (67%) had ATS plaques and 28 (52%) valvular calcifications, comparable with data in the literature (Table II).

The results of the linear regression present that IMT was directly associated with age (p=0.0025, R=0.158), Charlson comorbidity index (p=0.0002, R=0.506), LVPW (p=0.0126, R=0.351), IVS (p=0.07, R=0.257), LVEDV (p=0.0062, R=0.394) and inversely with hemoglobin (p=0.05, R=0.168) and ferritin (p=0.0024, R=0.159). Patients with IMT > 0.8 mm had higher DCCA (p=0.0240) and a tendency toward lower cholesterol (p=0.06) and LDL cholesterol (p=0.0532) in comparison with those with IMT ≤ 0.8 mm.

Parameter	Values
Intima media thickness (mm)	0.72 ± 0.2
Diameter of common carotid artery (mm)	8.91 ± 1.26
ATS plaques (%)	67
Valvular calcifications (%)	52
Left ventricle mass index (g/m²)	117.09 ± 40.45
LVPW (mm)	12 ± 1.72
IVS (mm)	12.99± 1.84
LVEDV (ml/m²)	84.87±35.86
LVESV(ml/m²)	41.03±24.83
Diastolic disfunction (%)	80
Low EF (%)	13

Table II. Ultrasonographic parameters

Parameter	p	R
Age (years)	**0.0025**	**0.158**
Charlson index	**0.0002**	**0.506**
Hb (g/dl)	**0.05**	**- 0.168**
Albumin (g/dl)	**0.08**	**- 0.250**
Ferritin (µg/dl)	**0.0024**	**- 0.159**
IVS (mm)	**0.07**	**0.257**
LVPW (mm)	**0.0126**	**0.351**
LVEDV (ml)	**0.0062**	**0.394**
LVESV (ml)	**0.0075**	**0.377**

Table III. Correlations between IMT and biochemical and ultrasonographic changes parameters

DCCA was directly associated with age (p= 0.0327, R=0.309), height (p=0.0396, R=0.298), Charlson comorbidity index (p=0.0335, R=0.307), erythropoietin/body weight/week (p=0.0422, R=0.294), systolic BP (p=0.048, R=0.287), diastolic BP (p=0.0268, R=0.320), mean arterial pressure (p=0.0296, R=0.314), LVEDV (p=0.0011, R=0.461), LVESV (p=0.0036, R=0.412), IVS (p=0.0367, R=0.302) and LVPW (p=0.0075, R=0.381) and inversely with HD vintage (p=0.0270, R=0.319), hemoglobin (p=0.0003, R=0.502) and albumin (p=0.05, R=0.284). (Table IV)

LVMi was directly associated with phosphorus (p=0.0146, R=0.348), CaxP (p=0.05, R=0.270), erythropoietin/body weight/week (p=0.0415, R=0.289), systolic BP (p=0.017, R=0.331), diastolic BP (p=0.037, R=0.293) and mean arterial pressure (p=0.016, R=0.335), and inversely with total cholesterol (p=0.0358, R=0.301), VLDL cholesterol (p=0.0239, R=0.333) and triglycerides (p=0.0151, R=0.345).(Table V)

Patients with ATS plaques in comparison with those without were older (p=0.0273), had

Parameter	p	R
Age (years)	**0.0327**	**0.309**
HD vintage (months)	**0.0270**	**- 0.319**
Charlson index	**0.0335**	**0.307**
Hb (g/dl)	**0.0003**	**- 0.502**
Epo (UI/bw/wk)	**0.053**	**0.053**
Albumin (g/dl)	**0.0558**	**- 0.284**
IVS(mm)	**0.0367**	**0.302**
LVPW (mm)	**0.0075**	**0.381**
LVEDV (ml)	**0.0011**	**0.461**
LVESV (ml)	**0.0036**	**0.412**
SBP (mmHg)	**0.048**	**0.287**
DBP (mmHg)	**0.0268**	**0.320**
MBP (mmHg)	**0.0296**	**0.314**

Table IV. Correlations between DCCA and biochemical and ultrasonographic changes parameters

Parameter	p	R
Cholesterol (mg/dl)	**0.0358**	**- 0.301**
VLDL (mg/dl)	**0.0239**	**- 0.339**
Triglycerides (mg/dl)	**0.0151**	**- 0.345**
Epo (UI/bw/wk)	**0.0415**	**0.289**
P (mg/dl)	**0.0146**	**0.348**
CaxP (mg²/dl²)	**0.05**	**0.270**
SBP (mmHg)	**0.017**	**0.331**
DBP (mmHg)	**0.037**	**0.293**
MBP (mmHg)	**0.016**	**0.300**

Table V. Correlations between LVMi and biochemical and ultrasonographic changes parameters

higher Charlson comorbidity index (p=0.0025), IMT (p<0.0001), DCCA (p=0.016), a tendency toward higher LVEDV (p=0.057), LVESV (p=0.072) and higher frequency of valvular calcifications (p<0.0001)(Table VI).

Patients with valvular calcifications had higher HD vintage (p=0.0233), Charlson comorbitity index (p=0.059), and IMT (p=0.0330) and higher frequency of ATS plaques (p<0.0001)(Table VII).

Systolic and diastolic function were not associated with cardiovascular risk factors studied.

Discussion

IMT. The correlation between IMT and age is similar to the data in literature and reflects the progression of ATS changes with age [4]. The correlation between IMT and Charlson comorbidity index is probably influenced by cardiovascular morbidities. IMT is inversely associated to hemoglobin, the role of anaemia being known in

Parameter	Patients with ATS plaques	Patients without ATS plaques	p
Number of patients	36	15	
Age (years)	62.40± 9.34	55.95± 10.81	**0.0273**
Charlson index	4.97± 1.03	3.72± 1.41	**0.0025**
IMT (mm)	0.80± 0.19	0.55± 0.11	**<0.0001**
DCCA (mm)	9.19±1.21	8.24± 1.16	**0.016**
Patients with valvular calcifications	26	2	**<0.0001**
LVEDV (ml)	89.41± 35.51	75.52 ±35.80	**0.057**
LVESV (ml)	42.09± 18.39	38.85±35.21	**0.072**

Table VI. Comparison between patients with and without ATS plaques

Parameter	Patients with valvular calcifications	Patients without valvular calcifications	p
Number of patients	28	26	
HD vintage (months)	40.50± 54.29	57.84 ±54.94	**0,0233**
Charlson index	4.97± 1.03	3.72± 1.41	**0,059**
IMT (mm)	0.80± 0.19	0.55± 0.11	**0,0330**
Patients with ATS plaques	27	10	**<0,0001**

Table VI. Comparison between patients with and without valvular calcifications

cardiovascular disease in HD patients [3].

The correlation between IMT and IVS and LVPW demonstrates that subclinical ATS can appear during cardiac remodeling, while the correlation between IMT and LVEDV and LVESV underline the role of hypervolemia in the appearance of vascular abnormalities. These associations reflect the reciprocal influence of cardiac and arterial changes.

The association with ATS plaques confirms that IMT is a real marker of ATS in this group of patients. Patients with increased IMT have also increased DCCA, because chronic increase of systemic blood flow, characteristic in HD patients, leads to enlargement of arterial diameter as well as increase in arterial thickness [3].

We found an inverse association of IMT with albumin, suggesting that hypoalbuminemia is associated to incipient atherosclerosis. Increased IMT is associated with higher mortality in HD patients [5,6,7], thus the inverse association between IMT and cholesterol, apparently paradoxical in comparison to data in the general population, might at least partially explain the contraintuitive U-shape mortality curve in relationship with cholesterol in hemodialysis patients. Malnutrition might be the factor that can explain the observation that outcomes can be more favourable in HD patients with higher cholesterol [8]. The same association between IMT and cholesterol is noted in the study of Kato et al [5], while there are other studies in HD patients that show positive correlations between IMT and total cholesterol [6].

We haven't found correlations between blood pressure and IMT, which can be explained by the fact that the majority of HD hypertensive patients have long-term antihypertensive treatment, with a possible beneficial effect on arterial wall.

Other studies have shown associations between IMT and male gender, arterial hypertension, smoking, dialysis vintage, BMI, CRP, diabetes mellitus and dialysis dose [4,5,9]. Some studies had found associations between IMT and P, CaxP product, PTH [10,11], while others, have not found this correlations (5,12). These associations were not found in our study.

We can underline that, except for age, we did not find any correlation between intima-media carotid thickness and traditional risk factors considered (gender, body mass index, blood pressure, diabetes). From the nontraditional risk factors, malnutrition seems to be important, since we observed an inverse correlation between IMT and serum albumin and cholesterol in our HD patients. As far as anemia is concerned, there is an inverse correlation between IMT and hemoglobin, as previously shown.

DCCA. It is well known that internal dimensions of the big arteries are influenced by age, height and blood pressure [3]. These associations have been found also in this study. The inverse

relationship between DCCA and hemoglobin and direct correlation with erythropoietin dose and LVEDV and LVESV might be explained by the fact that arterial diameter enlarges due to the chronic increase of systemic blood flow. In HD patients the increase in systemic blood flow is due to anaemia and hyperhydration.

We have found an association with hypoalbuminemia, albumin concentration being an independent factor in reducing arterial compliance [13].

The correlations of DCCA with IVS and LVPW reflect the interrelations between cardiac changes and those of the arterial system. We found higher DCCA in patients with ATS plaques which might be explained by the fact that ATS in advanced stages can lead to arterial stiffnes, while the increase in stiffness leads to lesions of arterial wall, which favours ATS [3]. There are though studies showing that the two processes are independent and that they frequently appear with the same localisation but without any causal relationship [14].

DCCA is inversely associated to time on dialysis, being higher in patients with a shorter dialysis period. It has been demonstrated that the arteries are already enlarged in patients that start dialysis, which suggests arterial remodelling starts in more incipient stages [3]. Probably the arteries stop dilatation while arterial calcification develops and HD vintage increases.

ATS plaques. The data obtained are similar to those shown in literature, that is no significant association between the presence of ATS plaques and traditional risk factors in dialysis patients, except for the increase of prevalence of plaques by age [3].

The association between ATS plaques and increased IMT and DCCA shows the interdependence of these changes. The magnitude of each parameter seems to rely on the presence of others. We also observed association with valvular calcifications, which are known as marker of systemic ATS [15]. The association with increased ventricular volumes show that cardiac and vascular changes occur simultaneously.

LVMi. The direct correlation between LVMi and erythropoietin dose and blood pressure reveals the importance of anaemia and arterial hypertension, in concordance with literature that show anaemia and arterial hypertension as risk factors most constantly associated with echocardiographic changes in HD patients [2].

LVMi obtained by echocardiography after dialysis is influenced by changes in effective intravascular volume. LVMi reduces during intradialytic ultrafiltration because of the changes in internal diameters of LV that correspond to intravascular volume reduction. LVMi is considered to be a surrogate marker of cardiovascular risk, so HD patients could be incorrectly evaluated to be or not to be at risk, depending of intravascular volume and hydration status [16].

The direct correlation with P and CaxP product reflects the influence of calcium-phosphorus metabolism in cardiac remodelling. We surprisingly found an inverse correlation of LVMi with cholesterol and triglycerides which suggests a possible influence of malnutrition in increase of LVM.

Valvular calcifications. The dialysis vintage is important for the development of valvular calcifications. The association between valvular calcifications, increased IMT and the presence of ATS plaques can lead us to conclude that valvular calcifications can be considered markers of systemic ATS.

Conclusion

In HD patients, carotid and cardiac ultrasonographic changes are highly prevalent. Remarkably, except for age, traditional cardiovascular risk factors, such as smoking, diabetes mellitus, arterial hypertension or obesity were not associated with carotid ultrasonographic changes, while nontraditional cardiovascular risk factors like malnutrition, anemia and calcium-phosphate imbalance are strongly associated with these abnormalities. Considering cardiac ultrasonographic abnormalities, nontraditional cardiovascular risk factors such as malnutrition, anemia and calcium-phosphate imbalance seem more important while amongst traditional risk factors only blood pressure is associated with the described echocardiographic abnormalities.

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