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Intima Media Thickness of Common Carotid Arteries is Associated with Traditional Risk Factors and Presence of Ischemic Heart Disease in Hemodialysis Patients

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Summary

Patients with chronic renal failure are prone to cardiovascular complications. The mechanisms and the assessment of the risk of cardiovascular diseases (CVD) in this population are of interest. The purpose of this study was to investigate the traditional and potential risk factors for the development of CVD and their contribution to ischemic heart disease (IHD) and variation in carotid intima media thickness (IMT) in hemodialyzed patients (HD). Twenty-one chronically HD patients and nineteen healthy volunteers were recruited. Studied parameters were intima-media thickness, body mass index (BMI), mean arterial blood pressure (MAP), hemoglobin, fibrinogen (Fbg), serum lipids, lipoprotein (a) [Lp(a)], total homocysteine (tHcy). Mean carotid IMT, tHcy, Fbg and Lp(a) were higher in HD patients compared to the control group. There were no differences in cholesterol (tCh) and triglycerides between these groups. Patients with ischemic heart disease were older and they had higher values of carotid IMT, tCh, triglycerides, Fbg and Lp(a). There were no differences in MAP, time on dialysis and tHcy between the two subgroups (with vs without IHD). Carotid IMT correlated positively with age ($r=0.68$, $p=0.001$), BMI ($r=0.50$, $p=0.02$), tCh ($r=0.58$, $p<0.01$), LDL- cholesterol ($r=0.55$, $p=0.01$) and Fbg ($r=0.57$, $p<0.01$) but not with tHcy or Lp(a) in the patients group. Carotid intima media thickness thus reflects the risk for ischemic heart disease in hemodialyzed patients. Elevated fibrinogen concentration and dyslipidemia influence arterial remodelling.

Key words

Intima-media thickness • Cardiovascular risk factors • Hemodialysis • Renal failure

Introduction

End-stage renal disease (ESRD) patients, especially dialysis-dependent ones, have a much higher risk of development of vascular diseases than the general population (Sarnak and Levey 1999, Baigent *et al.* 2000). Hemodialyzed patients have some uremia-related cardiovascular risk factors and probably because of this their risk of cardiovascular death is 10-20 times higher than in general population (Sarnak and Levey 1999). The

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most common causes of death are complications of atherosclerosis, including ischemic heart disease (IHD). It is noteworthy that almost 30 % of HD patients with symptoms of angina pectoris have no typical atherosclerotic lesions in their coronary arteries (Rostand *et al*. 1984). Such data have caused a continuous interest in investigating the mechanisms and methods of assessment of cardiovascular disease (CVD) risk in ESRD patients.

One of the methods is measurement of carotid intima media thickness (IMT). It is a noninvasive, ultrasonographic method of evaluating carotid arterial remodeling. It reflects changes taking place during the process of arteriosclerosis and/or early atherosclerosis.

The aim of our study was to investigate the association of traditional and some potential risk factors [homocysteine, lipoprotein (a)] with the presence of CVD and to assess their contribution to changes in carotid IMT in a population of HD patients.

Methods

The study was performed on 21 non-smoking, clinically stable, HD patients (15 men, 6 women, mean age 49.6 years, range 19-73) and healthy age-, sex- and body mass index (BMI)-matched control group (19 persons, 12 men, 7 women). Patients were on a chronic maintenance HD (three times a week for 4-4.5 hours per HD procedure). All HD patients were receiving treatment with polysulphone membranes and bicarbonate based dialysate with heparinization. The mean time on HD was 40.3±36.6 months (range 2.6-141.3 months). The causes of ESRD varied between chronic glomerulonephritis (n=11), polycystic kidney disease (n=1), diabetes mellitus (n=4), tuberculosis (n=1) and other or unknown causes (n=3). Among HD patients the IHD group was selected. The inclusion criteria were as follows: the presence of typical angina pectoris, a history of myocardial infarction (MI), typical changes in coronary angiograms or ischemic changes in electrocardiogram. The IHD group consisted of 10 patients (47.6 %). Arterial hypertension was diagnosed in 17 patients (81 %). Healthy control subjects were recruited from hospital staff and their families. Each subject gave an informed consent, and the Local Ethical Committee approved the study. Table 1 shows the basic characteristics of investigated subjects.

All subjects underwent measurements of carotid artery intima-media thickness by high-resolution real-time B mode ultrasonography with 7.5 MHz linear transducer (SSH 140A Toshiba, Japan). Each subject was examined in supine position. The carotid arteries were investigated bilaterally in longitudinal projections. The examination included the segment of the common carotid artery adjacent to a carotid bulb approximately 3 cm in length. Areas with calcified plaques were avoided. IMT was defined as the distance between the leading edge of the first echogenic line (lumen-intima interface) and the second echogenic line (media–adventitia interface) of the far wall. Four measurements from both sites were averaged to give the mean IMT. The same, experienced ultrasonographist unaware of any clinical data of the subjects performed all measurements.

Table 1. Basic clinical and laboratory characteristics of the two examined groups. Values are expressed as means ± S.D. or numbers (%). HD the group of hemodialysis patients; NS not significant; BMI body mass index; IHD ischemic heart disease; MAP mean arterial blood pressure; KT/V dialysis adequacy index; Hb hemoglobin; EPO erythropoietin; tCh total cholesterol; TG triglycerides; LDL low density lipoprotein; HDL high density lipoprotein

	HD	**Control**	**P value**
Age (years)	49.6±16.7	45.7±10.6	NS
Gender (M/F)	15/6	12/7	NS
BMI (kg/m^2)	24.7±5	24.5±3	NS
IHD (%)	47.6	-	-
Hypertension (%)	81.0	-	-
MAP (mmHg)	109.8±9	95.1±5	p<0.0001
KT/V	1.02±0.2	-	-
Hb (g/l)	110±15	-	-
EPO (%)	57	-	-
Albumins (g/l)	39±3	-	-
tCh (μmol/l)	4.6±0.9	5.5±0.8	NS
TG (μmol/l)	1.3±0.7	1.1±0.7	NS
LDL (μmol/l)	2.9±0.7	-	-
HDL (μmol/l)	1.2±0.5	-	-

Analyzed clinical parameters included: age, sex, BMI, mean arterial blood pressure (MAP) was calculated as MAP = diastolic + (systolic – diastolic)/3, time on dialysis. In the patient group, three predialysis blood pressure measurements were taken for calculation of MAP. Blood for biochemical analyses was drawn in the fasting state between 8:00 and 9:00 h to avoid circadian variations. The following biochemical parameters were assessed: hemoglobin, fibrinogen (Fbg), urea (for calculation of dialysis adequacy index KT/V), albumin,

total cholesterol (tCh), triglycerides (TG), HDL-cholesterol (HDL) by means of routine laboratory methods. Concentration of LDL-cholesterol (LDL) was calculated using the Friedewald formula (Friedewald *et al.* 1972). Blood samples (collected into 3.8 % sodium citrate in volume ratio of 9:1) intended for measurements of tHcy and lipoprotein (a) [Lp(a)] concentrations were centrifuged immediately and plasma was stored at –70 °C until assayed. tHcy concentrations were estimated by enzyme immunoassay (EIA) using commercially available kits (Axis Biochemicals ASA, Oslo, Norway). This method is as reliable as the reference method of high performance liquid chromatography (Quintana *et al.* 2000). Lp(a) concentration was estimated by the immunoenzymatic method using commercially available kits from American Diagnostica (USA).

Data were expressed as means ± S.D. The examination of the distribution normality of variables was done using the Shapiro-Wilk W test. Comparison between groups was done by Student t-test and Mann-Witney U test in cases of non-normal distribution of variables. Correlation between carotid IMT and other variables were evaluated by Pearson's or Spearman's test as appropriate. Values of $p<0.05$ were taken as statistically significant.

Results

Mean carotid IMT was higher in HD patients when compared to the control group (0.76±0.14 mm *vs.* 0.55±0.07 mm, Fig. 1). Mean tHcy concentration was higher in the patients group than in the control group (27.1±11.9 μmol/l *vs.* 11.4±6.1 μmol/l, $p<0.001$). In the group of patients taking folic acid (n=7, 15 mg per day) tHcy concentration was lower when compared to those without folate (18.4±5.4 μmol/l *vs* 31.5±12.0 μmol/l, $p<0.01$). Concentrations of Fbg [7.9±2.2 μmol/l (269.2±74.7 mg/dl) *vs.* 6.6± 1.2 μmol/l (224.1±40.2 mg/dl), $p<0.05$] and Lp(a) [0.6±0.5 μmol/l (169.4±134.1 mg/l) *vs.* 0.2± 0.1 μmol/l (50.4±25.8 mg/l), $p<0.001$] were higher in patients when compared to the control group. There were no differences in tCh and TG levels between the two groups (Table 1).

Patients with IHD were older than those without it (60.5±9.1 years *vs.* 39.7±16.1 years, $p<0.01$) and they had higher values of carotid IMT (0.85±0.14 mm *vs.* 0.68±0.08 mm, $p<0.01$, Fig. 2), higher concentrations of tCh [5.0±0.8 μmol/l (194.5±31.0 mg/dl) *vs.* 4.2±0.9 μmol/l (160.6±34.7 mg/dl), $p<0.05$] and LDL [3.3±0.7 μmol/l (126.0±25.6 mg/dl) *vs.* 2.5±0.6 μmol/l (97.5±24.2 mg/dl), $p<0.05$], higher levels of Lp(a) [0.9±0.5 μmol/l (241.8±152.0 mg/l) *vs.* 0.4±0.2 μmol/l (96.9±56.7 mg/l), $p<0.05$] and Fbg [9.0±2.2 μmol/l (307.0±75.2 mg/dl) *vs.* 6.9±1.7 μmol/l (234.8±57.7 mg/dl), $p<0.05$]. There were no differences in MAP (109.6±8.9 mm Hg *vs.* 110.0±9.8 mm Hg), duration of dialysis (37.7±42.9 months *vs.* 42.7±31.8 months) and in concentration of tHcy (26.0±7.9 μmol/l *vs.* 28.1±15.0 μmol/l) between the two subgroups.

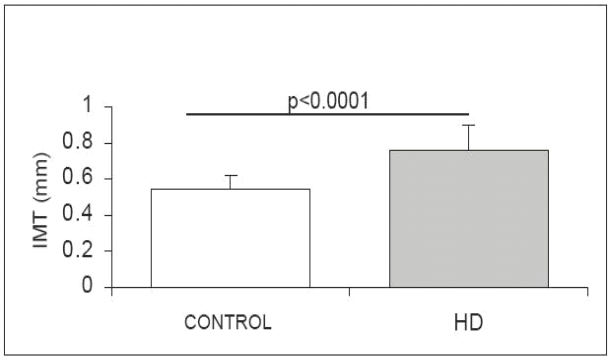

Fig. 1. Intima-media thickness (IMT) in hemodialyzed (HD) patients and control group.

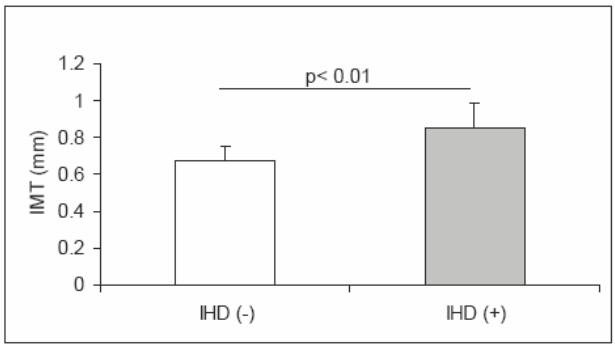

Fig. 2. Intima-media thickness (IMT) according to the presence of ischemic heart disease (IHD) in hemodialyzed patients.

Carotid IMT positively correlated with age (r=0.68, p=0.001), BMI (r=0.50, p=0.02), concentration of tCh (r=0.58, p<0.01), LDL (r=0.55, p=0.01), Fbg (r=0.57, p<0.01) (Fig. 3) but not with tHcy (r=0.13), Lp(a) or with MAP in the group of patients. There was no relationship between plasma fasting glucose values and IMT (data not shown).

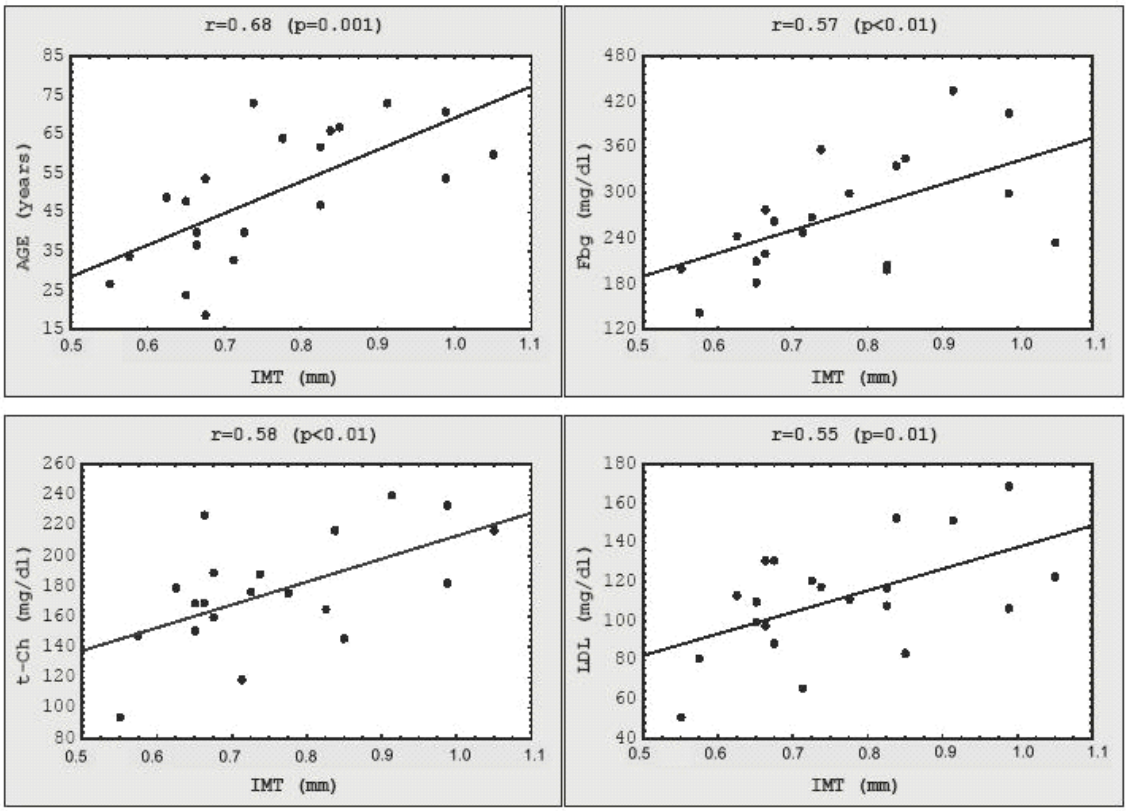

Fig. 3. Correlations of intima-media thickness (IMT) and age, plasma lipids and fibrinogen in hemodialyzed patients.

Discussion

In our study, higher values of carotid IMT in ESRD patients on HD were found than in the age- and sex-matched control group. These results are in accordance with other authors (Kawagishi *et al.* 1995) and prove extensive remodeling of a 'vascular tree' in this population of patients. It results in a high risk of cardiovascular complications reported in ESRD. Increased carotid IMT is considered as a marker of early atherosclerotic changes (Grobbee and Bots 1994). In the general population, there is a relation between carotid IMT and traditional cardiovascular risk factors such as arterial hypertension, diabetes mellitus, smoking, or hyperlipidemia (Crouse *et al.* 1996). Increased carotid IMT is a predictive factor for stroke and acute coronary syndromes (Bots *et al.* 1999, O'Leary *et al.* 1999). However, the interpretation of ultrasonographically revealed thickening of the artery wall demands a comment. Atherosclerosis and arteriosclerosis initially affect different parts of the vessel wall (London *et al.* 2000). It is important to point out that this method is unable to differentiate thickening of the intima of the artery (atherosclerosis) from medial hypertrophy (arteriosclerosis). Nevertheless, in the light of many clinical studies showing an association between carotid IMT and CVD this a non-invasive method seems to be useful for assessment of cardiovascular risk (Chambless *et al.* 1997). Surprisingly, several studies failed to identify hypertension as a strong risk factor for cardiovascular mortality in a population of ESRD patients (Locatelli *et al.* 2004). The answer for this apparently unexpected observation is a problem of the so-called case-mix phenomenon. HD patients with a previous long-lasting, and often variable history of hypertension, diabetes mellitus, chronic renal failure, and renal replacement therapy (all athero/arteriogenic states) suffer from ventricular dysfunction resulting in relative hypotension or normotension. On the contrary, hypertension has substantial influence on heart and vessels morphology and function before the initiation of dialysis. It is the possible explanation of no relation between MAP and IMT (surrogate of CVD) in the population of the present study.

The higher values of carotid IMT in the group of patients with symptoms of IHD were found. It confirms the coincidence of remodeling of carotid arteries in presence of IHD also in HD patients. However, it should be stressed that carotid IMT was correlated with age and patients with IHD were older than those free of the

disease. Observed relation between carotid IMT and age is in accordance with literature (Kawagishi *et al.* 1995, Smilde *et al.* 1998) and reflects a progression of athero/arteriosclerotic changes following a natural ageing process. Because of the small number of cases, we did not apply statistical multivariate analysis, which could evaluate the influence of age as a covariate.

Mild hyperhomocysteinemia (tHcy >15 μmol/l) is related to a higher risk of cardiovascular events in the general and ESRD population (Bostom *et al.* 1997, Malinow *et al.* 1999). We found a higher mean concentration of tHcy in HD patients compared with healthy subjects. Moustapha *et al.* (1999) found hyperhomocysteinemia in more than 90 % of HD patients in their study. Such results could be expected since renal function is one of the main factors determining tHcy concentration (Wollesen *et al.* 1999, Brzosko *et al.* 2001a,b). It should be noted that we found neither any differences in concentration of tHcy between patients with or without IHD nor a correlation between carotid IMT and levels of tHcy in HD patients. The small number of analyzed patients undoubtedly makes the interpretation of these negative results difficult. Oishi *et al.* (2000) did not find any differences in tHcy concentration between HD patients either with or without IHD. In spite of many experimental studies concerning toxic properties of hyperhomocysteinemia on vascular endothelium and unfavorable arterial remodeling, epidemiological data are not clear (Malinow *et al.* 1999, Brattsrom and Wilcken 2000).

There is growing evidence that hyperhomocysteinemia may not be a cause but a consequence or at least an epiphenomenon of athero/arteriosclerosis (Brattsrom and Wilcken 2000). For example, hypertension (and/or other established risk factors like smoking, hypercholesterolemia) and subsequent arterial changes in the kidneys (nephrosclerosis with a subsequent decline in renal function) could be responsible for the rise of tHcy concentration, since glomerular filtration rate (GFR) is the strongest predictor of tHcy (Wollesen *et al.* 1999). Indeed, plasma tHcy is related to blood pressure, which is a major risk factor in atherosclerosis and nephrosclerosis. The matter is even more elusive in view of the results of the study showing no improvement in endothelial function (measured by biochemical or ultrasonographical methods – flow-mediated dilatation) after 40 weeks of folate, which effectively decreased tHcy levels in HD patients (van Guldener *et al.* 1998).

As mentioned earlier, GFR is a major determinant of plasma tHcy, but even in patients with ESRD other important factors (besides vitamins B and folate) may be relevant. The study performed in Karolinska Institute (Suliman *et al.* 2000) showed a quite strong relation between concentrations of plasma tHcy and nutritional status in HD patients. Malnutrition was a strong predictor of death in this group of patients. Patients with IHD had an even lower concentration of tHcy (but still higher than the control group) and simultaneously malnutrition and hypoalbuminemia were more often observed in this group. This study was similar to the study performed by Sirrs *et al.* (1999), who observed a worse survival in HD patients with lower plasma tHcy concentrations. Plasma tHcy may be the next factor expressing the reverse causality in this population. This phenomenon is well described by a four fold higher mortality in a group of HD patients with total cholesterol concentration below 2.6 μmol/l (100 mg/dl) than the group with total cholesterol above 250 mg/dl (Lowrie and Lew 1990). Such an observation does not imply that hypercholesterolemia is not harmful but rather that low total cholesterol is a marker of severe stage of the disease (Zoccali 2000).

The patients studied by us were not seriously malnourished (mean concentration of albumin was 39 g/l, mean concentration of total cholesterol 4.6 μmol/l (176.7 mg/dl). Thus, it is also possible that in the population with ESRD on renal replacement therapy, i.e. in the late stages of 'arterial vascular disease', homocysteinemia might not have a strong influence on arterial remodeling. Another explanation is that hyperhomocysteinemia might affect plasma clotting factors (such as factor VII activity) and can thus predispose to thrombotic complications of atherosclerosis (Al-Obaidi *et al.* 2000).

Both, the relation between IHD, concentration of tCh and LDL and the correlation between these lipid risk factors and carotid IMT prove the important role of „traditional" risk factors for arterial remodeling (Prichard 1999). In the analyzed population, only three patients were receiving statins, so that any conclusions concerning the influence of treatment modalities of hyperlipidemia are elusive. BMI was also correlated with IMT of the common carotid arteries in studied patients. These results are consistent with the notion that body adiposity is a risk factor for atherosclerosis.

In the group of HD patients, the concentration of Lp(a) was higher than in the control group. These results are in accordance with other authors (Koch *et al.* 1997).

The role of Lp(a) in the development of CVD, although conceivable, still remains to be proved. There are studies showing a relation between concentrations of Lp(a) above 1.1 μmol/l (300 mg/l) and IHD, MI and stroke in the general population (Harjai 1999). However, in a Physician's Health Study performed on more than 14 000 subjects there was no correlation between concentration of Lp(a) and the occurrence of MI or stroke (Ridker *et al.* 1993, 1995). In the ESRD population the results are even more equivocal (Koch *et al.* 1997, Koda *et al.* 1999). We have shown the coincidence of IHD and elevated concentration of Lp(a) but we were unable to find any relation between Lp(a) and carotid IMT. Koda *et al.* (1999) in a prospective study performed on almost 400 HD patients showed that Lp(a) was an independent risk factor for cardiovascular death. It is possible that in atherogenesis, more important than Lp(a) concentration is the phenotype of apolipoprotein (a) (Kronenberg *et al.* 1996) which is a protein part of a moiety of Lp(a).

Fbg is a generally acknowledged, independent risk factor for CVD (Harjai 1999). In 1980, the paper informing about the relation between increased concentration of Fbg and a higher cardiovascular mortality was published for the first time (Meade *et al.* 1980). Fbg concentration rises with ageing, it is an acute phase protein and interleukin-6 stimulates its synthesis. Besides being an indicator of an inflammation, it can potentially exert deleterious effects such as an increase of plasma viscosity, enhancement of erythrocyte and platelets aggregation, fibrin formation, infiltration of vascular wall and proliferation of myocytes (Harjai 1999). Physicochemical properties of the blood are an important factor determining development of vascular changes (Koenig and Ernst 1992, Brzosko *et al.* 2001). In a group of patients, as expected, concentration of Fbg was higher than in the control group. Patients with IHD had significantly elevated its concentration that also correlated with IMT. These results corroborate the essential role of this protein in vascular complications, also in ESRD patients (Koch *et al.* 1997).

We are aware of the limitations of this study, which concern its cross-sectional design and the small number of participants. However, it seems conceivable that IMT reflects the risk for ICH in HD patients. Reliable conclusions cannot be drawn from some negative although not exclusive findings, such as the absence of association between tHcy or MAP and IMT. The role of hyperhomocysteinemia still remains to be elucidated in ESRD patients. Elevated Fbg concentration and dyslipidemia (in HD patients without malnutrition) have essential influence on arterial remodeling.

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