Factors associated with carotid and femoral atherosclerosis in non-diabetic hemodialysis patients

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Abstract

Information on different stages of atherosclerotic changes has been obtained by combining information from B-mode ultrasonography recordings of the common carotid (CCA) and femoral arteries (FA). The aim of our study was to analyze the potential risk factors associated with different B-mode ultrasonography measurements on CCA and FA in non-diabetic hemodialysis (HD) patients.

In a cross-sectional study we examined 67 non-diabetic, asymptomatic HD patients. All patients underwent high resolution B-mode ultrasonography of the CCA and FA. We compared the ultrasonographic findings in patients stratified according to various cut off levels for each clinical and biochemical parameter (mean value of one year laboratory data).

The intima media thickness (IMT) exceeded the upper limit of normal range in 97.5% on CCA and in 100% of patients on FA. Atherosclerotic plaques (AP) were detected in 43.3 and 55.2%, and were calcified in 20.9 and 13.4% of the patients on CCA and FA, respectively. An increased CCA-IMT was found in older patients (> 50 years and > 45 years at start of HD), with lower (< 1.2) kt/V, higher (> 1.5 mmol/L) phosphate and LDL (> 2,8 mmol/L) levels. An increased FA-IMT was only associated with HD duration > 72 months.

Male gender, kt/V < 1.2, systolic blood pressure (SBP) > 150 mmHg and pulse pressure (PP) > 70 mmHg were associated with increased CCA and FA internal diameter (ID). An increased CCA-ID was revealed in older patients (>50 years and > 45 years at the start of HD) and those with body mass index (BMI) > 23 kg/m^2. Mean arterial pressure (MAP) > 100 mmHg was associated with an increased FA-ID.

Higher frequency of CCA and FA-AP were detected in older patients (> 50 years and > 45 years at start of HD), and higher total serum calcium (Ca) > 2,4 mmol/L. The finding of CCA-AP was associated with male gender and lower (< 150 pg/ml) serum intact parathyroid hormone (iPTH), while the presence of FA-AP was associated with higher (> 70 mmHg) PP and serum C-reactive protein (CRP) levels (> 3 mg/L). The gender, age (> 50 years and > 45 years at start of HD), PP > 70 mmHg and iPTH < 150 pg/ml were associated with higher presence of calcified CCA and FA-AP. The calcified CCA and FA-AP were associated with lower (< 0.9 mmol/L) HDL and higher (> 3.5 mmol/L) Ca x phosphate product, respectively.

The atherosclerotic changes on CCA and FA were frequently found in our cohort of asymptomatic, non-diabetic HD patients, implying the need for examination of this group at risk for cardiovascular disease. Age, gender, blood pressure, dialysis adequacy, bone markers and serum lipid disorders were associated with the atherosclerotic lesions in our patients. Timely management of the associated factors may be beneficial in preventing of atherosclerosis.

Key words: dialysis, atherosclerosis, ultrasonography

Introduction

The association between uremia and increased risk of atherosclerotic disease has been documented in many investigations (1). Atherosclerotic damage of large arteries is major contributory factor to the high cardiovascular morbidity and mortality of hemodialysis (HD) patients (2). Since cardiovascular complications are a common cause of death in HD patients, the early detection and prevention of atherosclerosis are desirable. Arterial intima calcification represents an advanced stage of atherosclerosis and is associated with development of plaques and occlusive lesions (3). Moreover, the vascular calcification in advanced atherosclerosis is a common feature in HD patients (4).

It is assumed that the atherosclerotic changes in carotid artery may reflect the general atherosclerosis (5). High resolution B-mode carotid ultrasonography is a fundamental technique for the noninvasive investigation of atherosclerosis in HD patients, combining the data from measurements of the carotid and femoral arteries (5,6). The investigation of the carotid artery with this technique is important not only for the assessment of its structural alterations but also because the extent of atherosclerosis of this vessel reflects the severity of arterial damage in other districts (6). Increased common carotid artery intima-media thickness (IMT) is a marker of early atherosclerosis (7).

Traditional risk factors for atherosclerotic disease can not completely explain the excess of cardiovascular disease (CVD) in HD patients (5). Among a variety of pathophysiological conditions, age, gender, HD duration (5), hypertension (8,9), diabetes (10), chronic inflammation (11,12), malnutrition (13), abnormalities in lipid composition (14), serum calcium (Ca), hyperphosphatemia, calcium-phosphorus product (Ca x P) (15-17) and intact parathyroid hormone (iPTH) concentrations (18), have been closely associated with atherosclerotic changes in HD populations. However, further information about the possible factors associated with atherosclerosis is needed in order to better prevent and control development of CVD.

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The primary endpoint of present study was to analyze the association between B-mode ultrasonography findings in the carotid and femoral arteries and the possible risk factors for atherosclerosis in our non-diabetic HD population. Secondary endpoint was to assess the presence of atherosclerotic changes in the carotid and femoral arteries in our non-diabetic, asymptomatic HD patients.

Patients and methods

Patients

In a cross-sectional study we examined 67 patients (at least 12 months on HD), with no records and symptoms of CVD (19), infection or diabetes. The patients were dialyzed with low-flux synthetic membranes, bicarbonate dialysate (1,75 mmol/l calcium), on erythropoietin therapy to maintain pre-dialysis hemoglobin between 100 and 120 g/l, regular supplementation with iron, and calcium carbonate ($CaCO_3$) use to maintain pre-dialysis serum phosphate levels < 1,8 mmol/l. The duration of HD was individualized (4-5 hours, thrice weekly) to control body fluids and blood chemistries. Systolic (SBP) and diastolic blood pressure (DBP) was recorded monthly before HD, at the same day for blood sampling, and averaged for the last 12 months prior to the B-mode ultrasonography for statistical analysis. Brachial pulse pressure (PP) and mean arterial pressure (MAP) were calculated by the formula PP = SBP-DBP; MAP = DBP + (SBP-DBP) / 3. Body mass index (BMI), prescription for vitamin D (μg/weekly) and $CaCO_3$ (g of elemental Ca/day) prescribed to each patient were recorded from the patients' files. The demographic data on age at inclusion and start of HD, gender, HD duration, smoking, and dialysis adequacy were also recorded in the database.

Blood chemistries

Pre-dialysis hemoglobin, leukocyte, serum Ca, phosphate, albumin, triglycerids, total, HDL and LDL cholesterol and C-reactive protein (CRP) were determined once monthly. Serum iPTH and ferritin were measured every 4 months. The values of biochemical data considered in the study were averaged over the last 12 months preceding the B-mode ultrasonography measurements.

Ultrasonography

All patients underwent bilateral B-mode ultrasonography (Toshiba HDI 3000 with 7,5 MHz transducer) of the common carotid arteries (CCA) and femoral arteries (FA) for the evaluation of IMT, internal diameter (ID), atherosclerotic plaque (AP) detection and the presence of calcified AP. CCA measurements were made 2 cm beneath the bifurcation (20) and included approximately 4 cm of the CCA, and FA was examined approximately 4 cm below the inguinal ligament at the site where the artery divides into the superficial and the profound FA (5). IMT measurements were made on the far walls at the same level as the ID measurements (20). IMT was defined as the distance between the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far walls (5). Abnormal IMT is defined as IMT > 0,8 mm (6). A localized echo-structure encroaching into the vessel lumen was considered to be AP if the IMT was > 50% thicker than neighboring sites (20). Measurements of IMT and ID were always made in AP-free arterial segments (20).

Statistical analysis

Variables were expressed as frequencies, percentages for assessed factors and mean values ± SD for normally distributed continuous parameters.

Patients were divided into 2 groups as a result of different cut off levels of each parametric variable and different code of nonparametric variables, respectively. Fifty years at inclusion, 45 years at the start of HD, 72 months HD duration, Kt/V ≥ 1.2, SBP ≥ 150mmHg, DBP ≥ 90mmHg, MAP ≥ 100mmHg, PP ≥ 70mmHg, BMI ≥ 23 kg/m2, $CaCO_3$ ≥ 3g Ca/day, hemoglobin ≥ 110g/L, leukocyte ≥ $6x10^9$/L, serum albumin ≤ 40 g/L, total serum Ca ≥ 2.4mmol/L, serum PO_4 ≥ 1.5mmol/L, Ca x P product ≥ 3.5mmol/L, iPTH ≥ 150 pg/ml, TG ≥ 1.9 mmol/L, cholesterol ≥ 4.8mmol/L, HDL ≥ 0.9mmol/L, LDL ≥ 2.8mmol/L, ferritin ≥ 500mg/L and CRP ≥ 3.0mg/L were determined for cut off values. Gender (0-male, 1-female), vitamin D treatment, smoking, AP detection and presence of calcified AP (0-no, 1-yes) were used as categorical variables. Ultrasonography findings (IMT, ID, plaque detection and presence of calcified plaques) were compared among the groups.

Statistical comparison between the groups was performed with Student *t*-test for continuous variables, and chi-square analysis for the categorical variables.

Statistical analysis was performed with standard statistical package (SPSS for Windows version 9.0). For all comparisons, a *P*-value < 0.05 was considered statistically significant.

Results

This is the first study performed in our dialysis patients using high-resolution B-mode ultrasound for evaluation of the atherosclerotic changes in CCA and FA.

The intima media thickness (IMT) exceeded the upper limit of normal range in 66 (97.5%) on CCA and in 100% of patients on FA. Atherosclerotic plaques (AP) were detected in 29 (43.3) and 37 (55.2%), and were calcified in 14 (20.9) and 9 (13.4%) of the patients on CCA and FA, respectively. Ultrasonographic findings on CCA and FA of the whole study group are presented in Table 1.

Table 1. Ultrasonograpic characteristics of all patients

CCA-IMT (mm)	1.46±0.29	FA-IMT (mm)	1.43±0.23
frequency of CCA-AP (%)	43,28	Frequency of FA-AP (%)	55.22
Freq. of calcified CCA-AP (%)	20.9	freq. of calcified FA-AP (%)	13.43
CCA-ID (mm)	7.36±0.99	FA-ID (mm)	7.43±1.05

Age: When divided according to age (>50< years) the older patients (n=37) had mean age of 60.9±7.2 years (range 51-74) as compared with 41.4±6.3 years (range 26-49) in the younger group, while patients (> 45 years) at start of HD

(n=35) had mean age of 55.3±7.0 years (range 45-67) as compared with 33.7±7.7 years (range 19-44) in the younger patients. Both older groups of patients showed significantly increased CCA-IMT, CCA-ID, higher frequency of CCA and FA-AP, calcified CCA and FA-AP (the last being at borderline of significance for age at start of HD) (Table 2).

Table 2. Ultrasonograpic characteristics of patients divided according to age (>50< years)

age at inclusion	**> 50 years**	**< 50 years**	***P***
CCA-IMT (mm)	1.53±0.27	1.37±0.29	0.02
CCA-ID (mm)	7.62±1.02	7.04±0.88	0.01
frequency of CCA-AP (%)	22/37 (59.46)	7/30 (23.33)	0.000
freq. of calcified CCA-AP (%)	13/37 (35.13)	1/30 (3.33)	0.000
frequency of FA-AP (%)	25/37 (67.57)	12/30 (40.0)	0.03
freq. of calcified FA-AP (%)	8/37 (21.62)	1/30 (3.33)	0.04
age at start of HD	**≥ 45 years**	**< 45 years**	***P***
CCA-IMT (mm)	1.55±0.27	1.37±0.28	0.009
CCA-ID (mm)	7.68±1.01	7.01±0.87	0.005
frequency of CCA-AP (%)	20/35 (57.14)	9/32 (28.12)	0.001
freq. of calcified CCA-AP (%)	13/35 (37.14)	1/32 (3.12)	0.000
frequency of FA-AP (%)	23/35 (65.71)	14/32 (43.75)	0.04
freq. of calcified FA-AP (%)	7/35 (20.0)	2/32 (6.25)	0.07

Gender: Male patients (n=43) had significantly increased CCA-ID, FA-ID, higher frequency of CCA-AP, calcified CCA-AP and calcified FA-AP when compared with female patients (n=24) (Table 3).

Table 3. Ultrasonograpic characteristics of patients divided according to the gender

Gender	**Male**	**Female**	**P**
CCA-ID (mm)	7.60±0.96	6.92±0.93	0.006
FA-ID (mm)	7.84±0.98	6.69±0.72	0.000
frequency of CCA-AP (%)	24/43 (55.81)	5/24 (20.83)	0.005
freq. of calcified CCA-AP (%)	12/43 (27.91)	2/24 (8.33)	0.04
freq. of calcified FA-AP (%)	9/43 (20.93)	0/24 (0.0)	0.02

Dialysis adequacy and HD duration: CCA-IMT, CCA-ID and FA-ID were significantly lower in patients (n=37) with higher (> 1.2) kt/V (mean 1.37±0.14, range 1.21-1.76) as compared to the patients with kt/V ≤ 1.2 (mean 1.08±0.1, range 0.81-1.2). Patients (n=33) with longer (> 72 months) HD treatment (mean 130±47, range 72-236) in comparison with patients being shorter on HD (mean 47±15, range 14-68) showed significantly increased FA-IMT (Table 4).

Table 4. Ultrasonograpic characteristics of patients according to dialysis adequacy and HD duration

dialysis adequacy	**kt/V ≤ 1.2**	**kt/V > 1.2**	**P**
CCA-IMT (mm)	1.54±0.26	1.39±0.29	0.03
CCA-ID (mm)	7.74±0.87	7.04±0.99	0.003
FA-ID (mm)	7.91±0.96	7.05±0.97	0.000
HD duration	**≥ 72 months**	**< 72 months**	**P**
FA-IMT (mm)	1.49±0.19	1.37±0.24	0.028

Blood pressure: The patients (n=33) with higher (≥150mmHg) SBP (mean 162±11, range 151-190) presented with significantly increased CCA and FA-ID as compared with patients with lower SBP (mean 124±14, range 91-145). Significantly higher FA-ID

Table 5. Ultrasonograpic characteristics of patients divided according to the blood pressure

SBP	**≥ 150 mmHg**	**< 150 mmHg**	**P**
CCA-ID (mm)	7.60±1.03	7.12±0.92	0.049
FA-ID (mm)	7.74±1.06	7.13±0.96	0.01
MAP	**> 100 mmHg**	**< 100 mmHg**	**P**
FA-ID (mm)	7.69±1.08	7.18±0.98	0.049
PP	**≥ 70 mmHg**	**< 70 mmHg**	**P**
CCA-ID (mm)	7.65±0.92	7.19±1.01	0.06
freq. of calcified CCA-AP (%)	8/24 (33.33)	6/43 (13.95)	0.018
FA-ID (mm)	7.85±0.98	7.19±1.03	0.012
frequency of FA-AP (%)	18/24 (75.0)	19/43 (44.19)	0.016
freq. of calcified FA-AP (%)	6/24 (25.0)	3/43 (6.98)	0.028

measurements were found in patients (n=33) with MAP > 100mmHg (mean 115±7, range 103-130) as compared with those with lower MAP (mean 89±9, range 63-100). Patients (n=24) with higher (≥ 70 mmHg) PP (mean 77±8, range 70-100) tended to have increased CCA-ID, while FA-ID, FA-AP, calcified CCA and FA-AP were significantly higher when compared to the patients with lower PP (mean 52±9, range 31-61) (Table 5).

BMI: Significantly higher CCA-ID was shown in patients (n=33) with an increased (> 23 kg/m^2) BMI (mean 27.1±3.5, range 23.0-35.7) as compared with patients having lower BMI (mean 20.5±1.5, range 16.4-22.7) (Table 6).

Table 6. Ultrasonograpic characteristics of patients divided according to BMI

BMI	**> 23 kg/m^2**	**< 23 kg/m^2**	**P**
CCA-ID (mm)	7.69±1.11	7.17±1.11	0.04

Bone mineral metabolism parameters: Patients (n=31) with an increased (≥ 2.4 mmol/L) serum Ca (mean 2.49±0.08, range 2.4-2.8) had significantly higher frequency of CCA-AP and FA-AP being at borderline of significance in comparison with patients with lower Ca (mean 2.25±0.12, range 1.84-2.39). CCA-IMT was significantly increased in patients (n=34) with serum phosphate ≥ 1.5 mmol/L (mean 1.8±0.22, range 1.5-2.32) when compared with patients with lower phosphate levels (mean 1.23±0.18, range 0.86-1.47). Calcified FA-AP tended to be more frequent in patients (n=35) with serum Ca x P > 3.5 mmol/L (mean 4.27±0.62, range 3.51-5.84) as compared with patients with lower Ca x P product (mean 2.89±0.49, range 1.71-3.46). Patients (n=36) with lower serum iPTH < 150 pg/ml (mean 64.5±33.2, range 11.5-140) showed significantly higher frequency of CCA-AP, calcified CCA and FA-AP in comparison with patients with higher iPTH (mean 298.1±130, range 150-599) (Table 7).

Table 7. Ultrasonograpic characteristics of patients divided according to the bone mineral metabolism parameters

total serum Ca	**≥ 2.4 mmol/L**	**< 2.4 mmol/L**	**P**
frequency of CCA-AP (%)	16/31 (51.62)	10/36 (27.78)	0.04
frequency of FA-AP (%)	21/31 (67.74)	16/36 (44.44)	0.07
serum phosphate	**≥ 1.5 mmol/L**	**< 1.5 mmol/L**	**P**
CCA-IMT (mm)	1.53±0.29	1.39±0.27	0.04
Ca x P product	**> 3.5 mmol/L**	**< 3.5 mmol/L**	**P**
freq. of calcified FA-AP (%)	7/35 (20.0)	2/32 (6.25)	0.06
serum iPTH	**> 150 pg/ml**	**< 150 pg/ml**	**P**
frequency of CCA-AP (%)	11/31 (35.48)	18/36 (50.0)	0.05
freq. of calcified CCA-AP (%)	2/31 (6.45)	12/36 (33.33)	0.019
frequency of calcified FA-AP (%)	1/31 (3.23)	8/36 (22.22)	0.03

Serum HDL and LDL cholesterol: Significantly lower frequency of calcified CCA-AP was observed in patients (n=36) with higher (> 0.9mmol/L) HDL cholesterol (mean 1.17±0.25, range 0.92-1.94) as compared with patients lower HDL (mean 0.77±0.08, range 0.57-0.88); while significantly increased CCA-IMT was found in patients (n=33) with higher (≥ 2.8mmol/L) serum LDL cholesterol (mean 3.42±0.57, range 2.8-4.92) in comparison with patients with lower LDL (mean 2.11±0.38, range 1.43-2.77) (Table 8).

Table 8. Ultrasonograpic characteristics of patients divided according to the lipid parameters

serum HDL cholesterol	**< 0.9 mmol/L**	**> 0.9 mmol/L**	**P**
frequency of calcified CCA-AP (%)	11/31 (35.48)	3/36 (8.33)	0.04
serum LDL cholesterol	**≥ 2.8 mmol/L**	**< 2.8 mmol/L**	**P**
CCA-IMT (mm)	1.56±0.34	1.39±0.32	0.04

Serum CRP: Patients (n=33) with low (≤ 3.0 mg/L) serum CRP (mean 1.63±0.84, range 0.25-3.0) had significantly lower frequency of calcified FA-AP as compared with patients with high CRP (mean 7.02±4.89, range 3.07-30.0) (Table 9).

Table 9. Ultrasonograpic characteristics of patients divided according to CRP levels

serum CRP	**> 3 mg/L**	**≤ 3.0 mg/L**	**P**
frequency of FA-AP (%)	19/34 (55.88)	10/33 (30.3)	0.03

Other variables: When divided according to various cut off levels of parameters like DBP, daily dose of $CaCO_3$, blood hemoglobin and leukocyte, serum albumin, ferritin, triglycerides and total cholesterol, there was no significant difference between the groups of patients, neither for comparison of the use of vitamin D or smoking.

Discussion

The results of this study confirm that atherosclerotic changes on CCA and FA in asymptomatic, non-diabetic HD patients are rather frequent, implying the need for examination of

systemic atherosclerosis in HD patients even they are free of symptoms. Moreover, the higher risk of cardiovascular mortality was reported to be associated with IMT of CCA obtained by ultrasonographic measurement (6). The present data has confirmed previous reports that age, gender, blood pressure, dialysis adequacy, bone mineral markers and serum HDL/LDL cholesterol disorders in HD patients are predominantly associated with their atherosclerotic lesions (8,9,14-17).

Increased CCA-IMT in our patients was associated with traditional risk factors such as older (> 50 years) age at inclusion, and (> 45 years) at start of HD, worse dialysis adequacy (kt/V levels < 1.2), higher (> 1.5 mmol/L) phosphate and LDL (> 2.8 mmol/L) levels. In many studies no relationship was found between CCA and FA-IMT and the duration of HD (5). However, we found that increased FA-IMT was associated with longer (> 72 months) HD duration, although for better explanation we need a further statistical evaluation with multiple regression analysis. Male gender, lower kt/V (< 1.2), higher (> 150 mmHg) SBP and PP (> 70 mmHg) were associated with increased CCA and FA-ID. Increased CCA-ID was also associated with an older age at inclusion and at start of HD, and increased (> 23 kg/m^2) BMI. Higher (> 100 mmHg) MAP was also associated with an increased FA-ID.

Higher frequency of CCA and FA-AP in our patients was associated with an older age at inclusion and at start of HD, as well as an increased total serum Ca levels (> 2.4 mmol/L). The last could be possibly explained by the high (1.75 mmol/L) concentration of calcium in the dialysis fluid, and calcium influx during each of the sessions. In addition, a higher frequency of CCA-AP was also associated with male gender and lower (< 150 pg/ml) iPTH, and a higher presence of FA-AP was found in patients with higher (> 70 mmHg) PP and serum CRP levels (> 3 mg/L). Calcified CCA and FA-AP were most frequently observed in males, older patients, with higher PP and lower iPTH levels. A recent epidemiological survey on bone markers in our HD population has shown adynamic bone disease (ABD) as most frequent renal bone disease (21). It was concluded that the use of high (1.75 mM) dialysate Ca concentration, calcium carbonate and vitamin D treatment might be associated with development of ABD. Hence, the over-suppression of PTH and ABD as predominant type of renal osteodystrophy (ROD) contribute to high levels of calcium and phosphorus in the blood, which are strongly associated with cardiovascular disease, a major cause of mortality and morbidity (22). This is also in line with our study data that higher presence of calcified CCA and FA-AP was associated with lower HDL and an increased Ca x P product, respectively.

DBP, serum albumin, ferritin, triglycerides, cholesterol and the amount of ingested $CaCO_3$, vitamin D intake and smoking did not show significant associations with CCA and FA ultrasonographic findings in our patients. Here, the possible explanation could be a regular supplementation with parenteral iron therapy if needed, prescription of hypolipemics upon strict indication and precautious treatment with $CaCO_3$ and vitamin D.

In line with the previous reports that IMT is a strong predictor for cardiovascular events in the HD population (23), and that CCA-ID, but not CCA-IMT predict overall mortality and cardiovascular outcomes in HD patients (6), we need further keep trying to get under control the atherogenic factors like disorders of mineral metabolism (abnormalities in plasma Ca, phosphorus and iPTH concentration), blood pressure, HDL/LDL cholesterol, inflammation (CRP), and to improve the dialysis adequacy. The case if we can't establish any association between ultrasonographic findings and other atherogenic factors do not release us to keep up controlling further nutritional and inflammation markers, serum triglycerides and cholesterol, and the amount of ingested Ca from $CaCO_3$, vitamin D intake and smoking.

Conclusions

The measurement of IMT on CCA and FA in the present study demonstrated that atherosclerosis in asymptomatic non-diabetic HD patients is frequent. Our results suggest a few emerging risk factors for atherosclerosis such as older age, male gender, impaired dialysis adequacy, longer HD duration, increased BMI, SBP, MAP and PP, increased serum Ca, phosphate and Ca x P product, lower iPTH and HDL and higher LDL. We need to examine atherosclerotic conditions of CCA and FA in HD patients even if they are asymptomatic. The management of these associated factors may be beneficial in preventing of atherosclerosis and CVD development in this population at risk.

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