

Atherosclerosis in hemodialysis patients: traditional and nontraditional risk factors

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ABSTRACT

Aim: To determine the significance of the relationship between some traditional risk factors (age, arterial hypertension, smoking, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides) and some nontraditional risk factors (lipoprotein[a], apolipoprotein A, apolipoprotein B, homocysteine, calcium, phosphorus, parathyroid hormone) and asymptomatic atherosclerosis in hemodialysis patients.

Methods: Ninety-one hemodialysis patients were included in the study. Using B-mode ultrasonography, we measured intima-media thickness and plaque occurrence in the carotid arteries in these patients. Biochemical parameters were determined in all participants according to standard laboratory procedure, systolic and diastolic blood pressure was measured, and information on smoking habits was obtained by questionnaire.

Results: A correlation between intima-media thickness and age of the hemodialysis patients was found. Intima-media thickness values also correlated with total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B. Compared to those without plaques, patients with plaques were statistically significantly older; had higher concentrations of total cholesterol, low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B; and had lower concentrations of high-density lipoprotein cholesterol. The number of plaques correlated with age, total cholesterol, low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B. Using multivariate models (linear or logistic regression) of traditional and nontraditional risk factors, a relationship was found between intima-media thickness, plaque occurrence, number of plaques, and age of the hemodialysis patients. With the same multivariate statistical analysis of nontraditional risk factors, a relationship was found only between intima-media thickness, plaque occurrence, number of plaques and apolipoprotein B.

Conclusion: The results indicate that hemodialysis patients showed advanced atherosclerosis that is associated with traditional as well as nontraditional risk factors such as apolipoprotein B.

KEY WORDS

atherosclerosis, carotid arteries, hemodialysis, intima-media thickness, plaques, risk factors, ultrasound

Introduction

Hemodialysis (HD) patients belong to the group of patients with a high prevalence of cardiovascular dis-

ease, and about half of the deaths in HD patients are attributed to cardiovascular disease (1, 2). Atheroscle-

rosis is the most frequent cause of cardiovascular morbidity in patients with end-stage renal disease (ESRD) (3).

It is assumed that the atherosclerotic changes in the carotid artery mirror pathologic events of generalized atherosclerosis. Ultrasound measurements of intima-media thickness (IMT) and plaque occurrence in the carotid arteries were used as indicators of coronary atherosclerosis in previous studies in the general population as well as in studies involving patients with ESRD (4–11). The pathogenesis of cardiovascular damage in HD patients is complex. These patients were found to have traditional risk factors of advanced atherosclerosis as well as nontraditional ones that occur in patients with chronic renal failure. Previous studies reported data on the impact of traditional risk factors in asymptomatic atherosclerosis HD patients, but less is known about the impact of nontraditional risk factors in these patients (12–16).

The aim of this study was to investigate the possible

association of traditional and some nontraditional risk factors in asymptomatic atherosclerosis (IMT, plaque occurrence, and number of plaques) in HD patients.

Patients and methods

This study included 91 HD patients, 52 males and 39 females; the mean age was 53 years \pm 14.3 (range 19–79 years). They had been treated with hemodialysis for an average of 45 months \pm 45 (range 1–217 months).

Ultrasonographic scanning of the carotid artery was done with high-resolution echo color Doppler ultrasonography with a multifrequency 5–10 MHz linear probe (ATL HDI 3000, Advanced Technology Laboratories, High Definition Imaging; Bothell, WA, USA). All subjects lay supine with their necks slightly hyperextended and rotated away from the imaging transducer. Several images were captured in real time on the cine-loop frame grab-

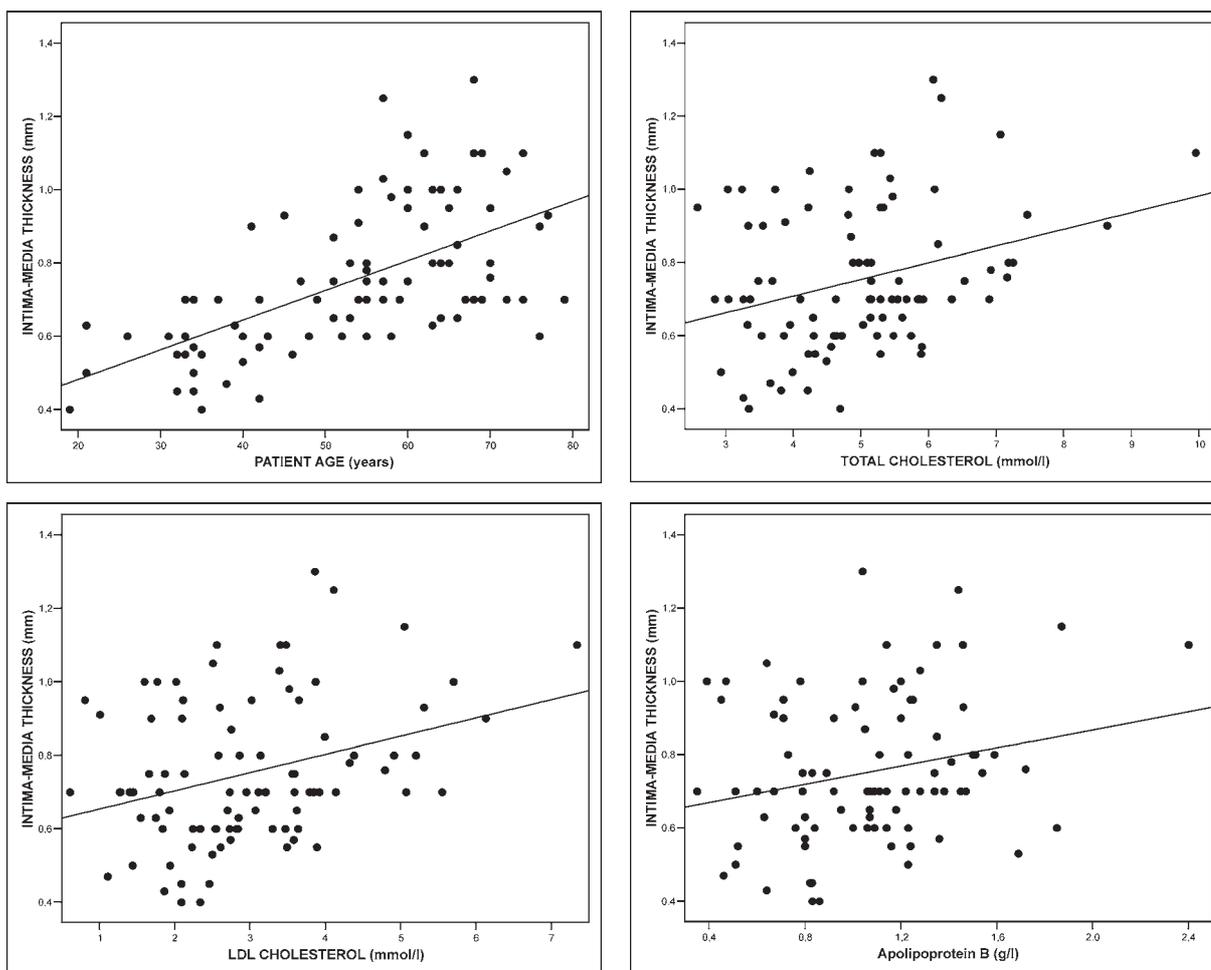


Figure 1. Correlation between intima media thickness (IMT) values and HD patient age, total cholesterol, LDL cholesterol, and apolipoprotein B.

ber and the three most clearly visible ones were used for measurements. Images were displayed with a constant fourfold magnification. Both carotid artery systems were scanned. We investigated IMT, plaque occurrence, and numbers of plaques in the common carotid arteries. In line with prior reports, IMT was defined as the distance between the leading edge of the lumen-intimal interface and the leading edge of the media adventitia interface of the far wall (5, 7, 9, 11). IMT was measured in the plaque-free section. Three digitized still images from the same section of the artery were measured and the average value was calculated. The mean value was also calculated from the left and right carotid artery.

Systolic and diastolic blood pressures were routinely measured before and after each dialysis. The results are reported as the mean of one month's measurements. Hypertension was defined by the administration of anti-hypertensive agents, systolic blood pressure greater than 160 mmHg, or diastolic blood pressure greater than 95 mmHg (4).

Information on smoking habits was obtained by questionnaire. HD patients were divided into two subgroups: smokers (present or former) and nonsmokers.

Serum cholesterol (total cholesterol, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol), triglycerides, lipoprotein(a) (Lp[a]), apolipoprotein A (apo A), apolipoprotein B (apo B), homocysteine, calcium, phosphorus, and parathyroid hormone (PTH) were measured by routine laboratory methods. PTH was measured by radioimmunoassay.

Table 1. Correlation between intima-media thickness (IMT) in carotid arteries and risk factors, traditional and nontraditional; *r*: Pearson's correlation coefficient, statistically significant difference*.

Risk factor	Unit	<i>r</i> value	<i>p</i> value
TRADITIONAL			
Age	year	0.589	0.0001*
Total cholesterol	mmol/l	0.305	0.003*
HDL cholesterol	mmol/l	-0.099	0.351
LDL cholesterol	mmol/l	0.317	0.002*
Triglycerides	mmol/l	0.172	0.102
NONTRADITIONAL			
Lipoprotein (a)	g/l	0.048	0.652
Apolipoprotein A	g/l	-0.078	0.463
Apolipoprotein B	g/l	0.230	0.028*
Homocysteine	g/l	-0.126	0.235
Calcium	mmol/l	0.028	0.790
Phosphorus	mmol/l	0.000	0.997
Parathyroid hormone	pg/ml	-0.156	0.140

All data are presented as mean \pm SD. Pearson's correlation coefficient was used to find the association between IMT and the number of plaques with various risk factors concerning the distribution of data. The Mann-Whitney test was used to assess the difference in IMT values or number of plaques between patients with arterial hypertension and those without and between smokers and nonsmokers. The same test was used to compare HD patients with plaques and those without plaques and different variables. Differences in plaque occurrence between smokers and nonsmokers and patients with arterial hypertension or without it were compared with a chi-square test. Multiple linear regression analysis was used to assess the influence of different variables on IMT values and the number of plaques in HD patients. Multiple logistic regression was used to assess the influence of different variables on plaque occurrence in the same patients. The differences were considered statistically significant at $p = 0.05$. Statistical analysis was carried out using SPSS 11.0 software.

The study protocol was conformed with ethical guidelines and informed consent was obtained from each participant.

Results

The mean IMT value was 0.75 ± 0.2 mm. The measurements ranged from 0.4 to 1.3 mm. In 59 of 91 HD

Table 2. Correlation between the number of plaques in carotid arteries and risk factors, traditional and nontraditional; *r*: Pearson's correlation coefficient, statistically significant difference*.

Risk factor	Unit	<i>r</i> value	<i>p</i> value
TRADITIONAL			
Age	year	0.530	0.0001*
Total cholesterol	mmol/l	0.335	0.001*
HDL cholesterol	mmol/l	-0.196	0.063
LDL cholesterol	mmol/l	0.391	0.0001*
Triglycerides	mmol/l	0.235	0.025*
NONTRADITIONAL			
Lipoprotein(a)	g/l	-0.019	0.860
Apolipoprotein A	g/l	-0.057	0.593
Apolipoprotein B	g/l	0.287	0.006*
Homocysteine	g/l	-0.053	0.621
Calcium	mmol/l	-0.069	0.516
Phosphorus	mmol/l	-0.010	0.923
Parathyroid hormone	pg/ml	-0.137	0.197

patients (65%) plaques were found (1–9 per patient). Correlations between IMT values and patient age were found ($p < 0.0001$). The IMT values correlated with total cholesterol ($p < 0.003$), LDL cholesterol ($p < 0.002$), and apo B ($p < 0.028$) (Figure 1). All correlations between IMT values and traditional and nontraditional risk factors are also shown in Table 1. No statistically significant difference was found in IMT values or number of plaques between patients with arterial hypertension and those without ($p = 0.822$; $p = 0.841$). In addition, no statistically significant difference in IMT values or number of plaques between smokers and nonsmokers was found ($p = 0.486$; $p = 0.139$). The number of plaques correlated with patient age ($p < 0.0001$), concentration of total cholesterol ($p < 0.001$), LDL cholesterol ($p < 0.0001$), triglycerides ($p < 0.025$), and apo B ($p < 0.006$) (Table 2). Patients with plaques compared to those without were statistically significantly older ($p < 0.0001$), they had higher concentrations of total cholesterol ($p < 0.001$), LDL cholesterol ($p < 0.001$), triglycerides ($p < 0.0001$), and apo B ($p < 0.008$), and they had lower concentrations of HDL cholesterol ($p < 0.019$). No difference in plaque occurrence between smokers and nonsmokers or patients with and without arterial hypertension was found ($p = 0.099$; $p = 0.424$). With multiple linear regression analysis of all observed risk factors, a relationship was found between IMT and patient age ($p < 0.0001$). Multiple linear regression analysis also showed an association between the number of plaques and patient age ($p < 0.0001$). Multiple linear regression analysis of nontraditional risk factors only showed a relationship between apo B values and IMT ($p < 0.04$) and the number of plaques ($p < 0.007$). Multiple logistic regression analysis of all observed risk factors assessed the influence of patient age on plaque occurrence ($p < 0.0001$). When only nontraditional risk factors were considered, we found a relationship between plaque occurrence and apo B ($p < 0.011$).

Discussion

High resolution B-mode ultrasound scan is a reliable, reproducible, and noninvasive method for detecting and monitoring asymptomatic atherosclerosis (10, 17). Atherosclerotic changes in the carotid arteries measured by ultrasonography mirror atherosclerosis of coronary arteries in the general population and also in patients with ESRD (4, 6, 8, 11, 18). In some studies a significant increase was found in IMT and plaque occurrence in carotid arteries in HD patients compared to age- and sex-matched healthy control subjects. Also, a higher frequency of plaques in carotid arteries in HD patients was observed (4, 5, 7, 8). It is assumed that atherosclerosis is accelerated in HD patients. There are only a few studies showing advanced atherosclerosis

in patients with chronic renal failure (19, 20), but more is known concerning the atherosclerotic process in patients with chronic renal failure just before starting dialysis, where more advanced atherosclerosis was found compared to healthy control subjects (21).

Risk for coronary heart disease is high among patients with ESRD. The pathogenesis of cardiovascular damage in HD patients is far more complex than in the general population (20). However, this increase in the risk of coronary heart disease is not entirely explained by traditional risk factors for cardiovascular disease. The impact of some risk factors, including nontraditional ones, on asymptomatic atherosclerosis in HD patients is not well known.

Therefore, our study investigated possible correlations of some traditional risk factors (age, arterial hypertension, smoking, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) as well as some nontraditional risk factors (Lp(a), apo A, apo B, homocysteine, calcium, phosphorus, and PTH) with IMT, plaque occurrence, and the number of plaques in HD patients.

As in previous reports demonstrating that the IMT of the carotid artery correlated significantly with age in the general population (9, 10), we also established a significantly positive association between IMT, plaque occurrence, the number of plaques, and age in our HD patients. Our results confirm the results from the two previous studies evaluating atherosclerosis in HD patients using ultrasonography (4, 7). Cigarette smoking was shown to be a predictor of atherosclerosis in the general population (12). Kawagashi et al. (4) and London et al. (7) found an association between IMT and smoking in HD patients. Similar to the study of Burdick et al. (11), we were unable to confirm an association between cigarette smoking and IMT in HD patients. Nor could we confirm an association between cigarette smoking and plaque occurrence, or the number of plaques. Arterial hypertension, a well-established cardiovascular risk factor in the general population, is very common among patients with ESRD. Some studies have quantified the effect of arterial hypertension on survival in HD patients (20, 22). Previous studies did not confirm the role of blood pressure as a determinant of IMT in HD patients (4, 5, 7, 11). Our study confirms previous findings: no association was found between arterial hypertension and IMT, plaque occurrence, or the number of plaques. These results can be explained by the fact that most hypertensive HD patients received long-term antihypertensive treatment (having a possible beneficial effect on the arterial wall). Because blood pressure is often being unstable in HD patients, this hinders the evaluation of arterial hypertension as a risk factor for atherosclerosis (4). Kawagashi et al. found a correlation between IMT and serum levels of phosphorus and PTH in HD patients (4). Nakashima et al. found a correlation only between IMT and serum levels PTH in the same patients (23). These data suggest that im-

paired calcium metabolism in secondary hyperparathyroidism affects lipoprotein metabolism and may contribute to the acceleration of atherosclerosis (4). Contrary to these findings, we found no correlation between asymptomatic atherosclerosis and serum levels of calcium, phosphorus, and PTH, which is compatible with some recent studies (24–26). Hyperhomocysteinemia is known as an independent risk factor for atherosclerosis in HD patients (13, 14). In some of the previous studies, the IMT of the carotid arteries was associated with serum levels of homocysteine (27, 28), but others failed to find a significant correlation between the two (29, 30). Likewise, in our study no associations between homocysteine and IMT, plaque occurrence, or the number of plaques were found. Hypercholesterolemia and high LDL cholesterol levels are known risk factors for atherosclerosis (10, 11). In HD patients, correlations were found between IMT and total and LDL cholesterol (11). Hojs et al. found that IMT values correlated with total and LDL cholesterol (26). In the same study, associations were found between total and LDL cholesterol and plaque occurrence and the number of plaques. Plaque occurrence was also associated with triglycerides (26). Others have failed to find a relationship between IMT and serum cholesterol and triglycerides in HD patients (4, 7). The explanation could lie in the relationship of serum cholesterol to mortality, which is a U-shaped curve.

Malnutrition can mask hypercholesterolemia, explaining the observation that outcomes can be even more favorable in HD patients with higher cholesterol levels (1).

In this study, values of total and LDL cholesterol were found to be associated with IMT, plaque occurrence, and the number of plaques. Levels of HDL cholesterol and triglycerides associated only with plaque occurrence and the numbers of plaques. Some (15, 16) but not all (31, 32) clinical studies among HD patients have shown that higher levels of serum Lp(a) are associated with an increased risk of coronary heart disease. In a study by Kronenberg et al., apolipoprotein(a), a fragment of Lp(a), was associated with plaques in carotid arteries in HD patients (33). Contrary to these results, we found no correlation between Lp(a) and plaque occurrence,

number of plaques, or IMT. Elevated levels of serum apo B, as well as a reduced level of serum apo A, have been found to be independent risk factors for coronary heart disease in epidemiological studies in the general population (34), but there are no data available for HD patients. In a recently published study with a large number of patients with chronic renal failure, a high prevalence of some nontraditional risk factors including apo B was found, suggesting the importance of nontraditional risk factors in pathogenesis of cardiovascular disease in patients with chronic renal failure (35). This study found associations between IMT, plaque occurrence, the number of plaques, and apo B. Using multivariate statistical analysis, a relationship between IMT, plaque occurrence, the number of plaques, and apo B was also found, thus establishing apo B as an important nontraditional risk factor for atherosclerosis in HD patients.

Conclusions

The risk of coronary heart disease is higher among patients with ESRD than in the general population. However, increased risk of coronary heart disease cannot be entirely explained by traditional risk factors alone. HD patients reveal a number of additional co-existing risk factors, and so it is difficult to establish the importance of single risk factors. This study stresses the importance of nontraditional risk factors. Positive correlations of IMT were observed with some traditional risk factors (age, total cholesterol, and LDL cholesterol) and also with the nontraditional risk factor apo B. We found associations between plaque occurrence and age, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and apo B, and also correlations between the number of plaques and age, total cholesterol, LDL cholesterol, triglycerides, and apo B. Future studies including a higher number of patients are necessary to determine the impact of these risk factors, especially nontraditional ones, on cardiovascular disease in these patients. In the meantime, aggressive management to reduce these risk factors is a strategy for preventing cardiovascular disease in HD patients.

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