Changes in common carotid artery intima-media thickness over 1 year in patients on peritoneal dialysis

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Abstract

Background. Accelerated atherosclerosis and vascular calcifications increase cardiovascular morbidity and mortality in patients on dialysis. Common carotid artery (CCA) intima-media thickness (IMT) is considered useful for imaging atherosclerosis non-invasively. Since chronic inflammation may accelerate atherosclerosis in end-stage renal disease patients, the aim of this 1 year study was to assess changes in CCA-IMT in stable peritoneal dialysis (PD) patients, and to search for possible associations between these changes and selected cytokines, acute phase proteins and other risk factors of atherosclerosis.

Methods. Of the original cohort of 61 stable patients on PD—28 female, 33 male; mean age 50.4±13.6 years; dialyse for a median of 17.5 months at inclusion (range 1–96 months)—47 patients survived the 1 year period on PD. CCA-IMT was assessed at baseline and after 12 months. Pro-inflammatory cytokines (IL-6, TNFα), acute phase proteins (CRP, fibrinogen), calcium-phosphate balance and lipid profile were assessed at baseline and after 6 and 12 months. Anthropometric parameters (age, weight, BMI, waist-to-hip ratio) were measured at baseline.

Results. The mean CCA-IMT at baseline, 0.66±0.19 mm, increased by a mean of 0.098±0.17 to 0.76±0.21 mm (P<0.001) in 1 year. In 14 patients (29.8%) at least one plaque was found in the CCAs examined. At the end of follow-up: 28 patients (59.6%) had increases in CCA-IMT from 0.63±0.2 to 0.83±0.21 mm; P=0.03; and 19 (40.4%) remained stable or even showed slight, but non-significant, decreases of CCA-IMT from 0.72±0.17 to 0.66±0.17 mm, P=NS. The ‘progressors’ had significantly higher initial BMI (P<0.05), and mean concentrations of calcium (P=0.005), IL-6 (P=0.05), TNFα (P=0.01) and CRP (P=0.005) and lower HDL-cholesterol than ‘non-progressors’. In univariate analysis, ΔCCA-IMT correlated positively with age (R=0.32, P=0.03), BMI (R=0.29, P=0.05) and mean concentrations of CRP (R=0.37, P=0.01), TNFα (0.52, P=0.0002), but inversely with HDL-cholesterol (R=−0.37, P=0.01). In multiple regression analysis, however, only age appeared to be independently associated with increase in CCA-IMT (β=0.37, P<0.01; R² for the model 0.14).

Conclusions. Our results suggest a possible role of non-specific inflammation in the progression of atherosclerosis in patients treated with PD, in addition to age.

Keywords: atherosclerosis; chronic inflammation; intima-media thickness; peritoneal dialysis

Introduction

Cardiovascular (CVS) disease is one of the most significant co-morbid conditions affecting patients with chronic renal failure. CVS co-morbidity also accounts for more than 50% of deaths among patients treated with various renal replacement therapies, even including those with functioning renal grafts [1,2]. There is increasing evidence to suggest that CVS disease and mortality, as well as all-cause mortality in patients on dialysis largely depend on the initial (i.e. at the initiation of renal replacement therapy) serum levels of certain pro-inflammatory cytokines and acute-phase proteins as well as on their profiles during dialysis treatment [3–6]. It has been also well recognized that chronic inflammation is closely associated with atherogenesis, which to some extent may be considered an inflammatory (and under certain circumstances even infectious) disease [7].
Trends in CCA-IMT over 1 year in patients on PD

Recently, non-invasive techniques of vascular imaging have emerged which appear to be adequate for assessing atherosclerosis, based on comparisons with findings obtained by invasive techniques or histology [8,9]. These new methods—such as measuring intima-media thickness (IMT) with ultrasound, quantitatively assessing coronary artery calcium burden with electron beam or multi-slice spiral computed tomographies, or estimating aortic stiffness from aortic pulse wave velocity—have also been proven to predict outcomes for patients in different risk categories.

Among those methods, measuring the common carotid artery (CCA) IMT is the longest applied and the best validated one. The increasing thickness of the intima and media combined, the presence of plaques, and their numbers and sums of thicknesses were shown to be very powerful predictors of adverse outcomes (the onset of cardio-vascular episodes and death) in both the general population and patients with end-stage renal disease (ESRD) [10,11].

CCA-IMT has been shown to be associated with ‘traditional’ risk factors (such as obesity, lipid profile abnormalities, homocysteine), as well as with those that reflect the state of inflammation—fibrinogen, C-reactive protein (CRP), leptin, adhesion molecules, growth factors or serological markers of certain viral infections [10,12,13]. Most of the studies on atherosclerosis and its risk factors performed to date in the setting of ESRD were on patients being treated conservatively (predialysis) or by haemodialysis (HD), or on mixed cohorts [peritoneal dialysis (PD) and HD]. The majority of these studies were cross-sectional in design, although some of them explored the value of baseline IMT for predicting future outcome. Only a few follow-up studies have been done in ESRD patients that focused on trends in this parameter over specific periods of time [10,14]. Recently, an interventional study was published that showed in patients with advanced atherosclerosis a reduction in CCA-IMT after treatment with LDL-apheresis combined with haemodialysis using vitamin E-coated dialysis membranes [15]. To our knowledge no paper has been published to date on changes in CCA-IMT over time in patients treated exclusively with PD.

The aim of the present study was to assess the trends and dynamics of changes in CCA-IMT in a group of stable PD patients over 1 year and to search for possible associations between these changes and the 1 year profiles of selected cytokines, acute-phase proteins and other factors that may be considered risk factors for the development of atherosclerosis, such as anthropometric parameters, calcium-phosphate balance and lipid profile.

Methods

Study population

We started the study with 61 patients (28 women, 33 men), with a mean age of 50.4±13.6 years, on maintenance PD [38 on continuous ambulatory peritoneal dialysis (CAPD), 23 on automated peritoneal dialysis (APD)] dialysed for a median of 17.5 months (range 1–96 months). All patients were clinically stable over at least 2 months prior to their baseline assessments (i.e. they displayed no symptoms of acute coronary events, neoplasms, infectious or non-infectious inflammatory diseases, including dialysis-related peritonitis). Our reason for selecting these inclusion criteria was the desire to relate the possible elevation of cytokines/acute-phase proteins to ‘non-specific’ inflammation, caused by uraemia and possibly dialysis (malnutrition-inflammation-atherosclerosis syndrome), but to exclude any other specific, identifiable reasons for inflammation.

The aetiologies of ESRD in the analysed group were: chronic glomerulopathy in 17 subjects, amyloidosis in four, diabetes mellitus in seven, chronic pyelonephritis and polycystic kidney disease each in four cases, uric acid nephropathy and lithium nephropathy, one case of each. For 23 patients, it was impossible to establish the aetiology of underlying renal disease that led to uraemia, due to late referral to the dialysis unit. The patients were dialysed using Baxter Twin Bag and Fresenius A.N.D.Y Plus or stay safe systems (CAPD) or Baxter HomeChoice or Fresenius PD Night cyclers (APD). Only 21 out of 61 subjects (34.4%) had previously diagnosed ischaemic heart disease based on one or more of typical clinical symptoms or prior ECG or exercise test; and 14 patients (22.9%) were normotensive (blood pressure below 140/90 mmHg and no hypertensive drugs). The dialysis dose of each patient was adjusted to obtain a Kt/V of at least 1.8.

Of the 61 patients, 60 completed the entire study period, one patient died, 47 remained on PD (although five of them were switched from CAPD to APD) and three patients were transferred to HD; 10 patients were transplanted during the study period. We analysed the data on the 47 subjects who were dialysed on PD throughout the study period—25 males and 22 females, mean age 52.7±12.8 years, on PD for a median of 16.5 months (range 1–98 months).

Common carotid artery intima-media thickness

The CCA-IMT was assessed in the B-mode presentation using an Acuson 128 XP/10 with a 5/7 MHz linear transducer (Acuson Corporation, Mountain View, CA). IMT was defined as the distance between the leading edge of the lumen interface and the media–adventitia interface of the far wall, and it was measured on the far walls of the CCAs bilaterally, 2–4 cm proximal to the bifurcations, and during cardiac diastole. For the purpose of this analysis, the higher of the two results from each side was used. IMT assessment was performed in the plaque-free arterial wall (an atherosclerotic plaque being defined as an echo-structure protruding into the vascular lumen and a thickness greater by at least 50% than neighbouring sites). The method described above has previously been validated by many other investigators [4,10,14,16,17]. All IMT ultrasound studies were performed by the same investigator (A.K.), who was blinded to the patients’ clinical and laboratory data.

CCA-IMT was measured at the start of the study (baseline) and after 12 months under the same standardized conditions. In each patient the difference in IMT between these two points of time was calculated (ΔCCA-IMT). Patients in whom the follow-up CCA-IMT was higher than at baseline (‘positive’ value of ΔCCA-IMT) were considered...
immediately frozen and maintained at a temperature of 1000

intra-assay variabilities for leptin, IL-6 and TNF

Serum leptin was measured using radioimmunoassay (Human
techniche (Quantikine, R&D Systems, Minneapolis, MN).

pro-inflammatory cytokines, were assessed by the ELISA

and tumor necrosis factor alpha (TNF$_{a}$)

haematocrit were assayed with Sysmex XE-2100 equipment

products Corporation, Los Angeles, CA). Haemoglobin and

chemiluminescence using the Immulite 2000 kit (Diagnostic

(high-density lipoprotein (HDL) cholesterol, triglycerides

All of the mentioned analyses were performed in duplicates.

utilizes the bromcresol green method for albumin assay).

phase reactant and nutritional marker; it was measured

with a Hitachi 917 analyser (Roche Diagnostics, Division

Laboratory assessment

The fasting blood samples taken for analyses of leptin,
cytokines and acute-phase reactants were centrifuged at 4'C

at 1000g for 15–30 min. Serum or plasma samples were

immediately frozen and maintained at a temperature of

−70'C. The serum concentrations of interleukin 6 (IL-6)

tumor necrosis factor alpha (TNF$_{x}$), considered

pro-inflammatory cytokines, were assessed by the ELISA

technique (Quantikine, R&D Systems, Minneapolis, MN).

Serum leptin was measured using radioimmunoassay (Human

Leptin RIA Kit, Linco Research Inc., St. Charles, MO). The

intra-assay variabilities for leptin, IL-6 and TNF$_{x}$ measure-

d statistical analysis of the data was performed using the

Statistica 5.1 software (StatSoft Inc., Tulsa, OK). Shapiro-

Wilk's $W$ test of normality was used to analyse data

distribution. All variables that were distributed normally are

presented as mean±SD, those with non-normal distribution, as

median and range. For correlations between variables, the

Pearson test was used for normally distributed data and the

Spearman $R$ test for those with non-parametric distributions.

For inter-group comparisons, we used the Student $t$-test

for normally distributed variables or the Mann--Whitney $U$

test for non-normally distributed data. Depending on data distri-
bution, the comparison of follow-up data vs baseline was

performed using the Student $t$-test for dependent variables or

the Wilcoxon test. To assess the influence of tested parameters

on CCA-IMT as the dependent variable, backward linear

multiple regression analysis was performed. We considered

$P$ values below 0.05 as statistically significant.

Results

In Table 1 we provide the data concerning haemoglo-

bin, haematocrit, lipid profile and calcium-phosphate

balance, and in Table 2 the values of acute-phase

proteins, cytokines and leptin, obtained at baseline

and after 6 and 12 months of follow-up, as well as

mean values calculated from the three separate

measurements. After 1 year of follow-up the serum

levels of fibrinogen, IL-6 and TNF$_{x}$ of the subjects

increased significantly compared with their baseline

values, serum albumin, total serum cholesterol and

LDL-cholesterol decreased significantly, and all other

variables remained stable.

The mean CCA-IMT at baseline was 0.66±

0.19 mm, and increased by a mean of 0.098±0.17–

0.76±0.21 mm ($P<0.0001$) at the end of the follow-up.
In 14 patients (29.8%), at least one plaque in one of the examined CCAs was identified at baseline. At the end of follow-up, but not at baseline, the patients with atherosclerotic plaques were characterized by significantly higher IMT, they also differed slightly in CCA-IMT at the end of the follow up. No progression in IMT was noticed in the plaque-free subjects when considered as a separate group (although there were some plaque-free patients in the ‘progressor’ group; see below), whereas it was highly statistically significant in the subgroup with plaques (Table 3).

In the group of 47 patients who remained on PD for the entire observation period, two categories were distinguished: those whose CCA-IMT increased (progressed) over the 1 year (N = 28; 59.6%), and those in whom it remained stable (or who in fact, showed slight, but non-significant, decreases in CCA-IMT; N = 19, 40.4%). In Table 4 we presented the baseline and follow-up values of CCA-IMT for the respective groups, as well as the absolute increments/decrements in CCA-IMT (ΔCCA-IMT).

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Table 5 provides a summary comparison of common CVS risk factors, drug treatment, peritoneal transport status and dialysis adequacy between ‘progressors’ and ‘non-progressors’. The significant differences in tested biochemical parameters between the two groups are shown in Table 6.

A number of correlations found between analysed variables and ΔCCA-IMT in univariate analysis are summarized in Table 7.
A backward linear multiple regression analysis was performed with CCA-IMT as the dependent variable and age, HDL-cholesterol, CRP, TNFα and ΔTNFα, identified in univariate analysis, to test the independent influence of these parameters on CCA-IMT. In this analysis only age appeared to be independently associated with the increment in CCA-IMT ($b = 0.37$, $P < 0.01$; $R^2$ for the model 0.14).

Discussion

The mean baseline CCA-IMT in our patients equaled $0.66 \pm 0.19$ mm. In several studies published recently concerning subjects treated with either PD or HD, and comparable in age with our cohort (although for HD patients usually with longer dialysis vintage), this value ranged from $0.58 \pm 0.04$ to $1.06 \pm 0.24$ mm [10,11,17–19]. Results within the mentioned range were also obtained for patients with advanced chronic renal failure shortly before the initiation of dialysis [14]. In some of these reports, the CCA-IMT of patients differed significantly from measurements in control healthy subjects, whereas in others such a difference could not be demonstrated [4,10,17,19].

As in our paper, most of the studies report a highly significant association between the prevalence of plaques detected by ultrasound and CCA-IMT, and when applicable, a close association between the sum of thicknesses of plaques (plaque score) and IMT [4,10,14,17,20].

In our study, age was significantly correlated with CCA-IMT, and it was the only parameter that multiple regression analysis identified as being independently associated with IMT. Diabetics were also more prevalent in the 'progressors' group. Almost all other papers on the topic confirm the significance of age and diabetes in predicting CCA-IMT in ESRD patients [4,17,19–22]. In our study a marginally significant difference in dialysis vintage between 'progressors' and 'non-progressors' was found. Most of the studies in this area have not confirmed the impact of dialysis vintage on CCA-IMT value [4,17,23] (although there are also some papers available that have documented such an association [24,25]).

The groups with and without progression in CCA-IMT differed in mean serum calcium level; the $Ca \times P$ product was borderline higher in the ‘progressors’, and there was no differences were shown in phosphate levels. Similar results were obtained recently in another study of patients treated exclusively with PD. Okhuma et al. [18] found statistically significant association between CCA-IMT and serum calcium level, whereas no such association could be demonstrated for phosphates, $Ca \times P$ product or iPTH. Other studies of ESRD patients did not, however, demonstrate any association between IMT and any parameter of calcium-phosphate balance [19,22].

### Table 3. The baseline and follow-up CCA-IMT values in patients whose IMT progressed or remained unchanged on the follow-up assessment (progressors and non-progressors)

<table>
<thead>
<tr>
<th>Plaque(s)</th>
<th>Initial assessment</th>
<th>Follow-up assessment</th>
<th>ΔCCA-IMT</th>
<th>P (1 vs 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Present</td>
<td>0.75 ± 0.17</td>
<td>0.96 ± 0.15</td>
<td>0.21 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>$N=14$ (29.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Absent</td>
<td>0.63 ± 0.12</td>
<td>0.67 ± 0.17</td>
<td>0.05 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>$N=33$ (70.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P (I vs II)</td>
<td>NS</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CCA-IMT, common carotid artery intima-media thickness; NS, non-significant.

### Table 4. The baseline and follow-up CCA-IMT values in patients with or without plaques in CCA at baseline assessment

<table>
<thead>
<tr>
<th>Plaque(s)</th>
<th>Initial assessment</th>
<th>Follow-up assessment</th>
<th>ΔCCA-IMT</th>
<th>P (1 vs 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Present</td>
<td>0.75 ± 0.17</td>
<td>0.96 ± 0.15</td>
<td>0.21 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>$N=14$ (29.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Absent</td>
<td>0.63 ± 0.12</td>
<td>0.67 ± 0.17</td>
<td>0.05 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>$N=33$ (70.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P (I vs II)</td>
<td>NS</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CCA-IMT, common carotid artery intima-media thickness; NS, non-significant.
Table 5. The comparison of common cardiovascular risk factors, blood pressure, drug treatment, baseline peritoneal transport status, residual renal function and dialysis adequacy between patients whose IMT progressed or remained unchanged at the follow-up assessment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Progressors</th>
<th>Non-progressors</th>
<th>P &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F:M</td>
<td>12:16</td>
<td>10:9</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
<td>54.7±13.8</td>
<td>49.9±11</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>kg/m²</td>
<td>27.0±4.48</td>
<td>24.5±3.88</td>
<td>0.05</td>
</tr>
<tr>
<td>WHR</td>
<td>–</td>
<td>0.92±0.07</td>
<td>0.92±0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Dialysis duration</td>
<td>Months</td>
<td>12.5 (2–96)</td>
<td>3 (1–52)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N (%)</td>
<td>6/28 (21.4)</td>
<td>1/19 (5.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smokers</td>
<td>N (%)</td>
<td>2/28 (7.1)</td>
<td>2/19 (10.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Past smokers</td>
<td>N (%)</td>
<td>2/28 (7.1)</td>
<td>3/19 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Treated for hypertension</td>
<td>N (%)</td>
<td>24/28 (85.7)</td>
<td>14/19 (73.7)</td>
<td></td>
</tr>
<tr>
<td>Mean number of antihypertensive preparations a</td>
<td>per patient per day</td>
<td>1.96±1.29</td>
<td>1.56±1.26</td>
<td></td>
</tr>
<tr>
<td>Treated with lipid lowering drugs b</td>
<td>N (%)</td>
<td>21/28 (75)</td>
<td>11/19 (58)</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>mmHg</td>
<td>140.7±15.7</td>
<td>141.3±17.5</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>mmHg</td>
<td>86.7±8.95</td>
<td>89.4±9.56</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>mmHg</td>
<td>45.6±12.2</td>
<td>43.9±10.3</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>mmHg</td>
<td>104.7±10.2</td>
<td>106.7±11.6</td>
<td></td>
</tr>
<tr>
<td>D/P creat. (PET results) d</td>
<td>–</td>
<td>0.617±0.13</td>
<td>0.613±0.12</td>
<td></td>
</tr>
<tr>
<td>Kt/V (total) d</td>
<td>–</td>
<td>2.27±0.53</td>
<td>2.33±0.43</td>
<td></td>
</tr>
<tr>
<td>Weekly creatinine clearance (total) d</td>
<td>–</td>
<td>74.8±22.8</td>
<td>69.5±23.8</td>
<td></td>
</tr>
<tr>
<td>RRF d</td>
<td>ml/min</td>
<td>2.64±2.22</td>
<td>2.02±2.08</td>
<td></td>
</tr>
<tr>
<td>Residual urine volume d</td>
<td>l</td>
<td>0.82±0.65</td>
<td>0.7±0.60</td>
<td></td>
</tr>
<tr>
<td>Daily UF d</td>
<td>l</td>
<td>1.56±0.66</td>
<td>1.09±0.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

aMean number of antihypertensive medications used throughout the study period per patient per day (including diuretics, beta-blocking agents, alpha-blocking agents, ACEi, calcium-channel blocking agents and clonidine).

bStatins, except for two cases using fibrates in the ‘progressor’ group.

Mean from three consecutive assessments (baseline, and 6 and 12 months).

dBaseline values; no differences in baseline and follow-up total Kt/V and weekly CiCr values between groups as well as between baseline and follow-up values within groups. Stable total Kt/V and wCrCl sustained due to statistically significant increase of daily dialysis volume (P<0.00001) and switch from CAPD to APD in five cases. The significant increase of dialytic components of Kt/V and wCrCl compensated for the significant decrease of RRF, residual urine volume and ‘renal’ components of Kt/V and CrCl over 1 year.

eBorderline significant; median and range.

fNo difference between groups in sex, age, waist-to-hip ratio, smoking habit, treatment for hypertension and hyperlipidaemia, blood pressure, peritoneal transport status, dialysis adequacy, residual renal function and volume.

IMT, intima-media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; D/P creat., dialysate-to-plasma creatinine ratio; PET, peritoneal equilibration test; RRF, residual renal function; UF, ultrafiltration; NS, non-significant.

Table 6. The comparison of biochemical parameters between patients whose IMT progressed or remained unchanged at the follow-up assessment (‘progressors’ vs ‘non-progressors’); only statistically significant or borderline significant differences shown

<table>
<thead>
<tr>
<th>Parameter a</th>
<th>Units</th>
<th>Progressors</th>
<th>Non-progressors</th>
<th>P &lt; e</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-cholesterol b</td>
<td>mmol/l</td>
<td>1.19±0.27</td>
<td>1.34±0.24</td>
<td>0.05</td>
</tr>
<tr>
<td>ΔHDL-cholesterol b</td>
<td>mmol/l</td>
<td>−0.09±0.16</td>
<td>0.06±0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Calcium b</td>
<td>mmol/l</td>
<td>2.43±0.17</td>
<td>2.29±0.14</td>
<td>0.005</td>
</tr>
<tr>
<td>Ca × P product b</td>
<td>mmol²/l²</td>
<td>4.17±1.01</td>
<td>2.29±0.14</td>
<td>0.08</td>
</tr>
<tr>
<td>IL-6 d</td>
<td>pg/ml</td>
<td>6.97 (1.6–77.5)</td>
<td>4.0 (1.83–60.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>TNFα d</td>
<td>pg/ml</td>
<td>6.73 (3.1–19.2)</td>
<td>3.93 (0–7.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔTNFα d</td>
<td>pg/ml</td>
<td>2.6±3.95</td>
<td>−0.03±2.96</td>
<td>0.001</td>
</tr>
<tr>
<td>CRP d</td>
<td>pg/ml</td>
<td>10.5 (1.31–51.5)</td>
<td>3.75 (0.44–20.9)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

aHDL-cholesterol, calcium, Ca × P product, IL-6, TNFα, CRP are the mean from three consecutive measurements; ΔHDL-cholesterol, ΔTNFα are the difference between follow-up and baseline levels.

bMean±SD; Student t-test for independent variables.

cMedian and range; U Mann–Whitney test.

dBorderline statistically significant.

eNo differences found between groups in terms of mean total-cholesterol, LDL-cholesterol, TG, phosphates, iPTH, albumin, fibrinogen and leptin.

IMT, common carotid artery intima-media thickness; HDL-cholesterol, high-density lipoprotein cholesterol; Ca × P product, calcium-phosphate product; IL-6, interleukin 6; TNFα, tumour necrosis factor α; CRP, C-reactive protein.
In contrast, Oh et al., who analysed factors that may affect IMT in young adults with childhood-onset renal failure, found associations between CCA-IMT and the cumulative concentrations (i.e. the mean of all results available since the onset of disease) of calcium, phosphate and Ca × P product [21]. As it is well recognized, the lipid profile considered to be 'atherogenic' in the general population still is atherogenic in patients on maintenance dialysis; however, its impact on survival appears to be 'paradoxical' and exemplifies the phenomenon defined recently as 'reverse epidemiology' [3]. Those patients from our cohort whose IMT progressed were characterized by significantly lower mean serum HDL-cholesterol and a significant decrease in HDL-cholesterol within the study period; serum HDL-cholesterol was also inversely associated with ΔCCA-IMT in univariate analysis. This relationship existed despite the fact that 70.2% of the studied patients were treated with lipid-lowering drugs, mostly statins. In a cross-sectional study of patients treated exclusively with PD, significant correlations were found between total cholesterol, LDL-cholesterol and CCA-IMT, but these associations were not confirmed further in multivariate analysis [18]. Drüke and co-workers [22] demonstrated an independent association between LDL-cholesterol and CCA-IMT in 71 patients aged 56±16 years who were on HD for 76±75.5 months along with a similar association between CCA-IMT and triglycerides in the subset of patients over 60 years old. However, several studies report no significant associations between lipid profile and CCA-IMT in ESRD subjects, although some of them suggest such an association with lipoprotein (a) [4,18,20,21].

Several significant correlations emerged between ΔCCA-IMT and mean CRP and TNFα levels, calculated from three measurements, and ΔTNFα over 1 year; similarly, ‘progressors’ and ‘non-progressors’ differed significantly in mean serum levels of CRP, IL-6 and TNFα over the entire observation period, as well as in ΔTNFα over the same interval. The relationship of IMT with TNFα and ΔTNFα deserves special attention since this cytokine is considered a key substance in the inflammation-mediated vessel wall damage of atherosclerosis. Its atherogenic properties include the activation of macrophages that infiltrate vessel wall, the enhancement of the local expression of metalloproteinases and adhesion molecules, and the stimulation of CRP synthesis. The expression of scavenger receptors is also controlled by this cytokine. In addition, acting as a potent inhibitor of lipoprotein lipase, TNFα mediates the generation of the ‘substrate’ for foam cell formation [26].

An association between CCA-IMT and markers of inflammation was addressed previously by other authors. Ohkuma and co-workers [18] found statistically significant correlations between IMT, plaque score, and CRP, fibrinogen, TNF soluble receptor and IL-1 receptor antagonist. Patients within successive CRP tertiles differed significantly in both IMT and plaque score. In the multiple regression model, both investigated features of CCA were independently associated with CRP. Among the patients with advanced renal failure not yet on dialysis, whom Stenvinkel et al. [27] studied, those displaying symptoms of malnutrition were characterized by significantly higher values of the three different parameters derived from CCA ultrasound (cIMT, CCA diameter and the calculated intima-media area (cIMA) and higher serum CRP and fibrinogen). The mean values of CCA and cIMA were also significantly higher in subjects with serum CRP above 10 mg/l than in those with CRP below 10 mg/l. The patients with at least one plaque in their CCA were also characterized with higher CRP and TNFα and lower serum albumin than those who were plaque-free [27]. Albumin was also shown to be inversely and independently associated with CCA-IMT in some studies of patients treated with PD or HD [17,23]. Although there may be many different clinical circumstances that lead to hypoalbuminaemia in ESRD, one convincing explanation for the mentioned association is that albumin may represent the state of enhanced inflammatory response as a ‘negative’ acute-phase protein. We, however, found no difference in serum albumin between ‘progressors’ and ‘non-progressors’; we also did not find any association between ΔCCA-IMT and mean serum albumin or the change in its serum level, despite the fact that albumin concentration decreased significantly during the 1 year follow-up. The significant positive correlations between IMT, the sum of thicknesses of CCA plaques and concentrations of circulating adhesion molecules

### Table 7. Statistically significant correlations between ΔCCA-IMT and selected anthropometric and biochemical parameters (univariate analysis; only statistically significant correlations shown)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age</th>
<th>BMI</th>
<th>HDL-cholesterol</th>
<th>CRP</th>
<th>TNFα</th>
<th>ΔTNFα</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>0.32</td>
<td>0.29</td>
<td>−0.37</td>
<td>0.37</td>
<td>0.52</td>
<td>0.36</td>
</tr>
<tr>
<td>P</td>
<td>0.03</td>
<td>0.05</td>
<td>0.01</td>
<td>0.01</td>
<td>0.0002</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Initial value.

*Mean from three consecutive measurements.

Calculation as difference between follow-up and baseline levels.

CCA-IMT, common carotid artery intima-media thickness; BMI, body mass index; HDL-cholesterol, high-density lipoprotein cholesterol; CRP, C-reactive protein; IL-6, interleukin 6; TNFα, tumour necrosis factor α.
that studies of patients treated with both HD and PD found additionally support an ‘inflammatory’ concept of atherogenesis [4,23].

As we mentioned in the introduction to this paper, only limited data exist on changes in CCA over time detected by ultrasound of ESRD patients. In one of follow-up studies, Stenvinkel et al. [27] analysed this topic in patients with advanced renal failure shortly before the initiation of renal replacement therapy. In a group of 45 patients, they identified two subgroups: 22 patients in whom the calculated cross-sectional intima-media area (cIM) progressed over one year and 23 who remained stable—although no progression was noticed for the group as a whole. The patients who progressed did not differ from the non-progressors in terms of baseline age, BMI, prevalence of cardiovascular disease, diabetes, malnutrition, serum albumin or lipid profile. The patients who progressed had, however, a significantly higher baseline IL-6 concentration (P < 0.05) and prevalence of IgA antibodies against Chlamydia pneumoniae (59 vs 17%; P < 0.01). Similarly, patients with at least one CCA plaque had higher serum IL-6 than plaque-free subjects (6.0 vs 2.5 pg/ml, respectively; P < 0.001). The increment observed over a 1 year follow-up in cIM was associated with the initial IL-6 (r = -0.41, P < 0.01); log-transformed IL-6 concentration was the only variable that independently predicted this increment. Patients with high initial serum IL-6 (>10 pg/ml) were characterized by a significantly higher increase of cIM [14].

In another study that repeatedly assessed IMT in 90 subjects on long-term HD, the baseline CCA-IMT was associated with age, systolic blood pressure, serum CRP and markers of endothelial dysfunction, serum homocysteine and asymmetric dimethyl-arginine (ADMA). In this cohort, the increment in CCA-IMT observed after 15.1 ± 1.1 months was associated with the initial serum CRP and ADMA concentrations. Interestingly, the initial IMT was significantly and inversely correlated with ΔCCA-IMT over the follow-up period (r = -0.41; P = 0.001) [10]. Our results are very similar: in our patients the initial IMT is also inversely correlated with ΔIMT (R = -0.31; P = 0.03), and its initial value was lower in the ‘progressors’ than in the ‘non-progressors’, although not significantly (0.63 ± 0.2 vs 0.72 ± 0.17, respectively). This may suggest that patients who initially have advanced atherosclerosis tend to relatively ‘stabilize’ over time, and those with lower initial values tend to progress.

We should emphasize the very significant absolute increase in IMT after 1 year in our entire cohort (by 0.098 ± 0.17 mm), and particularly in the patients who progressed (0.2 ± 0.14 mm). Most of the studies in this area report an annual increase ranging between 0.04 and 0.05 mm. To our best knowledge, no follow-up study has been published or performed to date on patients treated with PD only, therefore, we can make no direct comparisons with other cohorts. Such a high progression in IMT probably reflects the highly expressed risk profile in our cohort of patients, but the ‘atherogenic’ nature of PD as renal replacement therapy cannot be ruled out.

We are aware of several limitations in our study, such as its relatively small sample size, short-term follow-up and its observational design. Nevertheless, in our opinion our results may add important information to the knowledge concerning progression in carotid atherosclerosis in PD patients.

In summary, we would like to emphasize that our study appears to be the first one in the available literature to provide data on the repeated measurement of CCA-IMT exclusively in patients on PD and that correlates these with ‘traditional’ and inflammatory risk factors for atherosclerosis collected not only at baseline, but also repeatedly over a follow-up period. Unlike in several, cross-sectional studies performed previously in different ESRD cohorts, our results did not confirm any independent association between the progression of atherosclerosis and chronic inflammation, or with other ‘traditional’ risk factors, except for age. One may doubt that age is a factor sufficient as a single variable to underlie such a significant progression. However, there are still many other variables that might have an impact on the progression of atherosclerosis, which we did not analyse in our present study. It appears to be noteworthy that, even in a group of individuals with high-risk profiles for the progression of atherosclerosis, such as ESRD patients on PD, there are individuals who display no increase in CCA-IMT.

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References


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