Advanced Coronary and Carotid Arteriopathy in Young Adults With Childhood-Onset Chronic Renal Failure

Jun Oh, MD; Rainer Wunsch, MD; Martin Turzer, BSc; Malte Bahner, MD; Paolo Raggi, MD; Uwe Querfeld, MD; Otto Mehls, MD; Franz Schaefer, MD

Background—Cardiovascular mortality is excessive in young adults with end-stage renal disease (ESRD). The factors contributing to ESRD-related vascular disease are incompletely understood. Young adults with childhood-onset chronic renal failure (CRF) are uniquely suited for risk factor assessment because of their long-term exposure at an age when vascular pathology in the general population is still minimal.

Methods and Results—We used novel noninvasive technologies to screen for coronary and carotid artery disease in 39 patients with ESRD aged 19 to 39 years with childhood-onset CRF presently treated by dialysis or renal transplantation. Coronary artery calcification burden was assessed by CT scan with ECG gating and the intima-media thickness (IMT) of the carotid arteries by high-resolution ultrasound. Coronary artery calcifications were present in 92% of patients; calcium scores exceeded the 95th age- and sex-specific percentiles 10-fold on average. Carotid IMT was significantly increased compared with matched control subjects. Both coronary calcium scores and IMT were associated with cumulative dialysis and ESRD time and the cumulative serum calcium-phosphate product. Coronary calcium scores were strongly correlated with C-reactive protein and \textit{Chlamydia pneumoniae} seropositivity, time-averaged mean serum parathyroid hormone, and plasma homocysteine. C-reactive protein and parathyroid hormone independently predicted coronary calcium accumulation. Smoking, obesity, and HbA1c were correlated with IMT in the control subjects but not in the patients.

Conclusions—Young adults with childhood-onset CRF have a high prevalence of arteriopathy associated with indicators of microinflammation, hyperparathyroidism, calcium-phosphate overload, and hyperhomocysteinemia but not traditional atherogenic risk factors. These risk factors persist even after successful renal transplantation. (\textit{Circulation}. 2002; 106:100-105.)

Key Words: atherosclerosis ■ calcium ■ carotid arteries ■ coronary disease ■ kidney
transferred to adult units at age 16 to 20 years. Of these, 42 had died and 49 were lost to follow-up (Figure 1). Fifty percent of the deceased patients had died of cardiovascular or cerebrovascular events. A total of 39 patients participated in this study. Underlying diseases were hereditary nephropathies in 12, obstructive uropathies in 11, glomerulonephritides in 11, and renal hypoplasia or dysplasia in 5 patients. At a mean age of 27.3 ± 5.9 years (range, 19 to 39), their mean duration of CRF was 19 ± 6.4 years (range, 7 to 34). Median cumulative dialysis time was 5 years (range, 0 to 22). Thirteen patients were presently being treated with dialysis, and 26 had undergone transplantation. Symptoms of cardiovascular disease were reported by 8 patients (20%), consisting of chest pain (n = 4), shortness of breath (n = 4), or congestive edema (n = 2).

The imaging procedures described below, an anthropometric assessment, and an atherosclerotic risk profile were performed (Table 1). The ethics committee of Heidelberg University approved the study protocol. All participants gave written informed consent. Two patients were unable to undergo the CT scan, and 2 others were unable to undergo the ultrasound examination because of technical or medical reasons. Two patients were unable to undergo the ultrasound examination because of technical or medical reasons. Ten patients were presently being treated with dialysis, and 26 had undergone transplantation. Symptoms of cardiovascular disease were reported by 8 patients (20%), consisting of chest pain (n = 4), shortness of breath (n = 4), or congestive edema (n = 2).

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tion (7 of 25; 28%) patients. The 7 posttransplantation patients with calcium scores >100 had higher serum PTH (P<0.0005) and CRP (P<0.05) levels than the 18 patients with no or mild lesions. Moreover, 6 of the 7 patients with more severe lesions were seropositive for *C pneumoniae*, in contrast to only 1 of 18 posttransplantation patients with calcium score <100 (P<0.0001). The 2 subgroups with higher and lower calcium scores did not differ with respect to present serum creatinine or the total duration of ESRD, dialysis, or transplantation periods.

The cardiovascular risk factor profile is given in Table 1. In the univariate correlation analysis (Table 2), calcium scores were positively associated with the duration of ESRD and cumulative duration of dialysis periods, time-integrated mean plasma intact-PTH, cumulative serum calcium and calcium-phosphate product since the onset of CRF, and present CRP (Figure 4A) and plasma homocysteine. Calcium scores were markedly higher in patients seropositive for *C pneumoniae* IgG (median, 174; iqr, 108 to 233) than in seronegative patients (median, 41; iqr, 19 to 82; P<0.0005) (Figure 4B). No association was found with seropositivity for other viral infections. Serum albumin tended to be inversely correlated with CRP (r=0.29, P=0.07) but not with calcium scores.

Stepwise linear regression analysis included CRP (partial $R^2=0.50$, $P=0.0001$), mean plasma intact-PTH (partial $R^2=0.15$, $P=0.0006$), cumulative serum calcium-phosphate product (partial $R^2=0.07$, $P=0.01$), and plasma homocysteine levels (partial $R^2=0.03$, $P=0.05$) as independent predictors in a model explaining 75% of the variation in coronary calcification. Patients with time-averaged mean PTH >250 pg/mL and CRP >5 mg/L exhibited >5-fold greater calcium scores than subjects below these cutoffs (Figure 5).

**Carotid Intima-Media Thickness**

Carotid IMT was elevated both in the dialyzed (0.66±0.12 mm, P<0.01) and posttransplantation

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**TABLE 1. Basic Clinical and Biochemical Characteristics of 39 ESRD Patients and Matched Healthy Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Dialysis Patients</th>
<th>Posttransplantation Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>Sex, m/f</td>
<td>7/6</td>
<td>18/8</td>
<td>25/14</td>
</tr>
<tr>
<td>Age, y</td>
<td>27.2±4.8</td>
<td>27.4±6.4</td>
<td>28±5.9</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>3 (23)</td>
<td>9 (35)</td>
<td>13 (33)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.6±5.8</td>
<td>22.8±4.1</td>
<td>21.5±2.4</td>
</tr>
<tr>
<td>Time-integrated mean arterial pressure, mm Hg</td>
<td>108.6±8.8</td>
<td>108.1±7.4†</td>
<td>102.7±7.8‡</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>9±3.6†</td>
<td>1.9±2‡</td>
<td>0.8±0.2§</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>41.1±4.9†</td>
<td>44.3±5.4§</td>
<td>47.3±3.2§</td>
</tr>
<tr>
<td>VLDL cholesterol, mg/dL</td>
<td>24±12</td>
<td>28±24</td>
<td>18±12</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>126±52</td>
<td>120±33</td>
<td>112±23</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>45±19†</td>
<td>48±16</td>
<td>56±14§</td>
</tr>
<tr>
<td>Glycosylated hemoglobin A₁, %</td>
<td>5.61±0.62</td>
<td>5.84±0.68†</td>
<td>5.33±0.62‡</td>
</tr>
<tr>
<td>Plasma homocysteine, μmol/L</td>
<td>26±10.6†</td>
<td>23.5±9.4†</td>
<td>13.8±3.5§</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>10.9±7.7‡</td>
<td>3.9±5.3§</td>
<td>2.8±1.1§</td>
</tr>
<tr>
<td><em>C pneumoniae</em> IgG positive, n (%)</td>
<td>7 (54)</td>
<td>7 (27)</td>
<td>7 (18)§</td>
</tr>
<tr>
<td>Time-integrated mean serum calcium, mmol/L</td>
<td>2.49±0.14†</td>
<td>2.47±0.15†</td>
<td>2.33±0.11§</td>
</tr>
<tr>
<td>Time-integrated mean serum phosphate, mmol/L</td>
<td>1.72±0.31†</td>
<td>1.55±0.36†</td>
<td>1.06±0.27§§</td>
</tr>
<tr>
<td>Time-integrated mean plasma intact PTH, pg/mL</td>
<td>364±204†‡</td>
<td>231±136‡§</td>
<td>45±18§</td>
</tr>
<tr>
<td>Duration of CRF, y</td>
<td>18.1±6.7</td>
<td>19.4±6.2</td>
<td>...</td>
</tr>
<tr>
<td>Duration of ESRD, y</td>
<td>15.3±6.6</td>
<td>12.6±4.8</td>
<td>...</td>
</tr>
<tr>
<td>Cumulative time on hemodialysis, y</td>
<td>6.9±6.3‡</td>
<td>2.3±3.5§</td>
<td>...</td>
</tr>
<tr>
<td>Cumulative time on peritoneal dialysis, y</td>
<td>2.5±3.1</td>
<td>1.5±2</td>
<td>...</td>
</tr>
<tr>
<td>Cumulative time with renal transplant, y</td>
<td>5.9±4.7</td>
<td>8.8±5.7</td>
<td>...</td>
</tr>
<tr>
<td>Cumulative calcium carbonate/acetate intake, kg</td>
<td>20.3±17.1</td>
<td>31.2±24.3</td>
<td>...</td>
</tr>
<tr>
<td>Cumulative calcitriol intake, mg</td>
<td>18.5±26.6</td>
<td>10.8±6.5</td>
<td>...</td>
</tr>
</tbody>
</table>

*Based on individual mean values calculated over total CRF observation period. In controls, mean of single values obtained at time of investigation is given.
†Significant difference from control subjects.
‡Significant difference from posttransplantation patients.
§Significant difference from dialysis patients.
∥All measurements since introduction of intact-PTH assay were considered.
(0.61±0.11 mm, P<0.05) patients compared with control subjects (0.54±0.08 mm) but did not differ significantly between dialyzed and posttransplantation patients.

IMT was higher in patients aged 28 to 43 years (0.67±0.12 mm) than in those aged 19 to 27 years (0.59±0.09 mm, P<0.05) but did not differ by age in the control subjects. Smoking tended to be associated with higher IMT in the control subjects (0.57±0.11 versus 0.52±0.06 mm, P=0.06) but not among the patients. IMT was not correlated with coronary calcification scores. Patients with clinical cardiovascular disease tended to have higher IMT than did control subjects (0.68±0.1 versus 0.61±0.11 mm, P=0.10).

In the healthy control subjects, carotid IMT was positively correlated with body mass index (r=0.3, P<0.05), daily cigarette consumption (r=0.34, P<0.05), and HbA1c levels (r=0.41, P<0.01). In the patients, IMT was associated with ESRD duration, cumulative dialysis time, and cumulative serum calcium, phosphate, and calcium-phosphate product since onset of CRF (Table 2).

In the multiple regression analysis of patients and control subjects combined, plasma homocysteine (partial R²=0.13, P=0.002), age (partial R²=0.07, P=0.01), C pneumoniae seropositivity (partial R²=0.05, P=0.03), and plasma C-peptide (partial R²=0.05, P=0.05) contributed independently to the variance of IMT. In the healthy control subjects, HbA1c (R²=0.29, P=0.001) and smoking (R²=0.14, P=0.01) were independent predictors of IMT. When only the patients were considered, cumulative serum calcium levels (partial R²=0.25, P=0.002) and the total duration of dialysis (partial R²=0.10, P=0.03) predicted IMT independently.

Discussion

This study provides a quantitative assessment of coronary calcifications and carotid IMT in young adult ESRD patients with childhood-onset CRF either undergoing dialysis or after transplantation. Our results indicate an advanced calcifying arteriopathy in this young population. Coronary calcifications were observed in 92% of patients, confirming and extending a recent EBCT study reporting coronary calcifications in 14 of 16 dialysis patients aged 20 to 30 years.3 Our comparison with a large cohort of age-matched healthy subjects provides evidence

<table>
<thead>
<tr>
<th>Calcium Score</th>
<th>IMT</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>0.25</td>
</tr>
<tr>
<td>ESRD duration</td>
<td>0.53†</td>
</tr>
<tr>
<td>Cumulative time undergoing dialysis</td>
<td>0.33‡</td>
</tr>
<tr>
<td>Time-integrated mean plasma intact-PTH</td>
<td>0.60§</td>
</tr>
<tr>
<td>Cumulative serum calcium</td>
<td>0.38‡</td>
</tr>
<tr>
<td>Cumulative serum phosphate</td>
<td>0.31</td>
</tr>
<tr>
<td>Cumulative serum calcium-phosphate product</td>
<td>0.36‡</td>
</tr>
<tr>
<td>CRP</td>
<td>0.62§</td>
</tr>
<tr>
<td>Plasma homocysteine</td>
<td>0.35‡</td>
</tr>
</tbody>
</table>

Only variables significantly associated with at least 1 of the 2 parameters are listed. Cumulative denotes the product of the time-averaged mean value and total observation time.

*P<0.005.
†P<0.0005.
‡P<0.05.
§P<0.0001.

Figure 2. Coronary calcium scores in 24 male and 13 female ESRD patients with childhood-onset CRF. Symbols denote present treatment modality (●, dialysis; ○, after transplantation). The broken and solid lines indicate the 75th, 90th, and 95th reference percentiles of calcium scores.

Figure 3. CT sections from 27-year-old male hemodialysis patient with extensive calcification in all 3 coronary arteries and aorta.

Figure 4. Association of Agatston calcification score with serum CRP (A) and C pneumoniae seropositivity (B).

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that calcium scores exceed the minimal calcifications present in 5% to 10% of the general population in the third and fourth decade of life by more than one order of magnitude. Hence, young adults suffering from CRF are relatively more affected by coronary calcium deposition than older individuals, in whom calcium scores were only 2.5-fold elevated compared with age-matched control subjects. Furthermore, carotid IMT was increased compared with matched control subjects, in keeping with findings in older patients undergoing dialysis and after transplantation. The clinical relevance of our findings is underlined by the observed association of high coronary calcium scores with manifest cardiovascular disease, which was present in 20% of the population.

Whereas a selected group of patients on long-term dialysis was examined by Goodman et al., the history of the patients studied here was more representative of the childhood-onset ESRD population, with a variable sequence of dialysis and transplantation periods and an average of 45% ESRD time spent undergoing dialysis. Coronary calcifications tended to be more severe in patients presently undergoing dialysis than in those with a functioning allograft. On the other hand, calcium scores were more closely correlated with total ESRD duration than with cumulative time of treatment with dialysis, and no inverse relationship of coronary calcification with the time elapsed since the most recent transplantation was evident. Analogously, carotid IMT was increased more markedly in patients presently undergoing dialysis but was also elevated in the posttransplantation patients compared with control subjects. Cardiac calcifications may rapidly progress in patients undergoing extended dialysis. Assuming that the lesions attained during dialysis are essentially irreversible, the less marked vasculopathy observed in renal transplant recipients may reflect the shorter total dialysis duration in this patient group. Alternatively, regression after renal transplantation may be possible but partly inhibited by the persistence of risk factors related to ESRD in general or specific to transplantation.

Multivariate risk factor analysis revealed microinflammation and alterations of mineral metabolism as the most important independent contributors to the risk of ESRD-related arteriopathy, irrespective of the treatment modality at time of examination. Hyperphosphatemia and hyperparathyroidism are independent predictors of mortality during hemodialysis. Within the last decade, calcium-containing compounds have replaced aluminum salts as phosphate binders and high doses of active vitamin D metabolites have been administered to suppress PTH. These medications have contributed to a high incidence of hypercalcemic episodes. Concerns have been raised that critical increases of the calcium-phosphate product may contribute to extraosseous calcifications in ESRD. These can either occur as diffuse depositions of amorphic calcium in soft tissues and arterial media layers or by formation of hydroxylapatite crystals in atherosclerotic lesions via an active, regulated process resembling bone formation. Excessive calcium deposition in atherosclerotic lesions occurs in coronary arteries of ESRD patients. A particular phenotype of coronary atherosclerosis has been described in uremic patients, characterized by preferential thickening and calcification of the tunica media. An animal model of uremic arteriopathy showed focal proliferation, degeneration, and calcification of media smooth muscle cells with minimal intimal lesions, suggesting that the pathomechanisms underlying uremic arteriopathy may be distinct from those causing atherosclerosis as part of the aging process.

In our study, the cumulative serum calcium-phosphate product over time was not only correlated with coronary calcification but also with carotid IMT. Both findings are in keeping with observations linking the calcium-phosphate product to coronary calcification, serum phosphate to carotid IMT, and calcium carbonate intake to increased carotid artery stiffness. Surprisingly, however, calcifications were more closely associated with time-averaged plasma PTH than with the calcium-phosphate product. PTH increases intracellular calcium and causes calcium overload in platelets and cardiomyocytes; increased calcium entry might also affect the metabolism, structure, and function of vascular smooth muscle cells. Such an action could explain the preferential calcification of the media layer in uremia. Notably, vascular calcifications can be prevented or reversed by parathyroidectomy.

The acute-phase protein CRP is chronically elevated in one third to two thirds of dialysis patients. CRP is considered a surrogate marker of a microinflammatory state and is a powerful predictor of general and cardiovascular mortality both in the general and in the ESRD population. We observed increased CRP in 70% of the dialyzed patients but also in 25% of posttransplantation patients. CRP levels have been linked with the severity of atherosclerosis in nonrenal disease and predialytic CRF and with cardiac valve calcification in CAPD patients. We demonstrate here that CRP is strongly correlated with coronary calcifications in young ESRD patients not only undergoing dialysis but also after renal transplantation.

Multiple inflammatory mechanisms are implicated in the initiation and propagation of atherosclerotic lesions. CRP may be directly involved as it binds to degraded LDL particles, is deposited at the intima-media interface, colocalizes with complement, and attracts monocytes to atherosclerotic lesions. Moreover, calcification of vascular cells and atheromatous lesions is directly stimulated by TNF-α, a proinflammatory cytokine that also promotes CRP release.

Furthermore, C pneumoniae may be causally involved in the pathogenesis of atherosclerosis; the presence of antibodies...
against this pathogen is correlated with atherosclerosis, the microorganism is detectable in atheromas, and inoculation leads to deposition in arterial walls and atherosclerosis-like lesions. C. pneumoniae present in coronary and carotid artery plaques attracts and activates macrophages.27 In our study, the presence of C. pneumoniae antibodies was associated with more severe coronary calcifications and a trend toward increased carotid IMT. These findings are in keeping with recent studies linking C. pneumoniae antibodies to increased carotid IMT in predialytic CRF.28 carotid plaque number in hemodialyzed and CAPD patients.29 and coronary disease in CAPD patients.30 Notably, we observed the strongest association in the posttransplantation group, where advanced coronary calcifications were almost exclusively found in patients seropositive for C. pneumoniae. We speculate that posttransplantation immunosuppression may facilitate persistent infection of vascular lesions with this pathogen.

The notion that uremic arteriopathy may be etiologically distinct from atherosclerosis is supported by the lack of correlation of the disease markers with most conventional cardiovascular risk factors, such as smoking, dyslipidemia, hypertension, obesity, and insulin resistance. Only hyperhomocysteinemia contributed significantly to coronary artery calcification, independently of CRP, PTH, and calcium-phosphate load. Homocysteine is elevated in CRF and remains increased after kidney transplantation.31,32 Homocysteine predicts cardiovascular mortality in ESRD and morbidity after transplantation.31,33 In conclusion, the arteriopathy observed in young adults with ESRD is associated with several risk factors specific to renal disease. Hyperparathyroidism, an increased serum calcium-phosphate product, microinflammation, and hyperhomocysteinemia predispose to vascular damage at young age. The effects of these risk factors persist in part even after successful renal transplantation.

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References

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