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

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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 *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. (Circulation. 2002; 106:100-105.)

Key Words: atherosclerosis ■ calcium ■ carotid arteries ■ coronary disease ■ kidney

Young patients with end-stage renal disease (ESRD) suffer from an excessive cardiovascular mortality, which is increased 700-fold in 25- to 34-year-old patients undergoing dialysis and >10-fold after renal transplantation.1 Chronic renal failure (CRF) is associated with hypertension, dyslipidemia, hyperphosphatemia, hyperhomocysteinemia, and chronic inflammation.2 The impact of these cardiovascular risk factors is likely to accumulate with disease duration. Because of their long-term risk exposure at an age when physiological age-related atherosclerosis is still minimal, young adult survivors of childhood-onset CRF represent a unique population to investigate the specific vascular sequelae of CRF.

Two recent studies using electron-beam computed tomography (EBCT) disclosed excessive coronary artery calcifications in young adults with childhood-onset CRF, opening a new avenue of research into a potentially life-limiting complication in this population.3,4 In those studies, small population sizes precluded a detailed risk factor analysis. Also, it is unclear whether vascular lesions in young adults are limited to the coronary arteries and whether regression can occur after renal transplantation. To additionally elucidate these issues, we assessed the vascular status of 39 young adult ESRD patients with childhood-onset CRF. Cardiac CT scan with ECG gating, a novel imaging technique with sensitivity and precision equal to EBCT, was applied to assess coronary artery and valvular calcifications.5 In addition, carotid intima-media thickness (IMT), an early marker of atherosclerosis and predictor of vascular events,6,7 was measured by high-resolution ultrasound. The results were quantitatively correlated with an array of traditional and novel, general, and ESRD-specific vascular risk factors.

Methods

 Patients
Two hundred eighty-three patients treated at our facility for advanced childhood-onset CRF between 1970 and 1997 had been
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, glomerulopathies 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 organizational problems. All patient records since start of CRF (defined by the first recorded increased serum creatinine) were reviewed to assess the individual cumulative exposure to assumed CRF-specific cardiovascular risk factors. Serum calcium, phosphate binder, vitamin D, and antihypertensive medication were recorded at monthly intervals. Time-averaged monthly means were used whenever more than one value per month was documented.

Control Subjects
In 39 healthy volunteers matched to the patients with respect to sex, age, body mass index, and smoking habits, carotid ultrasound and cardiovascular risk profile were obtained. Because ethics committee approval was not given for CT scan studies in healthy individuals, age- and sex-specific control data for coronary calcium scores were obtained from EBCT scans of 4336 healthy subjects aged 19 to 39 years in 8 centers in the United States. The individuals had been obtained from EBCT scans of 4336 healthy subjects aged 19 to 39 years. The individuals had been investigated in local reference studies to exclude congenital heart disease or, in few cases, in the diagnostic workup of atypical chest pain. The use of the EBCT control data was considered justified in accordance with the guidelines on interpretation of calcium scores proposed by Rumberger et al.9 lesions were minimal (score <10) in 1, mild (11 to 100) in 19, moderate (101 to 400) in 12, and severe and with high probability stenosing (>400) in 2 subjects. Calcium scores were higher in patients with manifest cardiovascular disease (median, 226; iqr, 205 to 293) than in asymptomatic patients (median, 44, iqr, 22 to 91; P < 0.0005). Calcifications of cardiac valves and aorta were observed in 12 (34%) and 11 (32%) patients, respectively.

Sequential CT Scan With ECG Gating
Data were acquired using a multilayer SOMATOM Volume Zoom CT scanner (Siemens) with a rotation time of 500 ms and a table feed of 4 × 2.5 mm/rotation. The tube current was 50 mAs at 120 kV. During the scan, the patient’s digitized ECG was continuously recorded, and image acquisition was performed with prospective ECG gating. A calcification score was calculated for each lesion by multiplying the lesion area in mm² by a density score determined from the peak CT scan number.8 A density score of 1 was applied for 130 to 200 HU, 2 for 201 to 300 HU, 3 for 301 to 400 HU, and 4 for >401 HU. Scores were determined for each main epicardial coronary artery, and the total calcium score was defined as the sum of the values of all lesions identified.

Carotid Ultrasound
The subjects were examined using a Sonoline Elegra Duplex Scanner (Siemens) equipped with a 12-MHz linear probe. A single well-trained person performed the B-mode ultrasound scanning. The diagnostic protocol involved examination of the carotid artery in both transverse and longitudinal planes. IMT was measured on the far wall of the common carotid artery 2 to 4 cm proximally to the bifurcation. IMT was defined as the distance between the leading edges of the lumen interface and the media-adventitia interface of the far wall. Both carotid arteries were examined, and the higher of the 2 IMT values was used for additional analysis. The intraobserver technical error of measurement was 0.05 mm (8.9%).

Laboratory Measurements
Serum biochemistry was performed with routine laboratory techniques. Only intact PTHs measured by the Nichols immunoradiometric assay were considered for evaluation of time-integrated PTH. In a cross-sectional analysis at the time of investigation, C-reactive protein (CRP) was measured by an ultrasensitive turbidimetric assay (detection limit 1 mg/L), total plasma homocysteine by HPLC, and antibodies against Chlamydia Pneumoniae, herpes simplex, hepatitis C, and cytomegalovirus by immunofluorescence assays.

Statistics
Data were checked for Gaussian distribution by the Shapiro-Wilk statistic. Parameters with Gaussian distribution are expressed as mean ± SD; between-group differences were assessed for significance by Student’s t test or ANOVA followed by Newman-Keuls test. Parameters with skewed distribution are expressed as median and interquartile range (iqr); Wilcoxon and Kruskal-Wallis testing was used for comparing 2 or more groups, respectively. Spearman correlation coefficients were used to express associations between parameters, and stepwise multiple linear regression to identify independent predictors of calcium score or IMT. Results
Coronary Artery Calcifications
Significant calcification of coronary arteries (calcium score >1) was noted in 34 of 37 patients (92%). Compared with healthy control subjects, median calcium scores exceeded the age-specific 95th normal percentiles on average 10-fold in male and 17-fold in female patients (Figures 2 and 3). According to the guidelines on interpretation of calcium scores proposed by Rumberger et al.9 lesions were minimal (score <10) in 1, mild (11 to 100) in 19, moderate (101 to 400) in 12, and severe and with high probability stenosing (>400) in 2 subjects. Calcium scores were higher in patients with manifest cardiovascular disease (median, 226; iqr, 205 to 293) than in asymptomatic patients (median, 44, iqr, 22 to 91; P < 0.0005). Calcifications of cardiac valves and aorta were observed in 12 (34%) and 11 (32%) patients, respectively.

Coronary calcifications were more marked in patients presently treated by dialysis (median, 156; iqr, 46 to 226) than in transplant recipients (median, 60; iqr, 23 to 103; P = 0.06). Moderate or severe lesions were more frequently observed in dialyzed (7 of 12; 58%) than in posttransplanta-
ion (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 R²=0.50, P=0.0001), mean plasma intact-PTH (partial R²=0.15, P=0.0006), cumulative serum calcium-phosphate product (partial R²=0.07, P=0.01), and plasma homocysteine levels (partial R²=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
(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=0.31, 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 $R^2=0.13$, $P=0.02$), age (partial $R^2=0.07$, $P=0.01$), *C pneumoniae* seropositivity (partial $R^2=0.05$, $P=0.03$), and plasma C-peptide (partial $R^2=0.05$, $P=0.05$) contributed independently to the variance of IMT. In the healthy control subjects, HbA1c ($R^2=0.19$, $P=0.007$) and smoking ($R^2=0.14$, $P=0.01$) were independent predictors of IMT. When only the patients were considered, cumulative serum calcium levels (partial $R^2=0.25$, $P=0.002$) and the total duration of dialysis (partial $R^2=0.10$, $P=0.03$) 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 that IMT is associated with *C pneumoniae* seropositivity.

**Table 2. Spearman Correlation Analysis of Coronary Calcification and Carotid IMT in Young Adult ESRD Patients With Childhood-Onset CRF**

<table>
<thead>
<tr>
<th></th>
<th>Calcium Score</th>
<th>IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.25</td>
<td>0.45*</td>
</tr>
<tr>
<td>ESRD duration</td>
<td>0.53†</td>
<td>0.32†</td>
</tr>
<tr>
<td>Cumulative time undergoing dialysis</td>
<td>0.33‡</td>
<td>0.37‡</td>
</tr>
<tr>
<td>Time-integrated mean plasma intact-PTH</td>
<td>0.60§</td>
<td>0.13</td>
</tr>
<tr>
<td>Cumulative serum calcium</td>
<td>0.38‡</td>
<td>0.47*</td>
</tr>
<tr>
<td>Cumulative serum phosphate</td>
<td>0.31</td>
<td>0.40†</td>
</tr>
<tr>
<td>Cumulative serum calcium-phosphate product</td>
<td>0.36‡</td>
<td>0.50*</td>
</tr>
<tr>
<td>CRP</td>
<td>0.62§</td>
<td>0.03</td>
</tr>
<tr>
<td>Plasma homocysteine</td>
<td>0.35‡</td>
<td>0.18</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.

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

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**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).
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 period. Our findings are consistent with previous reports and suggest that the calcification process is accelerated in ESRD patients undergoing dialysis but is also present in transplant recipients. Cardiac calcifications may rapidly progress in patients undergoing extended dialysis. Assuming that the lesions attained during dialysis are 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 amorphous 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. 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.

The effects of these risk factors persist in part even after successful renal transplantation. 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 product. Homocysteine is elevated in CRF and remains increased after kidney transplantation. Homocysteine predicts cardiovascular mortality in ESRD and morbidity after transplantation.

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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