Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease

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Abstract

This observational study was designed to verify the hypothesis that the treatment modality significantly affects the evolution of CKD-associated arteriopathy.

Patients. Paediatric patients (mean age 13.8 ± 4.2 years) with chronic kidney disease (CKD) stages 3–5, including 24 patients with mean GFR 54 ± 21 ml/min/1.73 m² (CKD group) and 32 patients in end-stage renal disease, of whom 19 received a renal allograft (D-Rtx) and 13 remained on dialysis (D-D).

Methods. Sonography of the common carotid artery was performed at baseline and after 12 months. Intima-media thickness (IMT) and the cross-sectional areas of the vessel wall (WCSA) and lumen (LCSA) were measured and normalized to age (SDS).

Results. At baseline IMT-SDS and WCSA-SDS were increased above normal, and were significantly higher in D than in CKD patients (P < 0.001). IMT-SDS increased over time in CKD and D-D patients (1.4 ± 1.7 to 2.1 ± 1.2, P = 0.05). In contrast, IMT-SDS (2.8 ± 0.6 to 2.0 ± 0.6, P < 0.005) decreased in those D-Rtx patients who had elevated values prior to transplantation. The total number of patients with elevated cIMT-SDS changed from 7 to 13 in the 24 CKD, from 8 to 11 in the 13 D-D and from 11 to 12 in the 19 D-Rtx patients. While IMT-SDS was independently correlated with blood pressure and serum phosphate in the CKD and D patients, only total dialysis vintage (r = 0.50; P < 0.05) and the IMT-SDS attained at the time of grafting (r = 0.46, P < 0.05) correlated with IMT-SDS 1 year post-Rtx.

Conclusion. While vascular lesions rapidly progress in CKD and D patients, abolition of the uraemic state by Rtx leads to stabilization or partial regression of CKD-associated arteriopathy. Cumulative dialysis duration and the degree of arterial damage prevalent at the time of grafting are the main determinants of persistent arteriopathy 1 year after Rtx.

Keywords: atherosclerosis; chronic kidney disease; hypertension; paediatrics; risk factors

Cardiovascular complications are one of the leading causes of long-term morbidity and mortality in patients with chronic kidney disease (CKD) [1–5]. Progressive renal dysfunction is associated with multiple biochemical and haemodynamic alterations that profoundly affect the cardiovascular system. CKD patients typically develop a calcifying arteriopathy affecting both the intima and the tunica media of large arteries [6–8]. Population-based studies have suggested that cardiovascular risk is increased significantly even with mild impairment of kidney function, and becomes excessive as renal failure progresses. Patients undergoing renal transplantation (Rtx) have a significantly better long-term survival than subjects remaining on dialysis. So far, a few uncontrolled studies have suggested that good graft function is associated with improved blood pressure control and decreases in left ventricular mass and carotid intima-media thickness (IMT) [9,10].

The paediatric age group is uniquely suited for the study of cardiovascular abnormalities in CKD since confounding comorbidities such as diabetes mellitus and age-related atherosclerosis are largely absent. Registry analyses have suggested that children with CKD are at high risk for cardiac and arterial disease, and that cardiovascular disease is a leading cause of death in this age group. In a recent cross-sectional study in children we noted an elevation of IMT as early as in stage 2 CKD, an inverse correlation of IMT with GFR, most marked carotid artery thickening in children on maintenance dialysis, and significantly lower IMT in renal allograft recipients [11]. Based on these observations we hypothesized that successful Rtx, by improving some of the metabolic alterations associated with uraemia, may permit regression of arteriopathic changes. In order to test this hypothesis we performed a longitudinal observational study in children with CKD and in dialyzed

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patients who either continued this treatment or received a renal allograft.

Methods

Patients

Fifty-six children with CKD stages 2–5 in Warsaw and Heidelberg were included in the trial. Of these, 24 patients (14 boys) aged 12.8 ± 4 years with mean initial GFR 55 ± 25 ml/min/1.73 m² were treated conservatively throughout the period of observation (CKD group). Of 31 patients who were on maintenance dialysis (haemodialysis in 15, CPD in 16) at the start of follow-up, 18 patients (7 boys) received a kidney allograft and one patient with CKD had preemptive kidney transplantation (D-Rtx group). Thirteen patients (11 boys) remained on dialysis (D-D group). Three patients in the D-D group were >20 years of age. The duration of CKD was defined as the time from the first detection of GFR <80 ml/min/1.73 m² calculated from Schwartz formula (Table 1). Exclusion criteria from the study included any clinically overt inflammatory disease at the time of screening, clinically significant over- or dehydration, acute rejection or rapidly progressive chronic allograft nephropathy at the time of second examination, presence of venous dialysis catheters near the site of ultrasonographic evaluation, and any clinically significant severe comorbidity such as diabetes, cardiac, metabolic or inflammatory systemic disease. Renal allograft recipients received standard triple immunosuppression using cyclosporine or tacrolimus (n = 2), mycophenolate mofetil and prednisone.

The study was approved by the local Ethical Committees in Warsaw and Heidelberg. A written informed consent was obtained from the parents and consent or verbal assent from the patients as appropriate.

Study protocol

The study design was prospective and observational. All measurements and biochemical analyses were performed at baseline (time point 0) and then after a mean time of 12.0 ± 4.4 months. In patients on haemodialysis, sonography was performed after the dialysis session on the midweek day. In the D-Rtx group a baseline measurement was performed on the day of renal transplantation. Blood samples were collected during routine visits on the day of sonographic assessment. Parathormone (PTH) concentrations were measured with the ELISA method (Diagnostic System Laboratories, Webster, TX, USA) (normal range: 12–62 pg/ml).

Sonographic measurements

The methodology of sonographic measurements was described previously [11]. All measurements were performed by the same observer in each centre (ML in Warsaw, CJ in Heidelberg). High-resolution ultrasound [Acuson Sequoia (Acuson Inc., Mountain View, CA, USA) or Philips ATL 5000 HDI (Royal Philips Electronics, The Netherlands)] using a linear array transducer adjusted to 12.5–13 MHz was performed with subjects in supine position with slightly overextended neck, following at least 10 min rest. Blood pressure was measured before starting the examination and again on the ipsilateral arm during M-mode examination of each common carotid artery.

B-mode measurements were performed on both common carotid arteries. The carotid arteries were assessed 1–2 cm proximal to the bifurcation over a range of 1 cm of the far wall. IMT was defined as the distance between the leading edges of the lumen–intima interface and the media–adventitia interface of the far wall. The scans with the far-wall image were frozen at diastole.

For the M-mode measurement, a B-mode image was used to direct the M-mode ultrasound beam perpendicular to the walls of the CCA segment with the same adjustments and transducer positions. Wall motion was recorded for five consecutive heartbeats. The freezing point was chosen so that all the structures of interest, the near-wall intima–lumen interfaces and the far-wall lumen–intima interfaces were clearly visible. The lumen diameters were measured for systolic and diastolic pulse phases. All B- and M-mode images were saved in digital form and analysed off-line by one investigator in each centre who was fully unaware of the health status of each subject (PR in Warsaw and CJ in Heidelberg). Only images accepted as of good quality were taken to further analysis.

For every variable at least five to six measurements were taken from each arterial scan. The results were averaged for each side and presented as the mean value of both arteries.

The reproducibility of sonographic measurements was calculated from repeated measurements of 10 subjects by the two observers and expressed by the repeatability coefficient: $RC = \Sigma D_i/n$, where $D_i$ is the difference between each pair of measurements and $n$ is the number of examined subjects [12]. The intra-observer RC for IMT was 4.5 µm, for systolic diameter 276 µm and for diastolic diameter 277 µm. The inter-observer RC was 2 µm for IMT, 370 µm for systolic and 119 µm for diastolic diameter. This level of reproducibility compares favourably with previous studies [12–14].

Calculations

Lumen cross-sectional area (LCSA) and wall cross-sectional area (WCSA) were calculated from values of diastolic and systolic diameters of artery and blood pressure according to previously published equations [12–14].

The following parameters were calculated:

Mean systolic diameter ($sD$) = $L_{sd} + R_{sd})/2$, where $L_{sd}$ is left and $R_{sd}$ right CCA systolic diameter.

Mean diastolic diameter ($dD$) = $R_{dd} + L_{dd})/2$, where $L_{dd}$ is left and $R_{dd}$ right CCA diastolic diameter.

Mean lumen cross-sectional area of the artery (LCSA) = $\pi (dD/2)^2/4$

Mean wall cross-sectional area (WCSA) = $\pi (dD/2 + IMT)^2 - \pi (dD/2)^2$

Statistics

Since carotid artery dimensions and blood pressure change with age during childhood and adolescence [15,16], the
sonographic and blood pressure measurements were normalized to standard deviation scores (SDS) for within- and between-group comparisons and correlation analysis. SDS were calculated using the LMS method of Cole and Green to account for the non-Gaussian distribution of the variables in the general population [17]. Recently published reference values from 250 healthy Polish and German school children and adolescents were used for comparison [15]. For the three patients who were <20 years of age (20, 21 and 23, respectively), IMT was normalized to values observed in 20-year-old healthy adolescents.

Results are expressed as mean and standard deviation (SD) when parameters showed Gaussian distribution. In the case of non-normal distribution, results are presented as median and interquartile range (i.e. PTH concentrations).

Homogeneity of variance was checked with the Levene test. Between-group comparisons of parameters with Gaussian distribution were performed by ANOVA followed by Student’s Newman Keuls testing. Parameters with non-normal distribution were compared using the Mann–Whitney U-test. Student’s paired t-testing was used to perform intragroup longitudinal comparisons. Spearman correlation coefficients were used throughout to express associations between variables.

Stepwise multiple regression analysis was performed to assess predictors of standardized IMT. *P < 0.05 was regarded as significant.

Statement of responsibility
The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient characteristics
The baseline and follow-up patient characteristics are given in Tables 1 and 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD n = 24</th>
<th>D-D n = 13</th>
<th>D-Rtx n = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>12.8 ± 3.9</td>
<td>16.5 ± 4.2*</td>
<td>13.2 ± 4</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td><strong>Duration of CKD (years)</strong></td>
<td>7 ± 5.2</td>
<td>6.6 ± 4.7</td>
<td>6.3 ± 4</td>
</tr>
<tr>
<td><strong>Duration of dialysis (months)</strong></td>
<td>39 ± 33</td>
<td>35 ± 25</td>
<td></td>
</tr>
<tr>
<td><strong>Underlying renal disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal hypoplasia/reflux nephropathy</td>
<td>12</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nephropathisis</td>
<td>1</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Other and unknown</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Significant difference between D-D and other groups, *P < 0.05.

Table 2. Comparison of blood pressure and biochemical characteristics in the three cohorts at baseline (upper rows) and follow-up examination (lower rows)

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD</th>
<th>D-D</th>
<th>D-Rtx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>113 ± 13ab</td>
<td>121 ± 18a</td>
<td>126 ± 16b</td>
</tr>
<tr>
<td><strong>Systolic BP SDS</strong></td>
<td>–0.1 ± 1.0ab</td>
<td>1.4 ± 2.0a</td>
<td>2.5 ± 2.2b</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>57 ± 9abc</td>
<td>71 ± 11a</td>
<td>71 ± 15b</td>
</tr>
<tr>
<td><strong>Diastolic BP SDS</strong></td>
<td>–0.6 ± 1.0ab</td>
<td>1.4 ± 1.5a</td>
<td>1.6 ± 2.3b</td>
</tr>
<tr>
<td><strong>No. of antihypertensive drugs</strong></td>
<td>1.4 ± 1.0</td>
<td>0.4 ± 0.6</td>
<td>1.8 ± 1.4a</td>
</tr>
<tr>
<td><strong>GFR (ml/min/1.73m²)</strong></td>
<td>1.7 ± 1.0c</td>
<td>0.7 ± 0.5</td>
<td>0.5 ± 0.5ac</td>
</tr>
<tr>
<td><strong>Ca (mmol/l)</strong></td>
<td>2.40 ± 0.10</td>
<td>2.40 ± 0.13</td>
<td>2.36 ± 0.19</td>
</tr>
<tr>
<td><strong>P (mmol/l)</strong></td>
<td>1.39 ± 0.33</td>
<td>1.73 ± 0.24</td>
<td>1.88 ± 0.63b</td>
</tr>
<tr>
<td><strong>PTH (pg/ml)</strong></td>
<td>37 (26–123)</td>
<td>14 (4–72)</td>
<td>174 (45–639bc)</td>
</tr>
<tr>
<td><strong>HsCRP (mg/l)</strong></td>
<td>2.0 ± 0.7</td>
<td>2.2 ± 0.7</td>
<td>0.9 ± 0.8</td>
</tr>
<tr>
<td><strong>Cholesterol (mg/l)</strong></td>
<td>175 ± 42b</td>
<td>191 ± 35</td>
<td>234 ± 62b</td>
</tr>
</tbody>
</table>

*Significant change from baseline within a group. Superscript letters denote differences (*P < 0.05) between groups within a row (*CKD versus D-D, #CKD versus D-Rtx, *D-D versus D-Rtx). The values are mean and SD for all parameters except PTH, which is expressed by median and range.

Carotid artery measures
At baseline, dialyzed patients exhibited significantly greater measures than CKD patients for IMT-SDS (2.2 ± 1.4 versus 1 ± 1.5) (Table 2, Figure 1), WCSA-SDS (2.6 ± 1.6 versus 0.7 ± 1.5) and LCSA-SDS (1.3 ± 1.3 versus –0.3 ± 1) (all *P = 0.001). Overall, IMT-SDS was above normal in 7 of 24 CKD patients, 8 of 13 D-D patients and 13 of 19 D-Rtx patients. In the patients who remained in CKD or on dialysis during follow-up, an increase of IMT-SDS (1.4 ± 1.7 to 2.1 ± 1.2, *P = 0.05) and WCSA-SDS (1.1 ± 1.6 to 1.7 ± 1.3, *P = 0.09) was observed over time. cIMT decreased in 4 CKD, 5 D-D patients and 11 D-Rtx patients.
Evolution of carotid IMT in children with CKD and ESRD

**Fig. 1.** Evolution of IMT-SDS between first and second observation in the three cohorts. Shaded area denotes normal range, with SDS −1.64, 0 and 1.64 corresponding to 5th, 50th and 95th percentile.

**Table 3.** Comparison of sonographic carotid artery measures in the three cohorts at baseline (upper rows) and follow-up examination (lower rows).

<table>
<thead>
<tr>
<th></th>
<th>CKD</th>
<th>D-D</th>
<th>D-Rtx</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (mm)</td>
<td>0.44 ± 0.06&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>0.50 ± 0.10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.50 ± 0.05&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IMT-SDS</td>
<td>1.0 ± 1.5&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>2.2 ± 1.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.3 ± 1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>WCSA (mm²)</td>
<td>7.2 ± 1.5&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>9.5 ± 2.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.4 ± 1.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>WCSA-SDS</td>
<td>1.2 ± 3.2&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>3.1 ± 2.7&lt;sup&gt;ac&lt;/sup&gt;</td>
<td>3.0 ± 1.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>LCSA (mm²)</td>
<td>18.2 ± 3.7&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>24.1 ± 5.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25.2 ± 6.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>LCSA-SDS</td>
<td>0.2 ± 1.0&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>1.1 ± 1.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4 ± 1.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Significant change from baseline within a group, P < 0.05.

Superscript letters denote differences (P < 0.05) between groups within a row (<sup>a</sup>CKD versus D-D, <sup>b</sup>CKD versus D-Rtx, <sup>c</sup>D-D versus D-Rtx). Numbers are mean ± SD.

At follow-up, 13 of 24 CKD patients, 11 of 13 D-D patients and 12 of 19 D-Rtx patients had cIMT values still above normal. The clinical characteristics of these patients (blood pressure, time in CKD, dialysis vintage, biochemical variables) did not differ from those of the other patients in the respective groups.

In contrast, in the D-Tx patients IMT-SDS decreased significantly (P = 0.019) (Table 3). In the patients with elevated IMT-SDS (>1.64) at baseline, both IMT-SDS (2.8 ± 0.6 to 2.0 ± 0.6, P < 0.005) and WCSA-SDS (3.5 ± 1.3 to 2.5 ± 1.3, P = 0.05) decreased significantly.

**Univariate and multivariate predictors of IMT**

The results of the univariate correlation analysis are summarized in Table 4. At baseline, IMT-SDS was inversely correlated in the total cohort with GFR and positively with systolic and diastolic BP-SDS (Figure 2), serum phosphate, LDL cholesterol and uric acid levels. In the patients who remained with renal failure (CKD or D) during the observation period, persistent correlations with GFR, serum phosphate and blood pressure were noted and in D-D patients also with dialysis vintage. In the 19 D-Tx patients, only dialysis vintage was significantly associated with IMT-SDS both at first and at second examination after transplantation. The total time spent on dialysis and the IMT-SDS attained prior to transplantation (r = 0.46, P < 0.01) were the only significant correlates of IMT-SDS at follow-up.

Stepwise multiple linear regression analysis disclosed that the mean IMT-SDS in the CKD/D-D patients was independently predicted by the mean systolic BP-SDS (β: 0.26, partial R²: 0.13, P < 0.05) and, with borderline significance, mean serum phosphate levels (β: 0.84, partial R²: 0.06, P = 0.13). In the D-Tx group, no variables other than the IMT-SDS attained at the end of the dialysis period were identified as additional independent predictors of IMT-SDS.

**Discussion**

This study provides evidence that successful renal transplantation may induce partial regression of the large-vessel arteriopathy associated with uraemia in children and adolescents within 1 year of follow-up. In contrast, continued
renal failure is associated with measurable progression of vascular lesions.

Sonographic IMT measurement is an accepted quantitative measure of atherosclerosis and vascular damage [18]. In adult dialysis patients the sonographic IMT status is an excellent prognostic marker that can be used for cardiovascular risk stratification [19]. Increased IMT has been reported in young adults with childhood-onset end-stage renal disease [20] and, more recently, in children with different stages of CKD. In cross-sectional comparisons [11,21] carotid IMT was most markedly elevated in children on dialysis, but was increased also in renal allograft recipients and even in children with stage 2–4 CKD [11]. The baseline assessment of the children followed in this study confirms that while the vascular pathology including the cross-sectional areas of the carotid wall and lumen is most marked and even in children with stage 2–4 CKD [11]. The base- line assessment of the children followed in this study confirms that while the vascular pathology including the cross-sectional areas of the carotid wall and lumen is most marked and even in children with stage 2–4 CKD [11]. The base- line assessment of the children followed in this study confirms that while the vascular pathology including the cross-sectional areas of the carotid wall and lumen is most marked and even in children with stage 2–4 CKD [11]. The base- line assessment of the children followed in this study confirms that while the vascular pathology including the cross-sectional areas of the carotid wall and lumen is most marked and even in children with stage 2–4 CKD [11]. The base- line assessment of the children followed in this study confirms that while the vascular pathology including the cross-sectional areas of the carotid wall and lumen is most marked and even in children with stage 2–4 CKD [11]. The base- line assessment of the children followed in this study confirms that while the vascular pathology including the cross-sectional areas of the carotid wall and lumen is most marked and even in children with stage 2–4 CKD [11].

The observed partial regression provides prospective confirmatory evidence to the impression from cross-sectional studies that, at least in some children and adolescents, arteriopathy is partially reversible by removal of the uraemic state. In contrast, in a single uncontrolled study performed in adult patients, significant regression of IMT did not occur before the third post-transplant year despite regression of left ventricular mass within 12 months [9]. Similarly, Zougias et al. did not observe a significant change in carotid IMT within 12 months after Rtx, although the elastic properties of the large arteries improved markedly [24]. The apparently more rapid reversal of the morphological changes observed here may be related to the shorter exposure of paediatric patients to conventional and uraemia-specific vascular risk factors, or indicate a better efficiency of repair mechanisms in children. Also, the D-Tx patients attained an almost normal GFR and were exposed relatively shortly to potentially vasculopathic effects of immunosuppressive drugs, hypertension and infections that may interfere with vascular recovery after transplantation. Finally, we cannot entirely exclude that the apparent decrease of IMT in the D-Rtx group was partially biased by a random regression to the mean phenomenon in this longitudinal study. However, such an effect was not seen in the other experimental groups.

It is difficult to assess the removal of which uraemic abnormality was most relevant to the regression of arteriopathy. Renal transplantation was associated with a slight decrease in blood pressure levels, at a substantially reduced need for antihypertensive medication. Also, hyperphosphataemia and the serum calcium–phosphorus ion product...
were normalized. However, such associations do not prove causality. Isbel et al. recently found that aggressive and targeted treatment of cardiovascular risk factors in adults with CKD stage 4–5, despite decreasing blood pressure and LDL-cholesterol, did not lead to a decrease of carotid IMT or cardiovascular events [25]. Moreover, none of the haemodynamic and metabolic parameters at the time of transplantation was predictive of IMT-SDS 1 year later. Only the IMT level attained at the time of grafting and the total duration of dialysis correlated with the later IMT score, compatible with the notion that the vascular damage caused by end-stage renal failure is multifactorial, time-sensitive and only partly reversible.

The relatively small number of patients studied limits to some degree the conclusions that can be drawn from this work. Another potential limitation is the wide age range studied, which increased sample heterogeneity by inclusion of variable age specific vascular risk factors, such as treatment non-adherence and tobacco smoking in the adolescent population. On the other hand, these factors should not affect the main conclusions obtained by intraindividual longitudinal comparison.

In summary, this longitudinal assessment of IMT changes over time in paediatric CKD patients provides substantial evidence that progressive vascular lesions occur even in children with moderate renal disease, and are in part reversible after successful renal transplantation. Our findings permit the conclusion that extended periods of dialysis should be avoided, and kidney transplantation performed as soon as possible in paediatric CKD patients in order to minimize the exposure to vasculopathogenic factors and improve the long-term cardiovascular prognosis of this patient population.

Acknowledgements. This study was supported by EU grant QLGI-CT-2002-00908, the Boehringer Ingelheim Stiftung and the Kuratorium für Dialyse und Nierentransplantation.

Conflict of interest statement. None declared.

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Received for publication: 16.4.07
Accepted in revised form: 29.1.08