Altered Morphologic Properties of Large Arteries in Children with Chronic Renal Failure and after Renal Transplantation

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Increased intima-media thickness of the carotid arteries (cIMT) has been found in young adults with childhood-onset chronic kidney disease (CKD). The disease stage at which these patients first develop abnormalities of arterial texture is unknown. The objective of this study was to determine the onset and character of arterial changes in children aged 10 to 20 yr with different stages of CKD and to identify risk factors for early arteriopathy. High-resolution ultrasonography was conducted of common cIMT and femoral superficial artery IMT. Fifty-five children with stages 2 to 4 CKD (GFR 51 ± 31 ml/min per 1.73 m^2), 37 on dialysis, and 34 after renal transplantation (Rtx; GFR 73 ± 31 ml/min per 1.73 m^2) were studied. Control subjects were 270 healthy children, matched for age and gender. Compared with control subjects, cIMT, femoral superficial artery IMT (both as absolute values and as SD score of median of normal value), wall cross-sectional area, and lumen cross-sectional area of carotid artery were significantly increased in all patient groups and most markedly abnormal in dialysis patients. cIMT in CKD and Rtx patients was significantly lower in comparison with dialysis patients. cIMT correlated with mean past serum Ca × P product, the cumulative dose of calcium-based phosphate binders, and the time-averaged mean calcitriol dose. The cumulative phosphate binder intake, time-averaged Ca × P product, and young age were independent predictors of an increased cIMT. In children with CKD, thickening of IMT occurs early in the course of disease and is most marked in dialyzed patients. The changes may be partly reversible after Rtx.

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Cardiovascular complications are the dominant cause of the excessive mortality observed among patients with chronic kidney disease (CKD) and particularly in ESRD (1,2). Cardiovascular morbidity and even mortality seems to be prevalent also among children and adolescents with ESRD, despite much lower exposure to "classical" risk factors for atherosclerosis, such as diabetes, smoking, and hyperlipidemia (3–6).

Increased intima-media thickness (IMT) of the large arteries is considered an early marker of athero-arteriosclerosis and a sensitive predictor of cardiovascular events both in the general population and in adult dialysis patients (7–9). Increased carotid IMT (cIMT) has been demonstrated in children who are considered at risk for cardiovascular disease as a result of hypertension, obesity, and hyperlipidemia (10–17). Increased IMT that develops in the course of CKD is associated with stiffening of the large arteries, an abnormality that is related directly to an increased load to the left ventricle and impaired peripheral blood flow (18).

Although thickening of IMT and/or stiffening of carotid arteries has been reported in young adults with childhood-onset ESRD (19,20) and children after renal transplantation (Rtx) (21), it is not known when in the course of CKD abnormalities of arterial texture first occur. In this study, we assessed large-artery morphology in a large patient population of children and adolescents with different degrees of CKD and treatment modalities. Results were compared with a control group matched for age, gender, and body composition.

Materials and Methods

Patients

Patients were recruited in two pediatric nephrology centers in Warsaw, Poland, and Heidelberg, Germany. Overall, 126 children (82 from Warsaw and 44 from Heidelberg), aged 10 to 20 yr, with different stages of CKD and treatment modality were included in the study. Underlying diseases were renal hypo/dysplasia ($n = 18$), obstructive nephropathy ($n = 21$), reflux nephropathy ($n = 19$), neurogenic bladder ($n = 15$), hereditary nephropathies ($n = 7$), glomerulonephritis ($n = 18$), and hemolytic uremic syndrome ($n = 10$). In 18 children, underlying primary renal disease was unexplained. Among dialyzed patients, 19 were on hemodialysis and 18 were on automated peritoneal dialysis. No one from transplanted patients had preemptive kidney transplantation performed.

Exclusion criteria from the study were any clinically overt inflam-

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matory disease at the time of investigation, clinically significant overhydration or dehydration, acute graft rejection, presence of large intravenous catheters near the site of ultrasonographic evaluation, and any clinically severe condition.

The control group consisted of 270 healthy normotensive children and adolescents who were recruited voluntarily from local schools and among hospital staff in Heidelberg and Warsaw (22). The distribution of age, gender, and body composition was identical in the two local subgroups.

Informed consent of the parents and study participants was obtained in all cases. The study has approval of local Ethical Committees.

The study included a detailed workup of the biochemical status and cardiovascular risk profile (Table 1). GFR was estimated in all patients and 70 healthy control subjects according to the Schwartz formula. Plasma homocysteine and lipid levels were available in 83 patients and 70 control subjects. In 45 patients (15 on dialysis and 30 with predialysis CKD), all files since start of CKD (defined by the date of diagnosis of CKD stage 2) were reviewed to assess the individual cumulative exposure to assumed CKD-specific cardiovascular risk factors. Serum calcium; phosphate and intact parathyroid hormone concentrations (Nichols assay); BP (predialytic values in hemodialyzed patients); and phosphate binder, vitamin D, and antihypertensive medication were recorded at monthly intervals.

Sonographic Measurements

Ultrasonographic measurements were performed in all patients by the same examiner in each center (M.L. in Warsaw, C.J. in Heidelberg). High-resolution ultrasound (Acuson Sequoia, Acuson, Mountain View, CA; or Philips ATL 5000 HDI, Royal Philips Electronics, Amsterdam,

Table 1. Basic clinical, anthropometric, BP, and biochemical characteristics of patients and control subjects[a]

	Controls	CKD	Dialysis	Rtx
n	270	55	37	34
% male	49	59	59	49
Age (yr)	14.2 ± 2.6	15.3 ± 2.6	14.3 ± 3.0	15.0 ± 2.7
Height SDS	−0.11 ± 1.04[c,d,e]	−0.72 ± 1.18[b,d,e]	−2.76 ± 1.71[b,c,e]	−2.22 ± 1.47[b,c,d]
BMI SDS	0.40 ± 1.1[c,d,e]	−0.32 ± 1.33[b,d]	−0.6 ± 0.9[b,c]	−0.06 ± 1.19[b]
Time in predialytic CKD (mo)	—	86 ± 63	63 ± 43	67 ± 60
Cumulative time on dialysis (mo)	—	—	26 ± 32	22 ± 26
Time since transplant (mo)	—	—	—	33 ± 38
Systolic BP (mmHg)	113 ± 12[c,d,e]	120 ± 16[b,d]	129 ± 15[b,c]	125 ± 13[b]
Diastolic BP (mmHg)	59 ± 6[d,e]	61 ± 13[d,e]	71 ± 15[b,c,e]	67 ± 10[b,c,d]
No. of antihypertensive drugs	0[c,d,e]	1.6 ± 1.3[b]	1.4 ± 1.4[b]	1.4 ± 0.9[b]
Serum creatinine (mg/dl)	0.8 ± 0.1[c,d]	2.7 ± 2.4[b,d,e]	8.6 ± 2.0[b,c,e]	1.5 ± 0.9[c,d]
GFR (ml/min per 1.73 m²)	102 ± 7[c,d,e]	51 ± 31[b,d,e]	<10[b,c,e]	73 ± 31[b,c,d]
Triglycerides	69 ± 37[b,c,e]	139 ± 75[b,d,e]	178 ± 103[b,c]	188 ± 141[b,c]
Total cholesterol	170 ± 37[d,e]	179 ± 33[d,e]	211 ± 58[b,c]	204 ± 46[b,c]
LDL cholesterol	104 ± 32[d]	122 ± 38	145 ± 44[b,e]	112 ± 36[d]
HDL cholesterol	51 ± 12	47 ± 9	53 ± 14	56 ± 15
Apolipoprotein A	1.29 ± 0.23	1.26 ± 0.29	1.48 ± 0.31	1.53 ± 0.29
Apolipoprotein B	0.79 ± 0.25[d,e]	0.97 ± 0.26[d,e]	1.39 ± 0.52[b,c]	1.22 ± 0.42[b,c]
Homocysteine	11.1 ± 3.1	12.7 ± 3.0	14.3 ± 6.5	13.8 ± 6.5
CRP (pM)	ND	5.1 ± 9.1	2.1 ± 2.1	2.2 ± 2.7
Current albumin (g/L)	ND	42.5 ± 4.3	41 ± 2.1	42.9 ± 5.6
Time-integrated mean albumin (g/L)	—	42.6 ± 3.6	38.8 ± 3.4	41.2 ± 5.1
Current calcium (mM)	ND	2.36 ± 0.12	2.43 ± 0.19	2.38 ± 0.16
Current phosphate (mM)	ND	1.37 ± 0.29[d]	1.62 ± 0.52[c,e]	1.25 ± 0.31[d]
Current Ca × P product (mM)	ND	3.22 ± 0.67[d]	3.89 ± 1.17[c,e]	2.97 ± 0.72[d]
Current PTH (pM)	ND	9.9 ± 9.4[d]	27 ± 37[c,e]	12.8 ± 15.4[d]
Time-integrated mean Ca (mM)	—	2.31 ± 0.18	2.43 ± 0.19	2.38 ± 0.16
Time-integrated mean P (mM)	—	1.37 ± 0.29[d]	1.62 ± 0.52[c,e]	1.25 ± 0.31[d]
Time-integrated mean Ca × P (mM²)	—	3.65 ± 0.35[d]	4.3 ± 0.54[c,e]	3.69 ± 0.60[d]
Cumulative episodes of Ca × *P* >4.5 mM²	—	0.26 ± 0.57	0.84 ± 0.99	0.60 ± 0.78
Time-integrated mean PTH (mM)	—	19.6 ± 15.8[d]	38 ± 28[c,e]	21 ± 17[d]
Cumulative calcitriol intake (μg/kg)	—	36 ± 55[d]	242 ± 359[c,e]	88 ± 126[d]
Cumulative P binder intake (g/kg)	—	0.3 ± 0.8[d]	157 ± 189[c]	85 ± 112[c]

[a]Data are given as mean ± SD. Superscript letters denote statistical significant differences at 5% error level between groups: [b]significant difference from control group, [c]from CKD, [d]from dialysis and [e]from Rtx group.

CKD, chronic kidney disease; Rtx, renal transplantation; SDS, SD score; BMI, body mass index; CRP, C-reactive protein; PTH, parathyroid hormone; ND, not determined.

The Netherlands) using a linear array transducer adjusted to 12.5 to 13 MHz was performed with subjects in supine position with slightly overextended neck, after at least 10 min of rest. The IMT was measured with manual cursor placement technique. BP was measured before starting 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 and both superficial femoral arteries. 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 far wall image were frozen at diastole The carotid arteries were assessed 1 to 2 cm proximal to the bifurcation over a range of 1 cm of the far wall. Femoral IMT (fIMT) was measured at the upper to middle third of the thigh on both sides. The measured values from right and left artery were averaged, and the mean was taken to analysis. The lumen systolic and diastolic diameters of each carotid artery were measured in M-mode presentation over at least six cardiac cycles. The values from both sides (right and left carotid artery) were averaged and then taken to analysis.

The reproducibility of sonographic measurements was calculated from repeated measurements of 10 subjects by the two observers and expressed by the repeatability coefficient: $RC = \Sigma Di^2/n$, where Di is the difference between each pair of measurements and n is the number of examined subjects (11). The intraobserver RC for cIMT was 4.5 μm, for fIMT was 4.5 μm, for systolic diameter was 276 μm, and for diastolic diameter was 277 μm. The interobserver RC was 2 μm for cIMT, 5 μm for fIMT, 370 μm for systolic diameter, and 119 μm for diastolic diameter. This level of reproducibility compares favorably with previous studies (10–12).

All images were saved in digital form and analyzed off-line by one investigator in each center who was fully unaware of the health status of each subject (P.R. in Warsaw and K.F. in Heidelberg). Only images that were accepted as of good quality were taken to further analysis.

Calculations

Lumen cross-sectional area (LCSA) and wall cross-sectional area (WCSA) were calculated from values of diastolic and systolic diameters of artery and BP according previously published equations (10,11). The following parameters were calculated:

Mean systolic diameter (sD) = (LsD + RsD)/2, where LsD is left and RsD is right common carotid artery (CCA) systolic diameter

Mean diastolic diameter (dD) = (RdD + LdD)/2, where LdD is left and RdD right CCA diastolic diameter

$$\text{Mean LCSA} = \pi(\text{dD})^2/4$$

$$\text{Mean WCSA} = \pi(\text{dD}/2 + \text{IMT})^2 - \pi(\text{dD}/2)^2$$

Statistical Analyses

As the IMT are age- and gender-dependent variables (22,23), measured values were normalized to SD scores (SDS) for 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 (24). Respective L, M, and S reference tables derived from the healthy children also used as control subjects in this study have been published elsewhere (22).

Homogeneity of variance was checked with the Levene test. Between-group comparisons of parameters with Gaussian distribution were performed by ANOVA followed by Student-Newman-Keuls testing. Parameters with nonnormal distribution were compared using the Mann-Whitney U test. Spearman correlation coefficients were used throughout to express associations between variables. Variables that showed significant association in the univariate analysis were included in a stepwise multiple regression analysis to identify independent predictors of IMT.

Results

Basic anthropometric, biographical, and biochemical characteristics of the patient groups and the healthy control subjects are given in Table 1. Whereas the groups were comparable in terms of age and gender distribution, all patient groups were significantly smaller and lighter and had higher BP and fasting triglyceride levels than control subjects. Patients on dialysis and after renal transplantation had higher total cholesterol and apolipoprotein B levels, whereas LDL cholesterol was selectively increased in the dialysis group. Current and mean past serum phosphate, calcium-phosphate product, and parathyroid hormone levels as well as the cumulative doses of calcitriol and calcium-containing phosphate binders ingested since onset of disease were higher in the dialysis than in the CKD and post-Rtx groups, respectively.

A detailed morphologic analysis of the CCA and fIMT are given in Table 2. The IMT and the derived WCSA and LCSA of the CCA were significantly increased in each of the three patient groups compared with control subjects and more markedly elevated in the dialyzed compared with the CKD and post-Rtx patients. CCA IMT were equal to or exceeded the 95th percentile of normative value in 89% of the dialyzed (33 of 37 patients), 61% of the predialysis CKD patients (35 of 57), and in 75% (22 of 29) of the post-Rtx patients.

The ratio of WCSA/LCSA was significantly increased in CKD patients in comparison with control subjects ($P = 0.0001$) and patients after Rtx ($P = 0004$). Such relative increase in carotid wall thickness in comparison with Rtx patients was dependent mainly on increased LCSA in Rtx patients. When compared with control subjects, increased WCSA/LCSA ratio in children with CKD was due to increased WCSA in CKD patients. fIMT was also increased compared with control subjects, albeit less markedly than CCA IMT and significantly only in the CKD and dialysis groups. The subgroups of patients on hemodialysis *versus* peritoneal dialysis did not differ with respect to arterial morphology, age, and anthropometric and biochemical variables.

In the healthy control subjects, carotid IMT SDS was positively correlated with body mass index SDS ($r = 0.21$, $P < 0.001$) and pulse pressure ($r = 0.30$, $P < 0.0001$) and inversely with HDL ($r = -0.38$, $P = 0.08$) and apolipoprotein A (apoA) levels ($r = -0.50$, $P < 0.05$). In the patients, carotid IMT SDS was positively correlated with the mean past serum calcium-phosphorus ion product ($r = 0.32$, $P < 0.05$), the percentage of measurements where the Ca × P product exceeded 5.5 mM^2 ($r = 0.36$, $P = 0.01$), the cumulative dose of calcium-based phosphate binders ($r = 0.32$, $P < 0.05$; Figure 1), and the mean past calcitriol dose ($r = 0.28$, $P < 0.05$). The mean past serum albumin concentration was inversely correlated with carotid IMT SDS ($r = -0.32$, $P < 0.05$). Multiple stepwise regression

Table 2. Comparison of carotid and superficial femoral artery dimensions[a]

	Controls	CKD	Dialysis	Rtx
CCA IMT (mm)	$0.39 \pm 0.04^{c,d,e}$	$0.44 \pm 0.06^{b,d}$	$0.48 \pm 0.05^{b,c,e}$	$0.43 \pm 0.05^{b,d}$
SDS	$0.03 \pm 1.0^{c,d,e}$	$1.3 \pm 1.7^{b,d}$	$3.1 \pm 2^{b,c,e}$	$1.0 \pm 1.2^{b,d}$
CCA WCSA (mm^2)	$6.6 \pm 1^{c,d,e}$	$7.7 \pm 1.9^{b,d}$	$9.2 \pm 1.6^{b,c,e}$	$8.2 \pm 1.4^{b,d}$
SDS	$0.0 \pm 1.0^{c,d,e}$	$1. \pm 1.5^{b,d}$	$2.6 \pm 1.3^{b,c,e}$	$1.73 \pm 1.48^{b,d}$
Systolic CCA diameter (mm)	$5.9 \pm 0.5^{d,e}$	$6.0 \pm 0.6^{d,e}$	$6.5 \pm 0.8^{b,c}$	$6.4 \pm 0.9^{b,d}$
SDS	$0.0 \pm 1.0^{d,e}$	$0.18 \pm 1.20^{d,e}$	$1.17 \pm 1.28^{b,c}$	$0.90 \pm 1.61^{b,d}$
Diastolic CCA diameter (mm)	$4.9 \pm 0.5^{d,e}$	$5.1 \pm 0.5^{d,e}$	$5.7 \pm 0.7^{b,c}$	$5.5 \pm 0.8^{b,d}$
SDS	$0.01 \pm 1.0^{d,e}$	$0.36 \pm 1.16^{d,e}$	$1.52 \pm 1.49^{b,c}$	$1.16 \pm 1.78^{b,d}$
CCA LCSA (mm^2)	$19.2 \pm 3.7^{d,e}$	$20.4 \pm 5.2^{d,e}$	$25.4 \pm 6.9^{b,c}$	$25.4 \pm 7.0^{b,d}$
SDS	$0.01 \pm 1.0^{d,e}$	$0.36 \pm 1.16^{d,e}$	$1.52 \pm 1.49^{b,c}$	$1.16 \pm 1.78^{b,d}$
CCA WCSA/CCA LCSA	$0.35 \pm 0.05^{c,d}$	0.38 ± 0.05^{e}	0.37 ± 0.05	0.35 ± 0.04
Femoral artery IMT (mm)	$0.33 \pm 0.06^{c,d}$	0.36 ± 0.07^{b}	0.37 ± 0.05^{b}	0.35 ± 0.05
SDS	$0.06 \pm 1.1^{c,d}$	1.2 ± 2^{b}	$1.44 \pm 1.9^{b,e}$	0.7 ± 1.4^{d}

[a]Data are given as mean ± SD of both absolute values and SDS relative to healthy control subjects (see the Materials and Methods section). Superscript letters denote statistical significant differences at 5% error level between groups: [b]significant difference from control group, [c]from CKD, [d]from dialysis, and [e]from Rtx group.

CCA, common carotid artery; IMT, intima-media thickness; WCSA, wall cross-sectional area; LCSA, luminal cross-sectional area.

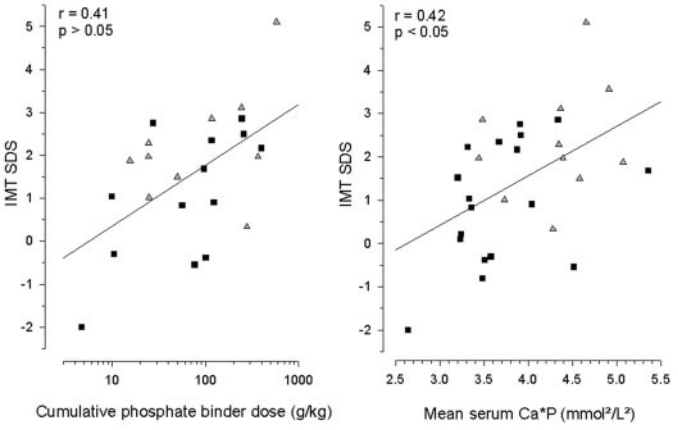

Figure 1. Correlation of carotid intima-media thickness (cIMT), normalized to SD score (SDS), with lifetime cumulative phosphate binder dose (in g/kg; left) and time-averaged mean serum calcium-phosphorus ion product (right). △, patients on dialysis treatment; ■, patients with a functioning renal allograft at time of examination.

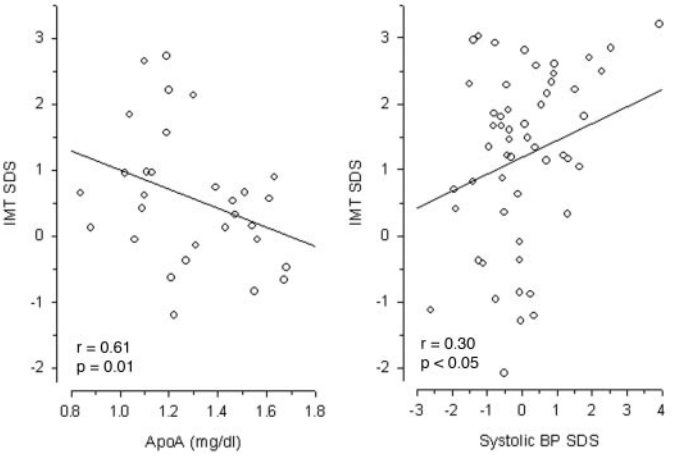

Figure 2. Correlation of cIMT, normalized to SDS, with serum apolipoprotein A levels (left) and systolic BP SDS (right) in children with stages 2 to 4 chronic kidney disease.

analysis identified the cumulative phosphate binder intake (part.R^2 = 0.21), the mean past calcium-phosphorus product (part.R^2 = 0.06), and young age (part.R^2 = 0.05) as significant independent predictors, together explaining 32% of the total variation of carotid IMT SDS.

When only CKD patients were considered, apoA ($r = -0.61$, $P < 0.01$), apoB ($r = -0.57$, $P < 0.05$), HDL ($r = -0.47$, $P = 0.06$), systolic BP ($r = 0.30$, $P < 0.05$; Figure 2), and current and mean past C-reactive protein levels ($r = 0.61$ and 0.70, both $P < 0.05$) but not the level of renal function, disease duration, or parameters of mineral metabolism showed associations with carotid IMT. In the post-Rtx patients, cIMT was correlated with the cumulative glucocorticoid dose ($r = 0.54$, $P < 0.05$) and the cumulative previous phosphate binder dose ($r = 0.44$, $P = 0.06$). The latter emerged as the only significant independent predictor of cIMT in multiple regression analysis.

Apart from the observed changes in arterial wall thickness, the luminal diameter and LCSA of the carotid artery were significantly increased in the dialyzed and the post-Rtx groups (Table 2). The standardized diastolic luminal diameter was significantly correlated with BP ($r = 0.36$, $P < 0.05$), cumulative phosphate binder intake ($r = 0.38$, $P < 0.05$), and cumulative glucocorticoid intake ($r = 0.36$, $P < 0.05$).

Discussion

This controlled study was designed to assess the morphology of the large arteries in children and adolescents with different

stages of CKD. Our key finding is a significant increase of IMT in both elastic- and muscular-type arteries and the possibility of at least partial reversal of arterial wall thickening after Rtx. Although abnormalities were detected even in mild to moderate renal failure, arterial thickening was most marked in dialyzed children. Post-Rtx patients had less marked arterial pathology than dialysis patients despite similar dialysis vintage, suggesting partial reversibility of the CKD-associated arteriopathy in children.

Several measures were taken to ascertain optimal methodologic quality in this two-center pediatric imaging study. These included a standardized procedural protocol used in both centers, careful common training of the two sonographers involved resulting in excellent intra- and interobserver reproducibility ratings, and off-line evaluation of the scans and measurements by a third investigator who was blinded with respect to the health status of the imaged subjects. The physiologic changes of arterial dimensions during childhood and related to gender (22–26) were accounted for by calculation of age-independent SDS on the basis of normative data calculated from the healthy control subjects (22). A modified method of SDS calculation was used (LMS method) (23) to eliminate any bias from the non-Gaussian distribution of the parameters under study. Finally, the acquisition of a matched control group that lived in the same area and was examined by the same observers as the patients helped to minimize any source of non–disease-related variability.

Our study provides clear evidence that CKD is associated with morphologic alterations of both muscular- and elastic-type arteries as early as in the second decade of life. The degree of pathology depends on the degree of renal dysfunction and is most marked in patients on dialysis, but even 61% of children with stages 2 to 4 CKD had cIMT equal to or exceeding the 95th percentile for age.

Our IMT findings in dialyzed patients are in agreement with two small-sized published studies in children (21,27) and with a previous assessment of young adults with childhood-onset CKD in one of our institutions (19), whereas a Dutch multicenter study in young adult survivors of pediatric ESRD found normal cIMT (but because of older age of their patients, absolute values of IMT were higher than in our patients) despite significant arterial stiffening (20). The difference between our findings and those of Groothoff *et al.* (20) in a population on average 15 yr older than our patients may be explained by a survivor effect; many of the patients with most severe vascular pathology in adolescence may have had already died at the time of the follow-up examination at young adult age.

In Rtx recipients, IMT were less markedly increased than in the patients on dialysis, although dialysis and post-Rtx patients had spent similar cumulative times in predialytic CKD and on dialysis. Although definite conclusions cannot be drawn from a cross-sectional comparison of treatment modalities, our observation is compatible with the notion that the severe arteriopathy associated with CKD may be partially reversible after correction of the metabolic and hemodynamic alterations of uremia by successful Rtx. Indeed, de Lima *et al.* (28) noted a significant decrease of carotid IMT during 3 yr of follow-up in 22 adult allograft recipients. Suwelack *et al.* (29) observed that a post-Rtx decrease of cIMT in adults was correlated with lower BP and normoglycemia. Notably, despite lower values of cIMT, the diameter and area of the carotid lumen were increased in the post-Rtx patients to the same degree as in the dialysis patients and significantly greater than in the predialysis CKD group. Hence, global arterial dilation may be less reversible than arterial wall thickness, probably as a result of its closer relationship with BP, which usually remains elevated after Rtx.

Among the various potential biographic, anthropometric, and biochemical risk factors that were assessed, increased IMT was most consistently linked to abnormalities of mineral metabolism. The calcium phosphorus ion product in serum, expressed either as time-integrated mean or as the fraction of previous elevated Ca $\times$ P measurements, was significantly correlated with cIMT. This finding extends previous observations in young adults with childhood-onset chronic renal failure to the pediatric age range (9,19) and confirms significance of calcifications in pediatric patients described earlier by others (30). The arteriopathy associated with uremia is characterized by excessive vascular calcification, which seems to include both Moenckeberg-type diffuse calcium depositions along the tunica media and a more marked generation of hydroxyapatite crystals in intimal atherosclerotic plaques than observed in conventional atherosclerosis (31). Our findings suggest that even in children, calcium-phosphate deposition substantially contributes to the arterial wall thickening visualized by sonography. The observed correlations with the lifetime phosphate binder and calcitriol doses are compatible with a causal relationship between these medications and arteriopathy. However, the prescribed doses are also surrogate markers of the severity of hyperphosphatemia and hyperparathyroidism that necessitated their administration. Although we are unable to differentiate the relative impact of the medication on arterial thickening, it is of note that the cumulative phosphate binder dose and the calcium-phosphate product were independent predictors of cIMT. In adult dialysis patients, evidence for a causative role of calcium-containing phosphate binders in the calcifying arteriopathy of uremia was provided recently in the prospective Treat to Goal study (32).

Besides the impact of altered mineral metabolism, uremic arteriopathy has been linked to a state of chronic inflammation and malnutrition that is present in mostly elderly adult patients (33). Of note in this context, mean past serum albumin levels were inversely correlated and C-reactive protein concentrations at least in the CKD subgroup positively correlated with cIMT in this pediatric population. Low serum albumin may reflect malnutrition but may also play a direct role in calcium deposition by increasing the ionized, precipitable calcium fraction. In the patient population as a whole, these disease-specific factors outweighed any effects of "conventional" risk factors that clearly had an impact on cIMT in the healthy control subjects, such as relative obesity, high BP, and low HDL and apoA levels. In the CKD subgroup, where hyperphosphatemia and hyperparathyroidism were not yet prominent, BP as well HDL, apoA, and apoB levels showed significant associations with cIMT. An association between hyperlipidemia and coronary

artery disease in pediatric patients on hemodialysis and after Rtx was noted already by Pennisi *et al.* (34). Some recent reports indicate a role of HDL cholesterol in inhibiting cytokine-induced calcification of vascular cells (35,36). Hence, it seems that several pathomechanisms interact in the pathogenesis of uremic arteriopathy. The early increase of IMT in stages 2 to 4 CKD may be related to preatherosclerotic intimal changes, as observed in other pediatric patient groups at risk for early cardiovascular disease (10–17). As CKD progresses to ESRD, arterial thickening is amplified by excessive calcium-phosphate precipitation. It leads both to increased IMT and to arterial stiffening and increase of pressure load to left ventricle (9,37). With regard to therapeutic implications of our findings, the apparent contribution of cumulative calcium-containing phosphate binder intake already in children and adolescents is in keeping with but does not prove the concept of preferential usage of calcium-free phosphate binders, especially in young CKD patients, to minimize secondary cardiovascular morbidity from hyperphosphatemia and its treatment. The other observation of potential therapeutic relevance made in this study is the significantly lower IMT in renal allograft recipients compared with dialyzed patients, despite comparable cumulative periods on dialysis. This is remarkable because high calcium and phosphate exposure as well as inflammation-related molecular pathomechanisms that are active in the uremic state are believed to trigger not only passive tissue calcification but also a transdifferentiation of vascular smooth muscle cells to an osteoblast-like phenotype (38–40). Recently, it was observed that in the presence of high extracellular calcium and/or phosphate concentrations, vascular smooth muscle cells undergo vesicle-mediated calciphylaxis. This process was prevented by addition of normal plasma (41). Our clinical observation suggests that IMT thickening is partly reversible by resaturation of a normal calcium balance and withdrawal of the uremic milieu by successful Rtx. Because of the absence of confounding cardiovascular risk factors such as diabetes and smoking, the pediatric CKD population might be uniquely suited to evaluate prospectively the efficacy of the two vasculoprotective strategies: Prevention by calcium-free phosphate binders and reversal of vascular damage by kidney transplantation.

In conclusion, we demonstrated that CKD is associated with morphologic alterations of the large arteries as early as in the second decade of life. Whereas conventional cardiovascular risk factors such as hypertension and dyslipidemia are correlated quantitatively with the degree of arteriopathy in predialytic CKD, hyperphosphatemia and hyperparathyroidism and their treatment with calcium-containing phosphate binders seem to be predominant risk factors of early arteriosclerosis in children with CKD.

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