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Carotid intima–media thickness in children and young adults with renal transplant: Internal carotid artery vs. common carotid artery

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Abstract: Cardiovascular diseases are the main causes of morbidity and mortality following renal transplantation. Atherosclerotic structural changes, which can be detected by high-resolution B-mode ultrasonography, begin before clinical findings. However, little is known about the extent of these abnormalities in children after renal transplantation. We aimed to determine early structural changes of large arteries in renal transplant recipients without cardiovascular disease and to evaluate the role of clinical and laboratory features on IMT of carotid arteries. IMT and hemoglobin, serum levels of creatinine, acute phase proteins, lipid profile, and homocysteine were examined in 24 asymptomatic renal transplant recipients (median age 16.5 yr; range 8–25), and 20 healthy controls (median age 16 yr; range 9–24). CCA and ICA were evaluated in patients and controls with a high-resolution B-mode ultrasonography in multiple projections to optimize detection of carotid IMT. Measurement of IMT of both CCA [0.36 mm (range 0.16–0.48) vs. 0.28 mm (range 0.21–0.35), $p < 0.001$] and ICA [0.27 mm (range 0.16–0.48) vs. 0.22 mm (range 0.1–0.26), $p < 0.001$] were significantly higher in renal recipients than in healthy controls. Among several parameters assessed, only significant correlations were found between duration of CRF, duration of dialysis prior to transplantation and ICA-IMT ($p = 0.06$ and $p = 0.02$, respectively) and between mean past serum calcium–phosphorus ion product and CCA-IMT ($p = 0.002$). In conclusion, our observations indicate that vascular changes begin early in the course of CRF and are directly related to time on CRF and dialysis. These changes can be detected by measuring CCA/ICA-IMT ultrasonographically. We suggest that early renal transplantation can potentially avoid long-term cardiovascular events in children with end stage kidney disease.

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Key words: chronic renal failure – pediatric kidney transplantation – intima-media thickness – common carotid artery – internal carotid artery

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Abbreviations: AZA, azathiopurine; BMI, body mass index; CCA, common carotid artery(ies); CKD, chronic kidney disease; CRF, chronic renal failure; CRP, C-reactive protein; CsA, cyclosporine A; ESR, erythrocyte sedimentation rate; ESRD, end stage renal disease; GFR, glomerular filtration rate; HDL, high density lipoprotein; ICA, internal carotid artery(ies); IMT, intima-media thickness; LDL, low density lipoprotein; MI, myocardial infarction; MMF, mycophenolate mophetil; PRED, prednisone; SIR, sirolimus; TAC, tacrolimus.

Cardiovascular disease is a major cause of morbidity and mortality in children after renal transplantation and is one of the most important determinants of long-term transplantation outcome (1). The main reason for cardiovascular disease is accelerated atherosclerosis and coronary artery disease in renal transplant recipients.

Atherosclerotic changes begin before clinical findings, which can be detected by high-resolution B-mode ultrasonography, an easy, non-invasive, and reliable method (2). Measurement of carotid artery IMT by ultrasound is now widely used as a marker for early carotid atherosclerosis. It has been previously reported that an increased IMT in the general population correlates with an increased risk of angina, MI, aneurysm, and peripheral vascular disease (3) and that each 0.1 mm increment in IMT lead to an 11% risk increase in MI (4). The CCA is frequently used for this purpose. However, data on cardiovascular risk associated with ICA-IMT are very limited. It has been proposed that IMT measurement from ICA may detect early athero-structural changes and may be a better estimate of early atherosclerosis than measurement from the CCA (5). This has been supported by data from the Cardiovascular Health Study in which the associations of ICA-IMT with MI and stroke have been found as strong as those for CCA-IMT (5, 6). By contrast, in a recent study, it has been shown that measurement of IMT in ICA, CCA and carotid bifurcation has the same ability to predict future MI (7).

In the present study, we aimed (i) to determine early structural changes of large arteries in renal transplant recipients without clinical evidence of cardiovascular disease, (ii) to evaluate whether clinical and laboratory parameters have any impact on IMT of carotid arteries, and (iii) to determine which site (CCA vs. ICA) is clinically relevant for detecting early atherosclerotic changes.

Patients and methods

Patients

Twenty-four renal transplant recipients (14 males, 10 females; aged 8–25 yr) who have currently been followed up at Department of Pediatric Nephrology, Hacettepe University Faculty of Medicine, were enrolled into the study. Twenty (10 males, 10 females; aged 9–24) healthy normotensive children served as controls.

Any myocardial disease including left ventricular hypertrophy was excluded by echocardiography. All patients had stable graft function for more than one yr with a GFR of ≥75 mL/min/1.73 m^2, which was estimated by the Schwartz formula. Exclusion criteria from the study were any clinically overt inflammatory or infectious disease, acute graft rejection, and any clinically severe co-morbid condition. Underlying diseases were structural diseases (n = 11), glomerulonephritis (n = 8) and others (n = 5). Dialysis modalities employed before transplantation were continuous ambulatory peritoneal dialysis (n = 11) and hemodialysis (n = 8). Pre-emptive kidney transplantation was performed in six patients.

All patients received triple immunosuppressive regimen consisted the combination of: TAC, CsA, AZA, MMF, SIR, and PRED as follows: TAC + AZA/MMF + PRED (n = 15), CsA + AZA/MMF + PRED (n = 7), SIR + AZA/MMF + PRED (n = 2).

The study was approved by the local Ethical Committee. Informed consent/assent of the parents and/or the patients was obtained.

Demographic and clinical information was obtained on the day of carotid IMT measurement.

Body weight (kg) and height (m) were determined, and BMI (kg/m^2) was calculated.

Blood pressure measurements were based on three independent readings using a digital blood pressure monitor after the subjects rested in the seated position at least 10 min. The subjects' right or left arms (depending on the presence of a dialysis fistula) were used to obtain blood pressure measurements. The cuff sizes selected were based on the fourth report on diagnosis, evaluation, and treatment of high blood pressure in children and adolescents (8). *Z*-scores for both systolic and diastolic blood pressures of each patient were calculated as described elsewhere (8).

After an overnight fast, blood samples for hematocrit, serum creatinine, calcium, phosphorus, lipid profile, homocysteine, high-sensitivity CRP, and ESR were drawn from each patient. For each patient, all hospital records from the beginning of CKD stage-2 were reviewed to assess the patient cumulative exposure to cardiovascular risk factors associated with CKD, which include serum calcium, phosphorus, intact parathyroid hormone levels, phosphate binders, calcitriol, and antihypertensive medication used prior to transplantation.

IMT measurement

The carotid arteries were evaluated in all patients and control subjects, with a high-resolution B-mode ultrasonography (Antares, Erlangen, Siemens) using a 13.5-MHz multidimensional linear transducer in multiple projections to optimize detection of carotid IMT. The ultrasonographic examination was performed by an experienced radiologist who was blinded to the study groups. The ultrasonographic scanning was performed with the subject in the supine position, examining the CCA and ICA bilaterally in every subject. The carotid arteries were explored with longitudinal and transverse scans (Figs. 1 and 2). The transducer was

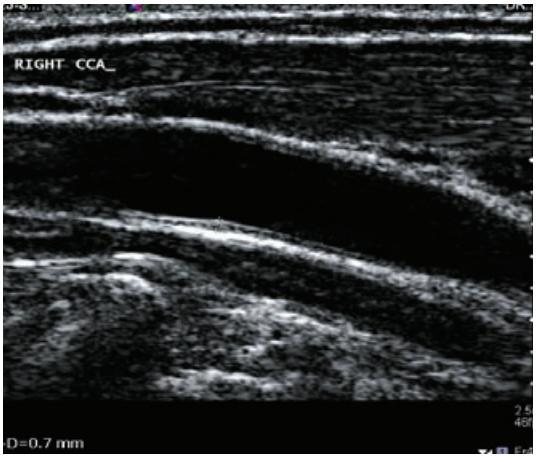

Fig. 1. Longitudinal scan of the right CCA by B-mode ultrasonography.

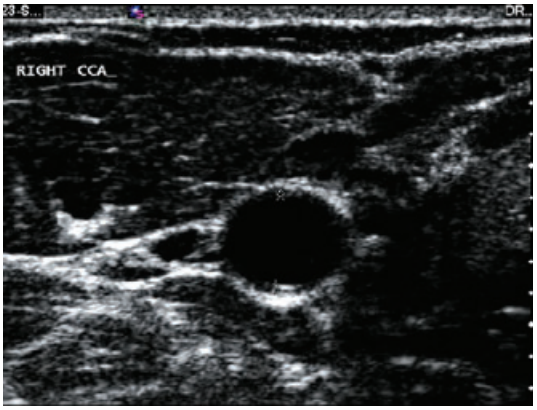

Fig. 2. Transverse scan of the right CCA by B-mode ultrasonography; right CCA demonstrating increased wall thickness.

manipulated so that the near and far walls of the CCA and ICA became parallel to the transducer footprint, and the lumen diameter was maximized in the longitudinal plane. A region 10-mm proximal to the carotid bifurcation for CCA and a region 10-mm distal to the carotid bifurcation for ICA were identified, and the IMT of the far wall was evaluated as the distance between the lumen–intima interface and the media–adventitia interface (Fig. 2). The IMT measurement was obtained from both sites. The average of the four measurements for CCA and ICA each were used for analyses. All measurements were made manually on still images obtained during the sonographic scanning (Fig. 2). The coefficients of variation of the measurements were less than 3%.

Statistical analysis

The results were analyzed using the SPSS version 11.0 (SPSS, Inc., Chicago, IL, USA) and were expressed as median (minimum–maximum) for data not showing normal distribution and as mean ± s.d. for data showing normal distribution. Parameters with non-normal distribution were compared using the Mann–Whitney *U*-test. Correlation analysis was carried out by the Spearman non-parametric correlation analysis. Variables that showed significant association in the univariate analysis, were included in a stepwise multiple linear regression analysis to identify independent predictors of IMT. $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics

The baseline characteristics of the study population are presented in Table 1. Whereas the groups were comparable in terms of age, gender, and BMI, patients had significantly shorter stature, higher diastolic blood pressure, higher fasting cholesterol, homocysteine, ESR, and CRP levels when compared with those in healthy controls (Table 1).

Eight patients received kidneys from deceased donors and 16 from living donors. All of the patients had their first transplantation. Twenty-two (92%) patients were being treated by chronic dialysis prior to transplant. The median time that had been spent in predialytic CKD period was 17 months (range 6–60) while the median duration on hemo- or peritoneal dialysis for ESRD was 6.5 months (range 1–84). Overall, the median duration from CKD (defined as GFR < 75 mL/min/m^2) including ESRD to renal transplantation was 36 months (range 8–96). Fourteen (58%) patients were on antihypertensive therapy.

Table 1. Clinical characteristics of the renal transplant recipients and controls†

Variable	Renal recipients (n = 24)	Control group (n = 20)	p
Age (yr)†	16.29 ± 4.44	15.7 ± 1.45	0.42
Sex (F/M)	10/14	10/10	ND
BMI (kg/m^2)†	21.24 ± 3.10	20.52 ± 2.43	0.65
Height†	153.2 ± 16.3	158.4 ± 13	0.23
Height *Z*-score†	−1.02 ± 0.64	−0.3 ± 0.4	<0.001*
Systolic BP (mmHg)	118.95 ± 6.66	115.5 ± 7.8	ND
Systolic BP (*Z*-score)	0.9891 ± 0.64	0.6149 ± 0.80	0.093
Diastolic BP (mmHg)	75.33 ± 4.86	69.25 ± 4.66	ND
Diastolic BP (*Z*-score)	1.0032 ± 0.48	0.4323 ± 0.33	<0.0001*
ESR (mm/h)	18.66 ± 13.58	8.45 ± 4	0.001*
CRP (mg/dL)	0.52 ± 0.17	0.38 ± 0	0.002*
Fibrinogen (mg/dL)	312.54 ± 88.22	284.65 ± 30.31	0.185
Cholesterol (mg/dL)	158.87 ± 44.97	117.7 ± 14.12	0.001*
Triglycerides (mg/dL)	117.33 ± 75.08	94.41 ± 17.15	0.189
LDL (mg/dL)	81.51 ± 34.45	65.51 ± 14.29	0.059
HDL (mg/dL)	53.29 ± 17.94	43.41 ± 8.48	0.029
Homocysteine (μmol/L)	14.17 ± 4.31	8.44 ± 1.58	<0.001*
Serum creatinine	0.87 ± 0.29	–	
Time in predialytic CKD (month)‡	17 (6–60)	–	
Cumulative time on dialysis (month)‡	6.5 (0–84)	–	
Duration after transplantation (month)‡	27 (12–122)	–	
Cumulative P binder intake (g/kg)	46.33 ± 38.93	–	
Mean past Ca × P product (mg/dL)	56.10 ± 5.7	–	

BP, blood pressure; Ca, calcium; CKD, chronic kidney disease; CRP, C-reactive protein; ESR, erytrocyte sedimentation rate; ND, not determined; P, phosphate.
†Data are given as mean ± s.d.; ‡Data are given as median (minimum–maximum).
*p-value < 0.05 is significant.

Laboratory parameters

IMT of both CCA [0.36 mm (range 0.16–0.48) vs. 0.28 mm (range 0.21–0.35), $p < 0.001$] and ICA [0.27 mm (range 0.16–0.48) vs. 0.22 mm (range 0.1–0.26), $p < 0.001$] were significantly higher in renal transplant recipients when compared with healthy controls (Figs. 3 and 4). ICA-IMT positively correlated with the duration of CRF including ESRD ($r = 0.548$; $p = 0.06$)

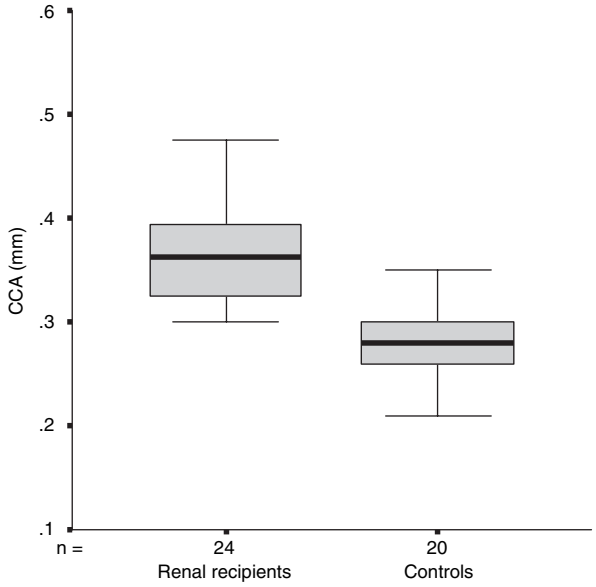

Fig. 3. CCA-IMT in the renal recipients and the controls.

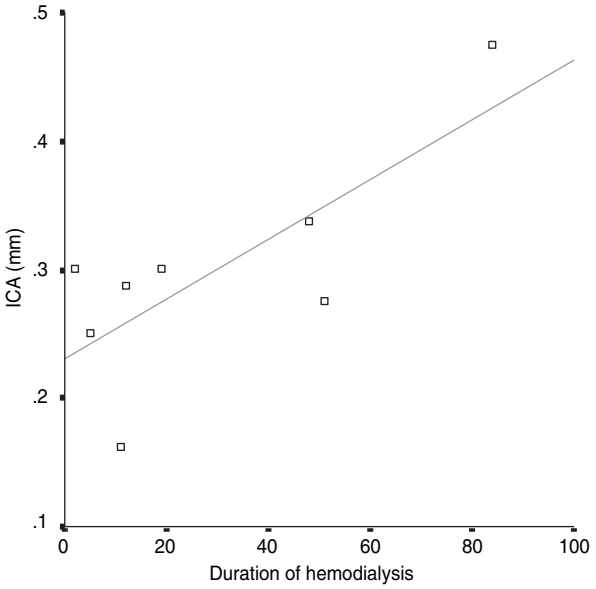

Fig. 5. Relationship between the duration of hemodialysis and ICA-IMT.

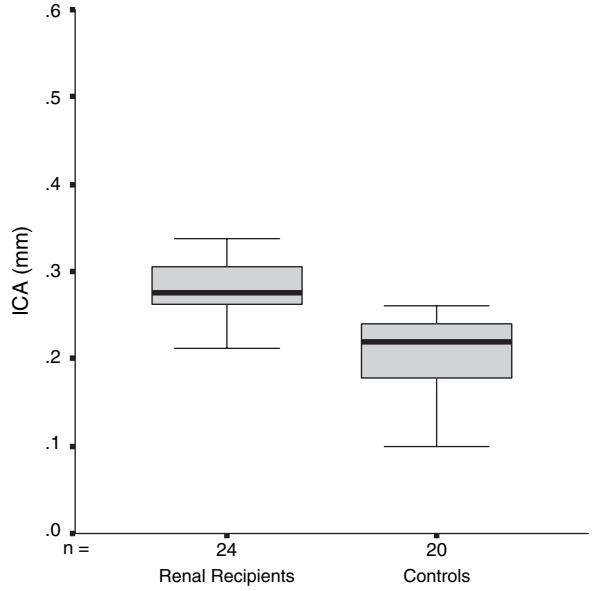

Fig. 4. ICA-IMT in the renal recipients and the controls.

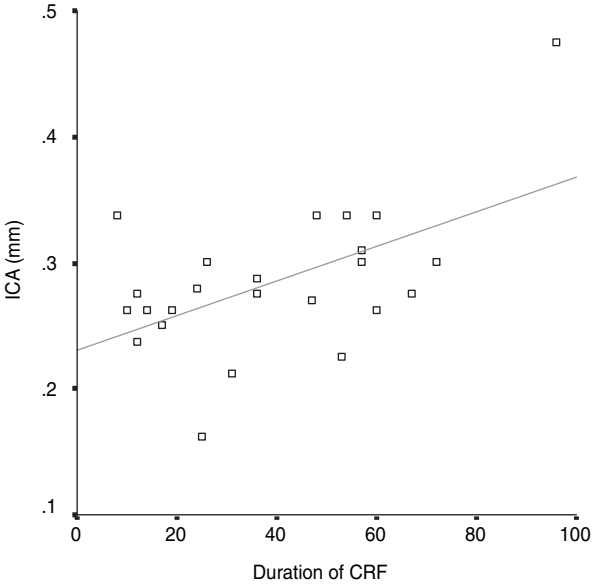

Fig. 6. Relationship between the duration of CKD including ESRD and ICA-IMT.

and with the duration of hemodialysis prior to transplantation ($r = 0.591$; $p = 0.02$) (Figs. 5 and 6). However, in the patient group, only CCA-IMT was positively correlated with the mean past serum calcium–phosphorus ion product ($r = 0.59$, $p = 0.002$) (Fig. 7). IMT values were comparable between subjects with deceased vs. live donor; hypertensive vs. normotensive patients; patients on antihypertensive medications vs. without; patients with structural disease vs. glomerulonephritis, and subjects on hemodialysis vs. peritoneal dialysis ($p > 0.05$). No correlation was found between IMT (both CCA and ICA) and mode of dialysis, cumulative dose of calcium-based phosphate binders, *Z*-scores of systolic and diastolic blood pressures, post-transplantation GFR, hematocrit, ESR, CRP, serum levels of homocysteine, calcium, phosphorus, and lipid profile.

A stepwise multiple linear regression analysis for CCA-IMT and ICA-IMT was performed separately using the following as independent variables: duration from ESRD to transplantation, ESR, serum phosphorus,

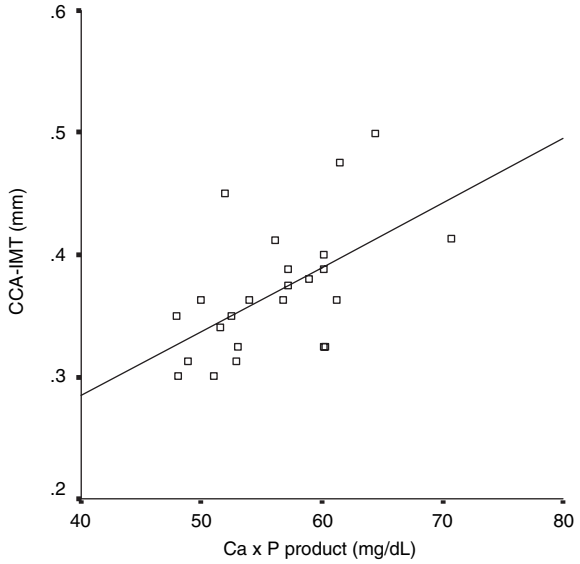

Fig. 7. Correlation of CCA-IMT with mean serum calcium–phosphorus ion product (Ca × P) before transplantation.

calcium, CRP, serum amyloid A, homocystein, LDL cholesterol, HDL cholesterol, intact parathyroid hormone, cumulative dose of calcium-based phosphate binders, and calcitriol used. This analysis identified serum phosphorus and duration from ESRD to transplantation for CCA-IMT (β coefficient = 0.065, t = 3.35, p = 0.003 and β coefficient = 0.001, t = 2.17, p = 0.042, respectively) and cumulative dose of phosphate binder used during CKD period for ICA-IMT (β coefficient = 0.001, t = 3.77, p = 0.001) as significant independent risk factors.

As the IMT variable was not dichotomized, a multiple stepwise regression analysis was performed with greater statistical power to compare the increase in IMT in patients vs. healthy controls and was adjusted for one variable at a time. *Z*-scores of systolic and diastolic blood pressures, ESR, serum levels of CRP, homocystein, cholesterol, and HDL cholesterol, which were found significant in univariate analysis, were included as independent variables into this model. Increasing in IMT in both CCA (β coefficient = -0.089, t = −6.498, p < 0.001) and ICA (β coefficient = −0.095, t = −5.673, p < 0.001) was found to be statistically significant in the patients when compared with those in the healthy controls.

Discussion

The present study demonstrates very important findings. Firstly, IMT, an early marker of atherosclerosis, in the carotid arteries could be found in the pediatric renal transplant recipients even in the asymptomatic period. Cardiovascular disease has been known to be a leading cause of mortality in the adult renal transplant population for decades (9). Recent studies have shown that cardiovascular morbidity, and even mortality, is also not rare among children and adolescents with ESRD and following renal transplantation, despite a much lower exposure to 'classical' risk factors for atherosclerosis, such as diabetes, smoking, and hyperlipidemia (10). In our study, we found significantly higher levels of serum cholesterol, CRP, homocysteine, and diastolic blood pressure in the renal transplant recipients than in the controls, all of which have been implicated in cardiovascular events either alone or in combination. More importantly, we clearly demonstrated that among the several parameters assessed, duration of CKD and duration of hemodialysis prior to transplantation correlated with IMT. This important finding, which is in agreement with previous studies in children and a previous assessment of young adults with childhood onset CKD stems from the fact that persistence of the cardiovascular alterations already present before the transplantation (11–13). Several factors can contribute to these alterations. In the present study, another important correlation was found between CCA-IMT and the mean serum calcium–phosphorus ion product before renal transplantation, which confirmed the significance of calcifications on arterial thickening in pediatric and adult patients with CRF as described earlier (13–15). In multivariate linear regression analysis, serum phosphorus and waiting time for transplantation for CCA-IMT and cumulative phosphate binder used during CKD for ICA-IMT were found significant independent risk factors, which further supported the detrimental effects of impaired calcium–phosphorus metabolism in CKD period. This finding is in agreement with the results of Treat to Goal study that has been conducted in hemodialysis patients (16). Litwin et al. (14) have recently demonstrated that CKD has been associated with morphologic alterations of both muscular and elastic type arteries as early as in the second decade of life. The authors have also noted that the degree of pathology depends on the degree of renal dysfunction and is most marked in patients on dialysis, but carotid IMT ≥ 95th percentile for age is also present in more than 50% of children in the earlier stages of CKD. The association between the period of dialysis therapy and IMT proves the detrimental role of

dialysis on arterial remodeling and the sequela in patients with ESRD.

In our study, the median value of CCA-IMT was 0.36 mm with a range of 0.16–0.48 mm in the renal transplant recipients whereas it was 0.28 mm with a range 0.21–0.35 mm in the healthy controls. Despite similar patient populations and measurement technique, Litwin et al. (14) reported a higher IMT value in their post-transplant patients when compared with our values. In their post-transplant patient cohort, predialytic CKD period and cumulative time on dialysis have been longer. Furthermore, systolic blood pressures, levels of serum creatinine, triglyceride, cholesterol, and LDL cholesterol have been higher, all of which could have impact on IMT, when compared with our patient population. Another point that requires clarification is the medications used and the dietary habits of their patients (i.e. high cholesterol intake) that could affect the IMT.

In a very recent report by Atabek et al. (17) from Turkey, the IMT of the carotid artery measured by a very similar technique, has been reported to range from 0.2 to 0.5 mm in healthy Turkish children, which is comparable with our IMT findings. However, our healthy controls have significantly lower IMT values when compared with those reported from the eastern part of Turkey (18). There are possible explanations for this discrepancy: Firstly, a 7.5-MHz B-mode ultrasonography has been employed in contrast to ours, which was 13.5 MHz multidimensional linear transducer. We lack a number of technical data and the intra/interobserver repeatability coefficient has not been provided that would have enabled further comparison. Furthermore, differences in IMT values of these studies may be explained by regional differences that might affect many environmental factors including dietary habits. Regional differences in subclinical markers of atherosclerosis have been studied previously by Jartti et al. (19), who found that middle-aged men born in eastern Finland had greater carotid IMT compared with men born in western Finland. Juonala et al. (20) have also demonstrated a greater IMT in young adults originating from east Finland and a lesser brachial artery flow-mediated dilation, functional marker of endothelial health, indicating reduced endothelial function in eastern subjects. Those differences have been found independent of environmental factors and accentuated when taking into account the subjects' family origin. Thus, they suggest that hereditable factors have a role in explaining the east–west difference in coronary heart disease mortality within Finland. Taking together, it is reasonable to suggest that IMT of the carotid artery may differ not only between countries but also from one region to another even in the same country, regarding with genetic background and environmental factors.

Another important finding of the present study is that measurement of ICA-IMT could be superior to the measurement of the CCA-IMT in detecting early atherosclerotic changes. The ICA-IMT appeared to overlap much more in cases and controls compared with CCA-IMT as seen in Figs. 3 and 4. However, when correlations were taken into account, only mean past serum calcium–phosphorus ion product was positively correlated with CCA-IMT among several parameters assessed. On the contrary, ICA-IMT, in fact, better correlated with duration of CRF including ESRD and hemodialysis, in which multiple factors contributed to arterio-structural changes are collectively present, when compared with those in CCA-IMT. There are several well-designed studies showing increased IMT in children with ESRD and renal transplantation, all of which are based on CCA-IMT measurement, but none of them have stressed which measurement of IMT is best suited for clinical use (12, 14). Recently, Mackinnon et al. (5) have clearly demonstrated that progression rates at the ICA rather than the CCA yield greater absolute changes in IMT and better correlations with vascular risk factors. The authors have also shown that vascular risk factors correlate more strongly with baseline IMT than with IMT progression like in a number of prospective cohort studies (21). We showed increased baseline IMT in both CCA and ICA in renal transplant recipients when compared with those in the controls; however, only ICA-IMT measurements correlated with duration of CRF and dialysis, in agreement with findings of Mackinnon et al. (5). From this aspect, our study is the first conducted work in a pediatric renal transplant population that showed that ICA-IMT measurement could be relevant for detecting early arterio-structural changes and that it correlates better with duration of CRF and dialysis. Measuring of baseline ICA-IMT rather than sequential measuring of CCA-ICA may be more appropriate as it may give a more accurate assessment of early vascular changes.

Conclusion

In conclusion, our observations indicate that vascular changes begin early in the course of CRF and are directly related to time on CRF and dialysis. These changes can be detected by

measuring ICA/CCA-IMT ultrasonographically. Taken together, the importance of early renal transplantation can potentially avoid long-term cardiovascular events in children with end stage kidney disease.

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