Carotid Intima-Media Thickness as a Cardiovascular Risk Marker in Pediatric End-Stage Renal Disease Patients on Dialysis and in Renal Transplantation

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ABSTRACT

Cardiovascular diseases are the principal cause of morbidity and mortality among young adults with chronic renal disease. Atherosclerotic structural changes as detected by high-resolution B-mode ultrasonography preceed clinical findings by several decades. The carotid intima-media thickness (cIMT) is being used as a marker of early atherosclerosis. We determined the cIMT of common carotid artery (CCA) in 8 asymptomatic children on dialysis or 12 after renal transplantation for comparison with 30 healthy controls. This prospective study of 40 children showed a mean age of 13.5 years (range, 8 to 18). We evaluated cIMT, hemoglobin, serum creatinine levels, lipid profile, and homeostasis model assessment (HOMA). The statistical analysis for variables with normal distribution was Student's t test. Parameters with a non-normal distribution were evaluated by the Mann–Whitney or Spearman correlation analysis with $P < .05$ considered statistically significant. The mean measurements of cIMT (mm) of both CCA were dialysis 0.450 ± 0.042; transplant 0.467 ± 0.033, and controls 0.380 ± 0.009 ($P < .03$). The homa levels of 2.45 ± 0.98 for dialysis and 1.8 ± 0.62 for transplant, were both significantly higher than the control group (0.8 ± 0.09; $P < .01$). The Ca $\times$ P product was higher in dialysis vs transplant group: 63.0 ± 10.0 versus 46.2 ± 2.2 ($P < .03$). The intact parathyroid hormone levels were 666.7 ± 276.7 versus 44.2 ± 2.8, respectively ($P < .008$). The low-density lipoprotein cholesterol was 129.0 ± 23.1 versus 80.8 ± 10.6, respectively ($P < .04$). The cIMT correlated with the duration of dialysis before transplantation. Changes in IMT can be detected by ultrasonography in early childhood in uremic patients. The etiology of atherosclerosis is multifactorial in children with end-stage renal disease. It seems possible to prevent or improve the factors related to cardiovascular risk in these patients.

CARDIOVASCULAR DISEASES (CVD) are the principal causes of morbidity and mortality among young adults with chronic kidney disease (CKD). Atherosclerotic structural changes detected by high-resolution B-mode ultrasonography preceed the clinical findings by several decades. Carotid intima-media thickess (cIMT) has been used as a marker for early atherosclerosis. The increased incidence of CVD is the consequence of a high prevalence of both traditional risk factors, uremia-related,[1,2] and "new factors," such as hyperhomocysteinemia, infections (herpes virus and *Chlamydia pneumoniae*) and oxidative stress, which increases atherosclerotic risk among these patients.[3–5] The objectives of this study were to determine the cIMT of the common carotid artery (CCA) and internal carotid artery thickness in asymtomatic children on dialysis and after renal transplantation compared with healthy controls.

PATIENTS AND METHODS

This prospective study enrolled 20 currently followed children between 8 and 18 years (mean, 13.5 years). Eight were on dialysis therapy and 12 had a kidney transplant. Twenty age- and gender-matched healthy normotensive children served as controls. In-

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formed consent was obtained from the parent/tutor. Demographic, laboratory chemistry, and clinical information were obtained on the day of cIMT measurement. The carotid arteries were evaluated with high-resolution B-mode ultrasonography using a 13.5-MHz multidimensional linear transducer (Philips IU 22) in multiple projections by an experienced radiologist who was blinded to the study group. The average of the IMT measurements obtained from CCAs was used for the analyses. After an overnight fast, we obtained blood samples for hemoglobin, serum creatinine, calcium, phosphorus, lipid profile, and HOMA test insulinemia * glycemia (mg/dL)/405. Patient cumulative exposure to cardiovascular risk factors associated with CKD included serum calcium, intact parathyroid hormone levels (iPTH) and time in chronic renal failure (CRF) and on dialysis.

Statistical Analysis

The analysis was performed using SPSS version 11.0. For variables with normal distribution we used, Student's *t*-test whereas those with a non-normal distribution were compared using the Mann–Whitney test. The Spearman test was used for correlation analysis. $P < .05$ was considered statistically significant.

RESULTS

Baseline characteristics are shown in Table 1. The groups were comparable in terms of age and gender. Patients on dialysis showed significantly shorter height, higher diastolic blood pressure, higher fasting cholesterol, and homa index compared with the healthy controls. The mean measurement of cIMT (mm) of both CCA in dialysis patients was 0.450 ± 0.042, in renal transplant recipients, 0.467 ± 0.033; and in a control group, 0.380 ± 0.009 ($P < .03$), values that were significantly higher among CKD patients than healthy controls (Fig 1). The homa index among dialyzed children was 2.45 ± 0.98 and in transplanted patients, it was 1.8 ± 0.62, both significatively higher than control group, 0.8 ± 0.09 ($P < .01$). The mean Ca × P product was higher among dialysis than the transplanted group, namely, 63.0 ± 10.0 versus 46.2 ± 2.2 ($P < .03$). There was no difference in Ca × P product between transplant 46.2 ± 2.2 and control groups 43.1 ± 1.4. The iPTH levels on dialysis were 666.7 ± 276.7 versus 44.2 ± 2.8 in the control group ($P < .008$). Low-density lipoprotein cholesterol (LDL-C) was higher among dialysis than transplant groups: 29.0 ± 23.1 versus 80.8 ± 10.6, respectively ($P < .04$). We observed a positive correlation between cIMT and CKD duration.

Table 1. Clinical, Biochemical, and Cardiovascular Characteristics

	Control	Transplant	Dialysis
Total cholesterol (mg/dL)	152.4 ± 3.9	171.4 ± 10.5*	174.3 ± 27.7*
HDL-C (mg/dL)	57.9 ± 2.6	58.4 ± 4.4	46.8 ± 2.8*
LDL-C (mg/dL)	81.2 ± 4.6	80.8 ± 10.6	129.0 ± 23.1*
VLDL-C (mg/dL)	13.7 ± 1.4	32.3 ± 8.4*	33.8 ± 2.5*
TG (mg/dL)	65.9 ± 4.4	161.1 ± 42.*	219.0 ± 29.4*
HOMA	0.82 ± 0.09	1.80 ± 0.62*	2.45 ± 0.98*
PTH (pg/dL)	44.2 ± 2.8	120.2 ± 15.2*	666.7 ± 276.7*
DBP (mm Hg)	63.2 ± 1.0	65.9 ± 2.9*	71.6 ± 3.1*
CCA-cIMT (mm)	0.380 ± 0.009	0.467 ± 0.033*	0.450 ± 0.042*

Abbreviations: CCA, common carotid artery; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; PTH, parathyroid hormone; TG, triglycerides; VLDL, very low-density lipoprotein.

*$P < .001$.

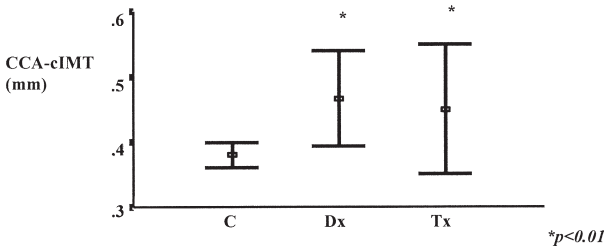

Fig 1. CCA-cIMT in the patients on dialysis (Dx), renal transplant recipients (Tx), and controls (C).

DISCUSSION

This study confirmed cIMT measurements evaluated by ultrasonography to be an early marker of atheroesclerosis in the carotid arteries of pediatric renal patients on dialysis therapy and even asymptomatic renal transplant recipients. Both atherosclerosis and coronary artery calcification which increase with age in the general population occur more frequently among adults with end-stage renal disease (ESRD). These changes have also been observed in younger adults receiving renal replacement therapy. This study reported that atherosclerotic changes could be demonstrated among children between 8 and 18 years with ESRD. The introduction of high-resolution ultrasonography has provided a reliable, reproducible, and noninvasive method to detect and monitor the progression of subclinical atherosclerosis. In our study, we observed significantly higher levels of serum cholesterol, iPTH, Ca × P, and diastolic blood pressure among patients with dialysis therapy compared with controls. All of these findings have been implicated in cardiovascular events either alone or in combination. Although renal transplanted recipients showed a better lipid profile than dialyzed patients, the cIMT was higher in both groups compared with a control group. These uremic patients have a chronic inflammatory status resulting from various factors: elevated cytokine production and reduced renal clearance, undetected persistent infections, and dialysis-related factors. C-reactive protein (CRP) is an excellent marker of systemic inflammation, but its role in the development of CVD is controversial. It has been considered an epiphenomenon rather than a pathogenic mechanism.[4] Lilien et al[6] reported that children on dialysis and after the transplantation show impaired endothelial function compared with healthy children. Accumulation of homocysteine and inflammation has been proposed as contributing factors in adults. A recent report in children did not observe a relationship between endothelial dysfunction and homocysteine or CRP levels.[1]

In conclusion, changes in cIMT can be detected by ultrasonography in early childhood among uremic patients.

The etiology of atherosclerosis is multifactorial in children with ESRD. It may be possible to prevent or improve the factors related to cardiovascular risk in these patients.

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