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Original Article

Risk Factors for Atherosclerosis and Carotid Intimal Medial Thickness as a New Marker for its Detection in Children With Chronic Renal Failure

Ali Abu Zeid, Doaa Twfeek, Doaa Mohamed, Naglaa Khalifa* and Tarek Sobhy**

Departments of Pediatrics, Clinical Pathology and Diagnostic Radiology**, Faculty of Medicine, Zagazig University, Egypt*

ABSTRACT

Background: The process of sclerosis and stiffening is the leading phenomenon of the arterial changes in uremia at young age which is usually followed by thrombus formation. Thus cardiac mortality is the main cause of death in patients with chronic kidney disease.

Objectives: To study the risk factors and new markers for diagnosis and follow up of atherosclerosis in children with chronic renal failure.

Methods: Fifty subjects were included in this work: 20 patients with end stage renal disease (ESRD) under regular hemodialysis (group A), 20 patients with chronic renal failure (CRF) under conservative treatment (group B) and 10 healthy age- and sex-matched children (group C). All groups were subjected to routine investigations (CBC, kidney function tests, serum albumin level, lipid profile, serum calcium and phosphorus level) and specific investigations (serum iron and ferritin, blood parathormone level (PTH), serum homocysteine (Hcy) and serum arginine leve). Finally Doppler ultrasound on the carotid arteries was done for all subjects.

Results: There was a highly significant difference in urea, creatinine, Ca x P, PTH and ferritin among the three studied groups with a significant increase of all in the patient groups than in the control group. Also, there was a significant decrease of serum arginine in the patient groups than in the control group while there was a significant increase in homocysteine level in the patient groups. There was a significant increase in carotid intimal medial thickness (CIMT) in patients with renal failure than in the control group with mean CIMT in group A under regular dialysis (0.79 ± 0.25 mm) and in group B (0.71 ± 0.18 mm) compared with the control group (0.38 ± 0.05 mm). There was a highly significant positive correlation between CIMT and age of patients, duration of disease, serum urea, Ca x P product, serum ferritin, triglycerides and homocysteine. While there was a highly significant negative correlation between CIMT and serum arginine, there was no significant correlation between CIMT and cholesterol or LDL levels.

Conclusions: There is accelerated atherosclerosis in children with chronic renal failure due to multiple risk factors. CIMT measurement can be used as an easy accurate and non-invasive method for early detection and follow up of atherosclerosis in these children.

INTRODUCTION

Cardiac mortality is the main cause of death in patients with chronic kidney disease[1].

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[2].

In young patients with ESRD, molecular data suggests that the process of sclerosis and stiffening is the leading phenomenon of the arterial changes in uremia at this age and is clinically more apparent and possibly more important than the process of atheroma formation. Current pediatric experience indicates that it is the 'sclerosis' part of atherosclerosis which is accelerated by ESRD, producing vascular changes for which the term 'uremic arteriopathy' might be more appropriate[3].

The cumulative serum calcium-phosphate product over time was not only correlated with coronary calcification but also with carotid intimal medial thickness (IMT). 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[4].

Endothelial cell dysfunction (ECD) is emerging as a common denominator for diverse cardiovascular abnormalities associated with inhibition of endothelial nitric oxide (NO) synthase (eNOS). Elevated levels of asymmetric dimethyl-arginine (ADMA), a potent eNOS inhibitor, are common in renal failure and may contribute to ECD[5].

Nitric oxide regulates vessel tone, inhibits platelet activation, adhesion, and aggregation, inhibits smooth muscle proliferation, and modulates endothelial cell-leucocyte interactions. Impaired bioavailability of nitric oxide in patients with chronic renal failure, may contribute to the pathogenesis of atherosclerosis in uremia. Although the precise mechanisms are unknown, uremic serum contains various substances that may either reduce endothelial production of nitric oxide or promote nitric oxide breakdown, including asymmetrical dimethylarginine, homocysteine, and oxidatively modified low density lipoproteins[6].

Arginine (ARG) is a substrate for endogenous nitric oxide (NO) production whereas its metabolite, asymmetric dimethylarginine (ADMA), acts as an inhibitor. Sufficient NO production is essential for cardiovascular key functions[7,8].

An increment of plasma homocysteine concentration is highly prevalent among patients under hemodialysis, and it is considered an independent risk factor for atherosclerotic complications of end-stage renal disease[9].

Hyperhomocysteinemia is closely linked to plasma folate and pyridoxine concentration. Once formed, homocysteine is either remethylated to methionine which requires vitamin B_{12}, folate and riboflavin as a cofactor, cosubstrate, and prosthetic group, respectively, or it undergoes a transsulfuration reaction to form cysteine. It was recently demonstrated that supplementation with high doses of folic acid reduced plasma homocysteine levels in chronic renal failure patients on regular hemodialysis[9].

The hypertriglyceridemia is the most common plasma lipid abnormality in patients with renal failure, and it has been considered as a risk factor for atherosclerotic vascular disease. The patients with endogenous creatinine clearance less than 20 ml/min/m^2 had low high density lipoprotein cholesterol (HDL-C) level. The HDL-C level was correlated inversely with serum triglyceride, the fatty acid pattern observed in chronic renal failure patients is indicative of an essential fatty acid deficiency. Polyunsaturated fatty acids decreased whereas saturated fatty acids increased in plasma and red blood cell membranes, altering the fluidity in the latter[10].

Increased levels of C-reactive protein (CRP) are significantly associated with the presence of vascular calcification in both aorta and hand arteries indicating evidence for a relationship between inflammation and vascular calcification in hemodialysis patients[11].

Carotid duplex ultrasound, indicating the presence of early arterial wall changes, may be useful for predicting other cardiovascular sequelae in hypertensive children[12].

Increased carotid intimal-medial thickness (CIMT) and coronary artery calcification (CAC) are used as two markers of early atherosclerosis, Carotid IMT may provide information in addition to CAC that can be used to identify young adults with premature atherosclerosis[12].

Carotid artery intima-media thickness: B-mode ultrasonography of the common and internal carotid arteries is a noninvasive measure of arterial wall anatomy that may be performed repeatedly and reliably in asymptomatic individuals. The combined thickness of the intima and media of the carotid artery is associated with the prevalence of cardiovascular risk factors and disease and an increased risk of myocardial infarction and stroke. This association is at least as strong as the associations observed with traditional risk factors[13].

AIM OF THE WORK

The aim of this work was to study the risk factors and new markers for diagnosis and follow up of atherosclerosis in children with chronic renal failure.

SUBJECTS AND METHODS

This study was carried out in the Departments of Pediatrics, Diagnostic Radiology and Clinical Pathology, Faculty of Medicine, Zagazig University in the period from July 2004 till December 2005.

The inclusion criteria were: A GFR less than 10 ml/min/1.73m^2 for group A and between 30-10 ml/min/1.73m^2 in group B.

The exclusion criteria were: familial hypertriglyceridemia, D.M., congenital heart disease, obesity and primary chest diseases.

The study included a total number of 50 subjects. They were selected and divided into 3 groups:-

Group A:

Comprised 20 patients with ESRD under regular hemodialysis (GFR less than 10 ml/min/1.73m^2).

- Their mean age was 11.7 ± 4.85 year.
- There were 11 females (55%) and 9 males (45%).

Group B:

Comprised 20 patients with chronic

renal failure under regular conservative non dialysis management. (GFR between 10-30 ml/min/1.73m^2). Their mean age was 11 ± 3.37 year.

- There were 11 females and 9 males.

Group C:

Comprised 10 healthy subjects as a control group with mean age of 10.7 ± 2.5 year. There were 5 females and 5 male.

All groups were subjected to:-

1- Full history taking

2- Thorough clinical examination

3- Routine investigations were done:

a. Complete blood count using automated cell counter system (KX-21).
b. Kidney function test, serum albumin, lipid profile done on Synchron CX7 autoanalyzer (Beckman Inst. Brca, California, USA).
c. Serum calcium and phosphorus using timed endpoint method on Synchron CX_5 system from Beckman (USA)[14,15].

4- Specific investigations were done:

a. Serum iron level[16].
b. Serum Ferritin: using ELFA technique enzyme linked fluorescent assay (Bio-Merieux).
c. Blood parathormone level:- The entire intact PTH assay procedure was done by Immulite analyzer[17].
d. Estimation of serum Hcy level by HPLC[18].
e. Estimation of serum Arginine level by HPLC[19].
f. Doppler ultrasound on carotid arteries.

The subjects were examined using a 12-MHz linear probe. Both carotid arteries were examined, and the median of the two IMT values was used for additional analysis[2]

Statistical Analysis

Data were entered checked and analyzed using Epi-Info version 6 and SPSS for Windows version 8[20].

RESULTS

Table (1) shows there is no significant difference in sex distribution among the three groups.

Table (2) shows the most common causes of CRF. In group A they are unknown followed by glomerulopathy while in group B the most common causes are unknown followed by SLE.

Table (3) shows a significant difference among the three groups as regards clinical manifestations.

Table (4) shows a significant difference as regards SBP, DBP, pulse and duration of the disease while there is no significant difference as regards age and weight.

Table (5) shows a highly significant increase as regards CIT (mean, right and left) among the three studied groups.

Table (6) shows a highly significant difference in urea, creatinine, hemoglobin, phosphorus, Ca x P, PTH, iron, ferritin among the three studied groups while there is a significant difference in Ca, cholesterol, triglycerides and LDL and a non-significant difference among them is found as regard platelets, WBCs, albumin and HDL.

Table (7) shows a highly significant difference as regards arginine and homocysteine among the three groups and by LSD there was no significant difference between group A and B as regards arginine level, while there was a highly significant

increase of homocysteine in group A compared with group B.

Table (9) shows no correlation between systolic or diastolic blood pressure and CIMT in all subjects.

Table (12) shows a highly significant relation between positive CRP and carotid intimal thickness.

Table 1: Distribution of sex in each group.

	Group A Patients on hemodialysis		Group B Patients on conservative		Group C Control group		Total No. = 50	X^2	p
	No. 20	%	No. 20	%	No. 10	%			
Male	9	45%	9	45%	5	50	23	0.32	> 0.05 NS
Female	11	55%	11	55%	5	50	27		

Table 2: Etiology of chronic renal failure in each group.

	Group A Patients		Group B Patients	
	No.	%	No.	%
Unknown	10	50.0	10	50.0
SLE	1	5.0	5	25.0
Glomerulopathy	7	35.0	1	5.0
Obstructive Uropathy	2	10.0	4	20.0

Table 3: Clinical descriptive data of the three studied groups.

Parameter		Chest pain	Cardiomegaly	Pallor	Murmur
Group A Patients on Hemodialysis (n = 20)	Present	9 (45%)	10 (50%)	6 (30%)	6 (30%)
	Absent	11 (55%)	10 (50%)	14 (70%)	14 (70%)
Group B Patients on conservative (n = 20)	Present	5 (25%)	6 (30%)	2 (10%)	2 (10%)
	Absent	15 (75%)	14 (70%)	18 (90%)	18 (90%)
Group C Control group (n = 10)	Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Absent	10 (100%)	10 (100%)	10 (100%)	10 (100%)
X2		4.1	6.4	20.5	23.1
P		**< 0.05 S**	**< 0.05 S**	**< 0.001HS**	**< 0.001HS**

Table 4: Clinical data of the studied groups.

	Group A Patients on Hemodialysis (Mean ± S.D. Range)	Group B Patients on Conservative (Mean ± S.D. Range)	Control (Mean ± S.D. Range)	F	p
Age (years)	11.7 ± 4.8 2–18	11.0 ± 3.4 4–15	10.7 ± 2.5 7–15	0.27	**> 0.05 NS**
Weight (kg)	30.7 ± 15.5 11–58	36.3 ± 14.6 12–58	39.0 ± 8.2 29–52	1.42	**> 0.05 NS**
SBP (mmHg)	124.0 ± 20.6 100–160	123.5 ± 17.3 100–150	108.0 ± 9.2 90–120	3.22	**< 0.05 S**
DBP (mmHg)	77.8 ± 15.3 50–100	76.0 ± 10.7 60–100	61.5 ± 11.6 50–80	5.78	**< 0.01 S**
Pulse (times/minute)	81.9 ± 9.6 70–105	82.6 ± 8.9 68–100	75.4 ± 5.4 68–83	2.71	**< 0.05 S**
Duration of disease in months	27.00 ± 14.24 5–52	17.15 ± 10.36 5–43		6.25	**< 0.05 S**

Table 5: Descriptive data of carotid intimal thickness (mean, right and left) among the three groups.

	Group A Patients on Hemodialysis Mean ± S.D. Range	**Group B Patients on Conservative** Mean ± S.D. Range	**Control** Mean ± S.D. Range	**F**	**p**
CIT (mean) mm	0.795 ± 0.251 0.400–1.280	0.712 ± 0.188 0.400–0.910	0.383 ± 0.050 0.300–0.480	14.54	**< 0.001 HS**
CIT Right mm	0.812 ± 0.267 0.300–1.310	0.730 ± 0.209 0.300–0.920	0.381 ± 0.050 0.300–0.460	13.67	**< 0.001 HS**
CIT Left mm	0.779 ± 0.256 0.400–1.250	0.695 ± 0.177 0.400–0.910	0.384 ± 0.052 0.300–0.490	13.37	**< 0.001 HS**

Table 6: Biochemical and hematological data among the three studied groups.

	Group A Patients on Hemodialysis Mean ± S.D. Range	**Group B Patients on Conservative** Mean ± S.D. Range	**Control** Mean ± S.D. Range	**F**	**p**
Urea (mg/dl)	133.25 ± 19.28 95–167	120.85 ± 30.34 80–132	16.00 ± 4.71 10–23	95.10	< 0.001 **HS**
Creatinine (mg/dl)	8.55 ± 1.85* 4.60–11.60	2.82 ± 2.06 1.50–8.60	0.46 ± 0.18 0.20–0.80	87.99	< 0.001 **HS**
Hemoglobin (g/dl)	9.47 ± 1.96 6.80–12.10	9.64 ± 1.65 7.90–12.20	12.80 ± 0.87 11.50–14.30	15.14	< 0.001 **HS**
Platelets (cells/mm^3)	254.3 ± 25.08 118–575	280.9 ± 81.0 119–437	293.6 ± 22.9 254–334	0.80	> 0.05 **NS**
White blood cells (cells/mm^3)	6.88 ± 2.27 4.3–14.0	8.12 ± 1.85 4.0–11.3	6.94 ± 2.22 3.9–11.0	2.02	> 0.05 **NS**
Albumin (g\dl)	4.14 ± 0.54 2.9–5.3	3.82 ± 0.45 2.6–4.5	3.90 ± 0.28 3.4–4.3	2.50	**> 0.05 NS**
Ca (mg\dl)	9.02 ± 1.56 7.30–13.20	9.09 ± 0.91 6.50–10.80	10.29 ± 0.45 9.70–11.00	4.54	**< 0.05 S**
Phosphorus (mg\dl)	6.18 ± 2.02 3.30–9.00	5.37 ± 0.94 3.80–6.90	3.64 ± 0.43 3.00–4.20	10.50	**< 0.001 HS**
Ca x P	54.74 ± 16.33 30.03–77.00	48.40 ± 7.30 32.76–57.96	37.47 ± 4.95 31.31–46.20	7.43	**< 0.001 HS**
PTH (µmol/L)	717.40 ± 165.75* 12–2320	87.00 ± 12.17 40–230	34.10 ± 2.98 18–52	11.38	**< 0.001 HS**
Iron (µg\dl)	87.91 ± 7.34 43.7–173	116.15 ± 22.71* 79–154	126.60 ± 32.06 85–164	7.62	**< 0.001 HS**
Ferritin (ng\ml)	780.48 ± 163.71* 82.6–2560	341.55 ± 44.52 99–750	142.50 ± 10.11 88–204	9.94	**< 0.001 HS**
Cholesterol (mg\dl)	140.20 ± 9.97 64–206	221.50 ± 24.67* 134–640	157.10 ± 9.61 144–170	6.153	**< 0.01 S**
Triglycerides (mg\dl)	148.70 ± 21.51 59–502	151.10 ± 13.39 78–244	85.50 ± 11.81 71–105	3.188	**< 0.05 S**
HDL (mg\dl)	40.63 ± 3.37 24.20–70.40	41.22 ± 12.66 24.86–69.30	49.61 ± 2.48 45.80–53.40	1.91	**> 0.05 NS**
LDL (mg\dl)	69.83 ± 9.16 17.68–141.46	150.06 ± 22.63* 48.90–532.00	90.39 ± 8.89 81.30–103.50	6.97	**< 0.01 S**

HDL = High density lipoprotein LDL = Low density lipoprotein

* Significant when comparing (group A) with (group B) by LSD.

Table 7: Arginine and homocysteine levels among the studied groups.

	Group A Patients on Hemodialysis Mean ± S.D. Range	**Group B Patients on Conservative** Mean ± S.D. Range	**Control** Mean ± S.D. Range	**F**	**p**
Arginine (µg\l)	71.58 ± 27.33 45.30–163.00	70.06 ± 16.19 45.60–114.80	114.56 ± 16.86 93.60–152.70	16.58	**< 0.001 HS**
Homocysteine (Before HD) (µg\l)	113.54 ± 13.29* 44.80–240.20	53.24 ± 15.51 25.90–80.10	9.83 ± 5.87 2.40–20.20	25.99	**< 0.001 HS**

Table 8: Correlation between CIMT and age of the patients and duration of disease and duration of dialysis in (group A).

	CMIT (mean carotid intimal medial thickness)		
	r	**p**	**Sig.**
Age	+ 0.588	< 0.001	**HS**
Duration of disease	+ 0.548	< 0.001	**HS**
Duration of dialysis DOD*	+ 0.439	< 0.05	**Sig**

Table 9: Correlation between systolic blood pressure, diastolic blood pressure and CIMT.

		CIMT
SBP	**r**	**0.17**
	p	**0.24 NS**
DBP	**r**	**0.19**
	p	**0.19 NS**

Table 10: Correlation between urea, ferritin and CIMT in the three groups.

	CIMT (carotid intimal medial thickness)		
	R	**p**	**Sig.**
Urea	**+ 0.558**	**< 0.001**	**HS**
Ferritin	**+ 0.561**	**< 0.001**	**HS**

Table 11: Correlation between carotid intimal thickness and calcium phosphorous product.

GROUP		Carotid intimal thickness	
		r	p
Group A	Ca x P	0.700	0.001 **HS**
Group B	Ca x P	0.588	0.006 **HS**
Control	Ca x P	-0.176	0.626 **NS**

Table 12: Relation between mean carotid intimal thickness and CRP.

GROUP		CRP negative	CRP positive	r	p
Group A	N	7	13	-3.6	0.002 HS
	Mean carotid IMT (mm)	0.58	0.91		
	SE	0.07	0.06		
Group B	N	14	6	2.9	0.008 HS
	Mean carotid IMT (mm)	0.64	0.87		
	SE	0.05	0.01		

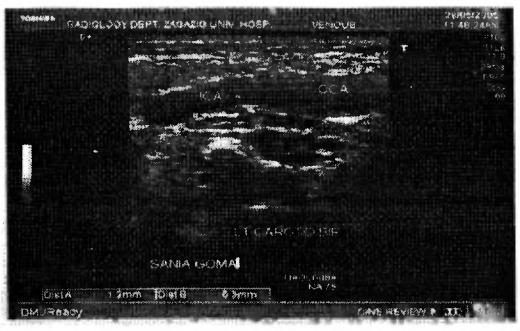


Fig. 1: One patient from Group A showing CIMT of left side 1.2 mm.

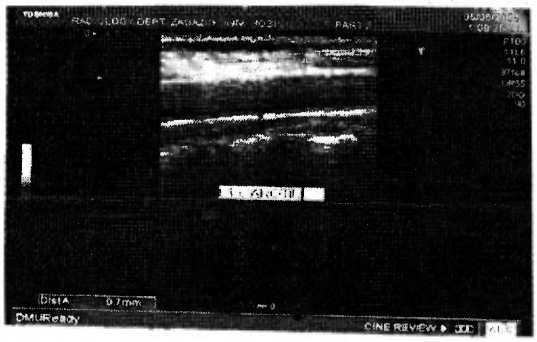


Fig. 2: CIMT of 0.7 mm in patient in Group B.

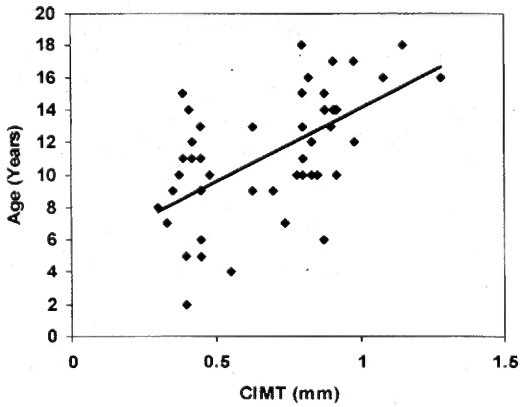


Fig. 3: A highly significant positive correlation between age and CIMT.

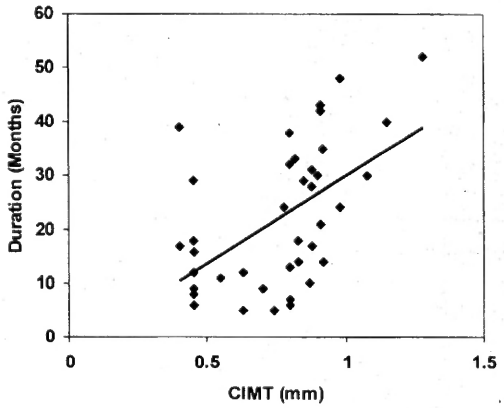
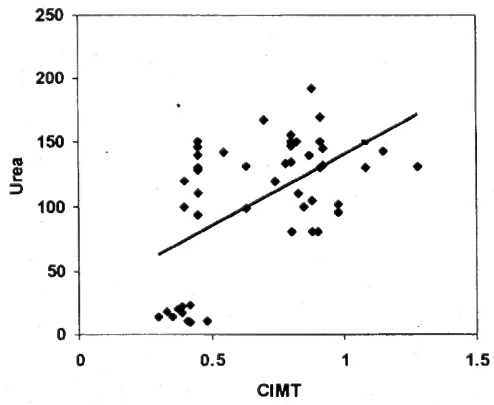


Fig. 4: A highly significant positive correlation between duration of disease and CIMT.



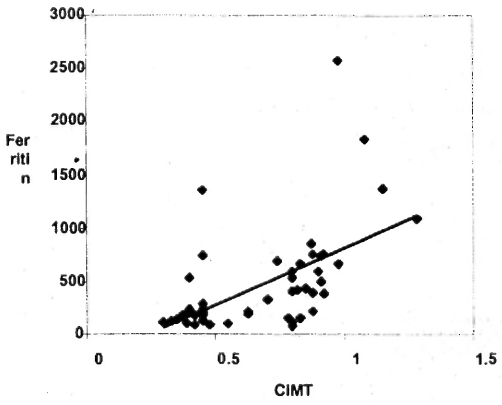


Fig. 5: A highly significant positive correlation between urea, ferritin and CIMT in the three groups.

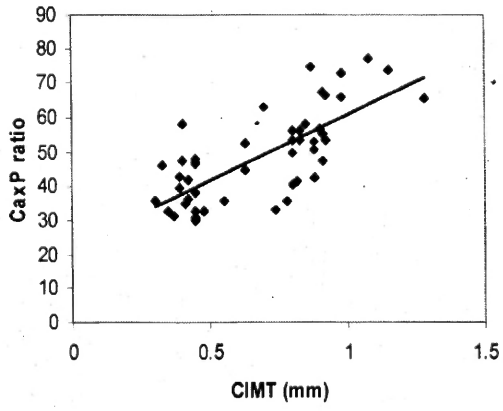


Fig. 6: There is a highly significant positive correlation between carotid intimal thickness and calcium phosphorus product in patients group.

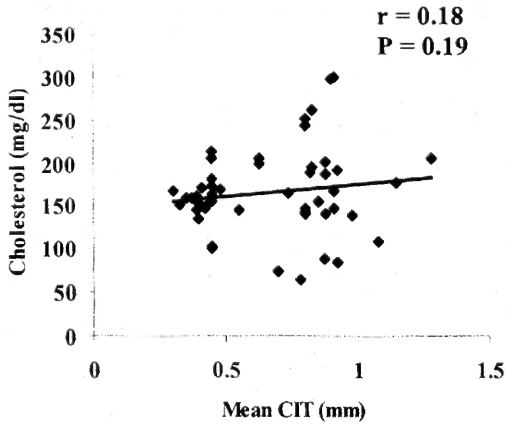


Fig. 7: No significant correlation between cholesterol and CIMT

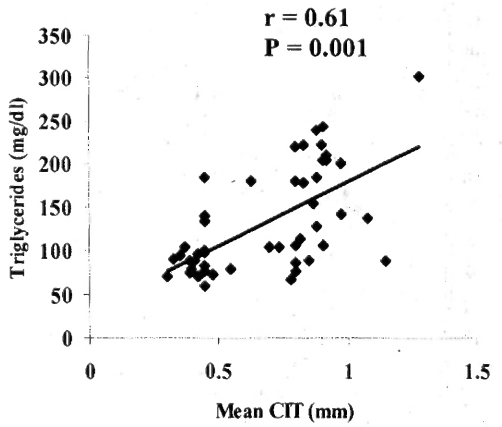


Fig. 8: A highly significant positive correlation between triglycerides and CIMT.

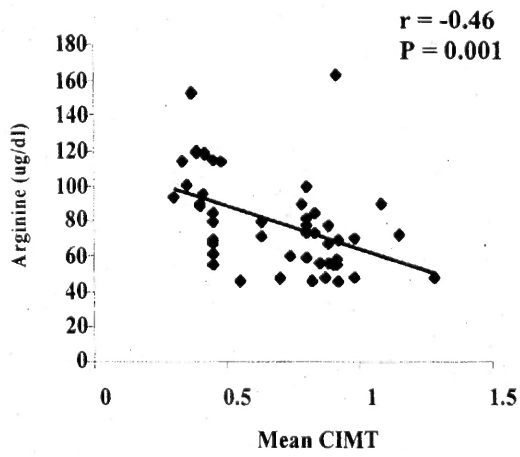


Fig. 9: A highly significant negative correlation between arginine and CIMT.

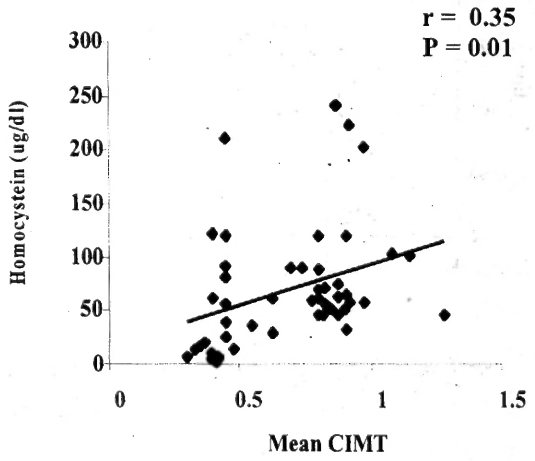


Fig. 10: A significant positive correlation between homocysteine and CIMT.

DISCUSSION

Cardiac mortality is the main cause of death in patients with chronic kidney disease[1], and these cardiovascular diseases in those patients cannot be explained entirely by the prevalence of traditional risk factors for atherosclerosis[21].

In this first-ever report of increased arterial stiffness in children on dialysis, that end-stage renal disease is associated with abnormalities in arterial wall elastic properties, comparable with adult levels, even in childhood. Most importantly, the absence of a discernible amelioration with dialysis implies that purely structural and not functional alterations lie behind the increased arterial stiffness[22].

The process of sclerosis and stiffening

is the leading phenomenon of the arterial changes in uremia and is clinically more apparent and possibly more important than the process of atheroma formation. Although risk factors are most likely to act in concert, producing both atheroma and sclerosis, this also implies that the driving force in this process is composed of a variety of factors leading to arterial stiffening, including hypertension, calcification and a decreased activity of endothelial relaxing factors. In more general terms, sclerosis develops faster than atheroma in young patients without significant co-morbidity[23].

We found that the calcium phosphorous product is higher in both groups of patients in comparison with the control group but there is no significant difference between both groups (those on hemodialysis and those on conservative management). This result is in accordance with almost all studies that discussed calcium and phosphorous in the serum of chronic kidney diseases patients[24] which state that prominent disturbances in calcium, phosphorus and vitamin D metabolism ultimately lead to alterations in parathyroid gland function and to various types of renal bone disease[24,25].

This study shows a highly significant increase in serum parathyroid hormone (PTH) level in patient group. Also, there is a highly significant difference between both groups A and B. This is in accordance with Blacher et al. (2001)[26] who explained this by hypocalcaemia, hyperphosphatemia and impaired renal 1, 25-dihydroxyvitamin D synthesis with attendant reductions in serum calcitriol concentrations and decreases in vitamin D receptor expression in the parathyroid glands each contribute to excess parathyroid hormone (PTH) secretion in patients with CRF.

This study also showed that there is a highly significant decrease in serum iron level and a significantly elevated serum ferritin when comparing patients on hemodialysis with those on conservative renal therapy and with the control group. This is in accordance with Silverberg et al.[26], and Fitzsimons and Brock[27] who say that the anemia of chronic renal failure is thought to result from a combination of erythropoietin deficiency and anemia of chronic disease. A further contribution may come from functional iron deficiency consequent on erythropoietin replacement for patients undergoing hemodialysis. In this setting and despite adequate ferritin concentration, the erythropoietic drive outstrips the ability of the reticuloendothelial system to release storage iron at a rate sufficient to satisfy the demands of the erythropoietin - stimulated bone marrow. This can be explained as anemia of chronic disease with low serum iron level due to poor nutrition, gastrointestinal malabsorption, uremic gastritis, and other co morbidity[28] and high serum Ferritin level due to poor utilization of seemingly adequate iron stores, excessive cytokines activation, and inhibited synthesis of Epo were common, suggesting that these are probably the most important factors closely connected with anemia of chronic disease, and the injudicious use of blood transfusion[29]. Inflammatory cytokines not only interfere with Epo gene expression, but also have a major impact on iron metabolism, determining the so-called reticuloendothelial iron block with defective iron supply to the erythropoiesis. The molecular

mechanisms responsible for this effect have been recently elucidated. Hepcidin is the key regulator for iron metabolism and mediator of anemia during inflammation. This small peptide is induced by inflammatory cytokines and its overproduction results in macrophage iron retention and, consequently, less iron is available for erythropoiesis. This reticuloendothelial iron block cannot be overcome by oral iron administration[30].

In this study we found as regards lipid profiles in patients with chronic renal failure, that there is a highly significant increase of cholesterol and LDL level in patients under conservative management in comparison with both those on hemodialysis and the control group and this is in agreement with Kagan et al.[31] who explained this on the basis of residual renal function increasing the lipid profile of CRF patients, especially serum levels of cholesterol-rich lipoproteins and that the residual renal function is higher in those under conservative management than those under hemodialysis. This is also in agreement with Manzi[32] and Manger et al.[33].

In our study there was a significant increase in triglycerides in chronic renal failure in both groups in comparison to the control group and this is in agreement with Massy et al.[34], who explained that hypertriglyceridemia is the most common plasma lipid abnormality in patients with renal failure, and it has been considered a risk factor for atherosclerotic vascular disease. A defective triglyceride removal due to low lipase activities may contribute to uremic hypertriglyceridemia in these patients with chronic renal failure.

However, in our study we found no significant difference as regards HDL among the three groups. This is in agreement with Kaysen et al.[35].

In this study we found that there is a highly significant decrease in blood arginine level in patients with CRF in both groups when comparing them with the control group and this is in agreement with Martens-Lobenhoffer et al.[36] who stated that plasma L-arginine levels of CRF patients also tended to be lower than that of the other groups. The explanation can possibly be a result of malnutrition or arginine loss caused by hemodialysis. Also the transport of L-Arginine, being rate-limiting for nitric oxide production, is extremely relevant to pathological conditions where NO synthesis and/or actions are affected[36].

In this study, there was a highly significant increase in homocysteine level in patients with chronic renal failure under regular hemodialysis compared with those under conservative management or the control group. That comes in agreement with Pastore et al.[37]. Boston et al.[38], who found that basal Hcy level in patients with ESRD on regular hemodialysis was markedly elevated. Homocysteinemia is a feature of ESRD in both children and adults[39].

This increase can be explained by abnormalities in sulfur amino acid metabolism which are present in chronic renal failure as part of the general alterations in amino acid metabolism in uremia[39]. Also the close relationship between plasma homocysteine and GFR suggests that homocysteine is cleared from the body by urinary

excretion through glomerular filtration, just like creatinine[40].

This study showed a highly significant correlation between CIMT and age of the patient. This is in agreement with Schmidt-Trucksäss et al.[41] who stated that that the CIMT increased with age and is also in agreement with Drüeke et al.[42] who stated that age was the major factor associated with CIMT. It was positively associated with iron dose, male sex, CCA diameter, and triglycerides.

We found a highly significant positive correlation between CIMT and duration of the disease in both group A and B. This is in agreement with Jun et al.[2] who stated that chronic renal failure (CRF) is associated with hypertension, dyslipidemia, hyperphosphatemia, hyperhomocysteinemia, and chronic inflammation. The impact of these cardiovascular risk factors is likely to accumulate with disease duration. Also this is in accordance with Milliner et al.[43], who stated that data from imaging studies and histological findings indicate that the amount and extent of vascular calcifications can be severe and are dependent upon the patient's age and duration of dialysis.

We also found a very highly significant positive correlation between CIMT and urea level in the three groups, and this is in accordance with Thambyrajah et al.[6] who found that endothelial function is abnormal in chronic renal failure, even in patients with biochemically mild renal insufficiency and in those without clinically evident atherosclerotic vascular disease. This suggests that uremia may directly promote the development of atherosclerosis early in the progression of chronic renal failure. Also uremic serum contains various substances that may either reduce endothelial production of nitric oxide or promote nitric oxide breakdown, including asymmetrical dimethylarginine, homocysteine, and oxidatively modified low density lipoproteins[44].

We also found that there is a positive correlation between calcium phosphorus product and PTH and carotid IMT in chronic kidney diseases. This can be explained by 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[45], and it is important because calcification of heart tissues resulting from deposition of excess Ca x P can cause arrhythmia, left ventricle dysfunction, coronary atherosclerosis, and death. Lung calcification can result in pulmonary hypertension, impaired gas exchange, and death[46]. Litwin et al.[47] stated that carotid IMT correlated with mean past serum Ca x 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 x P product, and young age were independent predictors of an increased CIMT.

Recent data has shown that calcification is a regulated process, and that smooth muscle cells in the media possess the capability to undergo transformation to osteoblast-like cells[48].

In this study we describe a highly significant positive correlation between

serum ferritin and CIMT. This is in agreement with London et al.[49] who described that parenterally administered iron may contribute to the oxidative stress observed in such patients, and it might play a role in arterial remodeling.

This can be explained by the fact the conditions favoring the generation of oxidative stress are present in patients on HD who may be exposed to the recurrent generation of oxidants and the origin of the oxidative stress is multifactorial.

Also It is, in part, due to the production of reactive oxygen species caused by the HD procedure, and as well as by other factors involved in chronic inflammation[41].

Our study shows no significant correlation between CIMT and cholesterol and LDL[50]. We failed to show significant relationships between carotid artery abnormalities and this element in children. Pirro et al.[50] described that non traditional factors are responsible for atherosclerosis in young ages in contrast to adults and also this is in agreement with Querfeld[3]. He explained this by the fact that there was no, or only a weak, correlation of cardiac death with hyperlipidemia, even though the lipoprotein profile is clearly atherogenic in chronic renal failure, on dialysis and after transplantation. This is in contrast with Clarkson et al.[51] who stated that hypercholesterolemia is a major risk factor for atherosclerosis in animal models and in man and may be associated with damage to the vascular endothelium which is involved in the initiation of the atherosclerotic process.

In this study, there is also a highly significant positive correlation between CIMT and triglyceride in both groups of chronic renal failure.

Also our study shows a significant negative correlation between HDL and carotid IMT in both chronic renal failure groups. This is in accordance with Okubo[52] who describe the HDL (Good Cholesterol) are proteins coated "packages" that carry fat and cholesterol through the body so with its decrease the protective effect will decrease.

In this study we found there is a highly significant negative correlation between arginine level and carotid IMT in both groups of chronic renal failure group A and B, and this is in agreement with Smirnova et al.[5]. The explanation of this correlation is the direct inhibitory effect of nitric oxide on the vessel wall atherogenesis and its dependency on Arginine[42].

In hypercholesterolemia in humans, acute intravenous administration of L-arginine may improve endothelial responses in resistance vessels in the peripheral and coronary circulation[53].

Our study also shows a significant positive correlation between carotid IMT and Homocysteine level. This goes with Temple et al.[54] who explained that homocysteine may act through many mechanisms, including direct injury to endothelial cells, platelet activation, and effects on clotting factors. This agrees with Mallamaci et al.[8].

Also this study shows a highly significant positive correlation between CIMT and CRP and this is in accordance with Jun et al.[2] who said that 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.

This can be explained by 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, co-localizes 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[53].

In conclusion there is accelerated atherosclerosis in children with chronic renal failure and it can be a result of multiple factors such as older age, long disease duration, high urea, calcium phosphorous product, ferritin, homocysteine, triglyceride and low arginine levels and inflammatory effects like a positive CRP. Also CIMT measurement can be used as an easy, accurate and non invasive method for early detection and follow up of atherosclerosis.

We recommend using carotid Doppler ultrasound for early detection and follow up of atherosclerosis in patients with CRF.

Follow up and trials to control all risk factors for atherosclerosis in these patients is suggested.

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