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Indicators of Vascular Dysfunctions in Children with End Stage Renal Disease under Regular Haemodialysis as Paediatric Emergency

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Abstract

Background: There is a necessity to predict cardiovascular diseases in children with end stage renal disease (ESRD) on regular haemodialysis. Objectives: to study biochemical, structural and functional indicators of vascular dysfunction in children with ESRD on regular haemodialysis (HD) and their correlations as early predictors of cardiovascular diseases in dialysis children.

Materials and methods: The present study was carried out on 30 children with ESRD on regular hemodialysis in Tanta University hospital and 30 healthy age and sex matched children as controls. All patients and control were subjected to history taking, clinical examination including, routine laboratory assessment measuring serum cholesterol, serum calcium and phosphorous, Ca × P product, serum alkaline phosphatase and serum intact parathyroid hormone (iPTH). Radiological assessment was done using B-mode ultras-onography to assess arterial calcifications, arterial stiffening by measuring mean CCA diameter in mm, carotid intima media thickness (CCA-IMT in µm), aortic PWV in cm/sec, Renal Resistance Index.

Results: Twelve (80%) of the studied patients showed calcifications in one or more of the studied different sites. There was a highly significant increase in the CCA diameter, CCA-IMT and Ao. PWV in studied patients as compared to the controls but there was no significant difference between patients and controls as regard renal RI (P>0.05).

Conclusion: Vascular calcifications in children with ESRD on regular haemodialysis are associated with increased stiffness of large, arteries. The extent of arterial calcification increases mainly with the duration of dialysis and abnormalities in Ca × P product.

Keywords: Atherosclerosis; Children; Haemodialysis; Chronic; Renal

Introduction

Cardiovascular disease accounts for one quarter of deaths in children and adult younger than 30 years old who started treatment of end stage renal disease (ESRD) as children [1-3]. Damage of large arteries is a major contributory factor to the high cardiovascular morbidity and mortality of ESRD patients [4,5]. The adverse effects of macrovascular disease are attributable to two principal mechanisms, the first is presence of occlusive lesions, principally atherosclerotic plaques, responsible for ischemic lesion, and the second is stiffening of arterial walls associated with arterial wall dilatation and hypertrophy leading to increased left ventricular mass [6].

Aim of work: To study biochemical, structural, and functional indicators of vascular dysfunction in children with end stage renal disease on regular haemodialysis (HD) and their correlations as early predictors of cardiovascular diseases in dialysis children as pediatric emergency.

Materials and Methods

Design of the study and setting

The present study was carried out after approval from research ethical committee centre of Tanta University Hospital and obtaining an informed consent from parents of included children, in Paediatric Nephrology Unit of Paediatric Department, Tanta University Hospital (TUH) from June 2016 to June 2017 on 30 children with ESRD on regular haemodialysis. 30 healthy children with matched age and sex were serving as control group. The patient's ages ranged from 4 to 19 years. They were 18 males and 12 females. All patients were undergoing haemodialysis three times per week, with each dialysis session lasting for three to four hours. Dialysis was started when GFR is equal or less than 15 ml/min./1.73 m^2. Patients were dialysed on Fresenius 4008 B dialysis machine (Germany) at blood flow rate=2.5 × weight (kg) + 100 ml/min., using polysulphane hollow fibre dialysers suitable for the surface area of the patients (Fresenius F3=0.4 m^2, F4=0.7 m^2, F5=1.0 m^2 and F6=1.2 m^2). Bicarbonate dialysis solutions were used. All patients were receiving supportive therapy in the form of SC. erythropoietin in a dose of 50 IU/Kg/session, IV iron dextran 100 mg/Kg/week, oral folic acid 1 mg/day, oral

calcium 1000 mg/day, oral vitamin D (one alpha) in a dose of 0.01-0.05 µg/Kg/day and oral antihypertensive medications for hypertensive patients.

Inclusion criteria

All children with ESRD and treated by regular haemodialysis were included in the study.

All patients and controls were subjected to the following:

- Thorough history taking including duration of dialysis.
- Clinical examination in the dialysis free day which includes:

Anthropometric measurements (weight, height and mid-arm circumference (MAC) by CDC growth charts developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Pretension and Health Promotion [7]. They were expressed as percent of ideal for age. Ideal measurement is defined as the 50th percentile for age.

Arterial blood pressure was measured by the auscultatory method using a mercury sphygmomanometer with the patient in the semi setting position after 10 minutes of rest, in the non-fistula arm using an appropriate sized cuff. Arterial blood pressure was taken as the mean value of 3 successive readings in 3 different days. The mean arterial blood pressure was measured using the following equation:

Mean arterial BP=Diastolic BP + 1/3 Pulse pressure

While, the pulse pressure equals systolic BP – diastolic BP [8].

- Indicators of vascular dysfunction

1) Biochemical indicators: The following laboratory investigations were done just pre-dialysis which include hemoglobin level, serum creatinine, serum albumin, serum cholesterol, serum calcium (ca) and phosphorous (p) and Ca × P product, serum alkaline phosphatase. serum intact parathyroid hormone (iPTH) levels [9].

2) Structural indicators by the following: Radiological assessment of arterial calcifications by high resolution B-mode ultrasonography, using (Siemens Sono-Line G60F, Germany with transducer frequency 5-10 MHz for superficial arteries as femoral and carotid and 2-5 MHz for aorta). Scanning of the near and the far walls of the common carotid artery (CCA) in a 4-cm segment preceding the carotid bifurcation. A 10 cm segment of abdominal aorta above its bifurcation was scanned, and the femoral arteries were examined distal to the inguinal ligament proximal to the site of the division of superficial and deep femoral arteries. Arteries were scanned longitudinally and transversely to determine the presence of plaques. A localized echostructure encroaching into the vessel lumen was considered to be plaque when the arterial wall was > 50% thicker than the neighbouring sites. Highly echogenic plaques producing bright white echoes with shadowing were considered to be calcifications [10]. Arterial calcifications in each arterial region were quantified qualitatively as absent (0) or present (1). The final overall score was obtained by the addition of calcifications from all studied zones. The final score ranged from 0 (absence of calcium deposits), to 3 (calcifications present in all arterial segments examined) [11].

Assessment of arterial stiffeness index by measurement of CCA diameter and CCA intima-media thickness (IMT): measured by high resolution B-mode ultrasonography (Siemens Sono-Line G60F, Germany, using 5-10 MHz transducer) enabling assessment of arterial wall displacement during the cardiac cycle which was measured on the far wall at the same level as the diameter measurements and were always performed in plaque-free arterial segments in CCA [11].

3) Functional Indicators: by the following: 3a) Aortic pulse wave velocity (PWV) which was determined using transcutaneous Doppler flow velocity recordings using 8 MHz transducer.

PWV in cm/second was defined by Moens-Kortweg equation, PWV= √(Eh/2pR), where E is Youngs modulus of the arterial wall, h is wall thickness, R is arterial radius at the end of diastole, and p is blood density [11].

Renal resistance indices (RRI): Measured by Coloured Doppler ultrasound (Siemens Sono-Line G60F, Germany using 2-5 MHz transducers) was used to evaluate intrarenal arterial blood flow and to obtain intrarenal Doppler spectra in each kidney and calculation of renal resistance indices. The ultrasound probe was positioned gently on the flank in an oblique projection, and the kidney was visualized as a longitudinal image. To examine the interlobar arteries, we obtain real-time colour coded Doppler mode images, in which intrarenal arterial and venous flows shown in different colours. Sample volumes were obtained to position the cursor of the pulsed Doppler mode at the mid portion of the interlobar arteries which flow along the renal pyramids. The pulsed Doppler mode was used to obtain quantitative measurement of velocity by placing a cursor along the course of interlobar arteries. We adjust our machine as the velocity scale was adjusted for the lowest flow possible. We minimize the pass filter to avoid eliminating any of flow colour information. The colour gain was increased to maximum and then reduced gradually until the disappearance of the background noise thus ensuring a range of colors inside the vessels. We used the angle correction menu of the apparatus. The peak systolic flow velocity (PSV) and the end-diastolic flow velocity (EDV) were calculated by the ultrasound apparatus. The renal resistive index (RI) was measured as follows: RI= (PSV – EDV)/PSV [12,13].

Statistical Analysis

Statistical analysis was performed with Statistical Package for Social Science (SPSS version 17). For quantitative data, the mean and the standard deviation were calculated, Chi-square was done for qualitative data, comparison between the studied groups was performed with student t-test, with $P<0.05$ were considered statistically significant. Correlation between variables was evaluated using Pearson's correlation coefficient [14].

Results

Tables 1 and 2 summarized demographic and laboratory data of the studied patients and controls. The decline in anthropometric measures of studied patients reflected that there was significant growth retardation in children with ESRD as compared to controls. There was a highly significant increase in the mean blood pressure of the patients group compared to the controls (P<0.001**). There was a highly significant increase in PTH of patients as compared to controls (P<0.001**).

Table 1 Demographic data of studied patients and controls.

Variables		Groups		Statistical test	
		Group 1 (Patients) (N=30)	Group 2 (Control) (N=30)	T or X2	P-value
Age (Years)	Range	Apr-19	Apr-19	t=0.00	1
	Mean ± SD	13.86 ± 3.83	13.8 ± 3.8		
Sex	Male No (%)	18 (60%)	18 (60%)	X=0.00	1
	Female No (%)	12 (40%)	12 (40%)		
Weight (kg)	Range	14-53	18-71	t=6.325	<0.001
	Mean ± SD	30.10 + 10.1	52.03 + 14.3		
Height (cm)	Range	95-157	103-170	t=9.201	<0.001**
	Mean ± SD	131 + 15.01	153.1 + 16.14		
MAC (cm)	Range	Dec-24	18.5 -27.5	3.944	<0.001**
	Mean ± SD	17.63 + 3.52	22.73 + 3.55		
Duration of Dialyses (months)	Range	Jun-84			
	Mean ± SD	24.95 ± 20.343			
Mean arterial blood pressure (mmHg)	Range	73-130	73-196	4.033	<0.001**
	Mean + SD	103.66 + 16.57	85.40 + 6.13		

No: Number; SD: Standard Deviation; MAC: Mid-Arm Circumference; T: Student T Test; $X^{2:}$ Chi Square Test; P: Probability; *Statistically Significant

Table 2 Biochemical parameters of studied patients and controls.

Parameter		Patients	Controls	t test	P value
Serum creatinine (mg/dl)	Range	4.5 - 9.4	0.3 - 0.8	19.642	<0.001**
	Mean + SD	7.38 + 1.32	0.633 + 0.154	--	--
Blood urea (mg/dl)	Range	6.96 + 1.37	0.63 + 0.15	19.632	0.001
	Mean + SD	95-164	15-35		
Serum albumin (g/dl)	Range	3.4-4.5	04-Jun	3.317	0.001
	Mean + SD	3.94 + 0.27	5.11 + 0.59		
Hb% (g/dl)	Range	6 - 10.6	11.5 - 13.5	9.052	<0.001**
	Mean + SD	8.5 + 1.471	12.29 + 0.658		
Cholesterol (mg/dl)	Range	185 - 285	150 - 193	5.635	0.019*
	Mean + SD	222.06 + 32.260	159.62 + 29.83		
Serum Calcium (mg/dl)	Range	7.5 - 8.9	9.1 - 11	9.954	<0.001**

	Mean + SD	8.23 + 0.449	10.033 + 0.532		
Phosphorus (mg/dl)	Range	4 - 7.8	3.5 - 4.5	5.68	<0.001**
	Mean + SD	5.440 + 1.028	3.880 + 0.270		
Alk.ph U/L	Range	85 - 640	55 – 123	1.823	0.079
	Mean + SD	202.53 + 155.6	86.20 + 6.88		
PTH pg/ml	Range	602 - 2220	23 – 63	7.63	<0.001**
	Mean + SD	1115.73 + 140.53	43.93 + 12.53		

Table 3 summarizes sites and scores of arterial calcifications detected in patients and controls, 24 (80%) of the studied patients showed calcifications in one or more of the studied different sites.

Table 3 Sites and scores of arterial calcifications detected in patients and controls.

Variables		**Patients No=30**	**Control No=30**	**Chi-Square**	**P-value**
Calcification sites	No calcification No (%)	6 (20%)	30 (100%)	20.336	0.001**
	FA No (%)	14 (46.8%)	0 (0%)		
	CCA No (%)	4 (13.3%)	0 (0%)		
	CCA + FA No (%)	2 (6.7%)	0 (0%)		
	CCA + FA + Ao No (%)	4 (13.3%)	0 (0%)		
Calcification score	0.00 No (%)	6 (20%)	30 (100%)	21.253	0.001**
	1.00 No (%)	18 (60%)	0 (0%)		
	2.00 No (%)	2 (6.7%)	0 (0%)		
	3.00 No (%)	4 (13.3%)	0 (0%)		

Table 4 Structural and functional parameters of vascular dysfunction in studied patients and controls.

Variables	**Parameter**		**Patients**	**Controls**	**t-test**	**P-value**
	Mean CCA diameter (mm)	Range	4.9 – 7.8	3.9 – 5.0	8.821	<0.001**
Structural indicators		Mean + SD	6.06 + 0.555	4.61 + 0.337		
	CCA-IMT (μm)	Range	350 - 770	225 - 415	6.869	<0.001**
		Mean + SD	612.3 + 153.78	336 + 52.8		
	Aortic PWV (cm/sec.)	Range	910 - 1280	880 - 925	3.526	0.025*
		Mean + SD	1010.2 + 126.3	910.2 + 14.09		
Functional indicators	Renal PSV (cm/sec)	Range	29.7 - 62.8	34.7 – 52.2	0.449	0.526
		Mean + SD	41.15 + 18.60	43.38 + 5.04		
	Renal Resistance Index	Range	0.42 – 0.92	0.39 – 0.68	1.254	0.358
	(Renal RI)	Mean + SD	0.680 + 0.309	0.537 + 0.099		

Table 4 summarized structural and functional indicators of vascular dysfunction of our studied patients and controls (mean CCA diameter, the mean CCA-IMT, the Aortic PWV, Calcification score, renal PSV and renal RI). There was a highly significant increase in the CCA diameter, CCA-IMT and Ao. PWV in studied patients as compared to the controls (P<0.05). But there was no significant difference between patients and controls as regard renal PSV and renal RI (P>0.05).

Table 5 Correlations between different studied parameters in patient group.

Variables		r	p
Calcification score	CCA diameter	0.514	0.050*
	CCA-IMT	0.918	0.001**
	Ao PWV	0.883	0.001**
	PTH	0.373	0.171
	CaXP	0.809	0.001**
	Dialysis duration	0.51	0.05*
	MAP	0.441	0.048*
CCA-IMT	PTH	0.255	0.236
	CaXP	0.722	0.002*
	Dialysis duration	0.552	0.033*
Ao PWV	PTH	0.709	0.007*
	CaXP	0.708	0.003*

Table 5 and Figures 1-5 showed correlations between different studied parameters in patients group, there is a significant positive correlation between calcification score and the mean CCA diameter, the mean CCA-IMT and the Aortic PWV (P<0.05). There is also a significant positive correlation between calcification score and Ca × P product, the dialysis duration and MAP (P<0.05) but there is no significant correlation between calcification score and the PTH level. There is a significant positive correlation between the CCA-IMT and the Ca × P product and the duration of dialysis (P<0.05) but there is no significant correlation between CCA-IMT and PTH. There is a significant positive correlation between the Aortic PWV and the PTH level and Ca × P product (P<0.05).

Discussion

Cardiovascular disease is the main cause of death in adults with ESRD 3. Damage of large arteries is a major contributory factor to the high cardiovascular morbidity and mortality of ESRD patients [4,5].

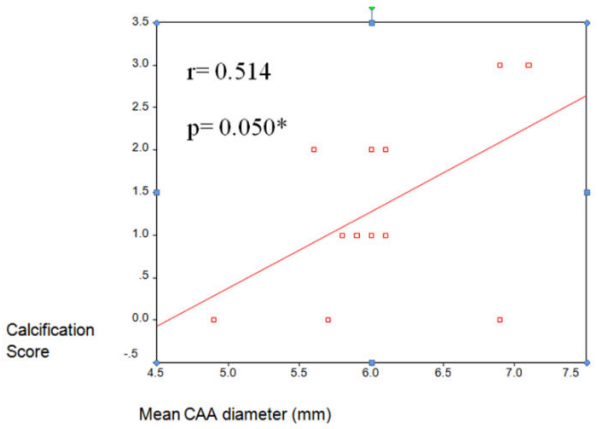

Figure 1 Normal value of pulse wave velocity (PWV) in healthy children and teenagers [12].

The adverse effects of macrovascular disease are attributable to two principal mechanisms, the first is presence of occlusive lesions, principally atherosclerotic plaques, responsible for ischemic lesion, and the second is stiffening of arterial walls associated with arterial wall dilatation and hypertrophy leading to increased left ventricular mass [6].

The present work was done to detect vascular disease in children with ESRD on regular haemodialysis particularly arterial calcification and stiffness [12].

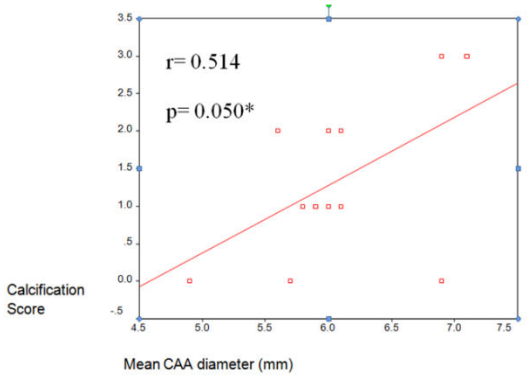

Figure 2 Correlation between calcification score and the mean common carotid artery (CCA) diameter in studied patients.

In the present work, we found vascular calcification in 80% of the studied patients in different arteries with the femoral arteries being the most frequently involved.

Little previous studies were done for detection of arterial calcification in paediatric patients with ESRD, while several studies were done in adult patients.

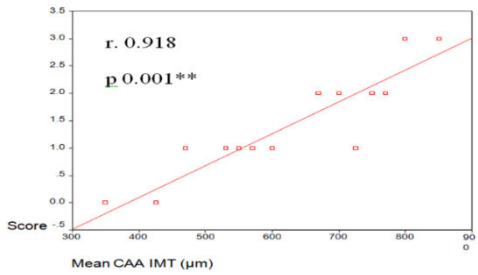

Figure 3 Correlation between calcification score and the mean common carotid artery intimal media thickness (CCA-IMT) in studied patients.

Hanada et al. studied 101 adult patients with predialysis CKD and among these subjects 82% had abdominal aortic calcifications [13].

Study of Groothoff et al. found only one male patient, in whom a hypercholesterolemia was well established, that showed wall irregularities and signs of calcified plaque formation in the CCA [14,15].

Temmar et al. studied adults with different stages of CKD and concluded that vascular calcifications appear early in patients with CKD and worsens as disease progresses [12].

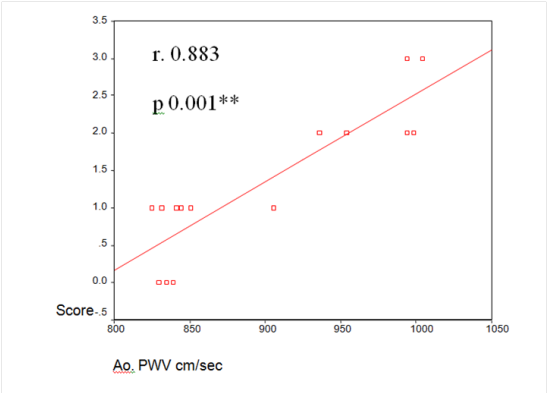

Figure 4 Correlation between calcification score and the aortic pulse wave velocity (PWV) in studied patients.

Honkanen et al. studied the presence of abdominal aortic calcifications in patients aged ≥ 18 years with duration of dialysis ≥ 3 months using lateral lumbar plain radiography. Calcifications were present in 81% of their studied patients [16].

Guerin et al. studied 120 ESRD patients on haemodialysis using B- mode ultrasonograhy, vascular calcification was detected in about two thirds of patients with one quarter of them having calcification score (4) [11].

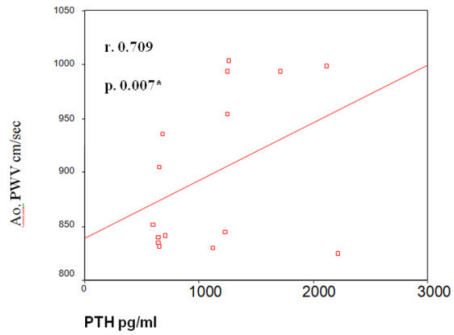

Figure 5 Correlation between the aortic pulse wave velocity (PWV) and the parathormone hormone (PTH) level in studied patients.

In the view of the above studies, vascular calcifications in adult patients under regular haemodialysis are well documented. We found vascular calcification is common in haemodialysis children. Our studied patients are relatively on dialysis for long time and non-optimal metabolic control; this may explain the high incidence of vascular calcification in those children.

In our study, we found a statistically significant positive correlation between calcification score and duration of dialysis, Ca × P product and mean arterial blood pressure, while there was no significant correlation between calcification score and PTH level.

The longer the time on dialysis, the more frequency of vascular calcification, this was also reported by other previous studies e.g. Guerin et al., Blacher et al. and Moe et al. [11,17,18].

In our study, Ca × P product was correlated positively with calcification score. In contrast, Savage et al. found negative correlation between Ca × P product and calcification score [10], while there was no correlation between them in study of Guerin et al. The difference in results may be related to the difference in the dialysis duration, level of calcium and phosphorus and the dose of $CaCO_3$ received [11].

Our patients have high Ca × P product and this increase was found to be due to hyperphosphatemia that results from insufficient dose of calcium containing phosphate binders. London et al. showed that the medial vascular calcification occurred in younger patients with longer duration of haemodialysis and derangement in their Ca × P products [19].

Increased intracellular phosphate appears to induce the formation of matrix vesicles. These matrix vesicles in turn, are known to be important in osteogenesis. High intracellular phosphate down regulates typical SMC genes and stimulates the production of Cbfα1, which is a central transcription factor in osteogenic differentiation [20].

In study of Guerin et al. study which included a well-controlled dialysis patients, phosphatemia was kept at a

reasonable level, so neither phosphatemia nor Ca × P product was associated with calcification score [11].

PTH showed no correlation to calcification score in our patients and this was also reported by Arad et al. and savage et al. [21]. Our results differ from that of Guerin, et al. showed a negative correlation between calcification score and PTH [10,11,21].

In the study of Guerin, et al. their patients were mainly of the adynamic bone disease type that occurs in elderly with hypoparathyroidism and extraosseous calcifications [11].

In our patients, the mineral bone disease (MBD)is typically of high bone turnover type with PTH level markedly high and most of patients have hyperphosphatemia rather than hypocalcemia, this type of MBD may be due to low dose of vitamin D supplementation, inadequate intake of oral calcium containing phosphate binders and poor drug compliance.

To assess arterial stiffness, we measured the CCA diameter, CCA-IMT and aortic PWV. We found increased CCA diameter, CCA-IMT and aortic PWV in our patients compared to controls.

Increased CCA-IMT in haemodialysis patients was also reported in adults [22] and in children. In the study of Mitsnefes et al. they found that children with ESRD who were on dialysis had a greater CCA-IMT than both CKD patients without dialysis and healthy control children [23,24].

In contrary to our study, Groothoff, et al. found that no difference in CCA-IMT between ESRD patients and controls. This may be explained by the shorter duration of their studied patients on dialysis when compared to our patients [15].

Covic et al. studied 14 children with ESRD on haemodialysis using aortic PWV and concluded that children on dialysis have already significant arterial wall structural abnormalities and as a consequence stiffer large arteries as reflected by a PWV 22% greater than controls [25].

In an attempt to find the factors increasing the risk of arterial stiffening, we found that CCA-IMT correlated positively with the duration of dialysis and Ca × P product while it had no significant correlation with the PTH level.

As the Ca × P product increases, the arterial stiffness becomes more predicted; this was also previously reported by Mitsnefes et al. and Covic, et al. [23-25].

We found that the higher the calcification score, the higher the CCA diameter, CCA-IMT and aortic PWV. So, arterial stiffness in children with ESRD is highly dependent on the presence and extent of vascular calcification and this may be resulted from the biochemical alterations in calcium-phosphate metabolism occurred due to the disease, inadequate drug intake and the prolonged period of dialysis.

This relation between calcification and stiffness was also reported by other previous studies [17,11,26].

The arterial system in our patients is characterized by intima-media hypertrophy of large arteries (aorta and carotid) with calcification of elastic lamellae, increased extracellular matrix with more collagen and relatively less elastic fibre content as seen in experimental uremia [27,28]. This remodeling is associated with arterial stiffening leading to increased PWV and is responsible for an early return of wave reflections from the periphery to the ascending aorta during systole, causing an abnormal rise in aortic systolic blood pressure and decrease of diastolic blood pressure. This abnormal pressure pattern leads to left ventricular hypertrophy and altered coronary perfusion.

Guerin et al. reported that many factors contribute to stiffness in adults, rather than calcification includes age, tobacco smoking, blood pressure level, diabetes mellitus, hypercholesterolemia and low serum albumin which are known as ordinary cardiovascular risk factors in addition to extraosseous calcifications [11].

Our patients are relatively of young age and the detailed examination of the cardiovascular status, in a population considered free of other confounders associated with age, supports the importance of the uremic milieu in the pathogenesis of early and accelerated vascular remodelling and calcification.

Measurement of arterial stiffening and calcification parameters will explore both structural and functional properties and could help not only in risk management strategies but also in risk reduction strategies by monitoring those arterial parameters under different drug regimens.

Conclusion

The main cardiovascular risk factor in ESRD children on regular haemodialysis is vascular calcifications which is associated with increased stiffness of large capacitative, elastic type arteries like the aorta and CCA. The extent of arterial calcification increases mainly with the duration of dialysis and abnormalities in Ca × P product.

Recommendations

It is prudent to evaluate vascular dysfunction in children with ESRD more than recommended in general population. Early recognition of vascular calcifications might be of protective value against cardiovascular mortality It is recommended to decrease the risk of vascular calcification in pediatric patients with ESRD by optimal control of blood pressure, correct dosing of vitamin D and serum phosphate reduction which can be achieved by restrictive phosphate in diet, increasing phosphate binders, efficient dialysis or in combination.

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