Geget (2011) 11 (1) : r7 - 45

Original Article

Vitamin D as a Marker of Arterial Calcification and Cardiovascular Risk in Children on Regular Hemodialysis

Hany El Bayed, Doaa Mostafa, Ashgan Al (hobashy and Amal Fathy*

Departments of Pediatric Nephrodialysis and Medical Biochemistry, Faculty of Medicine, Zagazig University, Egypt.*

ABSTRACT

Background: Vitamin D is essential for promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and prevent hypocalcemic tetany. It has other roles including modulation of neuromuscular and immune function and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Decreased serum levels of vitamin D have been related to arterial stiffening and vascular calcifications in haemodialysis (HD) patients but the pathophysiology of this association is not yet clear.

Objectives: The aim of this study is to evaluate the relationship between vascular calcifications, cardiovascular risk factors especially (left ventricular mass index) and 25-hydroxyvitamin D3 [25(OH)D_3] and 1,25-dihydroxyvitamin D3 [1,25$(OH)_2D_3$] serum levels in children with chronic renal failure on regular haemodialysis.

Methods: The study was conducted on 30 children regularly haemodialyzed 3 times weekly and 3 hours per session by polysulfone membrane using citrate dialysate. All cases were subjected to detailed history taking, thorough clinical examination, laboratory investigations including assessment of serum 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 by thin layer chromatography. Echocardiography was done for evaluation of left ventricular mass index (LVMI) by Devereux's formula.

Results: There was a significant and a highly significant negative correlation between left ventricular mass index (LVMI) and 25-OH and 1-25$(OH)_2$ respectively. Increased left ventricular mass Index in patients without one alpha supplementation was found.

Conclusion: We conclude that deficiency of [25(OH)D_3] and [1,25$(OH)_2D_3$] is prevalent in hemodialyzed children and is associated with cardiovascular risk.

INTRODUCTION

Cardiovascular disease is one of the most common causes of death in dialysis patients[1]. Increasing evidence shows that abnormalities in mineral metabolism may play an important role in cardiovascular disease in patients with chronic kidney disease (CKD), as hyperphosphataemia, hypocalcaemia, high calcium—phosphorus product and secondary hyperparathyroidism have all been associated with increased mortality in dialysis patients[2,3]. Advanced CKD leads to divalent cation and metabolic derangements as well as decreased production of 1,25-dihydroxyvitamin D3 [1,25$(OH)_2D_3$] (calcitriol) all of which can cause

parathyroid gland hyperplasia and development of bone disease[4,5]. One of the major actions of vitamin D is to maintain calcium and phosphate serum concentrations in the normal range and to allow for mineralization of newly synthesized bone[4].

AIM OF THE WORK

The aim of this study was to evaluate the relationship between vascular calcifications, cardiovascular risk factors especially (left ` ventricular mass index) and 25-hydroxyvitamin D3 [25(011)D_3] and 1,25-dihydroxyvitamin D3 [1,25(OH)2D_3] serum levels in children with chronic renal failure on regular haemodialysis.

SUBJECTS AND METHODS

Our study was carried out at the Pediatric Nephrology Unit and Medical Biochemistry Department of Faculty of Medicine in Zagazig University. Forty children were in _ ludcd in this study. They were classified into two groups.

1. Group A "Control Group":

This group comprised 10 healthy children attending the Pediatric Outpatient Clinic in Zagazig University. They were 3 males and 7 females. Their ages ranged from 9 to 15 years. All were apparently healthy, 'ith normal clinical examination. They had юо history of chronic illness and did not ie^.:ive any medication.

2. Group B "Case Group":

This group comprised 30 children on regular hemodialysis 3 times weekly by acetate dialysate 3 hours every session at the Pediatric Nephrology Unit, Zagazig University Hospital. They were 11 males and 19 females. Their ages ranged from 7 to 15 years. All children were subjected to complete history taking, through clinical examination and laboratory investigations including complete blood count (CBC), kidney function tests, liver function tests, serum calcium and phosphorus levels, serum iron, ferritin and parathyroid hormone (PTH) levels. Research investigations included assessment of serum 25-hydroxy vitamin D3 and 1,25-dihydroxy vitamin D3 by thin layer chromatography (TLC, WinCATS Planar Chromatography, E. MERK KGaA, Switzerland Manufacturer) and echocardiography for evaluation of left ventricular mass index (LVMI) by Devereux's formula[°01] and signs of vascular calcification by aortic sclerosis or calcification, if any.

LVMI (g/m^2) = (1.04 [(IVST + LVID + PWT)^3 — $LVID^3$] — 14 g)/воду surface area.

(IVST): Interventricular septal thickness

(LVID): Left ventricular internal diameter

(PWT): Posterior wall thickness

Statistical Analysis: Data was analyzed using SPSS (Statistical Package for Social Sciences) version **10.**

RESULTS

Our results are she wn in Tables 1 to 19 and Figures 1 to 5. Table 1 shows the characteristic data of the studied groups as .,gard age, gender ar j d' ration of dialysis. '^'he etiology of chronic renal failure in the ^rdied group was shown in Table 2. The most common cause is unknown (36.7%), followed by focal segmental glomerulo-::clerosis (13.3%) and obstructive uropathy (6.7%). Tables 3 and 4 show the clinical and laboratory data of the gtudied groups. Table 5 shows the relation of blood pressure

to left ventricular mass index (LVMI), 25-OH and 1-25$(OH)_2$ in the hemodialysis group. There was a highly significant and significant positive correlation between LVMI and blood urea nitrogen and creatinine, respectively as shown in Table 6. Also, there was a significant negative correlation and a highly significant positive correlation between LVMI and hemoglobin and parathormone (PTH), respectively as shown in Tables 7 and 8. Tables 9 and 10 show significant and highly significant negative correlation between LVMI and 25-OH and 1-25$(OH)_2$ respectively. There was a significant positive correlation between LVMI and Duration of dialysis as shown in Table 12. Tables 13 and 14 show a significant positive correlation and a significant negative correlation between 25 -OH, 1-25 $(0H)_2$ and Calcium & Phosphorus and Ca*P product respectively. There was a significant negative correlation between 25-OH, 1-25$(OH)_2$ and PTH as shown in Table 16. A positive correlation between Ca*P product and PTH was shown in Table 19. Table 18 shows increased [25(OH)D_3] & [1,25$(OH)_2D_3$] levels in patients with one alpha supplementation and increased left ventricular mass index in patients without One alpha supplementation. Also, Table 17 shows nosignificant difference between patients with calcium supplementation and without calcium supplementation in studied group as regards different laboratory parameters. No significant correlation between LVMI and calcium, phosphorus, iron, albumin and ferritin was found as shown in Table 11. In addition, no significant correlation between 25-OH, 1-25$(OH)_2$ and iron & ferritin was found as shown in Table 15.

Table 1: Characteristics of the studied group.

	Cases N = 30	**Control N = 10**	**Test of Significance**
Age: (years)			
$\overline{X}$ ± **SD**	12.87 ± 2.43	12.70 ± 2.54	t = 0.186
Range	7-15	9-15	p = 0.854
Gender:			
Male	11 (36.7%)	3 (30%)	$\chi 2$ = 0.17
Female	19 (63.3%)	7 (70%)	p = 0.702
Duration of dialysis: (years)			
$\overline{X}$ ± **SD**	3.26 ± 2.22		
Range	1-7 yrs		

Table 2: Showing the underlying etiology of chronic renal failure in the studied group.

Etiology	No.	%
Familial Mediterranean fever	1	3.3
Steroid resistant nephrotic syndrome	2	6.7
Focal segmental glomerulosclerosis	4	13.3
Unknown	11	36.7
Chronic familial interstitial nephritis	2	6.7
Sickle cell nephropathy	1	3.3
Neurogenic bladder	1	3.3
Chronic interstitial nephritis	2	6.7
Diffuse proliferative glomerulonephritis	1	3.3
Rapidly progressive glomerulonephritis	1	3.3
Vesicouretric reflux	2	6.7
Juvenile nephronophthisis	1	3.3
Membranoproliferative glomerulonephritis	1	3.3
Total	30	100.0

Table 3: Clinical data of studied group on haemodialysis.

Clinical Manifestation	Number of Cases (Total = 30 case)
Blood pressure:	
Hypertensive	8
Hypotensive	10
Normotensive	12
Cardiomegaly	15
Pallor	14
Chest pain	3
Palpitation	11

Table 4: Showing the laboratory parameters of the studied groups.

	Cases (n = 30) on Hemodialysis			Control (n = 10)			t	p
	M ± SD	Range	Median	M ± SD	Range	Median		
Alb g/dl	3.39 ± 0.51	2 - 4.5	3.4	4.49 ± 0.72	3.5 - 5.5	4.65	- 4.468	0.001 **HS**
BUN mg/dl	63.59 ± 26.38	6 - 131.8	62	12.30 ± 5.12	5 - 20	12.5	10.095	0.000 **HS**
Creatinine mg/dl	7.57 ± 2.07	2.4 - 11.9	7.6	0.97 ± 0.35	0.5 - 1.5	0.95	16.769	0.000 **HS**
HB g/dl	9.63 ± 1.55	7.1 - 13.7	9.7	13.70 ± 1.16	12 - 15	14	- 7.615	0.000 **HS**
Platelet Count/cmm	243.77 ± 83.92	38 - 424	237.5	227.50 ± 96.07	100 - 400	200	0.512	0.611
Ca mg/dl	9.95 ± 14.26	4.9 - 8.5	7.2	10.10 ± 0.88	9 - 11	10	- 0.034	0.973
PO_4 mg/dl	6.01 ± 2.33	2.4 - 12.3	5.3	4.44 ± 0.75	3.6 - 5.6	4.3	3.217	0.003 **HS**
Ca*PO_4 mg/dl	45.82 ± 24.77	17.4 - 125.96	36.8	45.32 ± 11.05	32.4 - 61.6	40.75	0.061	0.952
PT seconds	17.73 ± 26.32	11.6 - 157	12.6	11.70 ± 1.57	10 - 14	11.5	0.718	0.477
PTT seconds	43.46 ± 16.72	3.8 - 89.8	40.25	38.20 ± 5.16	30 - 45	39.5	0.972	0.337
Fe mg/dl	68.92 ± 31.87	19.3 - 164.8	61.5	87.90 ± 22.75	50 - 120	92.5	- 1.735	0.091
PTH pg/ml	610.30 ± 736.92	25.5 - 3292	373.9	26.20 ± 16.45	7 - 53	21	4.338	0.000 **HS**
Ferritin ng/ml	1158.01 ± 1073.75	185.5 - 5018	958.5	72.10 ± 35.77	25 - 140	70	5.530	0.000 **HS**
25-OH ng/ml	25.91 ± 15.73	5 - 44	25.5	36.00 ± 17.13	10 - 60	37.5	- 1.719	0.094
1-25$(OH)_2$ ng/ml	47.01 ± 26.33	5 - 77	47.05	0.03 ± 0.09	0.02 - 0.05	0.03	9.772	0.000 **HS**
LVMI g/m^2	177.90 ± 96.86	71 - 392	150.5	36.41 ± 0.86	35 - 37.6	36.55	8.000	0.000 **HS**

Table 5: The relation of blood pressure to different parameters in the studied group.

	Blood Pressure			F	p
	Normotensive (n = 12) A	Hypertensive (n = 8) B	Hypotensive (n = 10) C		
LVMI g/m²	161.83 ± 89.48	239.00 ± 92.29	148.30 ± 95.83	2.445	0.106
25-OH ng/ml	27.48 ± 15.70	21.49 ± 18.59	27.57 ± 14.27	0.414	0.665
1-25(OH)₂ ng/ml	52.39 ± 25.95	39.26 ± 32.89	46.76 ± 21.87	0.580	0.567

Least significant difference between groups A,B B,C and A,C

LVMI

A versus B → p = 0.078

A versus C → p = 0.735

*B versus C → p = **0.048****

25-OH

A versus B → p = 0.421

A versus C → p = 0.989

B versus C → p = 0.431

1-25 (OH)₂

A versus B → p = 0.291

A versus C → p = 0.627

B versus C → p = 0.559

Normal LVMI= 35 - 37.6 g/m²

Normal 25-OH = 10 - 60 ng/ml

Normal 1-25(OH)₂ = 0.02 - 0.05 ng/ml

Table 6: Correlation between left ventricular mass index (LVMI), blood urea nitrogen and creatinine in the studied group.

	LVMI g/m²		Sig.
	r	p	
Blood Urea Nitrogen mg/dl	0.635	<0.001	HS
Creatinine mg/dl	0.402	0.028	S

Table 7: Correlation between left ventricular mass index and hemoglobin in the studied group.

	LVMI g/m^2		Sig.
	r	p	
Hemoglobin g/dl	- 0.523	0.003	S

Table 8: Correlation between left ventricular mass index and PTH in the studied group.

	LVMI g/m^2		Sig.
	r	p	
Parathormone pg/ml	0.695	< 0.001	HS

Table 9: Correlation between left ventricular mass index and 25-OH in the studied group.

	LVMI g/m^2		Sig.
	r	p	
25-OH ng/ml	- 0.584	0.001	S

Table 10: Correlation between left ventricular mass index and 1-25(OH)$_2$ in the studied group.

	LVMI g/m^2		Sig.
	r	p	
1-25(OH)$_2$ ng/ml	- 0.766	< 0.001	HS

Table 11: Correlation between left ventricular mass index and calcium, phosphorus, iron, albumin and ferritin in the studied group.

	LVMI g/m^2		Sig.
	r	p	
Calcium mg/dl	0.152	0.422	NS
Phosphorus mg/dl	0.316	0.089	NS
Iron mg/dl	0.035	0.854	NS
Albumin g/dl	0.016	0.934	NS
Ferritin ng/ml	0.130	0.493	NS

Table 12: Correlation between left ventricular mass index and duration of dialysis in the studied group.

	LVMI g/m^2		Sig.
	r	p	
Duration of dialysis	0.498	0.005	S

Table 13: Correlation between 25-OH, 1-25(OH)$_2$ and calcium & phosphorus in the studied group.

	25-OH			1-25(OH)$_2$		
	r	p	Sig.	r	p	Sig.
Calcium mg/dl	0.576	0.001	S	0.404	0.027	S
Phosphorus mg/dl	0.398	0.030	S	0.503	0.005	S

Table 14: Correlation between 25-OH, 1-25(OH)$_2$ and Ca*P product in the studied group.

	25-OH			1-25(OH)$_2$		
	r	p	Sig.	r	p	Sig.
Ca*PO$_4$ Product mg/dl	-0.369	0.045	S	-0.521	0.003	S

Table 15: Correlation between 25-OH, 1-25(OH)$_2$ and iron and ferritin in the studied group.

	25-OH			1-25(OH)$_2$		
	r	p	Sig.	r	p	Sig.
Iron mg/dl	-0.027	0.885	NS	0.117	0.537	NS
Ferritin ng/ml	0.070	0.713	NS	-0.004	0.981	NS

Table 16: Correlation between 25-OH, 1-25(OH)$_2$ and parathormone in the studied group.

	25-OH			1-25(OH)$_2$		
	r	p	Sig.	r	p	Sig.
Parathormone pg/ml	-0.422	0.020	S	-0.383	0.037	S

Table 17: Correlation between calcium supplementation and studied parameters.

	Calcium Supplementation		t	p
	No (n = 12)	Yes (n = 18)		
LVMI g/m^2	162.33 ± 94.03	188.28 ± 99.99	0.713	0.482
25-OH ng/ml	35.68 ± 11.81	19.39 ± 14.81	3.188	0.004 HS
1-25(OH)$_2$ ng/ml	48.37 ± 28.18	46.11 ± 25.83	0.226	0.823
ALB g/dl	3.42 ± 0.47	3.37 ± 0.54	0.305	0.763
BUN mg/dl	55.92 ± 29.57	68.71 ± 23.49	1.318	0.198
Creatinine mg/dl	7.27 ± 2.62	7.78 ± 1.66	0.656	0.517

Table 18: Correlation between one alpha supplementation and studied parameters.

	One Alpha Supplementation		t	p
	No (n = 10)	Yes (n = 20)		
LVMI g/m^2	184.75 ± 96.42	164.20 ± 101.45	0.541	0.593
25-OH ng/ml	22.36 ± 17.06	27.69 ± 15.16	0.870	0.391
1-25(OH)$_2$ ng/ml	33.73 ± 27.33	53.66 ± 23.78	2.060	0.049 S
Albumin g/dl	3.51 ± 0.48	3.33 ± 0.52	0.917	0.367
BUN mg/dl	49.40 ± 25.23	70.69 ± 24.52	2.221	0.035
Creatinine mg/dl	6.93 ± 2.42	7.89 ± 1.85	1.213	0.235

Table 19: Correlation between Ca*P product and PTH in the studied group.

	PTH		
	r	p	Sig.
Ca*PO$_4$ Product mg/dl	0.267	0.153	NS

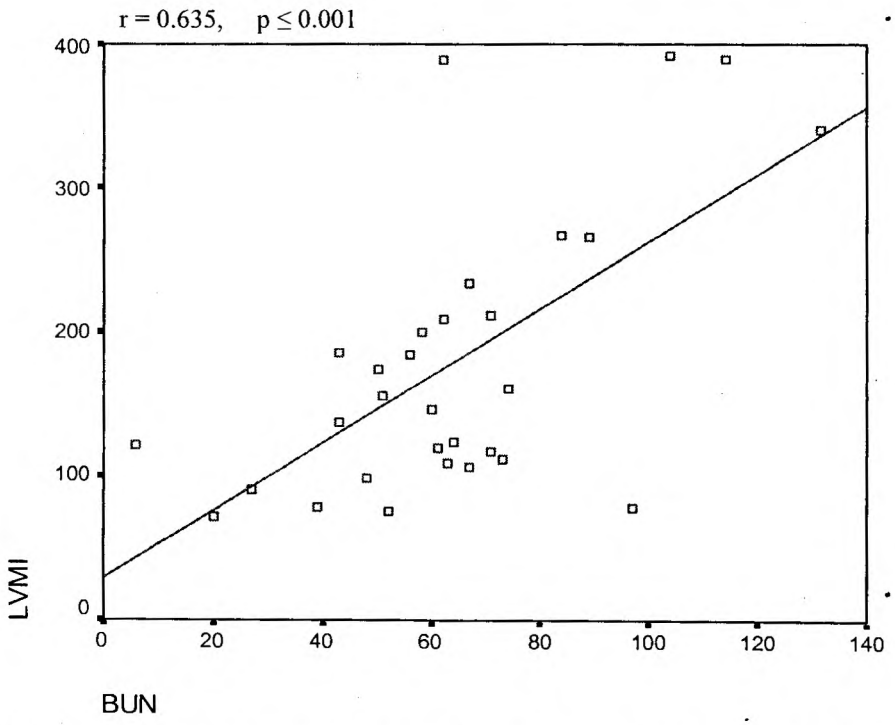

Fig. 1: Showing a highly significant positive correlation between LVMI and BUN.

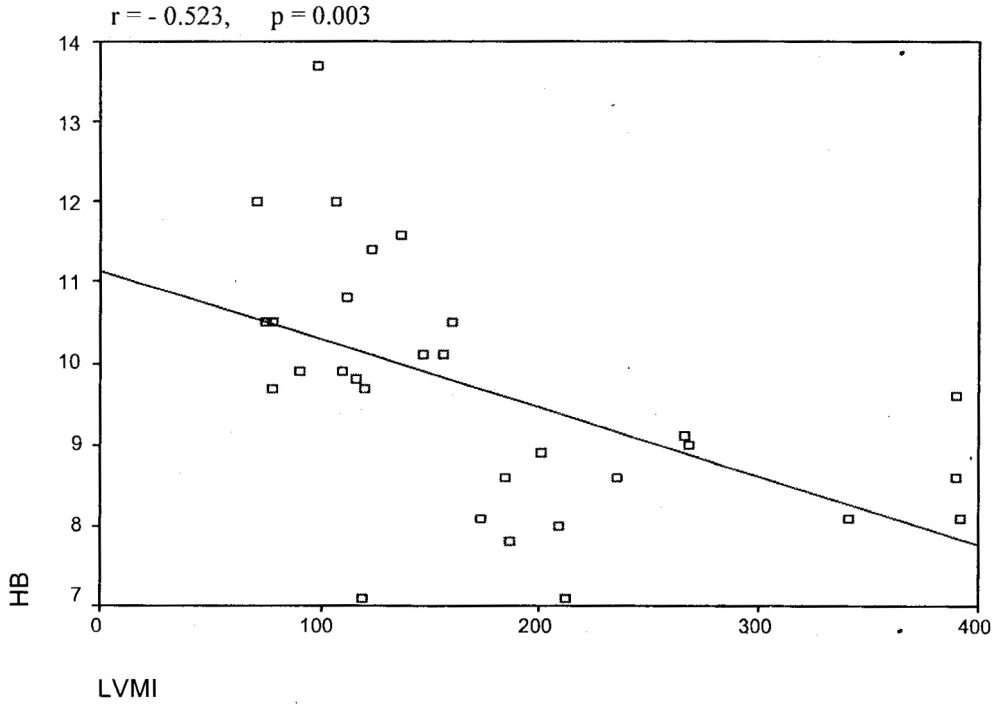

Fig. 2: A significant negative correlation between LVMI and HB.

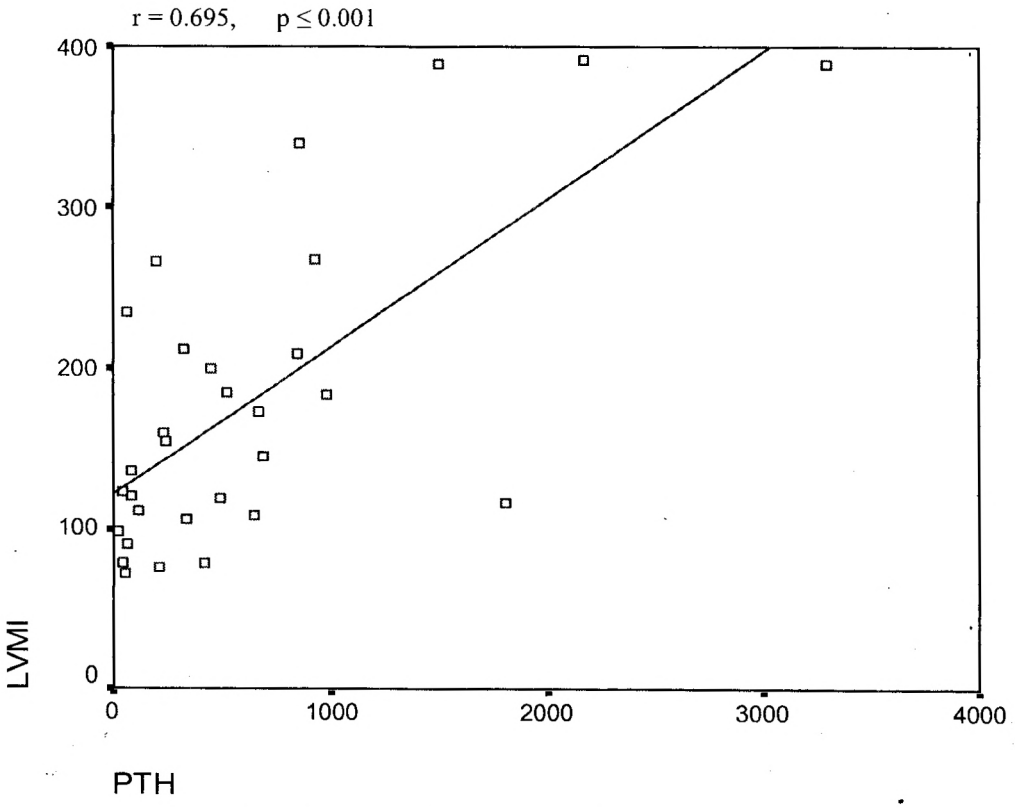

Fig. 3: A highly significant positive correlation between LVMI and PTH.

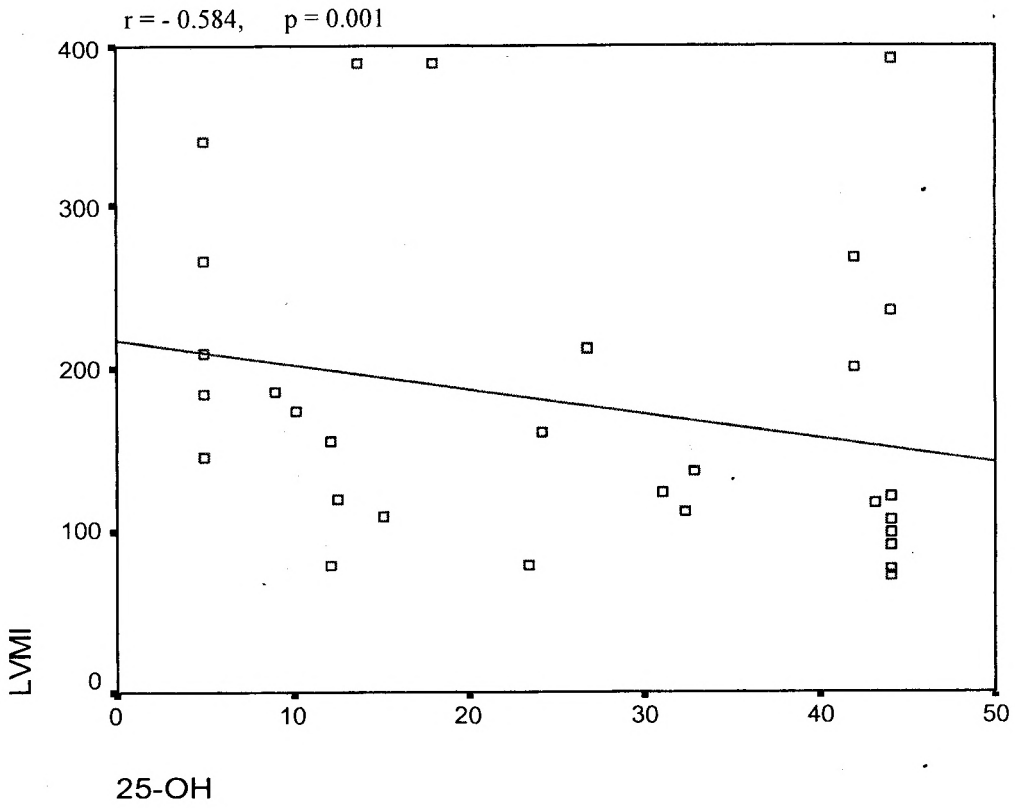

Fig. 4: A significant negative correlation between LVMI and 25-OH.

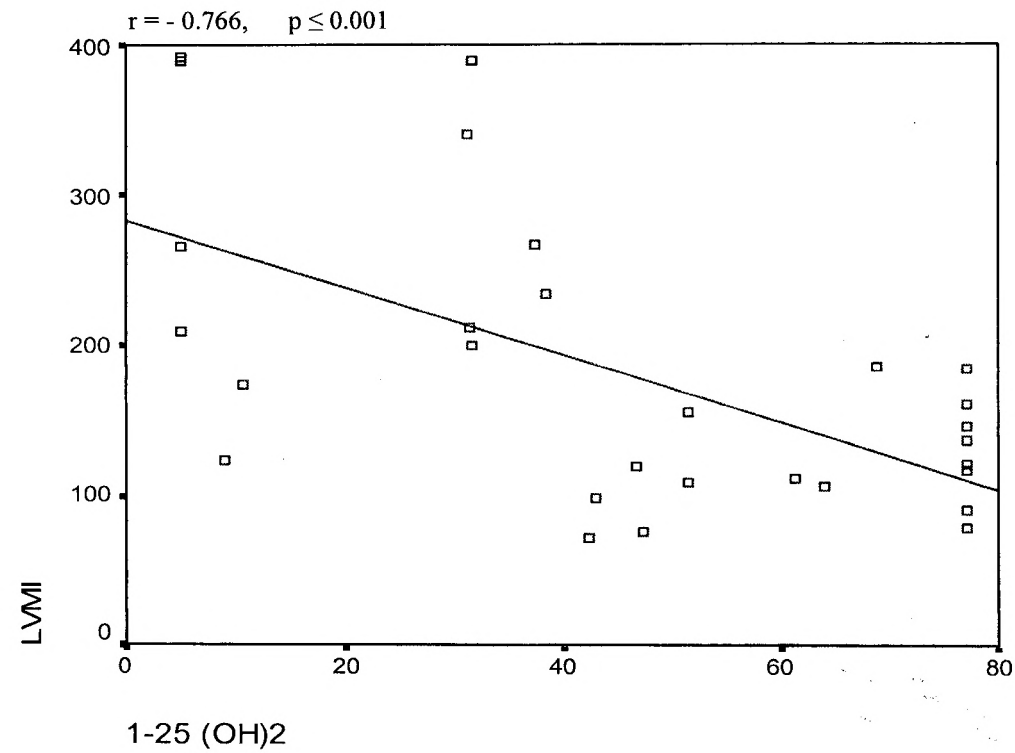

Fig. 5: A highly significant negative correlation between LVMI and 1-25$(OH)_2$.

DISCUSSION

Vitamin D, the sunshine vitamin, is so vitally important. It is a single nutrient and can have such a vast number of health benefits. First, it is important to realize that vitamin D is not "just a vitamin" but rather the only known substrate for a potent, pleiotropic (meaning it produces multiple effects) repair and maintenance hormones that serves multiple gene-regulatory functions in the body[8]. Arterial wall stiffness is a recognized complication in children with chronic kidney disease (CKD). Vascular abnormalities in these patients are shown to be followed by the development of cardiac abnormalities like left ventricular hypertrophy and diastolic dysfunction. The pathophysiology of the vascular abnormalities in these patients is not clear. Recently there has been increasing evidence on the role of vitamin D affecting the cardiovascular system, the vascular calcification process in particular. There is a high prevalence of vitamin D deficiency in the pediatric CKD population. 25-hydroxyvitamin D is the principal circulating storage form of vitamin D and reflects `nutritional' vitamin D status, in contrast to 1,25-dihydroxyvitamin D which reflects the `hormonal' status. There is a relationship between various parameters of calcium-phosphorus metabolism including 25-hydroxyvitamin D and arterial wall stiffness in pediatric patients with CKD[9]. Vitamin D deficiency may radically hamper the overall health. Just one example of an important gene that vitamin D up-regulates is the ability to fight infections including the flu. It produces over 200 anti microbial peptides, the most important of which is cathelicidin, a naturally occurring broad-spectrum antibiotic[8]. Optimizing vitamin D levels can also help you to prevent as many as 16 different types of cancer including pancreatic, lung, breast, ovarian,' prostate, and colon cancers. But perhaps most important to note is that vitamin D can lower the risk of dying from any cause, according to a new European meta-analysis published in the Archives of Internal Medicine in 2007. Another group of researchers have calculated that simply increasing levels of vitamin D3 could prevent diseases that claim nearly 1 million lives throughout the world each year, as the widespread vitamin D deficiency seen today is now thought to fuel an array of common chronic, diseases, such as cancer, hypertension, heart disease, autism, obesity, rheumatoid arthritis, diabetes 1 and 2. SO, Vitamin D is the "Master Key to Optimal Health" and therefore, monitoring of serum vitamin D considered so beneficiah[8].

We studied the relationship between vascular calcification, cardiovascular risk factors especially left ventricular mass index and 25-hydroxyvitamin D3 [25(OH) D_3] and 1,25-dihydroxyvitamin D3 [1,25 $(OH)_2D_3$] serum levels in children on regular haemodialysis.

We found that there was a deficiency of [25(OH)D_3] and [1,25$(OH)_2D_3$] serum level in the patient group, This result was in agreement with Patange et al., 2010, who show that serum 25-hydroxyvitamin D levels were low and whose study conducted in pediatric patients with CKD that suggests nutritional vitamin D deficiency as a possible cause of arterial stiffness, and the cardiac complications develop later in the course of the disease[9]. Also, the study by

Belostotsky et al., 2007, proved vitamin D deficiency in children with renal disease. A high proportion of renal patients were vitamin D deficient/insufficient, particularly children of South Asian origin[10].

Another study done by Shroff et al., 2008, showed that patients on peritoneal dialysis and hemodialysis had significantly lower 1,25$(OH)_2$D levels. Both low and high levels of 1,25$(OH)_2$D were associated with abnormal vascular measures. Patients with 1,25$(OH)_2$D in the normal range had carotid intima-media thickness (cIMT) levels comparable to those in the control subjects, but those with I ,25$(OH)_2$D <_40 or> 150 pmol/L had significantly higher cIMT. A strong quadratic relationship was found between cIMT and 1,25$(OH)_2$D and between the calcification score and 1,25 $(OH)_2$D, and thus vitamin D levels correlated with vascular measures[11]• Seeherunvong et al. 2009, reported that vitamin D insufficiency and deficiency are very prevalent in pediatric patients across all stages of O(D[12]. Cardiovascular disease is a major cause of death among patients with chronic kidney disease and vitamin D deficiency is a common problem among these patients[13].

In our study the most common clinical manifestations in hemodialyzed children is cardiomegaly, and by echocardiography there was increased left ventricular mass index (M + SD = 177.90f 96.86 g/m^2) comparing with control group (M t SD = 36.41 + 0.86 g/m^2). Several studies have reported elevated left ventricular mass index in children those on dialysis as follows: Kandil et al., 2009, reported that herodialysis is associated with accumulation of cardiovascular risk factors since left ventricular hypertrophy (LVH) was highly prevalent in pediatric patients on hemodialysis. Low fractional shortening (FS) and increased left ventricular mass index (LVMI) remain relatively good indicators and predictors of mortality in chronic hemodialysis pediatric patients. LVMI > 51 g/m^2 is highly sensitive while > 97 g/m^2 is highly specific as a short-term mortality predictor and FS < 28% was an excellent predictor of mortality in studied pediatric patitints[14]. Lumpaopong et al., 2005, indicated that left ventricular hypertrophy and abnormal LV geometry in chronic dialysis children were common. They reported that left ventricular hypertrophy (LVH) was defined as LVMI > 51 g/m^2 which in agreement with our study[15].

Another study reported that both children with chronic renal insufficiency (CRI) and those on dialysis had elevated LVMI compared with control subjects. Dialyzed children had significantly higher LVMI and higher prevalence of LVH when compared with children with CRI. Both the CRI and dialysis groups had greater cIMT, higher LVM index, and poorer diastolic function than the control subjects. Children who were on dialysis had greater carotid artery intima-media thickness (cIMT) and higher LVM index than those with CRI and greater arterial stiffness than both CRI patients and control subjtcts[16]. LVH was defined as LVMI > 95[tl]' percentile for normal children and adolescents[17]

In our study, we have a highly significant positive correlation between left ventricular mass index (LVMI) and parathormone (PTH) (r = 0.695 p < 0.001) which

run with Mitsnefes et al., 2005, who reported that LVMI in children with CRI and those on dialysis was positive correlated with PTH (r = 0.39, p 0.003)[16]. In our study, we have a significant negative correlation between left ventricular mass index and hemoglobin (r = .- 0.523, p = 0.003). Our result was in agreement with Mitsnefes et al., 2005, who reported that LVMI in children with CRI and those on dialysis was significant negative correlated with hemoglobin (r = - 0.48, p < 0.0001), Stepwise multivariate analysis demonstrated that higher PTH level and lower hemoglobin level were independent predictors of increased LVMI[16].

We found that there was a significant positive correlation (+ve correlation) between left ventricular mass index and duration of dialysis (r = 0.498, p = 0.005). The longer the duration of dialysis, the more the increased left ventricular mass index (and vice versa) but our result was against Kandil et al., 2009, and Lumpaopong et al., 2005, who found no significant correlation between LVMI and duration of dialysis(1 л,15>

We found a significant negative correlation between left ventricular mass index and 25(OH)D_3 and a highly significant negative correlation between left ventricular mass index and 1,25$(OH)_2D_3$). Our results were 'in agreement with Matias et al., 2010, who reported that lower circulating vitamin D levels correlated with increased BP and LVMI. There study had shown that the correction of vitamin D deficiency with vitamin D precursors, namely cholecalciferol, can decrease LVMh [18]. Lower circulating vitamin D levels correlated with increased BP and LVMI in humans(19,20>

In our study, there was a significant relation between blood pressure and left ventricular mass index "increased blood pressure lead to increased left ventricular mass index". The same was found by Lumpaopong et al., 2005, who showed that systolic, diastolic blood pressures, index systolic diastolic blood pressures (ISBP) and index diastolic blood pressures (IDBP) were significantly high in LVH patients (chronic dialysis children) and blood pressure had positive correlation with left ventricular mass[15]. However, Mitsnefes et al., 2005, reported that blood pressure was not significantly correlated with LVMh [16]

In our study, there was no significant correlation between left ventricular mass index and phosphorus and calcium this run with[15]. Calcium, phosphorus and calcium / phosphorus products tended to be high in LVH group but not statistically significant and this against Mitsnefes et al., 2005, who reported significant positive correlation between left ventricular mass index (LVMI) and Phosphorus (r = 0.27, p

Other investigators as Kandil et al., 2009, found that children undergoing chronic hemodialysis have increased LVMI with no significant correlation between LVMI and any of the clinical or laboratory data of the patients such as age, height, body mass index, duration of dialysis, dialysis session duration, dialysis flow, blood urea nitrogen, creatinine concentration, calcium, phosphorus, albumin, hemoglobin concentration, glomerular filtration rate and blood pressure[14].

We found that there was a significant negative correlation between [25(OH)D_3] &

[1 ,25$(OH)_2D_3$J serum level and Parathormone this result run with Belostotsky et al., 2007, whose study reported a high proportion of renal patients were vitamin D deficient/insufficient particularly children of South Asian origin and high PTH values might be due to vitamin D deficiency[10].

Also Shroff et al., 2008, said that intact PTH (iPTH) level inversely correlated with 1,25$(OH)_2D$ which rune with our results'[1]. Low I ,25$(OH)_2D$ results in an increase in PTH levels that can promote soft tissue calcification through its effect on calcium absorption and an efflux of Ca and P04 from a high-turnover bone state[21-23]

We studied the role of vitamin D as a marker of arterial calcification. We used Ca x P04 product and echocardiography as indicators of vascular calcification in the studied group. Our result indicate that there was significant negative correlation between Ca x P product and both [25$(OH)D_3$] and [1,25$(OH)_2D_3$] serum level. Some investigators studied a bimodal association of vitamin D levels and vascular disease in children on dialysis and reported that 1,25 $(OH)_2D_3$ showed a linear correlation with Ca x P04 product at the time of the study[11]. Calcification was most frequently observed in patients with the lowest 1 ,25$(OH)_2D_3$ and the highest high sensitivity C-reactive protein[11].

In our study, there was 8 cases had high Ca x P04 product (> 55 mg/dL) with significant increase in PTH levels and significant decrease in vitamin D and by echocardiography they had Aortic sclerosis as a marker of arterial calcification. Therefore, vitamin D deficiency may play a role in vascular calcification in herodialysis patients.

Cozzolino et al., 2005, studied the effect of increased calcium-phosphate product in arteriopathy and showed that a passive process is implicated in vascular calcification, i.e. calcium-phosphate precipitation in the vessel walls, associated with an active biological process "ossification" of the vascular wall structure. Important contributors to these calcifications are hyperphosphatemia and an increased calcium-phosphate product (> 55 mg/dl). At the same time, high levels of phosphate and/or calcium directly activate genes associated with osteoblastic functions in the smooth muscle cells (e.g. bone matrix protein 7, a2-HS glycoprotein, and matrix GLA protein)[26]. Some investigators study the role of vitamin D in vascular calcification in chronic kidney disease in some in vitro studies and proved that calcitriol has induced vascular calcification, by over suppression of PTH and induction of a low-turnover bone disease state, or by 'increased calcium-phosphorus (Ca x P04) product[27]. Shroff et al., 2008, showed that both low and high 1 ,25-dihydroxyvitamin D levels are associated with adverse morphological changes in large arteries, and that these changes may be mediated by the effects of 1 ,25$(OH)_2D$ on Ca—PO_4 homeostasis and inflammation[11].

Vitamin D analogues (paricalcitol, doxercalciferol, maxacalcitol) are capable of effective parathyroid suppression; they are structurally modified for fewer . calcemic and phosphatemic effects[13]. In a study by Cardus et al., 2007, demonstrated that paricalcitol has different effects on vascular

calcification compared with calcitriol. Both compounds raised the serum calcium and Ca x P product compared to control, but only calcitriol caused an increase in the calcification of the abdominal aorta[28]. Different VDR activators exert differential effects on vascular calcification independent of serum calcium, phosphorus and Ca x P product[13]. London et al., 2007, showed that [25(OH)D3] levels significantly negative correlated with markers of arteriolosclerosis and endothelial dysfunction in dialysis patients[29]. Low vitamin D levels were associated with increased carotid intima—media thickness[22].

Increased arterial calcification and stiffness may at least in part explain the very high morbidity and mortality in end-stage renal disease patients[13].

Epidemiological observational studies have shown that the currently used doses of different vitamin D metabolites and analogues have been associated with an improvement in vascular function and survivah[3,29]. Another study showed that serum [25(OH)D_3] levels were negatively correlated with vascular calcificationst[30]. Both [25(OH)D_3] and [1,25$(OH)_2D_3$] serum levels were negatively correlated with aortic pulse wave velocity and positively correlated with brachial artery distensibility suggesting a protective role for vitamin D in vascular funetion[29].

Unlike the study by London et al., 2007, who did not find a correlation between vitamin D levels and vessel stiffness. The greater plasticity of children's vessels and their shorter dialysis duration may allow for compensatory mechanisms that can maintain normal vessel function in the face of early structural damage to the vessel. Vessels from children provide an ideal model to study uremic influences on the arterial wall, because they do not have the confounding proatherosclerotic risk factors that are prevalent in the adult CKD population[29].

Our study showed a correlation between Ca x P product, vitamin D and PTH levels as decreased vitamin D with increased Ca x P product and PTH levels may contribute in calcification process. Raggi and Kleerekoper, 2008, explained that 1 ,25-Dihydroxyvitamin D3 levels begin to drop early in the course of kidney disease, leading to elevated parathyroid hormone levels and disrupted mineral metabolism. Impaired mineral metabolism seems to be associated not only with bone disease but also with vascular calcification[31].

Other studies reported that worsening carotid artery intima media thickness (cIMT) and a higher prevalence of coronary artery calcification (CAC) present with higher mean serum PO4 and Ca x PO4 levels, and higher doses of Ca intake from PO4 binders and vitamin D compoŭnds[11,32] Other Studies suggesting that dysregulated mineral metabolism is central to the vasculopathy of CKD. A , strong linear correlation between mean serum PO_4 and cIMT in pediatric dialysis patients is present; every 1 mmol/L difference in serum PO4 was associated with a 0.15-mm increase in cIMT, also, children on dialysis with mean levels of parathyroid hormone (PTH) more than twice the upper limit of normal (> 2 ULN) were more likely to have thicker cÏMT, stiffer vessels and increased

calcification than were those with PTH levels below 2 ULN[11]. We study the underlying etiology of chronic renal failure in the studied group "30 cases". We found the most common cause was unknown (36.7%) followed by focal segmental glomerulosclerosis (13.3%) and obstructive uropathy (6.7%). Contrary to our results, another study at the Center of Pediatric Nephrology and Transplantation, Pediatric Hospital, Cairo University included 30 Egyptian children with CKD on regular hemodialysis , showed that the etiology of CKD in the studied patients was urinary tract disorders in 14 patients (46.7%), followed by nonidentifiable cause in 10 patients (33.3%), congenital anomalies in 4 (13.3%) and glomerulonephritis in 2 (6.7%)A[41]. Two congenital abnormalities, posterior urethral valves and hypoplastic/ dysplastic kidneys, and a third disorder, focal segmental glomerulosclerosis (FSGS) are the primary causes of long-term kidney failure in children[241]. Obstructive uropathy with associated renal dysplasia is one of the most common causes of ESRD in children. The cause of ESRD in children varies acco>iding to the age of the child. At all ages, renal dysplasia with or without obstructive uropathy is a common cause of ESRD, whereas congenital nephrotic syndrome, cortical necrosis, autosomal recessive polycystic kidney disease, and hemolytic uremic syndrome also cause ESRD in infants and young children. ESRD in the school-age child and adolescent is more commonly caused by renal .dysplasia with or without obstructive uropathy, glomerulonephritis, focal segmental glomerulosclerosis, and various forms of polycystic kidney disease[25]. The differences among these studies may be explained by variability in geographic distribution, age, sex and hereditary factors.

Conclusion: We conclude that deficiency of [25(OH)D_3] and [1,25(OH)2DJ] is very prevalent in hemodialysis children and is a cardiovascular risk marker in those patients, since they are associated with increased left ventricular mass index and vascular calcification. Active vitamin D therapy seems to protect patients from this risk. Serial echocardiography and long term follow up should be done in those patients for early detection and prevention of cardiovascular morbidity and mortality.

REFERENCES

1. **Foley, R.; Parfrey, P. and Sarnak, M. (1988):** Clinical epidemiology of cardiovascular disease in chronic renal disease. Am. J. Kidney Dis.; Vol. 32, pp: 112-119.
2. **Block, G.; Klassen, P.; Lazarus, J.; Ofsthun, N.; Lowrie, E. and Chertow, G. (2004):** Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J. Am. Soc. Nephrol.; Vol. 15, pp: 2208-2218.
3 **Kalantar-Zadeh, K.; Kuwae, N.; Regidor, D.; et al. (2006** Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int.; Vol. 70, pP: 771-780.
4. **Heady, G.; Hruska, K.; Mathew, S.; et al. (2006):** New insights into mineral and skeletal regulation by active forms of vitamin D. Kidney Int.; Vol. 69, pp: 218-223.
5. **Andress, D. (2006):** Vitamin D in chronic kidney disease. A systemic role for selective vitamin D receptor activation. Kidney Int.; Vol. 69, pp: 33-43.
6. **Devereux, R. and Reichek, N. (1997):** Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation; Vol. 55, pp: 613-619.
7. **Devereux, R.; Alonso, D.; Lutas, E.; Gottlieb, G.; Campo, E.; Sachs, I. and Reichek, N.**

(1986): Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am. J. Cardiol.; Vol. 57, pp: 450-458.
8. Mercola, J. (2009): Vitamin D: The master key to optimal health.
9. Patange, A.; Pettersen, M.; Valentini, R. and Wei, Du (2010): Vitamin D deficiency and arterial wall stiffness in children with chronic kidney disease. American academy of pediatrics. Abstract No. 9574.
10. Belostotsky, V.; Mughal, M.; Berry, J. and Webb, N. (2007): Vitamin D deficiency in children with renal disease. Arch. Dis. Child. doi: 10.1 l3б/adc.2007.134866 (dr.vladimir(chdoctors.net.uk).
11. Shroff, R.; Egerton, M.; Bridel, M. and Shah, V. (2008): A Bimodal association of vitamin D levels and vascular disease in children on dialysis. J. Am. Soc. Nephrol.; Vol. 19, pp; 1239-1246.
12. Seeherunvong, W.; Abitbol, C.; Chandar, J.; Zilleruelo, G. and Freundlich, M. (2009): Vitamin D insufficiency and deficiency in children with early chronic kidney disease. The Journal of Pediatrics; Vol. 154, Issue 6, pp: 906-911.
13. **Colic,** A.; Voroneanu, L. and Goldsmith, D. (2010): The Effects of vitamin D therapy on left ventricular structure and function — Are these the • underlying explanations for improved CKD patient survival? Nephrol. Clin. Pract.; Vol. 116, No. 3, c 187-c 195.
14. Kandil, M.; Hussein, G.; Bazaraa, H.; Abdel Rahman, A. and Rasheed, M. (2009): Left ventricular hypertrophy and cardiac Troponin I in pediatric hemodialysis. J. of Clin. and Basic Cardiology; Vol. 12 (Issue 1-4), pp: 5-10.
15. Lumpaopong, A.; Tuntrakool, C.; Thirakhupt, P. and Chulamokha, Y. (2005): Left ventricular hypertrophy and LV geometry in chronic dialysis children and adolescents. J. Med. Assoc. Thai.; Vol. 88 (Suppl 3), pp: S202-205.
16. Mitsnefes, M.; Kimball, T.; Kartal, J.; Witt, S.; et al. (2005): Cardiac and vascular adaptation in pediatric patients with chronic kidney disease: Role of calcium-phosphorus metabolism. Am. Soc. Nephrol.; Vol. 16, pp: 2796-2803.
17. De Simone, G.; Devereux, R.; Daniels, S.; et al. (1995): Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict CV risk. J. Am. Coll. Cardiol.; Vol. 25, pp: 1056-1062.
18. Matias, P.; Jorge, C.; Ferreira, C. and Borges, M. (2010): Cholecalciferol supplementation in hemodialysis patients: Effects on mineral metabolism, inflammation, and cardiac dimension parameters. Clin. J. Am. Soc. Nephrol.
Adragao, T.; Ferreira, A.; Frazao, J.; et al. (25-hydroxyvitamin D deficiency: a new cardiovascular risk factor in hemodialysis patients? Nephrol. Dial. Transplant.; Plus, Vol. 1 (Sнppl 2), pp: 337.
20. Lind, L.; Hanni, A.; LitheII, H.; et al. (1995): Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-age men. Am. J. Hypertens.; Vol. 8, pp: 894-901.
21. Brown, A.; **Dusso,** A. and Slatopolsky, E. (2002): Vitamin D analogues for secondary hyperparathyroidism. Nephrol. Dial. Transplant.; Vol. 17, Suppl. 10, pp: 10-19.
22. **Dusso,** A.; Brown, A. and Slatopolsky, E. (2005): Vitamin D. Am. J. Physiol. Renal Physiol.; Vol. 289, pp: F8-F28.
23. Feldman, D.; Glorieux, F. and Pike, J. (2005): Vitamin D, 2°d Ed., Elsevier Academic Press.
24. Warady, B. (2002): End-stage renal disease in children: What causes it? Thig article originally appeared in the January 2002 issue of aakpRENALIFE, Vol. 17, No. 4.
25. Andreoli, S.; Brewere, E.; Watkins, S.; Fivush, A.; et al. (2005): American Society of Pediatric Nephrology Position Paper on Linking Reimbursement to Quality of Care. J. Am. Soc. Nephrol.; Vol. 16, pp: 2263-2269.
Cozzolino, M Brancaccio, D.; Gallieni, M.; et al. (2005 Pathogenesis of vascular calcificationin chronic kidney disease. Kidney Int.; Vol. , pp: 429
27. Wolisi; Godwin, 0. and Moe, M. (2005): The role of vitamin D in vascular calcification in chronic kidney disease. Sem. Dial.; Vol. 18, pp: 307-314.
28. Cardus, A.; **Panizo, S.;** Parisi, E.; et al. (2007): Differential effects of vitamin D analogs on vascular calcification. J. Bone Miner Res.; Vol. 22, pp: 860-866.
29. London, G.; Guerin, A.; Verbeke, F.; Pannier, B.; et al. (2007): Mineral metabolism and arterial functions in end-stage renal disease: Potential role of 25-hydroxyvitamin D deficiency. J. Am. Soc. Nephrol.; Vol. 18, pp: 613-620.
30. Cannata-Andia, J.; Rodriguez-Garcia, M.; Carrillo-L; 'Opez, N.; et al. (2006): Vascular calcifications: pathogenesis, management, and impact on clinical outcomes. J. Am. Soc. Nephrol.; Vol. 17, pp: 5267-5273.
31. Raggi, P. and Kleerekoper, M. (2008): Contribution of Bone and Mineral Abnormalities to Cardiovascular Disease in Patients with Chronic Kidney Disease. Clin. J. Am. Soc. Nepbrol.; Vol. 3, pp: 836-843.
32. Briese, S.; Wiesner, S.; Will, J.; Lembcke, A.; Opgen—Rhein, B.; Nissel, R.; et al. (2006): Arterial and cardiac disease in ,young adults with childhood-onset end-stage renal disease-impact of calcium and vitamin D therapy. Nephrol. Dial. Transplant.; 2006, 21: 1906-14.