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Peripheral Vascular Calcification in Patients on Regular Hemodialysis in relation to Parathyroid Hormone Abnormalities

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Abbreviation

PTH	Parathyroid hormone
Ca++	Calcium
Po^{-4}	Phosphate
HD	Hemodialysis
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease – mineral bone disorder
ESRD	End - stage renal disease
K/DOQI	kidney disease outcome quality initiative
KDIGO	Kidney disease improving global outcome
PVC	Peripheral vascular calcification
HTN	Hypertension
DM	Diabetes mellitus
ADPKD	Autosomal dominant polycystic kidney disease
CPN	Chronic Pyelonephritis
AKI	Acute Kidney Injury
N.S.	Nephrotic Syndrome
CRP	C. reactive protein

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Abstract:

Background:
Peripheral vascular calcification (PVC) commonly develop in patients on hemodialysis (HD) and associated with increase risk of morbidity and mortality.
Aim of study: To study risk factors of developing peripheral vascular calcification in patients on hemodialysis especially in relation to parathyroid hormone abnormalities.
Patients and Methods:
Cross sectional (observational) study on 54 patients on regular hemodialysis and divided into 2 groups according to abdominal X-Ray.
Results:
54 patient: 32 female, 22 male; mean age = 51.59 +/- 17.61, mean duration of HD = 44.83 +/- 38. 4 months
Peripheral vascular calcification by lateral lumbar X-Ray is 12 patients i.e 22.22%
We studied effects of many risk factors and appeared significant effects of age, duration of HD and use of calcium containing oral phosphate binders. Also there is some effects of increased serum calcium and phosphate, hypertension and DM but statistically not significant.
PTH abnormalities also affect on PVC especially in low level of PTH (a dynamic bone disease) but statistically not significant.
In this study, no apparent effect of inflammation on calcification.
Conclusion:
Peripheral vascular calcification, commonly present in patients on hemodialysis and associated with increase risk of morbidity and mortality, with many risk factors causing increase peripheral vascular calcification which can be prevented and treated

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INTRODUCTION

The most common cause of death in dialysis patients is cardiovascular disease (CVD). Increasingly it is appreciated and accepted that this may be due in part to the presence of excess vascular calcification. (1-5)

Many diverse but also potentially interlinked factors has been incriminated.

Many studies found association between PTH and minerals abnormalities and increase mortality and morbidity. (6-9)

Despite the ongoing concern about the role of calcium loading (e.g calcium containing oral phosphate binders OPB), such calcification was commonly noted in patients with renal disease during periods when calcium containing OPB, were not yet available.

Additional clinical factors include vitamin D therapy, increasing age and dialysis vintage. (10)

The 2009 KDIGO guidelines have endorsed the use of plain lateral abdominal X-Ray films to detect vascular calcification. (11)

2003 K/DOQI guidelines suggest if arterial calcification is identified by plain X-Ray in the abdominal aorta, then involvement of another

site should be investigated (12) 2003 K/DOQI recommendations are (opinions): (13)

1. Therapy of elevated phosphate level (> 5.5 mg/dl) that is refractory to dialysis and diet can be initiated with either calcium or non-metal salt based phosphate binders
2. The use of cocktail of oral phosphate binders is strongly encouraged, with a limit of 1.5 grams of calcium salts.
3. Calcium salts should be avoided in patients with sustained intact PTH levels of < 150 pg/ml , or plasma calcium levels > 9.5 mg/dl .
   vitamin D compounds should also avoided or terminated in patients with calcium levels > 9.5 mg/dl
4. Non-calcium based phosphate binders are preferred with severe vascular calcification or soft tissue calcifications
5. S.ca++ should be maintained at the lower end of the normal range (8.4 – 9.5 mg/dl)
6. Ca++ x $po4^-$ product should be kept less than 55 mg^2/ml^2
   2009 KDIGO guidelines are:
   1. S.po4 should be maintained in the normal range for patients with CKD stages 3-5 but not on dialysis and should be lowered to the normal range in those on dialysis
   2. Among dialysis patients, the desired range for PTH should be 2-9 times the upper limit of normal reference laboratory range.
   3. S.ca++ should be maintained in the normal range.
   4. Ca++ x $po4^-$ product should not be used to help guide therapy, and its use should be abandoned .
   5. Trends in biochemical parameters as well as absolute values should be closely followed .
   6. The dose of calcium salts can be considered for restriction in patients with hypercalcaemia, a dynamic bone disease, vascular calcification and/or low serum PTH levels.
   7. Not routinely screening all patients for vascular calcification and, if individual patients need to be assessed for this , reminding clinicians that lateral X-Ray of the lumbar spine and echo cardiography are excellent tools to use to detect , if not quantify, vascular calcification (17)

PATIENTS AND METHODS:

Cross sectional (observational) study performed on 62 patients on regular hemodilaysis in Ibn-Sina teaching hospital, Mosul city from June 2019 till December 2019.

Inclusion criteria involve all patients with chronic kidney disease on regular hemodilysis more than 3 months.

With exclusion of acute kidney injury and chronic kidney disease of less than 3 months duration with exclusion of 8 patients. Because of death of 2 patients, and incomplete data of 6 patients, 54 patients were asked about age, duration of dialysis (months) underlying causes of ESRD and use of drugs.

Investigations were done for them including bl.urea (mg/dl) , s.creatinin (mg/dl)

s.ca++ (mg/dl) , s.po^{-4} (mg/dl) , s.PTH (pg/ml) , s.albumin and CRP.

Lateral lumbar X-Ray for abdominal aorta for any degree of calcification.

And compare 2 groups, first group with vascular calcification (positive)

Second group without calcification (negative).

And Compare both groups according to risk factors including age, duration of dialysis, s.ca^{++},

s.po4^{-} , s.ca++ × s.po4^{-}, s.PTH, CRP (inflam.) , drug use and according to cause like DM,HT

STATISTICAL ANALYSIS:

All the results were expressed as data of all patients with duplicates and percentages and t-test for two independent samples and Chi-square test using SPSS V16, Differences with Pvalue < 0.01 were considered as statistically significant.

RESULTS:

The study involve 54 patients, 32 female and 22 male, mean age= 51.59 +/- 17.61 year, mean duration of HD = 44.83 +/- 38.64 months, mean blood urea =148.55+/- 95.67 mg/dl, means s.creatinin = 8.76 +/- 3.15 mg/dl, mean corrected s.ca++ = 7.92 +/- 1.33 mg/dl, mean s.po4 = 5.96 +/- mg/dl, mean CRP=9.47 +/- 13.67.

Most common causes of ESRD was hypertension 37% followed by D.M.15% (table1).

Percentage of abdominal aorta calcification, (i.e peripheral vascular calcification) was 22.22% (table 2) (12 patients with PVC from total no. of 54) named as group A. and those 42 patients without PVC named as group B.

Group A: 12 patients with PVC, 5 male, 7 female, mean age = 60.9 +/- 14.95 year (table 3) mean duration of HD = 69.5 +/- 50.75 months, (table 5).

-Hypertension in 42%, DM in 8%. (table 2)

-using calcium salts 100%, one-alpha 92%, and sevelamer 0% (table 11) .

-s.ca++ : 8% with hypercalcemia (table 11)

-s.po^{-}4 : 92% with hyperphosphatimea (table11) .

PTH: < 160 pg/ml = 42 % of patients

160-720 pg/ml = 50% of patients, > 720pg/ml = 8% of patients (table 12)

-CRP: >6 (inflam.) = 25%

CRP <6(without inflam) = 75% (table 11)

Group B: patients without PVC, no.= 42 patients, 17 male, 25female, mean age = 48.928+/- 17.56 year (table 3)

Mean duration of HD = 37.787 +/- 31.787 month (table 5)

-hypertension in 36%, DM in 16% (table 2)

-using calcium salts 95%, one-alpha 50 % and sevelamer 24% (table 11)

-s.ca++= 2% with hypercalcemia (table 11)

-s.po4 = 79% with hyper phosphatemia (table 11)

-PTH= 41% with value lower than 160pg/ml

45% within normal range 160-720 pg/ml

14% with > 720 pg/ml (table 11)

- CRP = (inflammation) >6 : 36%
- CRP < 6 (with inflame.) : 64 % (table 11)

  Comparison between 2 groups:
- Mean age group A = 60.9+/- 14.9 Vs group B mean age = 48.92 +/- 17.56. p-value 0.003

  Mean duration of HD group A = 69.5+/- 50.75 Vs group B =37.78+/- 31.78. p-value = 0.007
- Hypertension in group A = 42% Vs group B 36%. p-value = 0.025%
- DM in group A = 8% Vs group B = 16%, p-value = 0.034%.
- Hypercalcemia 8% in group A Vs 2% in group B with p-value 0.364
- Hyperphosphatemia: 92% in group A Vs 2% in group B with p-value =0.364
- S.ca++ x s.po^{-}4 > 55: 42% in group A Vs 26% in group B with p-vale = 0.3

PTH = <160 = 42 % in group A, 41% in group B

160-720 = 50% in group A, 45 % in group B

>720= 8% in group A, 14% in group B with p-value = 0.859

- Using calcium salts 100% in group A Vs 95% in group B with p-value = 593
- Using one-alpha = 92% in group A Vs 50% in group B with p-value = 0.01
- Using sevelamer 0% in group A Vs 24% in group B with p-value = 0.061

Table 1 causes of ESRD (54 patients)

	No.	**percentage**
HTN	20	37%
DM	8	15%
ADPKD	6	11%
Obst.Uropathy	5	9%
CPN	3	6%
Neurogenic bladder	2	4%
Post AKI	1	2%
Lupus Neph.	1	2%
N.S.	1	2%
Unknown	7	13%
	54	100%

Table 2

Variables	**12 positive**		**42 negative**		**P. value**
	No.	**percentage**	**No.**	**percentage**	
HTN	5	42%	15	36%	0.025
DM	1	8%	7	16%	0.034

Table (3) Age

Age	**12 positive**		**42 negative**		**P. value**
	mean	**Std. deviation**	**mean**	**Std. deviation**	
	60.9167	14.95726	48.9286	17.56020	0.003*

Table (4) Sex

Sex	**12 positive**		**42 negative**		**P. value**
	No.	**percentage**	**No.**	**percentage**	
M : 22	5	23%	17	77%	0.941
F : 32	7	22%	25	78%	

Table (5) duration of HD months

Duration of HD months	12 positive		42 negative		P. value
	mean	Std. deviation	mean	Std. deviation	
	69.5000	50.75521	37.7875	31.78705	0.007*

Table (6)

Variables		positive		negative		P. value
		mean	Std. deviation	mean	Std. deviation	
S.ca++	Normal(8.4-10)	9.2800	0.81976	9.0769	0.57468	0.558
	Hyper (>10)	10.8	0.00000	10.88	0.00000	---
S.po4 -	Normal(3-4.5)	4.41	0.00000	4.35	1.30576	0.966
	Hyper (>4.5)	6.5909	1.07653	3.8250	0.54968	0.000*
S.ca++ × S.po4 -	(<55mg²/dl²)	44.0057	6.89860	38.9906	10.27289	0.229
	(>55mg²/dl²)	65.7120	6.91569	64.8673	8.78519	0.853

Table (7) PTH

Level(pg/ml)	12 positive		42 negative		P. value
	mean	Std. deviation	mean	Std. deviation	
< 160	49.43333	41.65154	80.3000	46.62120	0.168
160 - 720	357.0000	112.73864	355.3947	157.56223	0.983
> 720	2284.0000	0.00000	1267.6667	565.17915	0.157

Table (8) CRP

Level	12 positive		42 negative		P. value
	mean	Std. deviation	mean	Std. deviation	
> 6	15.7444	10.43589	21.1643	19.93292	0.462
< 6	2.1667	0.75719	2.3964	1.34976	0.776

Table (9) Drugs

Variables	12 positive		42 negative		P. value
	No.	percentage	No.	percentage	
Calcium	12	100%	40	95%	0.000*
One alpha	11	92%	21	50%	0.077
Sevelamer	0	0%	10	24%	0.011

Table (10)

Variables		mean	Std. deviation
Age / years		51.5926	17.61487
Duration of HD months		44.8333	38.64485
S.ca++		7.9237	1.33489
S.po4 -		5.9631	1.61324
S.ca++ × S.po4 -		47.3861	14.87070
PTH		372.0222	489.21425
CRP		9.4741	13.67550
Sex	M	22	41%
	F	32	59%
Calcium	+	52	96%
	-	2	4%
One alpha	+	32	59%
	-	22	41%
Sevelamer	+	10	19%
	-	44	81%
Bl.urea	+	**148.55**	**95.67**
S.creatinin	-	**8.76**	**3.15**
S.Albumin	+	**38.22**	**5.85**

Table (11)p

Difference between (12 positive) and (42 negative).

		A		B		
Variables		**12 positive**		**42 negative**		**P-value**
		No.	**percentage**	**No.**	**percentage**	
Sex	M : 22	5	23%	17	77%	0.941
	F : 32	7	22%	25	78%	
S.ca++	Normal(8.4-10)	5	42%	13	31%	0.423
	Hyper (>10)	1	8%	1	2%	
S.po4 -	Normal(3-4.5)	1	8%	8	19%	0.364
	Hyper (>4.5)	11	92%	33	79%	

S.ca++ × S.po4 -	(<55mg²/dl²)	7	58%	31	74%	0.300
	(>55mg²/dl²)	5	42%	11	26%	
PTH	< 160	5	42%	17	41%	0.859
	160 - 720	6	50%	19	45%	
	> 720	1	8%	6	14%	
CRP	> 6	3	25%	15	36%	0.487
	< 6	9	75%	27	64%	
Calcium	+	12	100%	40	95%	0.593
	-	0	0%	2	5%	
One alpha	+	11	92%	21	50%	0.010*
	-	1	8%	21	50%	
Sevelamer	+	0	0%	10	24%	0.061
	-	12	100%	32	76%	

	A		**B**		
Age / years	**12 positive**		**42 negative**		**P-value**
	mean	**Std. deviation**	**mean**	**Std. deviation**	
	60.9167	14.95726	48.9286	17.56020	0.003*

Duration of HD months	**12 positive**		**42 negative**		**P-value**
	mean	**Std. deviation**	**mean**	**Std. deviation**	
	69.5000	50.75521	37.7875	31.78705	0.007*

DISCUSSION:

Peripheral vascular calcification (PVC) were noticed in 22.22% of patients on regular hemodilysis (HD).

Age was a significant risk factor for PVC:

Mean age in group A = 60.9+/- 14.9 Vs group B mean age =28.92+/- 17.56, p-value= 0.003.

Also duration of HD has significant effect for PVC as : mean duration of HD in group A = 69.5 +/- 50.75 Vs group B = 37.78+/- 31.78, with p-value = 0.007

Treatment with one-alpha also has significant effect on PVC as: 92% in group A use one alpha Vs 50% of group B use one alpha with p-value = 0.01.

Other risk factors like hypercalcemia, hyperphophatemia , hypertension, DM, and use of calcium salts, have some effect and increase risk of calcification but statistically not significant.

Also PTH abnormalities have risk of calcification especially in low PTH, (a dynamic bone disease) but statistically not significant.

As explained down:

1- Hypercalcemia 8% in group A Vs 2% in group B , p-value = 0.423
2- Hyperphosphatemia : 92% in group A Vs 79% in group B with p-value = 0.364
3- PTH : < 160 = 42% in group A Vs 41% in group B

160-720= 50% in group A Vs 41% in group B

>720= 8% in group A Vs 14% in group B with p-value= 0.859

4- S. ca++ x s.po4 > 55= 42 % in group A Vs 26% in group B with p-value = 0.3
5- Hypertension in group A 42% Vs 36% in group B with p-value = 0.025
6- DM in group A 8% Vs 16% in group B with p-value = 0.034
7- Use of calcium salts : 100% in group A vs 95 % in group B with p-value = 0.593

In this study. no apparent effect of inflammation on PVC as : inflammation (CRP> 6) in group A 25% vs in group B 36% with p-value = 0.487

CONCLUSION:

Peripheral vascular calcification were common in patients on regular hemodilaysis which associated with calcification in another site, and increase risk of cardiovascular disease.

Peripheral vascular calcification increased by many factors especially old age, long duration of hemodialysis, use of calcium and Calcium containing phosphate binders.

Also hypertension, DM may increase risk of calcifications.

PTH in low-level, hypercalcaemia and hyperphosphatemia have some role in increase PVC.

RECOMMENDATIONS:

1- Make s.ca++ s. po^{-4} on normal range
2- Control of hypertension and DM
3- Avoid exclusive use of containing phosphate binders
4- Preferable to use non calcium containing phosphate binders like sevelamer
5- Lateral lumbar X-Ray for searching for PVC

Bone biopsy stay a definite diagnosis of a dynamic bone disease

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