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PREVALANCE AND PROGRESSION OF CARDIOVASCULAR CALCIFICATIONS IN HAEMODIALYSIS PATIENTS

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ABSTRACT Chronic kidney disease (CKD) is an important global public health problem affecting approximately 10% of the global population. However the poorer outcomes from CKD are not related to kidney failure but also include a wide array of morbidity and mortality related to complications, particularly from decreased kidney function and cardiovascular diseases (CVD).

MATERIALS AND METHODS: Prospective observational study done at government general hospital Vijayawada. From may 2016 to august 2017. Valvular calcification: Two dimensional assessment of the aortic valve and mitral valve by 2D- echo, together with continuous-wave doppler ultrasonography, was performed according to parasternal long-axis and short axis views. Echocardiography is a sensitive and specific method for the detection of valve calcifications. Cardiac valve calcification is defined as bright echoes of more than 1 mm on 1 or more cusps of the aortic ormal mitral valve or mitral annulus. Three grades were established according to the calcification area: score:0 for no calcification,score:1 for mild calcification, when there were only small, isolated areas; score:2 for moderate and severe calcifications, when calcification was extensive and diffuse.

KEYWORDS :

INTRODUCTION

Chronic kidney disease (CKD) is an important global public health problem affecting approximately 10% of the global population (Kidney Disease: Improving Global Outcomes [KDIGO] Chronic Kidney Disease Working Group, 2013). More than 2 million people are estimated to be receiving treatment with dialysis or transplantation for chronic kidney disease and this population has been growing at an approximate rate of 7% per year (Lysagth et al., 2002). However the poorer outcomes from CKD are not related to kidney failure but also include a wide array of morbidity and mortality related to complications, particularly from decreased kidney function and cardiovascular diseases (CVD). Some authors suggest that an inverse relationship exists between glomerular filtration rate (GFR) estimated with the modification of diet in renal disease (MDRD) and mortality and cardiovascular (CV) events (Levy et al.,1999). This relationship is due in part to the presence of excess vascular calcification (VC), particularly in the form of extensive coronary artery calcification (CAC), a frequent complication of CKD patients which can be observe even in very young dialysis patients(Sigrist et al., 2007). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines published in 2009 suggest that stage 3-5D CKD patients with vascular/ valvular calcifications may be considered to be at highest CV risk (Kidney Disease: Improving Global Outcomes [KDIGO] CKD – MBD Work Group, 2009). In a multicentre study conducted in 47 European dialysis centres, during a 2 year follow up, there were 234 deaths and 91 non fatal cardiovascular events. The risk of adverse event increased 3.7 fold in patients with an Abdominal Aorta Calcification(AAC) score of 5-15 (mid tertile) and 8.6 fold in 2 patients with a score of 16- 24 (top tertile) compared to lowest tertile(Verbeke et al., 2010). In a study by Okuno et. al, during the study period there were 103 deaths from all causes and the cardiovascular event rate was greater in patients with AAC (27.8% vs 9.8% death rate; and 11.6% vs 3.1% cardiovascular event rate respectively). VC is highly prevalent in CKD patients, although the case reports dating from 1885 to 1945 (Mulligan, 1947) were typically a consequence of severe hypercalcemia, the analysis of the subsequent studies suggest that factors other than calcium intake and abnormalities of mineral metabolism may promote the risk of VC. Among CKD stage 3-5(not on dialysis) patients, 47%- 83% had CV calcifications. This is thought to be related to the increasing age, diabetes mellitus, the dialysis vintage, and the use of calcium containing phosphate- binders or elevated phosphorus levels. Regarding age, VCs are present even in children on dialysis therapy, with a prevalence of almost 20% in a study by (Shroffet al.), in young adults receiving dialysis age ranges 20-30 years and in another study, with childhood onset CKD and age ranges 19-39 years, VC prevalence was 87.5% and 92% respectively (Goodmanet al., Oh et al.,). VCs has been found in upto 70% of patients entering dialysis treatment and upto 92% in patients on long term dialysis (Block et al., Blacher et al., Raagi et al.,). The progression of VC has been reported to vary from 50% to 60% in ESRD patients (Goodman et al., Chertow et al.,) and with normal renal function it is 20% to 36% (Budoff et al., and Raagi et al.,). In a cohort of strictly controlled patients on dialysis, calcification scores nearly double in 3 young adults on dialysis for a mean of 20 months (Goodman et al.,) and increased by 14% and 25% after 26 and 56 weeks respectively. Vascular calcification mechanism are not fully understood. Recent studies suggest that it also involves inflammation, active cell-mediated process, FGF-23 and low concentrations of glycoprotein such as fetuin-A. The purpose of this study is, to know the extent of cardiovascular calcifications and its out comes in hemodialysis patients, which was done in a tertiary referral hospital, as there is limited data available on cardiovascular calcifications from India and especially from south India.

Study population:

Patients with chronic kidney disease stage-5D

Inclusion criteria:

1. Patients on hemodialysis for at least more than 3 months.
2. Age more than 18 years.

Exclusion criteria:

1. Pre existing chronic viral infections (HbsAg, HCV,HIV)
2. Previous moderate systolic dysfunction
3. Patients with cirrhosis of liver, malignancies
4. Patients on immunosuppression medications
5. Patients previously on continuous ambulatory peritoneal dialysis.
6. Pregnant chronic kidney disease stage -5D 26

METHODS:

1. All patients are subjected to lateral abdominal X-ray at the beginning and at the end of the study.
2. All patients are subjected to 2D-echo at the beginning and at the of the study.
3. 25OH vitamin D, Serum iPTH and serum fibroblast growth factor-23 (FGF-23) done once during the study period.
4. Heamogram, serum calcium, serum phosphorus, serum alkaline phosphatase, and lipid profile were repeated every 3 months.

Serum iPTH was done by chemiluminescence, two step sandwich immunoassay at Ranbaxy diagnostics, Mumbai. Serum FGF- 23 was measured by using an ELISA according to the manufacturers protocol (SEA 746 HU kit, cloud – clone corp; Houston, texas 77082, USA. This is a second generation two site monoclonal antibody ELISA which estimates the intact FGF-23, it has a detection range of 15.6 pg/ml – 1000pg/ml. For grading the abdominal aorta calcifications scores Kauppila scores are used on lateral abdominal plain x-ray. 27

Valvular calcification: Two dimensional assessment of the aortic valve and mitral valve by 2D- echo, together with continuous-wave doppler ultrasonography, was performed according to parasternal long-axis and short axis views. Echocardiography is a sensitive and specific method for the detection of valve calcifications. Cardiac valve calcification is defined as bright echoes of more than 1 mm on 1 or more cusps of the aortic or mitral valve or mitral annulus. Three grades were established according to the calcification area: score:0 for no calcification,score:1 for mild calcification, when there were only small, isolated areas; score:2 for moderate and severe calcifications, when calcification was extensive and diffuse. Statistical analysis: Abdominal aorta calcifications are divided into quartiles according to the kauppila calcification scores, the laboratory values are distributed according to their calcification scores. If there is significance between the quartiles ANOVA is applied to know the statistical significance. For correlation pearsons correlation is applied by using SPSSA software version 23. P value of less than 0.05 is taken as significant.

OBSERVATION AND RESULTS:

Baseline characteristics of study population N:82

Age (yrs)	46.23 ± 10.08
Male	57(69.51%)
Female	25 (30.48%)
BMI (kg/m²)	20.03 ± 3.46
Systolic BP (mmHg)	140.54 ±8.61
Diastolic BP (mmHg)	96.8 ± 7.74
Hemoglobin% (gm%)	7.75 ± 1.02
S.Ferritin (ng/ml)	745.11±642.41
S.Albumin (gm/dl)	2.93±0.41
S.Calcium (mg/dl)	8.65±0.46
S.phosphorus (mg/dl)	3.79±0.61
S.Alkaline phosphatase (IU/L)	91.27±14.67
25 OH Vit D (ng/ml)	37.11±14.56
S. iPTH (pg/ml)	299.37±225.8
S. FGF23 (pg/ml)	193.81±128.52
T. Chol (mg/dl)	157.23±17.07
HDLc (mg/dl)	35.66± 4.02
Initial AV calcification score	0.24± 0.43
Initial MAC calcification score	0.68± 0.51
Initial AA calcification score	3.62± 2.84
IVSd (mm)	11.56± 1.00
LVPWd (mm)	11.78± 0.97
EF%	56.29± 4.66

Tab:1. (IVSd: Interventricular septum dimension, LVPWd: left ventricular posterior wall dimension, AV: Aortic Valve, MAC: mitral annular calcification, AA: Abdominal Aorta).

Total 89 patients were taken into the study, 7 were dead within one year on entering the study period, so they were excluded for final analysis. Out of 82 patients, males and females are n: 57 (69.51%) and n: 25 (30.48 %) respectively with whole group mean age is 42.23 ± 10.0yrs. The mean hemoglobin, serum albumin and serum ferritin are 7.75 ± 1.02 gm%, 2.93 ± 0.41 gm% and 745.11 ± 642.41 respectively. The means of serum iPTH and serum FGF23 are 299.37 ± 22.8 pg/ml and 193.81 ±128.52 pg/ml respectively with means of initial aortic valve, mitral valve and abdominal aorta calcification kauppila scores are 0.24± 0.43, 0.68± 0.51 and 3.62± 2.84 respectively shown in table 1.

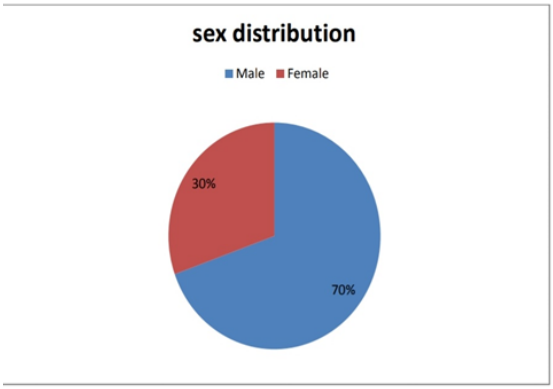

Figure 2: Sex Distribution

Table: 2 Laboratory results according to Quartiles of final abdominal aorta calcification scores (AAC) and their p values using ANOVA analysis.

Variable	AAC Quartile 1 (< 5)	AAC Quartile 2 (5.1 -8)	AAC quartile3 (8.1-11.25)	AAC Quartile4 (>11.26)	P Value
S.Ferritn (ng/ml)	691.28 ± 438.94	707.56±292.42	776.65±680.96	818.69±351.30	0.79
S.Calcium (mg/dl)	8.42±0.23	8.58±0.42	8.55±0.42	9.13±0.45	0.001
S.phosphorus (mg/ml)	3.51±0.53	3.70± 0.58	3.75±0.49	4.29±0.59	0.001
S.Alkaline phosphatase (IU/L)	84.5±11.94	90.67±11.19	87.32±11.30	104.95±14.88	0.001
25 OH Vit D (ng/ml)	43.43±15.42	36.21± 10.39	31.67±11.61	34.09±16.13	0.81
S.iPTH (pg/ml)	184.83±121.40	232.72±150.85	297.87±171.90	511.15±285.65	0.001
S.FGF23 (pg/ml)	99.03±63.62	183.63±71.09	166.46±71.09	360±113.93	0.001
Diastolic dysfunction					
Normal function	n21	n1	n0	n0	0.001
Stage I	n6	n14	n13	n6	0.001
Stage II	n1	n0	n6	n7	0.003
Stage III	n0	n0	n0	n7	0.001
mortality	2	1	3	9	0.02

Abdominal aortic calcification scores are divided into quartiles, table 2 shows different laboratory and 2D –Echo findings with their means and standard deviations distributed according to their final abdominal aorta calcification quartile scores. Lowest quartiles have lower means for different parameters and normal diastolic function By ANOVA analysis across quartiles of Abdominal Aorta Calcification (AAC) kauppila scores, serum ferritin and 25OH vitD are not significant. The means of 32 serum iPTH and serum FGF-23 are high in 4th AAC quartile and is associated more calcification burden which is significant (P value 0.001) shown in table:2. Diastolic dysfunction is more severe in 4th quartile which is associated with more mortality. (p values 0.001 and 0.02 respectively). But when compared among different stages of diastolic dysfunction and mortality (Table 4), stage III diastolic dysfunction is associated with significant mortality compared to other stages (p value 0.05).

Table:3. Severity of valvular calcification and mortality.

calcification score	Aortic valve			Mitral annulus		
	Age	survivors	non survivors	Age	survivors	non survivors
0	47.35±10.83	41	2	48.56±14.13	7	2
1	44.61±9.41	24	7	37.47±13.21	40	4
2	46.5±8.65	2	6	33.0±15.12	20	9
P Value	0.001			0.57		

Table: 4. Diastolic dysfunction and mortality

Diastolic dysfunction	survivors	N0n survivors	P value
Normal function	20	2	0.192
Stage I	35	4	0.73
Stage II	9	5	0.64
Stage III	3	4	0.05

Vascular calcifications in chronic kidney disease and hemodialysis patients had already been related to vascular stiffness113,114, cardiovascular disease115,116 , and cardiovascular mortality113,114 and these complications are more common than in general population 115. The burden of vascular calcifications are usually estimated by more sensitive tools like electron beam computed tomography (EBCT) and 36 multislice computed tomography with ECG gating, these methods differ in sensivity, availability and cost117. KDIGO 2009 clinical practice guide lines for diagnosis and assessment of vascular calcifications recommend lateral abdominal X-ray in CKD stage 3 – 5D patients. KDIGO considers CKD stage 3- 5D patients having valvular or vascular calcifications as high risk patients. The subjects in this cohort are from low socioeconomic group, the mean age in this cohort is 46.23± 10.08 yrs with male to female percentages 69.51% and 30.48% respectively. When compared with other cohorts, this cohort had younger subjects. Most of the studies like Accelerated mortality on renal replacement (ArMORR) study118, Orlando M. Gutierrez and Ravi Thadhani et. Al group119, on vascular calcifications are from developed countries which have prolonged life expectancy and prevalent patients on hemodialysis are older. Younger subjects in general population will have lesser vascular calcification when compared to older. In general population, older persons will have

atherosclerotic associated vascular intimal calcifications compared to medial calcifications in CKD population120. Older population will have other comobities like hypertension diabetes mellitus and 38 coronary artery diseases. So in younger CKD patients vascular calcifications are usually associated with disease process. The mean body mass index in this cohort is 20.03± 10.08 kg/m², compared to western population, who are more prone for obesity and metabolic syndrome. This cohort is mainly from low socioeconomic group and CKD can cause malnutrition, inflammation as reflected in results like high serum ferritin, hypoalbuminemia and low serum cholesterol which might be the cause for low BMI compared to other studies or from western data. The male and female percentages in this cohort 69.51% and 30.48% respectively. Gender is an important factor associated with development and progression of CKD. According to the USRDS Annual Data Report, there is preponderance in the prevalence of all-cause ESRD in favor of men, but this has not been reported to be so marked in Europe. In most CKD studies and meta-analyses, women have a slower rate of progression compared with men121 . There is no significant correlation for serum ferritin, 25OH vitD, and HDLc for cardiovascular calcification in this study. The same was observed in various studies done by Cristianne Tomiyama, et al, Antonio Bellasi et al, and Nilgul Akalin et al Jehu S. Mathew et al and Blai Coll et al. Ferritin is a positive inflammatory marker which is a non specific marker for vascular pathology, some studies used hs CRP which is a specific marker for vascular inflammation and is well correlated with vascular calcification (p values 0.01). 39 Inflammation is another important mechanism in the pathogenesis of vascular calcification. Associations of circulating levels of pro-inflammatory factors such as tumor necrosis factor-alpha (TNF-α), interleukin-1β and interleukin-6 with arterial calcification have been observed in general population and in patients with CKD. The actions of vitD occurs through the binding of its active metabolite, 1,25 di(OH) vitD (calcitriol) to the vitamin D receptor (VDR), although effects mediated by other metabolites such as 25(OH)D and 24,25-dihydroxyvitamin D are also possible. In addition to the endocrine effects of VDR activation by circulating calcitriol, local 1,25di(OH) vit D production can also activate VDRs expressed in many tissues via an autocrine mechanism, including endothelial cells and VSMCs122'123 . Calcitriol can increase the expression of the VDR and decrease the proliferation of VSMCs124. At high doses, it also can promote VSMC migration, transition into an osteoblast-like phenotype and calcification, together with up-regulation of proteins regulating mineralization and calcium transport. A study done by Chertow et al., 125 where the coronary artery calcification (CAC) progression attenuated with LDL-C reduction. Luminal diameter would not be reduced, as demonstrated in prior coronary regression trials with lipid lowering therapy. The attenuation in progression of coronary calcium by EBCT was recently demonstrated with statins in non ESRD patients. This suggests that LDL-C is a principal determinant of VC126. This process is ongoing in the media and adventitia with little vascular calcification (VC) change occurring near the lumen. Early in the course of atherosclerosis, calcification becomes detectable by high resolution imaging such as EBCT. However, late in the course of atherosclerosis (and likely 40 operative in CKD/ESRD), heavy calcification, which can be seen on plain x-rays, is associated with lower lipid levels and more stable atherosclerotic plaques.

Limitations of the Study 1. Fibroblast growth factor -23 and iPTH was done only once during the study period. (done during the 8th month of study period). 2. No control cohort to compare. 3. No hospitalization data of the patients during the study period.