ORIGINAL ARTICLE

MITRAL ANNULAR CALCIFICATION IN STAGE 5 CHRONIC KIDNEY DISEASE ON DIALYSIS THERAPY

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Background: Mitral Annular Calcification (MAC) is a degenerative process involving the mitral valve and is a marker of advanced cardiovascular disease. Prevalence in the general population is upto 10% and increases in advanced age, diabetes mellitus, chronic kidney disease (CKD), end stage renal disease (upto 40%) and mitral valve prolapse.The aims of this study were to assess the prevalence of MAC in CKD5D patients and correlate with patients' characteristics. **Methods:** Echocardiograms were obtained in 84 hemodialysis patients. Association of MAC with various patient characteristics was studied. Data was analysed using SPSS-22. **Results:** The mean age of the patients was 63.38±12.3 years and 48 (57%) were males. Sixty-eight patients (81%) had DM and 79 (94%) had hypertension. MAC was present in 37 out of 84 (44%) patients. Sixty-four (72%) had IHD. The presence of MAC correlated significantly with IHD (Odds Ratio 6.42, *p*=0.006). Mean follow up of the patients was 30.30±29.22 months and 37 (44%) suffered mortality during this period. Patients on dialysis for longer than 36 months had an elevated risk of developing MAC (OR=3.32, *p*=0.019). Patients with the following risk factors: serum PO4 greater than 5.5 (OR=2.03), DM (OR=1.95), HTN (OR=3.35), Age >60 (OR=1.83), AFIB (OR=1.28); had an observable increase in incidence of MAC with time but they weren't statistically significant. **Conclusion:** Mitral Annular Calcification is common in hemodialysis patients and correlates significantly with IHD. Our findings support the recommendation by KDIGO 2017 guidelines on Mineral and Bone Disease on the use of echocardiography for the detection of valvular calcification.

Keywords: Chronic Kidney Disease; Cardiovascular disease; Mitral Value; Annular calcification

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INTRODUCTION

On cardiac imaging like echocardiography, Mitral annular calcification (MAC) is usually an occasional finding. Mitral Annular Calcification is a degenerative process and may be caused by a process similar to atherosclerosis. It is usually seen on the parasternal or apical views. It is determined as an echo dense band or mass in the atrioventricular groove, on transthoracic echocardiography, and is seen throughout systole and diastole.[1] Mitral Annular Calcification C most commonly affects the posterior annulus. Limiting mobility, the extent of calcification can be from the annulus onto the leaflets. Calcification can be extensive so much so that the posterior leaflet is encased in calcium and it hardly moves.

The presence of MAC is affected by certain factors such as advancing age and the presence of other risk factors. Mitral annular calcification has also been detected in Egyptian Mummies.[2] The Framingham study found out that MAC was high in the elderly population. It was up to 14%.[3] In another study conducted at a preventative health clinic, the prevalence was 8%.[4]

Other studies have shown lower prevalence rates (2.8%) among patients free of clinical coronary heart disease.[5] With a mean age of 59 years, the occurrence of MAC was almost equal in both males and females. It was found out to be 5.6% in men and 4.6 % in women in the Atherosclerosis Risk in Communities (ARIC) study. [6] It further showed that as the age increases, the prevalence of MAC also increases. Mitral annular calcification was found in 15% of men and 10% of women at the age of 70 years.

According to the Multi-Ethnic Study of Atherosclerosis (MESA) Study, the occurrence of MAC was more in females as compared to males in the age group 45–84 yrs. MAC was found in 12% of women and 8% of men in the study.[7]

Increasing age, High blood pressure, raised cholesterol levels, diabetes mellitus and chronic kidney disease have been reported to accelerate calcification of mitral annulus specifically in association with mineral and bone disease. In one study of 275 patients, those with calcification of aortic valve and mitral annulus, had a higher abdominal aortic calcification score.[8]

Many studies have been done to find out the about the findings of MAC and its relationship with cardiovascular events. 1197 subjects were studied for 16 years in the Framingham Study and showed a positive relationship between MAC and CVD, death due to

cardiovascular events, and death from all causes. The study also concluded that for each 1 mm increase in MAC, the risk of cardiac events, death due to cardiovascular disease, and death from all causes increased by about 10%.[6]

The Belgrade Atrial Fibrillation Study, a large prospective study analysed the Mortality data in patients with MAC and nonvalvular atrial fibrillation. The study had a long duration of follow up and found significant associations between MAC and death from all causes, death from cardiovascular disease, and the compound endpoint of ischemic stroke, myocardial infarction, and all-cause death.[9]

According to USRDS, heart diseases are a prime cause of death in CKD 5/D-End Stage Renal Disease (ESRD) patients, making more than half of all deaths with known causes. Patients on haemodialysis have the highest development of these cardiovascular diseases.[10] In comparison with control subjects of similar age the occurrence of MAC is higher in patients who are on dialysis.[11–13]

The Framingham Heart Study showed that the development of MAC was significantly higher in chronic kidney disease (CKD) patients as compared to patients with normal renal function. Patients with chronic kidney disease were at a 50% more risk to have at least one calcified valve as compared to normal subjects. Adjustment for various factors such as age, gender, variation in blood pressure, serum cholesterol levels, hypertension treatment, diabetes, smoking status, body weight and height and heart disease was made. After adjustments of these factors, participants with CKD had 60% increased odds of MAC.[6]

Thus, findings of MAC on echocardiography should raise the suspicion of the presence of CKD in the physician's mind and to determine all risk factors in the progression of MAC. There is significant cardiovascular mortality and increased development of MAC in CKD patients and baseline echocardiograms have been suggested by Kidney Disease Improving Global Outcome (KDIGO). Kidney Disease Improving Global Outcome suggested that patients who are on haemodialysis should have echocardiography for the detection of valve calcification as well as valve calcification for risk stratification. Follow up echocardiogram are suggested to ascertain progression of MAC.[14]

Our study was done to determine the development of MAC in CKD Stage 5D patients and ascertain correlation between age, presence of ischemic heart disease, vintage of dialysis, serum calcium, phosphorus and intact parathormone level.

MATERIAL AND METHODS

We analysed 84 patients undergoing regular haemodialysis. Patients who were on dialysis for less than two months were excluded. Patients who had acute kidney injury were also not included in the study. Fresenius series dialyzers were used during dialysis of all the patients. Most of the patients were on twice a week HD due to financial or personal constraints. Written informed consent was taken from all participants for 2D Echocardiogram. The study protocol was accepted and approved by the Ethics Committee at the Doctor's hospital.

Diagnosis of valve calcification (VC) was based on the findings of echocardiography. Echocardiographic criteria for diagnosis include dense echoes in the mitral valve. Baseline data were recorded including age, sex, weekly frequency of dialysis, duration on dialysis before entering into the study, presence of diabetes mellitus (DM), Raised blood pressure, presence of ischemic heart disease (IHD), atrial fibrillation, biochemical indices of serum calcium, phosphorus and intact parathormone level. Majority of the patients were taking medicines common in dialysis patients, including blood pressure control medications, erythropoietin (EPO) and calcium based and non-calcium-based phosphorus binders.

Table-1: Patient characteristics

Characteristic	MAC +ve	MAC -ve
No. of patients	37	47
Age	65.4±13.3	61.81±11.32
Gender:		
Male	54.10%	59.6%
Female	45.90%	40.40%
DM	86.50%	76.60%
HTN	97.30%	91.50%
IHD	91.90%	63.80%
PCI	13.50%	10.60%
CABG	13.50%	8.50%
Ca	8.58±0.88	8.6±0.92
PO4	5.86±1.72	5.71±2.29
Intact PTH	391.45±336.47	427.93±280.22
Dialysis Vintage	39.6 ±38.4	23.17 ±16.77
Dialysis 1x a week	2.70%	6.40%
Dialysis 3x a week	29.70%	25.50%
Mortality	45.90%	42.60%

Association of MAC with patient age, DM, IHD, HTN, dialysis vintage, smoking, serum calcium, serum phosphate and iPTH was studied.

RESULTS

Our data was analysed using SPSS 22 for Windows (SPSS Inc., Chicago, IL). A p value of less than 0.05 was considered significant. Results were expressed as mean±SD. All subjects had an average age of 63.38±12.3 years. There were 36 (43%) females and 48 (57%) males. Sixty-eight patients (81%) had DM

and 79 (94%) had hypertension. Sixty-four (72%) were diagnosed with IHD. Mean follow up of the patients was 30.30±29.22 months.

Majority of the patients were on twice a week haemodialysis. Association of MAC with patient age, DM, hypertension, Ischemic Heart Disease (IHD), atrial fibrillation, mortality, duration of dialysis, serum calcium and phosphorus (PO4), iPTH was studied. Thirty-seven (44%) of the patients died during this period. Mitral annular calcification was present in 37 out of 84 (44%) patients. MAC was present in 47% female's vs 41% in males. The presence of MAC correlated significantly with IHD (Odds Ratio 6.42, p=0.006). Patients who were on dialysis for more than 36 months were also found to be at elevated risk of developing MAC (OR=3.32, p=0.019).

We also saw that patients with the following risk factors: serum PO4 greater than 5.5 (OR=2.03), DM (OR=1.95), HTN (OR=3.35), Age >60 (OR=1.83), atrial fibrillation (OR=1.28), had an increase in incidence of MAC but they weren't statistically significant. We did not find any relationship between MAC and serum Calcium and iPTH. Patients with MAC did not have a significantly higher mortality in our study.

DISCUSSION

According to our study the occurrence of MAC was high in CKD patients as has been shown in previous studies. In our study we found positive correlation between MAC and IHD. This has been shown in previous studies as well.[13]

Mitral annular calcification was shown to be related with heart disease in a group of one hundred and forty renal transplant candidates. Patients who had MAC had an increased concentration of Cardiac troponin T, N-terminal Pro-B-type natriuretic peptide.[12] We also found a positive correlation between MAC and dialysis vintage. This increase in prevalence of MAC with increased passage of time on dialysis has been shown in earlier studies.[11,15]

In another study of 205 maintenance dialysis patients, length of time on dialysis was positively associated with valvular calcification risk.[16]

We found a small correlation between MAC and age, mortality, diabetes, hypertension, serum phosphorus, atrial fibrillation and smoking which was not statistically significant. There was no correlation between serum calcium/iPTH and MAC.

There are many studies that highlight the importance of MAC in mortality in CKD 5 D patients. In a meta-analysis of 2686 patients involving 10 studies Wang and colleagues demonstrated that cardiac valve calcification is a strong independent predictor for death from all causes, and cardiovascular deaths among the chronic kidney failure patients on haemodialysis. The same correlation of cardiac valve calcification and mortality has been found in patients on peritoneal dialysis.[17,18]

In another study of 144 dialysis patients, adjustment for various risk factors such as age, sex, race, presence of diabetes mellitus, and history of Ischemic heart disease was made. In this study it was concluded that only calcification of mitral valve was independently related with death from all causes (hazard ratio [HR], 1.73.[19]

In our study we only found a small correlation of MAC with mortality in CKD 5D patients. However, in the normal subjects and in other studies with CKD 5D patients MAC is correlated with mortality. Chronic kidney disease 5D patients are complex, mortality is primarily related to cardiovascular causes. Lack of correlation in our study could be because of the inclusion of patients with systolic dysfunction, ongoing ischemia and the short follow up.

Larger randomized control trials with adequate power need to be conducted that evaluate the effect of MAC on patient outcomes and death in the setting of other cardiovascular morbidity (arrhythmia, systolic dysfunction, diastolic dysfunction, coronary artery disease etc) and biochemical parameters (calcium, PO4, iPTH). Although the current KDIGO guidelines suggest that serum calcium and phosphorus should be maintained in the normal ranges, past KDIGO guidelines suggested monitoring the calcium-phosphate product. The calcium phosphorus product was shown to correlate directly with the prevalence of MAC in some studies.[20]

Initially it was found out that high serum phosphate levels appear to affect calcification of the vessels just by increasing the calcium phosphate product. Further studies have suggested that hyperphosphatemia appears to have a direct role in vascular calcification by inducing human aortic smooth muscle cells to differentiate into an osteoblastic phenotype.[21]

In our study we also found that MAC was higher in patients with high PO4. Raised levels of FGF-23, and iPTH along with increased Calcium and phosphate product are all related with increased vascular and valvular calcification in patients with kidney disease and are almost always present in advanced CKD.[22] However, we did not find a correlation between serum calcium/iPTH and MAC.

Kidney Disease Improving Global Outcome guidelines suggest serial assessment of serum PO4

and calcium, to bring down high serum phosphate, limiting dietary phosphate and to keep calcium levels within limits.

Reducing Calcium levels in the dialysate showed to slow the progression of Coronary artery calcification (CAC) thus KDIGO suggests to keep the dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2C).

In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment KDIGO guidelines suggest to limit the dose of calcium-containing phosphate binders as CAC was highest in patients using a calcium containing phosphate binder.[23] The Total calcium score is much higher in patients in whom hyperphosphatemia was treated by calcium carbonate and not at all in non-calcium-based phosphate binder treated patients. As the calcium score increased, the process of calcification also increased.[24]

Thus, MAC is an important marker of CAD in CKD 5D patients. Measures should be taken to prevent MAC and to retard its progression. Echocardiography should be performed for early diagnosis and non-calcium containing phosphate binders should be used. Calcium balance should be evaluated in dialysis patients in relation to dialysate calcium concentration, calcimimetic treatment and active vitamin D analogue treatment. This will ensure that measures are taken to control progression of MAC. More trials that assess the effect of new non calcium containing phosphate binders in association with patient-related outcomes, their relation with calcification, and rates of cardiovascular events need to be conducted.

The results of future studies may help us to decrease the incidence and rate of progression this complication in CKD and CKD 5D patients and help to prolong the lives of these patients.

CONCLUSION

Mitral annular calcification is common in haemodialysis patients and correlates significantly with IHD. Aetiology of Mitral Annular calcification in CKD 5D/End Stage Renal Disease (ESRD) is multifactorial and needs to be analysed further. Our findings support the recommendation by Kidney Disease Improving Global Outcomes (KDIGO) 2017 guidelines on Mineral and Bone Disease on the use of echocardiography for the assessment of valvular calcification.

AUTHORS' CONTRIBUTION

AM: Write-up, study design, analysis. SS: Abstract. HN, AI, AM: Data collection, analysis. SS: Echo, analysis.

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