Association between Vascular Calcification and Residual Renal Function

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Authors' contributions

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ABSTRACT

Introduction: In chronic kidney disease patients, the leading cause of mortality is cardiovascular disease. In most cases, it is related to vascular calcification. Among multiple risk factors for vascular calcification, decline of residual renal function is an important one. So far, there is scarce

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information about the influence of residual renal function on vascular calcification in haemodialysis patients.

Objective: To determine the association between vascular calcification and left ventricular hypertrophy in haemodialysis patients with low residual renal function.

Methods: An observational study was performed on 60 chronic kidney disease patients on maintenance haemodialysis with low renal residual function attending in dialysis units of Chittagong Medical College Hospital in Bangladesh during the period from April 2018 to March 2019. Blood samples for biochemical analysis were collected in fasting condition. At the same day, lateral lumbar radiography and M mode echocardiography was done for vascular calcification score and left ventricular hypertrophy respectively.

Results: The prevalence of vascular calcification was present in 88.3% cases in patients with low residual renal function. Patients without vascular calcification had normal left ventricular mass index in 100% cases and those with vascular calcification had increased left ventricular mass index in 75% cases, which was very highly significant. The duration of dialysis, age, gender and smoking were not statistically significant for vascular calcification. There was positive correlation of vascular calcification with fasting blood sugar, C-reactive protein, intact Parathormone, Cholesterol, body mass index, serum calcium, serum phosphate, calcium phosphate product and systolic blood pressure but it was negative for serum albumin, diastolic blood pressure and 24 hours urinary total volume.

Conclusion: Vascular calcification is very common in patients with end stage renal disease on maintenance haemodialysis. Loss of residual renal function is an important risk factor for vascular calcification. Patients with vascular calcification had significantly raised left ventricular mass index.

ABBREVIATIONS

CKD	: Chronic Kidney Disease
HD	: Haemodialysis
RRF	: Residual Renal Function
MHD	: Maintenance Haemodialysis
LVH	: Left Ventricular Hypertrophy
FBS	: Fasting Blood Sugar
CRP	: C-Reactive Protein
iPTH	: Intact Parathyroid Hormone
BMI	: Body Mass Index
$Ca \times PO_4$	: Calcium Phosphate product
UTV	: Urinary Total Volume
ESRD	: End Stage Renal Disease
BP	: Blood Pressure
LVMI	: Left Ventricular Mass Index
RRT	: Renal Replacement Therapy
KDIGO	: Kidney Disease	Improving Global Outcomes
MI	: Myocardial Infarction
ICM	: Ischaemic Cardiomyopathy
PVD	: Peripheral Vascular Disease
CAC	: Coronary Artery Calcification
AAC	: Abdominal Aortic Calcification
VC	: Vascular Calcification
AV fistula	: Arterio-Venous Fistula
AACS	: Abdominal Aortic Calcification Score
HDL	: High Density Lipoprotein
LDL	: Low Density Lipoprotein

1. INTRODUCTION

Chronic kidney disease (CKD) is an irreversible deterioration in renal function that usually develops over a period of years. End stage renal disease (ESRD) is the stage 5 of CKD spectrum of diseases when death is inevitable without renal replacement therapy (RRT) [1]. According to KDIGO reports, prevalence of CKD is approximately 10% of the global population [2]. In CKD patients, the leading cause of mortality is cardiovascular disease and it accounts for more than half of all the deaths; with myocardial infarction (MI), ischemic cardiomyopathy (ICM), stroke and peripheral vascular disease (PVD) making up bulk of the deaths [3]. Most of this problem may relate to vascular calcification and arterial stiffness. In CKD stage 5 population, 80-85% of existing dialysis patients and 60% of new patients have some degree of Coronary Artery Calcification (CAC) or Aortic calcification [4,5]. Furthermore, it has been also reported that vascular calcification scores may be predictive of mortality, with lower survival in association with greater CAC [6]. A study showed, prevalence of vascular calcification (VC) is 92% after 16 years of haemodialysis [7]. Multiple risk factors are associated with VC in haemodialysis (HD) patients and residual renal function (RRF) is one of the major risk factors. There is general belief

that renal function rapidly declines after initiation of HD treatment. However, renal function can be preserved for several years after the start of HD in many patients, especially when ultrapure dialysis fluid and biocompatible dialyzers are used [8,9]. Previous observational studies have shown that, preservation of residual renal function in dialysis patients is a prognostic and independent factor in patient survival and quality of life [10,11]. So by preserving RRF, morbidity and mortality related to VC can be reduced. Several non-invasive methods e.g., plain radiography, computed tomography, vascular ultrasound and so on are present to measure severity of VC. AAC is one of the measurements of VC that can easily be obtained by a semi-quantitative measurement in lateral lumbar radiography. AAC is an easy and fast measurement of VC used in HD patients [12]. Components of AAC are age, duration of dialysis and cardiovascular disease [13]. Traditional determinants for atherosclerosis, such as dyslipidemia, hypertension, smoking, gender and age only partly explain the calcification that seems to be more linked to the uremic milieu and abnormalities in mineral metabolism [14]. Relevant literature proved association between loss of RRF and VC in peritoneal dialysis (PD) patients [15] but this association is still unclear in HD patients. The aim of this study is to find out the association between loss of RRF and VC in HD patients and also to establish the association of VC with LVMI to show the effect of VC on cardiac morbidity and mortality. Since loss of RRF increases the amount of extracellular fluid which is associated with hypertension and left ventricular hypertrophy in haemodialysis patients [16]

2. MATERIALS AND METHODS

This observational study was conducted in Chattogram Medical College Hospital, Chattogram during April 2018 to March 2019. The study population consisted of CKD patients undergoing haemodialysis at dialysis units of the hospital. Sampling was done by convenient method. The sample size was estimated using the formula:

$$n = \frac{Z^2 \text{pq}}{d^2}$$

Where;

n = Sample size
Z= z value of standard normal distribution (SND) at a given level of significance

p= Expected proportion of event or prevalence of the event.
q= 100-p
d= Allowable error or precision in the estimate of 'p' (proportion)

Here,
Z = 1.96 at 5% level
p = 70% [5]
q = 30% (100-p)
d = 10% of p or 7

So,

$$n = \frac{(1.96 \times 1.96) \times 70 \times 30}{7 \times 7} = 164.64 \approx 165$$

After adjustment for 5% patients loss to follow-up: final sample size was (165×0.05+165 = 173) 173 patients.

As it was an observational study, all patients during study period with informed consent and fulfilling eligible criteria at dialysis units in Chittagong Medical College Hospital were included in this study. However, due to time limitation total 76 patients were included in this study after taking written informed consent from them. Afterwards, 16 patients withdrew their consent. So, the total number of study participants at the end of the study was 60.

The selection criteria were as follows:

Inclusion criteria:

1. Adult patients (age≥18 years) of either sex.
2. Patients on haemodialysis through A-V fistula.
3. Ambulatory patients.
4. Patients with 24 hours urinary volume less than 200ml.

Exclusion criteria:

1. Patients on MHD for less than 3 months.
2. Patients on acute haemodialysis.
3. Patients on MHD through pump catheter.
4. Those who are not willing to participate.

Those patients who fulfilled the selection criteria were enrolled after convenience method of sampling and their records were reviewed. They were selected on the basis of measuring total amount of urine volume collected in the last 24 hours of a dialysis session. A 50-cc disposable syringe was used for urine volume measurement.

Blood samples for biochemical analysis were collected in fasting condition. At the same day, lateral lumbar radiography and M-mode echocardiography was done for vascular calcification score and left ventricular hypertrophy respectively. Lateral lumbar radiography and M-mode echocardiography was done in CMCH and biochemical tests were performed in a nearby reputed diagnostic laboratory. Demographic variables & haemodialysis duration were recorded after interviewing the patients. BMI was recorded after measuring weight by analog weight machine (Equinox BR 9201 weighing scale) and height by measuring tape (Foshan Guos Wintape measuring Tape Co. Ltd, China). Low RRF was considered in those patients with no urine output or 24 hours urine output less than 200 ml. Hypertension was defined as taking antihypertensive drugs without regard to the actual measurement of blood pressure, or having a systolic blood pressure reading greater than 140 mm Hg or a diastolic blood pressure reading greater than 90 mm Hg [25]. BP was measured with a standard mercury sphygmomanometer and cuffs adapted to arm circumference. Before recording BP, the subject was kept in recumbent position for 10 minutes. Diabetes mellitus was defined as use of insulin or oral hypoglycemic agent, or a fasting plasma glucose level of 126 mg/dL or more [26]. FBS was measured by auto analyzer Siemens Advia 1800. Venous blood was collected at morning after an overnight fast of at least 12 hours before starting a dialysis session. Whole blood was used for FBS and lipid profile. Serum was used for other biochemical analysis. Lipid profile, serum calcium & phosphate, serum albumin was assessed by automated clinical chemistry analyzer Siemens dimension EXL 200. Measurement of serum PTH was done by chemiluminescence's method and CRP by nephelometry method.

Detection of vascular calcification: Vascular calcification score of all patients were measured by a lateral lumbar radiography at the level of L_1 to L_4. Vascular calcification was graded as 0: no aortic calcific deposits; 1: small scattered calcific deposits less than one-third of the corresponding length of the vertebral level; 2: medium quantity of calcific deposits about one-third or more but less than two-thirds of the corresponding vertebral length; 3: severe quantity of calcifications of more than two-thirds or more of the corresponding vertebral lengths. The abdominal aorta score at each vertebra level was obtained by summing up the calcification of the anterior and posterior walls of aorta. Calcification score at each lumbar spine level was between 0 and 6. The scores of L_1 to L_4 were summed with a total AAC score ranging from 0 to 24. AAC was measured with the help of a radiologist who was blind about the study patients.

Detection of left ventricular hypertrophy: Left Ventricular Mass index estimated from the Echocardiography report of the patients by a cardiologist who was blinded regarding the patients. M-mode echocardiography was performed with a GE Vivid S5 using a 3 MHz transducer. Methods of American Society of Echocardiography was followed during measurement. M-mode measurements included left ventricular end-diastolic diameter (LVDd), left ventricular posterior wall thickness (PWT), and interventricular septal thickness (IVST). Left ventricular mass (LVM) was calculated according to the Penn convention using the formula: LVM = $1.04 \times [(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3] - 13.6$ g [24]. The left ventricular mass index (LVMI) was calculated as LVM divided by body surface area. LVMI above reference range (Male = 49-115 g/m^2, Female = 43-95 g/m^2) [27] was considered as raised LVMI. Body surface area was calculated using Mosteller formula [27].

Data were collected by face-to-face interview, recording physical examination and reports of laboratory investigations using a structured questionnaire containing all the variables of interest. All the data were compiled in a preformed structured case record form.

After collection, all the data were compiled, edited and analysed using Statistical Package for Social Sciences (SPSS) version 20. Continuous variables were expressed as mean and standard deviation, if normally distributed, or as median and interquartile range where data were skewed. Categorical variables were expressed as frequency distribution. Statistical analysis included unpaired t test for quantitative variables and x^2 test for categorical variables. To assess the individual and combined influence of variables on AAC score univariate & multivariate linear regression were used respectively. Data were presented in tables. Statistical significance was defined as $p < 0.05$ and confidence interval set at 95% level.

3. RESULTS

Table 1 demonstrates the socio-demographic variables, general and renal function-related

risk factors of the respondents. It was seen that, mean age of the respondents was 50.33 ± 11.21 years. Majority of the participants were males and hailed from rural areas, 43 (71.7%) and 39 (65.0%) respectively. Most of them were service holders by occupation, that is 34 (56.6%). As per as the general risk factors were concerned, maximum cases were non-smokers and non-diabetic, 37 (61.7) and 33 (55.0). In addition, 60 of the participants, meaning 100% were found to be hypertensive. With context to renal function-related risk factors, etiology-wise, diabetes mellitus was predominantly found, which is 27 (45.0%). Duration of dialysis was found less than 2 years in majority of the cases, i.e., 26 (43.3%) and lastly, RRF was mostly moderately lost meaning 24 hours urinary total volume was within 100-200 ml in 32 (53.3%) participants.

Table 1. Distribution of respondents according to socio-demographic characteristics, general risk factors and renal function-related variables (n=60)

Traits	Frequency (f)	Percentage (%)
Socio-demographic characteristics		
Age group (years)		
<40	10	16.7
40-60	42	70.0
>60	08	13.3
Mean age ± Standard deviation	50.33 ± 11.21	
Gender		
Male	43	71.7
Female	17	28.3
Residence		
Rural	39	65.0
Urban	21	35.0
Occupation		
Service holder	34	56.6
House wife	16	26.7
Businessman	10	16.7
General risk factors		
Smoking status		
Non-smoker	37	61.7
Smoker	23	38.3
Diabetes mellitus		
Non-diabetic	33	55.0
Diabetic	27	45.0
Hypertension		
Hypertensive	60	100.0
Non-hypertensive	00	0.0
Renal-function related variables		
Etiology of CKD		
Diabetes Mellitus	27	45.0
Hypertension	22	36.7
Glomerulo-nephritis	11	18.3
Duration of dialysis (years)		
<2	26	43.3
2-4	24	40.0
>4	10	16.7
Residual renal function		
Moderately lost [urinary total volume in 24 hours: 100-200 ml]	32	53.3
Severely lost [urinary total volume in 24 hours: <100 ml]	28	46.7

Table 2. Association between vascular calcification and left ventricular mass index among the respondents (n=60)

VC	Normal LVMI (f/%)	Raised LVMI (f/%)	Total (f/%)	p-value
No VC	7 (100.0)	0 (0.0)	7 (100.0)	
Mild VC*	6 (19.4)	25 (80.6)	31 (100.0)	<0.001[vhs]
Moderate VC**	2 (10.5)	17 (89.5)	19 (100.0)	
Severe VC***	0 (0.0)	3 (100.0)	3 (100.0)	
Total	15 (25.0)	45 (75.0)	60 (100.0)	

*AACS=1-8; **AACS=9-16; ***AACS=17-24; VHS=very highly significant

Table 2 illustrates the association between vascular calcification and left ventricular mass index among the study participants. It is evident that, among those having mild vascular calcification, most of them had raised LVMI, which is 25 (80.6) out of 31 cases, followed by moderate VC, where among 19 patients, 17 (89.5) of them had raised LVMI. The p-value was derived from conducting X^2 test which shows the association between VC and LVMI was statistically highly significant (p = <0.001).

Table 3 demonstrates the association between vascular calcification and residual renal function among the study respondents. In case of 31 out of 60 patients with mild VC, majority of the cases had moderately lost VC, which is 20 (64.5). It was also found that, out of those 19 patients who developed moderate VC, 14 (73.7) were detected to have severely lost RRF. The p-value was found by doing X^2 test and the association between VC and RRF was seen to be statistically significant (p = <0.01).

Table 3. Association between vascular calcification and residual renal function among respondents (n=60)

VC	Moderately lost RRF (f/%)	Severely lost RRF (f/%)	Total (f/%)	p-value
No VC	7 (100.0)	0 (0.0)	7 (100.0)	
Mild VC*	20 (64.5)	11 (35.5)	31 (100.0)	<0.01[hs]
Moderate VC**	5 (26.3)	14 (73.7)	19 (100)	
Severe VC***	0 (0.0)	3 (100.0)	3 (100.0)	
Total	32 (53.3)	28 (46.7)	60 (100.0)	

*AACS=1-8; **AACS=9-16; ***AACS=17-24; HS=highly significant

Table 4. Pearson's Correlation between vascular calcification scores (AACS) and other dependent variables (n=60)

Variables	Correlation Coefficient (r)	p-value
AACS and LVMI	+0.562	0.000[vhs]
AACS and UTV	-0.667	0.000[vhs]
AACS and CRP	+0.487	0.000[vhs]
AACS and duration of dialysis	+0.345	0.007[hs]
AACS and Serum Phosphate	+0.383	0.003[hs]
AACS and Ca x PO_4	+0.339	0.008[hs]
AACS and FBS	+0.271	0.036[s]
AACS and Serum Albumin	-0.103	0.432[ns]
AACS and Serum Calcium	+0.047	0.721[ns]
AACS and BMI	+0.117	0.375[ns]
AACS and Systolic BP	+0.037	0.778[ns]
AACS and Diastolic BP	-0.092	0.486[ns]
AACS and total Cholesterol	+0.016	0.902[ns]
AACS and Triglyceride	-0.081	0.539[ns]
AACS and HDL	+0.177	0.176[ns]
AACS and LDL	+0.132	0.314[ns]
AACS and Serum iPTH	+0.055	0.675[ns]

VHS = Very Highly Significant (p< 0.001); Hs = Highly Significant (p< 0.01); S = Significant (p<0.05); NS = Not Significant (p>0.05)

Table 4 shows Pearson's correlation vascular calcification scores (which is determined by Abdominal Aortic Calcification scores) and other dependent variables. It was clearly evident that, vascular calcification was significant positively correlated with LVMI, CRP, duration of dialysis, serum Phosphate and Ca x PO_4 product ($p > 0.05$). It was also seen that; VC was significant negatively correlated with Urinary Total Volume ($p < 0.05$).

4. DISCUSSION

This observational study conducted on 60 CKD patients on MHD, during the period of April 2018 to March 2019 at Chattogram Medical College Hospital revealed that, vascular calcification was affected by low residual renal function; and those with vascular calcification had significantly raised left ventricular mass index which reflected left ventricular hypertrophy.

Previous studies on chronic kidney disease and diabetes patients [17-20]. demonstrated that age, diabetes mellitus, hypertension, male gender and duration of dialysis are closely associated with vascular calcification. This study revealed similar results, except for the trait of duration of dialysis which could be for the fact of including most patients with shorter duration of dialysis.

Another study on general population [21] suggested that, men are particularly more prone to vascular calcification than women. Some studies on CKD patients [17-20] also found close association of vascular calcification with male gender. In this study, male had more vascular calcification score than female. So, it supports the above studies. But these results may owe to the fact of recruiting higher number (71.7%) of male participants.

Here, in case of respondents with loss of residual renal function, median abdominal aortic calcification score was significantly higher in severely lost group comparing with moderately lost group. This result is consistent with a study done at China Medical University Hospital on chronic haemodialysis patients [22].

A previous study on pre-dialysis chronic kidney disease (CKD) patients [23] showed that left ventricular mass increases parallel with the decrease in residual GFR. In this study, vascular calcification increased in proportional to reduced residual renal function and, patients with more severe vascular calcification status had more proportional loss of residual renal function. So, my result supports the above study.

CORD study [13] found no significant relationship between AACS and SBP, DBP, serum PO4, Lipid or CRP. However, in this study, I found positive correlation of AACS with SBP, serum PO4, serum Lipid and CRP, though none of these were statistically significant. In addition, this study found negative correlation of AACS with DBP. This correlation was also found in similar studies [17,18,22]. In this study, AACS is positively correlated with LVMI. This result is supported by other studies on chronic kidney disease and hypertensive patients [24,25]. It reflects the effect of vascular calcification that increases cardiac morbidity and mortality in maintenance haemodialysis patients [26,27].

5. CONCLUSION

In this observational study conducted among the HD patients with loss of RRF revealed that, patients with severe loss of RRF (24 hours UTV <100 ml) had significantly (p value <0.01) raised vascular calcification. The more was the RRF loss, the more was the vascular calcification score. The patients with higher calcification score had also significantly raised LVMI. Also, diabetic patients showed significant (p value <0.05) association with raised VC compared to non-diabetics.

6. LIMITATIONS

1. The study was performed in only one center and only based on prevalence at a single point, no follow up records were included.
2. There were relatively smaller sample size subgroups of vascular calcification which might have distorted the result of statistical analyses.
3. Certain data may appear unusual as there were no restrictions on supplementary calcium, phosphate-binder medication or phosphate rich diet.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

All patients during study period with informed consent and fulfilling eligible criteria at dialysis units in Chattogram Medical College Hospital were included in this study. However, due to time

limitation total 76 patients were included in this study after taking written informed consent from them.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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