

Vascular Calcification as a Predictor of Left Ventricular Hypertrophy in Haemodialysis patients with Low Residual Function

Abstract:

Introduction: In CKD 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 information about the influence of residual renal function on vascular calcification in HD patients. **Objective:** To determine the association between vascular calcification and left ventricular hypertrophy in HD patients with low RRF. **Methods:** An observational study was performed on 60 CKD patients on MHD with low RRF 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 LVH respectively. **Results:** The prevalence of vascular calcification was present in 88.3% cases in patients with low RRF. Patients without vascular calcification had normal LVMI in 100% cases and those with vascular calcification had increased LVMI 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 FBS, CRP, iPTH, Cholesterol, BMI, Serum Calcium, Serum Phosphate, Ca x PO₄ product and systolic BP but it was negative for Serum Albumin, Diastolic BP and 24 hours UTV. **Conclusion:** Vascular calcification is very common in patients with ESRD on MHD. Loss of RRF is an important risk factor for vascular calcification. Patients with vascular calcification had significantly raised LVMI.

Keywords: Chronic Kidney Disease; End Stage Renal Disease; Maintenance Haemodialysis; Vascular Calcification; Residual Renal Function; Left Ventricular Hypertrophy.

Introduction:

Chronic kidney disease is an irreversible deterioration in renal function that usually develops over a period of years. ESRD is the stage 5 of CKD spectrum of diseases when death is inevitable without RRT.¹ According to KDIGO reports, prevalence of CKD is approximately 10% of the global population². In CKD patients, the leading cause of mortality is cardiovascular disease and it accounts for more than half of all the deaths; with MI, ICM, Stroke and 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 VC is 92% after 16 years of haemodialysis.⁷ Multiple risk factors are associated with VC in HD patients and 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) patients¹⁵ 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

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:

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

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 $(165 \times 0.05 + 165 = 173)$ 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 \geq 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.⁴⁶ 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 more⁴⁷. 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 L₁ to L₄. 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 L₁ to L₄ 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: $LVM = 1.04 \times [(LVIDD + PWT + IVST)^3 - (LVIDD)^3] - 13.6 \text{ g}$.⁴⁵ The left ventricular mass index (LVMI) was calculated as LVM divided by body surface area. LVMI above reference range (Male = 49-115 g/m², Female = 43-95 g/m²)⁴⁹ was considered as raised LVMI. Body surface area was calculated using Mosteller formula.⁵⁰

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 χ^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 and figures. Statistical significance was defined as $p < 0.05$ and confidence interval set at 95% level.

UNDER PEER REVIEW

Results:

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 \pm Standard deviation	50.33 \pm 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 1 above 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 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)	<0.001 ^{vhs}
Mild VC*	6 (19.4)	25 (80.6)	31 (100.0)	
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 above 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 χ^2 test which shows the association between VC and LVMI was statistically highly significant ($p = <0.001$)

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)	<0.01 ^{hs}
Mild VC*	20 (64.5)	11 (35.5)	31 (100.0)	
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 3 above 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 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 PO₄ product ($p > 0.05$). It was also seen that, VC was significant negatively correlated with Urinary Total Volume ($p < 0.05$).

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 patients⁵¹⁻⁵⁴ 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 population⁵⁵ suggested that, men are particularly more prone to vascular calcification than women. Some studies on CKD patients⁵¹⁻⁵⁴ 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.⁵⁶

A previous study on pre-dialysis chronic kidney disease (CKD) patients⁵⁹ 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.

CARD study¹³ 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.^{22,55,60} In this study, AACS is positively correlated with LVMI. This result is supported by other studies on chronic kidney disease and hypertensive patients^{57,58}. It reflects the effect of vascular calcification that increases cardiac morbidity and mortality in maintenance haemodialysis patients.

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.

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.

4. Abbreviations

5. CKD: Chronic Kidney Disease
6. HD: Haemodialysis
7. RRF: Residual Renal Function
8. MHD: Maintenance Haemodialysis
9. LVH: Left Ventricular Hypertrophy
10. FBS: Fasting Blood Sugar
11. CRP: C-Reactive Protein
12. iPTH: Intact Parathyroid Hormone
13. BMI: Body Mass Index
14. Ca x PO₄: Calcium Phosphate product
15. UTV: Urinary Total Volume
16. ESRD: End Stage Renal Disease
17. BP: Blood Pressure
18. LVMI: Left Ventricular Mass Index
19. RRT: Renal Replacement Therapy
20. KDIGO: Kidney Disease | Improving Global Outcomes
21. MI: Myocardial Infarction
22. ICM: Ischaemic Cardiomyopathy
23. PVD: Peripheral Vascular Disease
24. CAC: Coronary Artery Calcification
25. AAC: Abdominal Aortic Calcification
26. VC: Vascular Calcification
27. AV fistula: Arterio-venous fistula
28. AACS: Abdominal Aortic Calcification Score
29. HDL: High Density Lipoprotein
30. LDL: Low Density Lipoprotein

References:

1. Stuart H. Ralston. Davidson's Principles and Practice of Medicine. In: B Conway, PJ Phelan, GD Stewart. Nephrology and Urology. Edinburgh: Elsevier, 2018: 415.
2. Neil Turner. Oxford Textbook of Clinical Nephrology. In: Adrian Covic, Mugurel Apetrii, Luminita Voroneanu, David J. Goldsmith. Vascular calcification. Oxford: Oxford University Press, 2016: 957.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am. J. Kidney Dis.* 1998; 32: S112-19.
4. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK. et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J. Am. Coll. Cardiol.* 2002; 39: 695–701.
5. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindberg J, Dreisbach A. et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int.* 2005; 68: 1815–24.
6. Matsuoka M, Iseki K, Tamashiro M, Fujimoto N, Higa N, Touma T, Takishita S. et al. Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis. *Clin. Exp. Nephrol.* 2004; 8: 54–8.
7. Goldsmith DJ, Covic A, Sambrook PA, Ackrill P. Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis. *Nephron* 1997; 77: 37–43.
8. Schiff H, Lang SM, Fischer R: Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. *Nephro Dial Transplant* 17: 1814 – 1818, 2002
9. McKane W, Chandna SM, Tattersall JE, Greenwood RN, Farrington K: Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. *Kidney Int* 61: 256 – 265, 2002
10. Shafi T, Jaar BG, Plantinga LC, Fink N E, Sadler J H, Parekh R S, Powe N R. et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for healthy outcomes in caring for End-Stage Renal Disease (CHOICE) Study. *Am J Kidney Dis.* 2010, 56: 348 – 358.
11. Liao CT, Chen YM, Shiao CC, Hu F C, Huang J W, Kao T W et al. Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long term peritoneal dialysis. *Nephrol Dial Transplant.* 2009; 24: 2909 – 2914.

12. Toussaint ND, Pedagogos E, Lau KK, Heinze S, Becker GJ, Beavis J et al. Lateral lumbar X-ray assessment of abdominal aortic calcification in Australian haemodialysis patients. *Nephrol* 2011; 16:389–95.
13. Honkanen E, Kauppila L, Wikstrom B, Pieter L, Krzesinski JM, Aasarod K, Verbeke F et al. Abdominal aortic calcification in dialysis patients: results of the CORD study. *Nephrol Dial Transplant: The Official Publication of the European Dialysis and Transplant Association-European Renal Association* 2008; 23:4009–15.
14. Goodman WG, London G, on Behalf of the Vascular Calcification Work Group. Vascular calcification in chronic kidney disease. *Am J Kidney Dis* 2004; 43: 572–579.
15. Wang AY, Lam CW, Wang M, Chan IH, Lui SF, Sanderson JE. Is valvular calcification a part of the missing link between residual kidney function and cardiac hypertrophy in peritoneal dialysis patients? *Clin J Am Soc Nephrol: CJASN* 2009; 4: 1629–36.
16. Fagugli RM, Pasini P, Quintaliani G, Pasticci F, Giau G, Cicconi F. et al. Association between extracellular water, left ventricular mass and hypertension in hemodialysis patients. *Nephrol Dial Transplant*, 2003; 18: 2332 – 2338.
17. Maxine A. Papadakis Stephen J. McPhee. *Current Medical Diagnosis & Treatment* 2017. In: Suzanne Watnick, MD, & Tonja C. Dirks, MD: *Kidney Disease*. Lange: McGraw Hill Education, New York, 2017: 925.
18. Keith, D. S., Nichols, G. A., Gullion, C. M, Brown JB, Smith DH. (2004). Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*, 164(6), 659–63.
19. Sigrist, M. K., Taal, M. W., Bungay, P, and Christopher W.M. (2007). Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney diseases. *Clin J Am Soc Nephrol*, 2(6), 1241–8.
20. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Wang W. et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N. Engl. J. Med.* 2000; 342: 1478–83.
21. Massy, Z. A. and Drueke, T. B. (2012). Magnesium and outcomes in patients with chronic kidney disease: focus on vascular calcification, atherosclerosis and survival. *Clin Kidney J*, 5(1), i52–i6.
22. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003; 18: 1731–1740.

23. Verberckmoes. SC, Persy. V, Behets, GJ, Hufkens A, Zebger-Gong H, Muller D et al. (2007). Uremia-related vascular calcification: more than apatite deposition. *Kidney Int*, 71(4), 298–303.
24. AY-M Wang and K-N Lai. The importance of residual renal function in dialysis patients. *Kidney International* 2006; 69: 1726 – 1732.
25. Maiorca R, Brunori G, Zubani R, Cancarini G.C, Manili L, Camerini C. et al. Predictive value of dialysis adequacy and nutritional indices for mortality and morbidity in CAPD and HD patients. A longitudinal study. *Nephrol Dial Transplant* 1995; 10: 2295 – 2305.
26. Covic, A., Kanbay, M, Voroneanu, L, Turgut F, Serban DN, Lacramioara I. (2010). Vascular calcification in chronic kidney disease. *Clin Sci (ond)*, 119(3), 111–21.
27. Simon, A., Megnien, J. L., and Chironi, G. (2010). The value of carotid intima-media thickness for predicting cardiovascular risk. *Arterioscler Thromb Vasc Biol*, 30(2), 182–5.
28. Reynolds, J. L, Skepper, J, McNair. R, Kasama T, Gupta K, Weissberg PL. (2005). Multifunctional roles for serum protein fetuin-A in inhibition of human vascular smooth muscle cell calcification. *J Am Soc Nephrol*, 16(10), 2920–30.
29. Lomashvili, K. A., Cobbs, S., Hennigar, R. A, Hardcastle K, O’neill WC. (2004). Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin. *J Am Soc Nephrol*, 15(6), 1392–401.
30. Lomashvili, K. A., Garg, P., Narisawa, S., et al. (2008). Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification. *Kidney Int*, 73(9), 1024–30.
31. Agatston, A. S, Janowitz, W. R, Hildner, F. J, Zusmer N. R, Viamonte M, Detrano R.(1990). Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*, 15(4), 827–32.
32. Kauppila, LI, Polak, JF, Cupples, LA., Hannan MT, Kiel DP, Wilson WF. (1997). New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. *Atherosclerosis*, 132(2), 245–50.
33. Milutinovic J, Cutler RE, Hoover P, Meijssen B, Scribner BH. Measurement of residual glomerular filtration rate in the patient receiving repetitive hemodialysis. *Kidney Int* 1975;8:185-90.
34. Van Olden RW, van Acker BA, Koomen GC, Krediet RT, Arisz L. Time course of inulin and creatinine clearance in the interval between two haemodialysis treatments. *Nephrol Dial Transpl: Official Publication of the European Dialysis and Transplant Association- European Renal Association* 1995; 10:2274–80.

35. Termorshuizen F, Korevaar JC, Dekker FW et al. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am J Kidney Dis: The Official Journal of the National Kidney Foundation* 2003;41:1293–302.
36. Van Olden RW, Krediet RT, Struijk DG, Arisz L. Measurement of residual renal function in patients treated with CAPD. *J Am Soc Nephrol* 1996; 7: 745-750.
37. Daniela R, Dumitru F, Carol D. The importance of residual renal function in chronic dialysed patients. *Journal of Medicine and Life*: 2009; 2:199-206.
38. Lest CG, Vanholder RC, Ringoir SM. Loss of residual renal function in patients on regular haemodialysis. *Int J Artif organs*.1989; 12: 159-164.
39. Van Stone JC. The effect of dialyzer membrane and etiology of kidney disease on the preservation of residual renal function in chronic haemodialysis patients. *ASAIO J*.1995; 41: M713- M716.
40. Davies SJ. Peritoneal dialysis in the patients with a failing renal allograft. *Perit Dial Int*. 2001; 21(Suppl 3): S280-S284.
41. Jassal SV, Lok CE, Walele A, Bargman JA. Continued transplant immunosuppression may prolong survival after return to peritoneal dialysis: results of a decision analysis. *Am J Kidney Dis*. 2002; 40: 178-183.
42. Shemin D, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. *Am J Kidney Dis* 2001; 38: 85–90.

UNDER PEER REVIEW