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Prevalence and Predictors of Aortic Valve Sclerosis in Chronic Hemodialysis Patients

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ABSTRACT

Background: Aortic valve sclerosis (AVS) is a serious public health issue, particularly among the elderly. It is linked to higher rates of acute cardiovascular events. In addition, cardiovascular diseases are common in chronic hemodialysis patients. **Objective:** To find out the prevalence of AVS in chronic hemodialysis patients and assess risk factors for AVS in these patients. **Patients and Methods:** The research involved 58 chronic hemodialysis patients from December 2019 to December 2020. They were categorized into group 1 (22 subjects) who did not have AVS and group 2 (36 subjects) who had AVS. Demographic data were gathered from all patients. Laboratory investigations and echocardiographic examinations were done for all the subjects. **Results:** Group 2 was older than group 1 ($p = 0.002$). In addition, diastolic blood pressure (DBP) was higher in group 1 than in group 2 ($p < 0.003$). Furthermore, group 2 exhibited greater serum alkaline phosphatase (ALP) levels than group 1 ($p = 0.011$). In contrast, group 2 had lower serum creatinine, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) than group 1 ($p= 0.049$, $p = 0.038$, $p = 0.01$, and $p = 0.01$, respectively). On multivariate regression analysis, greater age ($p = 0.014$), lower DBP ($p = 0.049$), and lower MCH ($p = 0.011$) were significantly predictive of AVS. **Conclusion:** 37.9% of hemodialysis patients had AVS in this study and the predictors for AVS included older age, lower DBP, and lower MCH.

Keywords: Aortic Valve Sclerosis, Chronic Kidney Disease, Hemodialysis, Mean Corpuscular Hemoglobin, Vascular Calcification.

INTRODUCTION

In older individuals, one of the most prevalent echocardiographic findings is aortic valve sclerosis (AVS). AVS is related to a higher prevalence of myocardial infarction leading to higher rates of mortality [(1)]. Moreover, the fatality rate from cardiovascular problems in chronic dialysis patients is greater than in the general population [(2)].

AVS has the same pathological features and risk factors as atherosclerosis [(3)]. Furthermore, mechanical stresses, including membrane stretching, blood pressure, and shear force, enhance the calcification process of the aortic valve [(4)]. Therefore, this study aimed to find out the prevalence of AVS in chronic hemodialysis patients and detect predictors of AVS in these patients.

PATIENTS AND METHODS

This cross-sectional study included 58 subjects from December 2019 to December 2020. They were end-stage kidney disease (ESKD) patients who had been on regular hemodialysis for at least 6 months. All subjects with a past history of parathyroidectomy, coronary artery bypass surgery, previous hospital admission for acute coronary syndrome, and advanced heart failure were excluded.

The contributors were sorted into two groups depending on the identification of AVS on echocardiography. Group 1 consisted of 22 patients who did not have AVS. They were 14 males and 8 females, and the ages varied from 27 to 82 years. Group 2 comprised 36 patients with a confirmed diagnosis of AVS. They were 21 males and 15 females, and the ages varied from 29 to 82 years. Medical histories were collected from all subjects. Clinical examination included weight, height, pulse, blood pressure, temperature, general examination, and local cardiac examination. Investigations included renal and hepatic function tests, bone profile, iron profile, fasting lipid profile, urea reduction ratio, complete blood count, serum vitamin B12, C-reactive protein, serum folate, troponin T, and erythropoietin resistance index (ERI). ERI was calculated as weekly erythropoietin dosage/weight of the patient/hemoglobin level [(5)]. All patients underwent echocardiographic examination by a skillful cardiologist and AVS was identified by the detection of irregular thickening of the aortic leaflet with a peak velocity across the valve <2.5 m/s.

Ethical approval:

The research was authorized by the Institutional Review Board of the Ethical Committee of Zagazig University and according to the Helsinki declaration ethical guidelines. Each participant signed informed consent to share in the study.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) version 26 was used to execute data analysis. The normality of continuous data was examined using the Shapiro Wilk test. Continuous variables with skewed distributions were presented as medians and interquartile ranges, while continuous variables with normal distributions were presented as means and standard deviations. Categorical data were expressed as numbers and percentages. The Student's t-test and the Mann-Whitney U test were employed to evaluate normally distributed and non-normally distributed continuous data, respectively. While

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the nominal variables were evaluated using the Chi-square test. P value less than 0.05 was considered significant. Backward logistic regression analysis was used to identify independent predictors of AVS. Multiple regression analysis was deemed for all variables having $P \leq 0.2$ on univariate analysis.

RESULTS

In the comparison of demographic data, group 2 was significantly older than group 1. In addition, diastolic blood pressure (DBP) was higher in group 1 than in group 2 as shown in table (1).

Table (1): Comparison of demographic and clinical data between the two studied groups

Variable	Group 1 (N=22)	Group 2 (N=36)	Test	p-value
Age (years), Median (IQR)	52 (33-64)	65 (54.5-71.8)	-3.055	0.002**
Male sex, No (%)	14 (63.6%)	21 (58.3%)	0.160	0.689
Weight (Kg), Median (IQR)	59.25 (43.8-73.4)	59.4 (48.5-73.6)	-0.2	0.841
SBP (mm Hg), Mean ± SD	156±25.4	149.9±24.5	0.912	0.366
DBP (mm Hg), Mean ± SD	87.2±13.4	74.3±16.3	3.105	0.003**
IDWG (Kg), Median (IQR)	2.35 (1.68-3.08)	2 (1.4-2.8)	1.558	0.119
Dialysis vintage (years), Median (IQR)	3 (1.5-3.6)	3 (1-7)	-0.798	0.425

(IQR): Interquartile range, (SD): Standard deviation, (SBP): Systolic blood pressure, (DBP): Diastolic blood pressure, (IDWG): Interdialytic weight gain. In the comparison of laboratory data, group 2 had higher serum alkaline phosphatase (ALP) levels than group 1. In contrast, Group 2 had lower serum creatinine, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) than group 1 as presented in table (2).

Table (2): Comparison of laboratory data between the two studied groups.

Variable	Group 1 (N=22)	Group 2 (N=36)	Test	p-value
ALT (IU/L), Median (IQR)	8.85 (5.6-11.78)	9.9 (6.3-12.4)	-0.722	0.47
Alkaline phosphatase (U/L), Median (IQR)	72.5 (52.9-90.72)	83 (67-154.5)	-2.532	0.011*
Serum total protein (g/dL), Mean±SD	6.97±0.5	6.87±0.65	0.611	0.544
Serum albumin (g/dL), Mean±SD	3.95±0.36	3.77±0.43	1.641	0.106
Serum calcium (mg/dL), Mean±SD	9.38±0.8	9.18±0.64	0.954	0.344
Serum phosphorus (mg/dL), Median (IQR)	1.64 (1.11-2.12)	1.61 (1.21-2.03)	-0.24	0.81
iPTH (pg/dL), Median (IQR)	250.8 (93.4-539.9)	270.2 (128-601)	-0.625	0.532
Serum creatinine (mg/dL), Mean±SD	11.13±2.88	9.54±2.94	1.995	0.049*
Urea reduction ratio (%), Median (IQR)	50.76 (38.49-60.59)	49.04 (44.72-57.7)	-0.032	0.974
Serum cholesterol (mg/dL), Mean±SD	150±28.2	154.3±35.6	-0.473	0.638
Serum triglycerides (mg/dL), Median (IQR)	139.8 (110.6-220)	106.6 (87.6-193.8)	-1.314	0.189
LDL (mg/dL), Median (IQR)	1.93 (1.48-2.58)	2.04 (1.57-2.6)	-0.361	0.718
HDL (mg/dL), Mean±SD	35.18 (28.6-44.85)	39.6 (30.9-50.65)	-1.491	0.136
Urea (mg/dL), Median (IQR)	112.3 (84.7-160.4)	100.9 (72-161)	-0.617	0.537
Hemoglobin (g/dL), Mean±SD	10.7±1.5	10.7±1.4	0.033	1.000
MCV (fL), Mean±SD	83.7±8.68	79.1±7.58	2.128	0.038*
MCH (pg), Mean±SD	24.9±3.47	22.7±2.78	2.665	0.01**
MCHC (gm/dL), Mean±SD	29.6±1.59	28.6±1.2	2.673	0.01**
Serum uric acid (mg/dL), Mean±SD	6.67±1.3	6.73±1.22	-0.175	0.862
WBC ($x10^3/mm^3$), Median (IQR)	6.5 (5.6-7.1)	6.39 (5.3-7.76)	-0.064	0.949
Platelets ($x10^3/mm^3$), Median (IQR)	236 (185-263)	206.65 (172-295.5)	-0.104	0.917
Serum folate (µg/L), Median (IQR)	9.02 (5.4-12.89)	8.8 (5.8-13.53)	-0.449	0.653
Serum vitamin B12 (pg/mL), Median (IQR)	627.5 (362.3-764.4)	525 (404.6-751.9)	-0.184	0.854
Serum iron (µg/dL), Median (IQR)	45.68 (35.7-72)	42.7 (33.5-59.1)	-1.002	0.317
TIBC (µg/dL), Mean±SD	186±29.37	180.7±34	0.611	0.544
Transferrin saturation (%), Median (IQR)	25.5 (18-41)	26.37 (19-31)	-0.866	0.387
Ferritin (ng/mL), Median (IQR)	624 (382-898.5)	531 (390-963.8)	-0.152	0.879
CRP (mg/L), Median (IQR)	17 (4.9-53)	7.7 (3-25.5)	-1.474	0.14
Troponin T (ng/mL), Median (IQR)	0.086 (0.054-0.172)	0.124 (0.07-0.211)	-0.866	0.387
ERI (IU/kg/week/g/dl), Median (IQR)	18.8 (9.6-29.5)	17 (12.9-26.4)	-0.016	0.987

(ALT): Alanine transaminase, (IQR): Interquartile range, (SD): Standard deviation, (iPTH): Intact parathyroid hormone, (LDL): Low density lipoprotein, (HDL): High density lipoprotein, (MCV): Mean corpuscular volume, (MCH): Mean corpuscular hemoglobin, (MCHC): Mean corpuscular hemoglobin concentration, (WBC): White blood cells, (TIBC): Total iron binding capacity, (CRP): C-Reactive protein, (ERI): Erythropoietin resistance index. In the comparison of echocardiographic findings, group 2 had a lower ejection fraction median value than group 1 as demonstrated in table (3).

Table (3): Comparison of echocardiographic findings between the two studied groups

Variable	**Group 1 (N=22)**	**Group 2 (N=36)**	**Test**	p-value
Ejection fraction (%), Median (IQR)	55 (55-61)	50 (45-55)	-2.472	0.013*
LVED (mm/m^2), Mean± SD	53.95±7.57	51.5±6.16	1.349	0.183
LVES (mm/m^2), Mean± SD	35.14±9.9	35.28±7.64	-0.061	0.952
Aortic size (mm), Median (IQR)	30 (27.8-30.5)	28 (28-30)	-0.998	0.318

LVED: Left ventricular end diastolic diameter, LVES: Left ventricular end systolic diameter.

Moreover, univariate analysis of predictors of AVS in all studied patients showed that the significant predictors were older age, lower DBP, lower MCV, lower MCH, and lower MCHC. Serum ALP, serum albumin, serum creatinine, and HDL were marginally statistically insignificant with p-values ≤0.2 as shown in table (4).

Table (4): Univariate logistic regression analysis of predictors of aortic valve sclerosis in all studied patients

Variable	β	SE	OR	95% CI	p-value
Age (years)	0.071	0.023	1.074	(1.027-1.122)	0.002**
Male sex	0.223	0.557	1.25	(0.419-3.727)	0.689
SBP (mm Hg)	-0.01	0.011	0.99	(0.968-1.012)	0.36
DBP (mm Hg)	-0.057	0.021	0.945	(0.907-0.984)	0.006**
Weight (Kg)	-0.002	0.014	0.998	(0.972-1.025)	0.89
Dialysis vintage (years)	0.077	0.075	1.08	(0.931-1.251)	0.31
ALT (IU/L)	0.013	0.031	1.013	(0.952-1.077)	0.688
Alkaline phosphatase (U/L)	0.012	0.007	1.012	(0.999-1.026)	0.069
Serum total protein (g/dL)	-0.029	0.046	0.972	(0.888-1.064)	0.537
Serum albumin (g/dL)	-0.123	0.078	0.884	(0.759-1.029)	0.113
Serum calcium (mg/dL)	-1.481	1.554	0.227	(0.011-4.786)	0.341
Serum phosphorus (mg/dL)	0.04	0.45	1.04	(0.431-2.515)	0.93
iPTH (pg/dL)	0.000	0.007	1.000	(0.987-1.013)	0.965
Serum creatinine (mg/dL)	0.002	0.001	0.998	(0.996-1.000)	0.06
Urea (mg/dL)	0.017	0.024	0.983	(0.938-1.03)	0.472
Urea reduction ratio (%)	0.003	0.02	1.003	(0.965-1.042)	0.872
Serum cholesterol (mg/dL)	0.155	0.322	1.167	(0.621-2.195)	0.631
Serum triglycerides (mg/dL)	-0.139	0.243	0.871	(0.54-1.403)	0.569
LDL (mg/dL)	0.105	0.383	1.11	(0.524-2.351)	0.785
HDL (mg/dL)	1.258	0.782	3.517	(0.76-16.28)	0.108
Serum uric acid (mg/dL)	0.001	0.004	1.001	(0.993-1.008)	0.859
Hemoglobin (g/dL)	-0.006	0.191	0.994	(0.684-1.444)	0.974
MCV (fL)	-0.072	0.035	0.931	(0.869-0.997)	0.042*
MCH (pg)	-0.232	0.095	0.793	(0.659-0.955)	0.014*
MCHC (gm/dL)	-0.519	0.216	0.595	(0.39-0.909)	0.016*
WBC ($x10^3/mm^3$)	-0.021	0.12	0.979	(0.773-1.24)	0.862
Platelets ($x10^3/mm^3$)	0.002	0.003	1.002	(0.996-1.008)	0.572
Serum folate (µg/L)	0.008	0.023	1.008	(0.963-1.055)	0.732
Serum vitamin B12 (pg/mL)	0.000	0.001	1.000	(0.998-1.003)	0.731
Serum iron (µg/dL)	-0.069	0.06	0.933	(0.829-1.05)	0.252
TIBC (µg/dL)	-0.03	0.048	0.971	(0.883-1.067)	0.537
Transferrin saturation (%)	-0.025	0.022	0.975	(0.935-1.017)	0.247
Ferritin (ng/mL)	0.000	0.001	1.000	(0.999-1.001)	0.9
CRP (mg/L)	-0.004	0.004	0.996	(0.989-1.003)	0.278
Troponin T (mg/L)	0.000	0.002	1.000	(0.996-1.004)	0.986
ERI (IU/kg/week/g/dl)	-0.008	0.021	0.992	(0.952-1.034)	0.719

(*): Significant, (**): Highly significant, (β): Regression coefficient, (SE): Standard error, (OR): Odds ratio, (SBP): Systolic blood pressure, (DBP): Diastolic blood pressure, (ALT): Alanine transaminase, (iPTH): Intact parathyroid hormone, (LDL): Low density lipoprotein, (HDL): High density lipoprotein, (MCV): Mean corpuscular volume, (MCH): Mean corpuscular hemoglobin, (MCHC): Mean corpuscular hemoglobin concentration, (WBC): White blood cells, (TIBC): Total iron binding capacity, (CRP): C-Reactive protein, (ERI): Erythropoietin resistance index.

All variables with p-values ≤0.2 were selected for multivariate regression analysis. Finally, significant predictors of AVS on multivariate regression analysis were older age, lower DBP and lower MCH as shown in table (5).

Table (5): Multivariate logistic regression analysis of predictors of aortic valve sclerosis in all studied patients

Variable	β	SE	OR	95% CI	p-value
Age (years)	0.067	0.027	1.069	(1.013-1.128)	0.014*
DBP (mm Hg)	-0.053	0.027	0.948	(0.899-1.000)	0.049*
MCH (pg)	-0.301	0.118	0.74	(0.587-0.933)	0.011*
Alkaline phosphatase (U/L)	0.013	0.008	1.013	(0.996-1.03)	0.13

(*): Significant, (**): Highly significant, (β): Regression coefficient, (SE): Standard error, (OR): Odds ratio, (DBP): Diastolic blood pressure, (MCH): Mean corpuscular hemoglobin.

DISCUSSION

Dialysis patients suffer from valvular heart diseases, which occur 5 times more frequently in these patients than in the general population [(6)]. This relationship results in higher death rates and poor prognosis in patients with chronic kidney disease (CKD). Moreover, the 5-year survival rate with mild aortic stenosis in CKD patients is approximately 40% while it reaches 69% in persons without CKD [(7)]. Therefore, the goals of this research were to find out the prevalence of AVS in chronic hemodialysis patients and assess risk factors for AVS in these patients.

This cross-sectional study included 58 subjects. They were classified into group 1 (22 patients without AVS on echocardiography) and group 2 (36 patients with a confirmed diagnosis of AVS on echocardiography). The median age of the patients in group 2 was 65 years with interquartile range of (54.5-71.8) years, which was significantly older than that of group 1. This agrees with **Sayarlioglu *et al.*** [(8)] but against **Sercelik and Besnili** [(1)]**.** The reason for this is that degenerative calcification occurs frequently with the aging process therefore older people have a higher prevalence of AVS [(9)]. Additionally, DBP was markedly higher in group 1 than in group 2. This corresponds to the findings published by **Cho *et al.*** [(10)]. In the general population, hypertension is related to accelerated calcification of the aortic valve [(11)]. However, in the dialysis population lower DBP is commonly associated with AVS because vascular calcification is greatly predominant in dialysis patients and it is linked to diastolic dysfunction of the left ventricle and reduced arterial elasticity resulting in lower DBP [(12)].

Regarding laboratory data, group 2 had higher levels of ALP than group 1. This is because ALP is frequently raised in the dialysis population, which is linked to higher death rates in ESKD patients. High levels of ALP enhance the hydrolysis of pyrophosphate, which is a strong suppressor of the process of vascular calcification therefore elevated ALP levels encourage vascular calcification [(13)]. In addition, group 2 had considerably lower serum creatinine than group 1, this is because CKD patients with lower levels of serum creatinine are at higher risk of vascular calcification due to poor nutritional condition and reduced muscular bulk [(14)]. Additionally, MCV, MCH, and MCHC were lower in group 2 than in group 1. This is inconsistent with the results obtained in the general population by **Vezzoli *et al.*** [(15)]. This can be explained by the fact that low red cell indices are very common in CKD patients and they result mainly from chronic inflammation and insufficiency of iron [(16)]. The reduced levels of MCV and MCH are closely related to the deficiency of Klotho [(17)]. Klotho deficiency enhances the expression of phosphate receptors (Pit-1 and Pit-2) leading to increased phosphate entry inside vascular smooth muscle cells and consequently osteogenic transdifferentiation [(18)]. Therefore, Klotho deficiency enhances vascular calcification in CKD patients [(19)].

In the comparison between the two groups regarding echocardiographic findings, group 2 had a lower ejection fraction than group 1. That is consistent with the result obtained by **Sayarlioglu *et al.*** [(8)]. That is because uremic toxins play important role in inducing AVS and uremic cardiomyopathy as uremic toxins stimulate peroxisome proliferator-activated receptors and G protein-coupled receptors and reduce oxidation of fatty acids leading to myocardial fibrosis and subsequent heart failure [(20)].

Moreover, univariate analysis of predictors of AVS in all studied patients showed that the significant predictors were older age, lower DBP, lower MCV, lower MCH, and lower MCHC. Finally, significant predictors of AVS on multivariate regression analysis were older age, lower DBP and lower MCH.

CONCLUSION

In hemodialysis patients, aortic valve sclerosis represents a significant health problem due to its association with atherosclerosis and acute cardiovascular events. In this study, 37.9% of hemodialysis patients had AVS and the predictors for AVS included older age, lower DBP, and lower MCH. Further studies on larger groups of hemodialysis patients are recommended, and the role of Klotho needs to be investigated as a risk factor for cardiac valvular calcification.

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