Cardiovascular

Intracranial and heart valve calcifications in hemodialysis patients—Interrelationship and clinical impact

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Abstract

Introduction: Arterial calcification is an integral component of active atherosclerosis and is an independent risk factor for cardiovascular disease. Atherosclerosis is a systemic, life-threatening disease that may occur at different sites and in various clinical presentations. Intracranial and valvular calcifications are common among dialysis patients and have been associated with poor cardiovascular outcomes. The aim of this study was to assess the clinical impact of valvular and intracranial arterial calcifications on mortality among chronic hemodialysis patients.

Methods: A blinded neuroradiologist graded intracranial calcifications (ICC) of all hemodialysis patients who underwent brain computerized tomography (CT) from 2015 to 2017 in our institution. Valvular calcifications were assessed by echocardiography. Only hemodialysis patients with available echocardiography and brain CT were included.

Findings: This study included 119 patients (mean age 70.6 ± 12.6 years, 57.1% men, and mean dialysis vintage 25.8 ± 42.6 months). Among the cohort, 19 (16%) had no cardiac or brain calcifications and 65 (54.6%) had both valvular and intracranial calcifications. Considering the patients with no calcification as the reference group yielded adjusted odds ratios for all-cause mortality of 3.68 (95%CI 1.55–8.75) among patients with any brain calcifications, p = 0.002. While valvular calcifications alone did not increase the 1-year mortality rate, ICC was the most important predictor of all-cause 1-year mortality in the study cohort.

Discussion: We found an independent association between ICC and the risk of death among hemodialysis patients. Assessing ICC may contribute to the risk stratification of hemodialysis patients. These calcifications are no less important than valvular calcifications.

KEYWORDS
arterial calcification, hemodialysis, intracranial calcification, valvular calcifications
BACKGROUND

Vascular calcification is an integral component of active atherosclerosis and an independent risk factor for cardiovascular disease.\(^1\)

A meta-analysis of prospective studies among 218,080 subjects with mean follow-up of 10 years demonstrated significantly more major adverse cardiovascular events (strokes, coronary events, all-cause and cardiovascular death) among those with vascular calcifications, as compared with subjects without vascular calcifications.\(^2\) This meta-analysis included different sites and types of vascular calcifications, diagnosed with different modalities, among several types of populations (asymptomatic general population, patients with end stage kidney disease and/or diabetes mellitus, and other cardiovascular risk factors).

Thus, it is not surprising that vascular calcifications in the brain are associated with cardiovascular events in the general population.\(^2\) Intracranial arterial calcification has a mean prevalence of about 90% in hemodialysis (HD) patients. Its severity is correlated with age, hemodialysis vintage and mineral bone disease and was found to be predictive of cardiovascular events.\(^2,3\)

Cardiac calcifications are another important site of vascular calcifications related to atherosclerosis. These include calcifications in the coronary arteries and in the heart valves. Coronary artery calcifications were evaluated thoroughly in MESA and other studies and were shown to be the strongest predictor of incident coronary heart disease.\(^1,2,4,5\) Heart valve calcifications have been investigated less often than coronary artery calcifications, and may also be considered a local manifestation of atherosclerosis. Their presence and severity were associated with increased cardiovascular morbidity and mortality in the general population.\(^6\) Mitral and aortic valve calcifications are frequent echocardiographic findings among dialysis patients, and are estimated to be four to five times more prevalent than in the general population.\(^7\)

Both intracranial and valvular calcifications have been associated with poor cardiovascular outcomes and are assumed to be a component of systemic atherosclerosis. Yet, vascular calcifications at different sites and of varying severities may play differential roles in plaque homeostasis and thus, have different effects on individual prognoses. The parameters of mineral bone disease, systemic inflammation, and uremic toxins, along with local environments, might also affect plaque homeostasis.\(^8,9,10\)

The aim of this study was to assess the clinical impact of valvular calcifications and intra-cranial calcifications (ICC) on mortality among chronic HD patients.

METHODS

This single-center, retrospective study included all chronic HD patients who had undergone brain non-contrast computerized tomography (CT) from January 1, 2015 to December 31, 2017, at Meir Medical Center. Chronic HD was defined as a minimum of 3 months on dialysis. Most of the chronic HD patients were treated using conventional HD schedules (thrice weekly sessions, 4 h each), with high-flux membranes. Clinical information and laboratory data were abstracted from the electronic medical records.

A neuroradiologist who was blinded to the clinical and laboratory information of study population performed repeated and directed radiologic assessments of brain CTs and scored the intracranial arterial calcifications. Thickness of the calcifications on the wall of both common carotid arteries was assessed using Barbiaz’s score\(^11\) from 0 to 4 as follows: 0. No calcifications; 1. Calcification 1 mm thick or stippled; 2. Calcification 2 mm thick, thin continuous, or thick discontinuous; 3. Calcification 3 mm thick, or thick continuous; and 4. Calcification >3 mm thick or with double tracts.

Valvular calcifications were assessed by trans-thoracic echocardiography. All echocardiographic examinations were conducted and analyzed by cardiologists specializing in cardiac imaging. Calcifications were graded 0 (no calcification on any heart valve), 1 (one calcified valve), and 2 (two and more calcified valves).

The primary endpoint of the study was all-cause mortality 1-year after the brain CT. Secondary endpoints were the presence of ICC and valvular calcifications and 30-day all-cause mortality after the brain CT. Mortality data were collected from the national social security records.

Statistical analysis

Data are presented as numbers and percentages for nominal parameters and as means and standard deviations for continuous parameters. Differences between the study groups were analyzed with chi-square or Fisher’s exact test, as appropriate. Continuous variables were examined for normality (Shapiro–Wilk test) and data were analyzed accordingly. Student t test or one-way ANOVA was used for normally distributed variables and the Mann–Whitney or Kruskal-Wallis test for nonparametric variables. Correlations were assessed using Spearman or Pearson tests, as appropriate. \(p < 0.05\) was considered statistically significant. Data were analyzed with SPSS Version 21 (IBM Corporation, Armonk, NY).
RESULTS

A total of 119 chronic HD patients were included in this study. Mean age was 70.6 ± 12.6 years and 57.1% were men. Patients were divided into four groups according to the presence or absence of valvular and intracranial calcifications. The demographics, comorbidities and baseline laboratory data of the patients according to these groups are shown in Table 1. Baseline calcium and phosphorus levels were comparable between the groups.

Valvular calcifications

Among 119 patients, 85 (71.4%) had any valvular calcification, 50 (42%) had calcifications on at least two heart valves and the rest had calcification on one valve.

Patients with valvular calcifications were older than those who did not have any valvular calcifications (74 ± 10 vs. 62.1 ± 15 years, p < 0.01). There were no statistical differences in dialysis vintage and comorbidities.

Age and prior stroke were the most important predictors of valvular calcification on multivariate analysis (Table 2).

Intracranial calcifications

Only 8 of 119 patients (6.7%) did not have intracranial calcifications. Of the remaining patients, 31 had an ICC score of 1, 25 had a score of 2, 31 had score of 3, and 24 patients had a score of 4. To estimate and compare differences between the 4 groups, patients with Barbiaz score 0 or 1 (as detailed in Section 2) were referred to as “no ICC” and patients with 2–4 points were analyzed as “ICC.”

Patients with intracranial calcifications were older than those who did not have ICC (75 ± 8.9 vs. 62 ± 15 years, p < 0.01). There was no significant difference in dialysis vintage or comorbidities.

| Variable                        | Valvular calcification (N = 85) | No valvular calcification (N = 34) |
|---------------------------------|---------------------------------|-----------------------------------|
|                                 | ICC (N = 65) | No ICC (N = 20) | p-value | ICC (N = 15) | No ICC (N = 19) | p-value |
| Age, years                      | 75.4 ± 8.7 | 69.2 ± 10.6 | 0.011 | 71.9 ± 9 | 54.4 ± 14.6 | 0.002 |
| Male sex                        | 37 (57%)  | 10 (30%)  | 0.586 | 10 (67%)  | 11 (58%)  | 0.601 |
| Dialysis vintage, months        | 30 ± 40.9 | 8.9 ± 11.1 | 0.05  | 28.1 ± 51.6 | 25.6 ± 58.2 | 0.864 |
| BMI                             | 31.1 ± 8.7 | 28.9 ± 10 | 0.985 | 30.5 ± 6.3 | 27.8 ± 8.2 | 0.456 |
| Ischemic heart disease          | 30 (47%)  | 7 (35%)   | 0.35  | 7 (47%)   | 3 (16%)   | 0.05  |
| Congestive heart failure        | 26 (41%)  | 8 (40%)   | 0.96  | 6 (40%)   | 5 (26%)   | 0.397 |
| Hypertension                    | 57 (89%)  | 19 (95%)  | 0.43  | 14 (94%)  | 14 (74%)  | 0.136 |
| Diabetes mellitus               | 41 (64%)  | 13 (65%)  | 0.93  | 14 (93%)  | 7 (37%)   | 0.001 |
| Prior stroke                    | 14 (22%)  | 4 (20%)   | 0.85  | 7 (47%)   | 4 (21%)   | 0.113 |
| Atrial fibrillation             | 17 (27%)  | 6 (30%)   | 0.763 | 3 (20%)   | 2 (11%)   | 0.439 |
| Peripheral vascular disease     | 10 (16%)  | 1 (5%)    | 0.219 | 5 (33%)   | 1 (5%)    | 0.033 |
| Smoking                         | 12 (19%)  | 8 (40%)   | 0.051 | 6 (40%)   | 8 (42%)   | 0.901 |

Baseline laboratory (serum)

| Variable                  | Valvular calcification (N = 85) | No valvular calcification (N = 34) |
|---------------------------|---------------------------------|-----------------------------------|
| Creatinine, mg/dL         | 5.2 ± 1.7                      | 5.5 ± 1.9                         | 0.657 | 5.5 ± 1.4 | 5.3 ± 1.8 | 0.442 |
| Albumin, g/dL             | 3.2 ± 0.8                      | 3.4 ± 0.5                         | 0.093 | 3.5 ± 0.4 | 3.5 ± 0.8 | 0.954 |
| Total calcium, mg/dL      | 8.5 ± 0.8                      | 8.5 ± 0.8                         | 0.895 | 8.2 ± 0.8 | 8.4 ± 0.7 | 0.704 |
| Phosphorus, mg/dL         | 5.2 ± 1.7                      | 5.8 ± 1.9                         | 0.5   | 5.6 ± 2.5 | 5.7 ± 1.6 | 0.314 |
| Ca*P product              | 43.8 ± 15                      | 48.4 ± 19.5                       | 0.262 | 50.5 ± 18.8 | 45.9 ± 14.4 | 0.427 |
| PTH, pg/mL                | 329 ± 202                      | 273 ± 156                         | 0.521 | 238 ± 131 | 388 ± 228 | 0.215 |
| Vitamin (25OH) D, nmol/L  | 49.8 ± 19                      | 38 ± 19.7                         | 0.956 | 34.3 ± 11.8 | 42.7 ± 16.2 | 0.254 |
| Vitamin (1,25OH) D, pmol/L| 33 ± 19.1                      | 31 ± 23.6                         | 0.481 | 37.8 ± 20.3 | 34.1 ± 23.1 | 0.794 |
| C-reactive protein, mg/dL | 8.5 ± 11                       | 5 ± 10.8                          | 0.32  | 8.985     | 3.6 ± 4.4 | 0.225 |
| Hemoglobin, g/dL          | 10.5 ± 1.5                     | 10.4 ± 1.3                        | 0.455 | 9.4 ± 0.97 | 11.2 ± 1.4 | 0.078 |

Abbreviations: ICC, intracranial calcification.

Note: Values are presented as absolute numbers (percentage) or as mean ± SD.
Age was the most important predictor of intracranial calcifications on multivariate analysis (Table 3). 

| Variable              | Odds ratio | p-value |
|-----------------------|------------|---------|
| Age (years)           | 1.06 (1.01–1.12) | 0.025   |
| Sex (male)            | 1.33 (0.39–4.53)  | 0.644   |
| Dialysis vintage, months | 1.06 (1.0–1.1)   | 0.94    |
| IHD                   | 2.03 (0.814–5.05) | 0.583   |
| CHF                   | 0.69 (0.23–2.13)  | 0.744   |
| DM                    | 1.1 (0.433–2.698) | 0.867   |
| Prior stroke          | 3.64 (1.02–13.16) | 0.047   |
| PVD                   | 1.35 (0.31–5.79)  | 0.282   |
| Hypertension          | 2.313 (0.686–7.79) | 0.176   |

Mortality

Of the total cohort, 19 (16%) had no valvular or intracranial calcifications and 65 (54.6%) had both valvular and intracranial calcifications. Patients with intracranial calcifications had significantly higher 1-year mortality rates compared to patients without intracranial calcifications (52.5% vs. 23.1%, p = 0.002, odds ratio [OR] 3.68, 95% confidence interval [CI] [1.55–8.75]). There was no significant difference in mortality rates after 30 days (23.8% vs. 12.8%, p = 0.163) or between patients with valvular calcifications compared to patients without valvular calcifications (41.2% vs. 47.1% after 1 year, p = 0.558, OR 1.27, 95%CI [0.57–2.83]).

Multivariate analysis showed that the most important predictors of 1-year mortality were ischemic heart disease (p = 0.007, OR = 3.36, 95%CI [1.4–7.9]) and intracranial calcifications (p = 0.004, OR 4.46, 95%CI [1.6–12.3]; Table 4).

Survival curves showed significant differences between subgroups (p = 0.001) (Figure 1). Patients with intracranial calcifications had the worst survival curve with median survival of 118 days, as compared with overall median survival of 527 days (p = 0.001).

**DISCUSSION**

This study assessed the impact of intracranial and valvular calcifications on the survival and all-cause mortality of chronic HD patients. We used uniform, quantitative measurements to assess heart valves and intracranial calcifications.

We found that valvular and intracranial calcifications are very prevalent and are important predictors of mortality in this population.

The high prevalence of vascular calcifications was similar to that described in previous studies in patients with end stage kidney disease. We found age to be an important predictor of both valvular and intra-cranial calcifications, as described in other studies. Chronic kidney disease (CKD) and age are well-known risk factors for vascular calcification. The coexistence of CKD, aging and vascular calcification has been identified as a poor prognostic factor, with an assumed synergistic effect of each component.

In our study, valvular calcifications were diagnosed using trans-thoracic echocardiography. This is a non-invasive, inexpensive exam, frequently performed in chronic HD patients to assess cardiac function. Valvular calcification is a common finding that, even in the absence of significant blood flow obstruction, should encourage nephrologists to treat and prevent...
progression of mineral-bone disease by controlling hyperphosphatemia and hyperparathyroidism in CKD patients.\textsuperscript{7,8} Calcification and sclerosis of heart valves may rapidly deteriorate to stenosis and obstruction of blood flow in HD patients. Valvular calcification shares common risk factors and pathogenic features with atherosclerosis. Thus, it is considered a local manifestation of this systemic disease. This may explain the doubly increased risk of death among dialysis patients with valvular calcifications involving aortic and mitral valves, as compared to patients with no valvular calcifications, as described by Raggi et al.\textsuperscript{7}

Intracranial calcifications are often considered incidental findings in brain imaging. They have been suggested to be noninvasive markers of atherosclerosis, because calcium deposits can be easily detected on noncontrast CT, and their severity is associated with adverse events.\textsuperscript{2,8,11–13} Most HD patients in our cohort had ICC. This is comparable to previous findings in the HD population. The adjusted OR for all-cause mortality was 3.68 (95%CI 1.55–8.75) among patients with any brain calcification, compared with no calcifications as the reference group. This finding is supported by other adverse events associated with ICC and by the hypothesis that ICC is part of systemic atherosclerosis but is not necessarily associated with acute ischemic stroke.\textsuperscript{2,3} Although cardiac calcifications are considered a strong predictor of cardiovascular morbidity and mortality, the significance and predictive value of ICC have not been studied or demonstrated as often.

The finding of calcifications either on cardiac echocardiography or at other vascular sites should encourage nephrologists to focus on this axis and try to slow calcification progression by intervening to balance calcium, phosphorus and parathyroid levels. For example, the ADVANCE study found attenuated progression of vascular and cardiac valve calcifications with the combination of a calcimimetic (cinacalcet) and low dose active vitamin D in patients on dialysis.\textsuperscript{14} Yet, no treatment has been proven to prevent or completely reverse vascular calcifications.

### Clinical implications

Both noncontrast CT and trans-thoracic echocardiography are noninvasive tests, frequently used in HD patients. Echocardiography is frequently performed while preparing patients for procedures, such as creation of AV access and kidney transplantation. Calcifications are sometimes an incidental finding in these exams, which were originally performed for a different reason. Yet, they provide valuable information regarding mortality risk and therefore, can provide physicians information regarding risk stratification. Vascular calcifications and hyperphosphatemia are known risk factors for mortality in patients with advanced CKD. Consequently, strategies have been evaluated to better control mineral bone disease. Elevated phosphate, calcium, PTH, and FGF23 levels and decreased klotho are all associated with vascular calcifications in patients with CKD and may directly promote calcifications. Klotho is an important biomarker for CKD and has a direct effect on vasculature. It is involved in FGF23 signal transduction (as a coreceptor), and its decrease with the progression of CKD contributes to vascular calcification.\textsuperscript{15}

This study had several limitations. First, since it was conducted retrospectively, CT and echocardiography were not performed at the same time. Second, the survival was calculated as days from CT, with adjustment for dialysis vintage and other variables, such as age. In
addition, it was a single center study with a relatively small cohort of 119 patients. Despite these limitations, this study provides interesting information derived from routine, inexpensive exams that contribute to risk stratification which is much needed in this specific high-risk population.

In conclusion, we found an independent association between ICC and the risk of death among HD patients. Assessing ICC with noncontrast CT may contribute to the risk stratification of HD patients. These calcifications are no less important than are valvular calcifications. Additional studies are needed to confirm these findings.

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None to declare.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT
Upon request.

ETHICS STATEMENT
The study was approved by the local Institutional Ethics Committee (0251-17-MMC) in keeping with the principles of the Declaration of Helsinki. In accordance with Ministry of Health regulations, the Institutional Ethics Committee did not require written informed consent because data were collected anonymously from the electronic medical records without active patient participation.

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