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Association of coronary artery calcium score and vascular dysfunction in long-term hemodialysis patients

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Abstract

Long-term hemodialysis patients are prone to an exceptionally high burden of cardiovascular disease and mortality. The novel temperature-based technology of digital thermal monitoring (DTM) of vascular reactivity appears associated with the severity of coronary artery disease in asymptomatic population. We hypothesized that in hemodialysis patients, the DTM and coronary artery calcium (CAC) score have a gradient association that follows that of subjects without kidney disease. We examined the cross-sectional DTM-CAC associations in a group of long-term hemodialysis patients, and their 1:1 matched normal counterpart. Area under the curve for temperature (TMP-AUC), the surrogate of the DTM index of vascular function, was assessed after a 5-minute arm-cuff reactive hyperemia test. Coronary calcium score was measured via electron beam computed tomography or multidetector computed tomography scan. We studied 105 randomly recruited hemodialysis patients (age: 58 ± 13 years, 47% men) and 105 age- and gender-matched controls. In hemodialysis patients vs. controls, TMP-AUC was significantly worse (114 ± 72 vs. 143 ± 80, $P = 0.001$) and CAC score was higher (525 ± 425 vs. 240 ± 332, $P < 0.001$). Hemodialysis patients were 14 times more likely to have CAC score >1000 as compared with controls. After adjustment for known confounders, the relative risk for case vs. control for each standard deviation decrease in TMP-AUC was 1.46 (95% confidence interval: 1.12–1.93, $P = 0.007$). Vascular reactivity measured via the novel DTM technology is incrementally worse across CAC scores in hemodialysis patients, in whom both measures are even worse than their age- and gender-matched controls. The DTM technology may offer a convenient and radiation-free approach to risk-stratify hemodialysis patients.

Key words: Chronic kidney disease, coronary calcification, digital thermal monitoring, hemodialysis, vascular disease

INTRODUCTION

Long-term hemodialysis patients are prone to an exceptionally high burden of cardiovascular disease and mortality.[1,2] Traditional cardiovascular risk factors, which are helpful in risk stratification of asymptomatic population without chronic kidney disease (CKD), may not fully

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account for this increased risk of adverse cardiovascular disease burden in end-stage renal disease (ESRD) patients undergoing maintenance hemodialysis (MHD).[3] This fact highlights the need to find novel nontraditional risk factors useful for identification of at-risk patients. A number of marker such as hyperhomocysteinemia, elevated C-reactive protein (CRP), low albumin, and coronary artery calcium (CAC) have been proposed to account for this increased cardiovascular risk in ESRD patients.[4–6]

Coronary artery calcium, an anatomic disease marker of calcified coronary atherosclerosis, is one of the strongest predictors of future adverse cardiovascular events and has been suggested to be incorporated into national guidelines for risk stratification of asymptomatic population.[7] It is also an independent predictor of mortality in long-term MHD patients beyond traditional cardiovascular risk factors.[8] Fingertip digital thermal monitoring (DTM) of vascular reactivity is a noninvasive, operator-independent test based on changes in fingertip temperature during and after arm-cuff occlusion. The fingertip DTM of vascular function during arm-cuff reactive hyperemia test correlates with the severity and extent of coronary artery disease in both asymptomatic and symptomatic population.[9,10] Vascular dysfunction is an early step in the development of atherosclerotic plaque formation that can be used for cardiovascular risk assessment.[11,12] The functional changes in vascular function precede the development of structural changes and reverse more quickly in response to therapies.[13,14]

The current study evaluates the hypothesis that CAC is associated with fingertip temperature-based DTM of vascular function in long-term MHD patients compared with an age- and gender-matched cohort without CKD (non-CKD). We also hypothesized that in MHD patients, the DTM and CAC score have a gradient association that follows that of subjects without kidney disease. However, we expected that this gradient is steeper in long-term MHD patients compared with subjects without CKD. As vascular dysfunction represents earlier stage in the atherosclerosis process and as MHD patients have higher burden of cardiovascular disease compared with the general population, we expected to find lower (worse) DTM in MHD patients, even in MHD patients with CAC score of zero, compared with non-CKD controls.

SUBJECT AND METHODS

Study population

The study population consisted of 105 long-term MHD patients who underwent a number of elaborate tests, including both CAC and DTM. MHD patients were selected from 10 Da Vita long-term dialysis facilities in South Bay Los Angeles area. Inclusion criteria were patients who had been on maintenance hemodialysis for at least 6 months, had an average monthly $Kt/V_{sp} > 1.4$ with a dialysis time between 3.5 and 5 hours, functioning arteriovenous (AV) graft or fistula and signed the Institutional Review Board approved consent form. Exclusion criteria for MHD patients included (i) peritoneal dialysis; (ii) terminal illnesses with life expectancy of <6 months, e.g., stage IV cancer or full-blown AIDS; (iii) MHD < 6 months after switching from peritoneal dialysis or renal transplant failure; (iv) likelihood of pregnancy or intention to become pregnant; (v) acute wasting condition or active systemic disease (e.g., acute flares of systemic lupus erythematosus, rheumatoid arthritis, or vasculitis); (vi) pulse chemotherapy; (vii) noncompliance with dialysis treatment; and (viii) dialysis catheter.

The matched cohort for comparison was selected from a previous study population that included 129 consecutive patients with suspected coronary artery disease who were referred to the cardiac imaging laboratory.[9] All subjects underwent CAC scanning and DTM as a part of the study. Patients with established cardiovascular disease, stroke, diabetic retinopathy, ESRD, Reynaud's syndrome, infection, cancer, immunosuppression, systemic inflammation, and end-stage liver disease were excluded. All non-CKD patients had normal glomerular filtration rate (GFR) at study entry and no history of renal disease. All patients had signed the informed consent approved by the Institutional Review Board of Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. These patients were matched on one-to-one basis with MHD patients based on age and gender. A total of 105 patients from MHD group and 105 patients from non–CKD-matched group were selected. All subjects underwent CAC scan and DTM test on the same day at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. These measurements were performed on nondialysis days.

Digital thermal monitoring

All DTM measurements were performed in a quiet, dimmed room at a controlled ambient temperature between 23.0 and 25.0°C.[9] Studies were conducted after an overnight fast of at least 10 hours (water was permitted) and abstinence from tobacco, alcohol, caffeine, vasoactive medications, exercise, high-fat foods, and vitamin C. The measurements were obtained with the subjects in sitting position and after 30 minutes of rest. Blood pressure measurement was recorded in the non–AV-fistula arm in a

sitting position 5 minutes before the DTM test (IntelliSense_ Professional Digital Blood Pressure Monitor, HEM-907XL; Omron Inc., IL, USA) in MHD patients and in control arm in non-CKD patients. DTM of both hands was obtained during 5-minute stabilization, 5-minute cuff inflation to 30–50 mmHg greater than systolic blood pressure, and 5-minute deflation using an automated, operator-independent protocol (VENDYS, Endothelix Inc., Houston, TX, USA). Thermal changes during a 5-minute arm-cuff-induced reactive hyperemia test were monitored continuously in the fingertip of both the occluded and the non-occluded arms using VENDYS software. The device consists of a computer-based thermometry system, with two fingertip resistance temperature detector fast response probes designed to minimize the skin-probe contact area and fingertip pressure, attached to the pulp of the index finger on both hands. The system includes a common automated sphygmomanometer cuff, cuff-inflation pump, and release valve to permit noninvasive measurement of arterial pressure and the control of occlusive hyperemia.

Coronary artery calcium score measurement

Coronary artery calcium scans were performed on E-Speed electron beam scanner (electron beam computed tomography [EBCT]) (GE-Imatron, South San Francisco, CA, USA) or 64-multidetector computed tomography (MDCT) (General Electric, Milwaukee, WI, USA) scanners. The coronary arteries were imaged with 30–48 contiguous 2.5–3 mm slices during mid-diastole using electrocardiogram-triggering during a 35-second breath hold. CAC measurements were performed on noncontrast studies by an experienced reader blinded to the patient information. Coronary artery calcium was defined as a plaque of at least 3 contiguous pixels (area of 1.02 mm^2) with a density of > 130 Hounsfield units. The lesion score was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield unit within this area, as described by Agatston et al.[15] Total calcium score was determined by summing individual lesion scores from each of the four main coronary arteries (left main coronary, left anterior descending coronary, left circumflex coronary, and right coronary arteries). CAC (Agatston score [AS]) were categorized as CAC 0, 1–100, 101–400, 401–1000 and >1000 AS.

Statistical analysis

The clinical information of the patient population was compared using *t*-test and chi-square test. The continuous variables were mentioned as mean ± standard deviation, whereas the categorical variables were presented as percentages or absolute numbers. CAC scores were categorized as increasing quartiles as follows: 0, 1–100,101–400,401–1000 and >1000. The association between CAC score quartiles and DTM of MHD and non-CKD cohort were presented using a bar graph. The relative risk of CAC was assessed for MHD patients according to the CAC score categories of 1–100,101–400, 401–1000 and >1000 using relative risk regression analysis. The non-CKD patients were used as reference group for this analysis. The results were adjusted for traditional cardiovascular risk factors, including age, gender, diabetes mellitus, hypertension, hypercholesterolemia, smoking, ethnicity and race. Similar to DTM, we determined the relative risk per standard deviation decrease in TMP-AUC in MHD patients compared with the non-CKD patients.

RESULTS

General characteristics of the patients are given in Table 1. Mean age of the MHD population was 58 ± 13 (range: 27–84 years; 47% men), and the non–CKD-matched cohort was 59 ± 8 (47% men). There were no statistically significant differences based on age, gender, body mass index, or diabetes among subjects with and without CKD (Table 1). Mean heart rates for MHD and non-CKD patients during DTM test were 71 ± 10 and 62 ± 10/minute, respectively ($P < 0.001$). Mean systolic and diastolic blood pressure for MHD and non-CKD patients during DTM test were 156 ± 26 and 145 ± 21 mmHg ($P = 0.002$), and 81 ± 13 and 79 ± 11 mmHg ($P = 0.21$), respectively. The prevalence of patients with CAC score of zero was 15 (14%) vs. 39 (37%) in MHD patients compared with the non-CKD patients. There were 72 (69%) patients with CAC > 100 AS in the MHD group compared with the non-CKD patients (26 patients, 25%). Mean hemoglobin level for MHD patients was 12.01 ± 1.16.

In long-term MHD patients vs. controls, TMP-AUC was significantly lower or worse (114 ± 72 vs. 143 ± 80, $P = 0.001$), and CAC score was higher (525 ± 425 vs. 240 ± 332, $P < 0.001$). After adjustment for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, smoking, ethnicity, and race, the risk for each standard deviation decrease in TMP-AUC was 1.46 (95% confidence interval [CI]: 1.12–1.93, $P = 0.007$) in MHD patients compared with the non-CKD patients. TMP-AUC was lower in each CAC score category (CAC 0, 1–100, 101–400, 401–1000, and >1000 AS) in MHD population compared with the non-CKD group ($P < 0.05$) (Figure 1).

Table 1 Demographic information of ACKD and non–CKD-matched cohort

	Non–CKD-matched cohort (n = 105)	ACKD cohort (n = 105)	P
Age (years)	59 ± 8	58 ± 13	0.50
Male, n (%)	48 (46.6)	48 (46.6)	1.0
Height (cm)	169.6 ± 7.5	161.7 ± 21.0	0.0004
Weight (kg)	90.5 ± 10.8	78.4 ± 22.8	<.0001
BMI (kg/m^2)	31.6 ± 4.4	30.7 ± 15.7	0.59
Hypertension, n (%)	101 (98.1)	81 (85.3)	0.01
Diabetes, n (%)	58 (56.3)	65 (64.4)	0.24
Family history of CAD, n (%)	40 (38.8)	23 (23.2)	0.02
Dyslipidemia, n (%)	65 (63.1)	34 (35.8)	<0.001
CAC score	240 ± 332	525 ± 425	0.0001
TMP-AUC	143 ± 80	114 ± 72	0.001

ACKD = advanced chronic kidney disease; BMI = body mass index; CAC = coronary artery calcium; CAD = coronary artery disease; CKD = chronic kidney disease; TMP-AUC = area under the curve of temperature.

The lowest mean value of TMP-AUC was among the MHD group with CAC > 1000 AS (Figure 1). When we compared the TMP-AUC of MHD patients with CAC score of zero, the TMP-AUC was found to be significantly lower than the non–CKD-matched cohort.

The relative risk of CAC increase from 0 to 1–100, 101–400, 401–1000, and >1000 AS was 5.29 (95% CI: 1.82–15.38, P = 0.002), 7.49 (95% CI: 2.45–22.85, P = 0.0001), 10.88 (95% CI: 3.82–31.03, P = 0.0001), and 13.98 (95% CI: 4.86–40.14, P = 0.0001) respectively, in MHD patients compared with non-CKD patients (Table 2). These results were adjusted for age, gender, diabetes, hypertension, hyperlipidemia, smoking, ethnicity, and race.

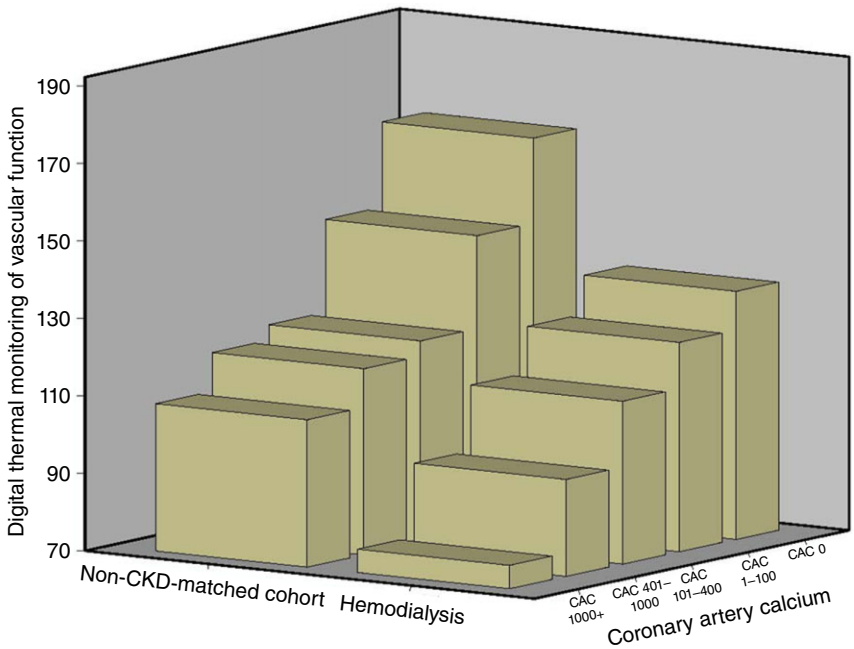

Figure 1 Association between coronary artery calcium (CAC) and digital thermal monitoring (DTM) of hemodialysis patients and non-chronic kidney disease (non-CKD)-matched subjects. Figure shows association between CAC and DTM of endothelial function measured in hemodialysis patients and non–CKD-matched cohort patients. DTM is lower (worse) within each CAC score category in hemodialysis patients compared with non–CKD-matched controls, with lowest being in patients with CAC score of >1000 Agatston score.

Table 2 Showing relative risk[a] of CAC scores for ACKD patients compared with non–CKD-matched patients

	Non-CKD-matched cohort	ACKD cohort
CAC 1–100	1.0 (Ref)	5.29 (95% CI 1.82–15.38), P = 0.002
CAC 101–400	1.0 (Ref)	7.49 (95% CI 2.45–22.85), P = 0.0001
CAC 401–1000	1.0 (Ref)	10.88 (95% CI 3.82–31.03), P = 0.0001
CAC > 1000	1.0 (Ref)	13.98 (95% CI 4.86–40.14), P = 0.0001

[a]These results were adjusted for age, gender, diabetes, hypertension, hyperlipidemia, smoking, ethnicity, and race.
ACKD = advanced chronic kidney disease; CAC = coronary artery calcium; CI = confidence interval; CKD = chronic kidney disease.

DISCUSSION

In this study of 105 MHD patients, we found that vascular reactivity measured via the novel DTM technology is incrementally worse across CAC scores in these patients, in whom both measures are even worse than their age- and gender-matched controls. Given these unprecedented findings, the novel DTM technology may offer a convenient and radiation-free approach to risk-stratify hemodialysis patients.

Traditional cardiovascular risk factors are important risk stratification screening parameters used in the general population such as obesity, hypercholesterolemia, and hypertension, but they appear to play a protective role in dialysis patients; a concept called "reverse epidemiology" where undernutrition is associated with adverse cardiovascular outcomes in long-term dialysis patients compared with the well-known association between overnutrition and poor outcome in the general population.[3] A possible explanation for this is that small numbers of patients reach MHD stage and may not share the same constellation of risk factors as those of their predecessor CKD patients. This fact highlights the need to identify novel markers of coronary atherosclerosis in long-term dialysis patients. The current shows the presumptive role of novel noninvasive, operator-independent, radiation-free DTM of vascular reactivity in risk stratification of at-risk long-term MHD patients.

CAC is an anatomic marker of coronary atherosclerosis that correlates with the presence and extent of coronary atherosclerosis.[16] CAC has been shown to be an independent predictor of mortality in a multivariable model after adjusting for age, gender, ethnicity, and cardiac risk factors in a registry of 25,253 asymptomatic populations.[17] The addition of CAC to traditional risk factors resulted in a higher concordance index compared with traditional risk factors alone (0.81 vs. 0.61, P < 0.0001, respectively). Detrano et al., in a population-based study of 6722 participants followed for a median period of 3.8 years for coronary events, demonstrated that a CAC score >300 AS was associated with adjusted risk of 9.67 (P < 0.001). CAC has also been shown to predict all-cause mortality in MHD patients. MHD patients having CAC scores of 101–400 and >400 were associated with hazard ratio for death of 8.5 and 13.3 compared with CAC score of zero, independent of demographics, comorbidities, lipids and other cardiovascular risks, surrogates of bone disease, nutritional and inflammatory markers, and dialysis dose.[8] There were only two deaths reported in patients with CAC score zero compared with 30 deaths in patients with CAC score >400. In the present study, we found that the relative risk of CAC increase in MHD patients with CAC score 101–400 was 7.5% and 11% for > 400 AS compared with the non-CKD population. The relative risk for >1000 AS CAC score was 14% in MHD population compared with non–CKD-matched population.

Vascular dysfunction is an early step in atherosclerosis process and precedes the actual development of atherosclerotic plaques.[11,12] Pathophysiology of endothelial dysfunction includes reduced bioavailability of nitric oxide, elevated levels of asymmetric dimethylarginine, oxidative excess, angiotensinogen II, hyperhomocysteinemia, and various mechanisms in diabetics.[18] The novel technology of DTM measures skin vascular response based on fingertip temperature reactivity. Skin vascular response is believed to be primarily due to microvascular reactivity. Studies have been conducted regarding the pathophysiology of skin vascular reactivity and its significance in patients with vascular disease.[19–22] Our previous study showed that vascular dysfunction measured by DTM was strongly correlated with Framingham risk score (FRS) and CAC independent of age, gender, and traditional cardiac risk factors, and was superior to FRS for the prediction of significant CAC in a group of 230 asymptomatic subjects.[10] This study also showed the superior and incremental predictive power of DTM in addition to FRS in the prediction of significant CAC ≥ 100 (0.79 for DTM vs. 0.66 for FRS vs. 0.89 for DTM + FRS, respectively). Similarly, in another study, DTM was shown to be associated with the presence and severity of coronary artery disease

measured by cardiac computed tomography angiography.[9] Endothelial dysfunction in coronary arteries has been shown to the associated with cardiovascular events in patients with and without coronary artery disease.[12,23,24] Caglar et al.[25] showed the presence of endothelial dysfunction in all stages[1–5] of CKD and association with reduction in estimated GFR using flow-mediated dilatation determined by high-resolution brachial ultrasonography. Perticone et al. showed impaired vasodilator response to acetylcholine associated with renal function loss in patients with essential hypertension.[26] These studies show the presence of vascular dysfunction in patients with different stages of CKD. Chung et al. showed a differential response of the vasculature obtained from nondialyzed and dialyzed CKD patients to various stimuli such as depolarization, agonist, and acetylcholine.[27] The current study shows that vascular reactivity measured via the novel DTM technology is incrementally worse across CAC score categories, even worse than their age- and gender-matched controls. The worse vascular function was noted in MHD patients with CAC score of 1000+. DTM vascular reactivity was also worse than their age- and gender-matched control group in MHD patients, with the absence of CAC (CAC = 0). The risk for each standard deviation decrease in TMP-AUC was 1.46 in the MHD patients compared with the non-CKD patients, after adjustment for cardiovascular risk factors. The cuff-induced reactive hyperemia DTM test of vascular reactivity, by virtue of its standardized, operator-independent, and automated technique is easy to use for risk assessment of long-term MHD patients. The ease-of-use and radiation-free approach, this novel fingertip temperature DTM of vascular function, is well suited for repeated measurements and following the effect of various therapeutic treatments in at-risk long-term MHD patients.

The following limitations of our study should be considered. (i) Despite the sample size, we were able to show significant differences in CAC and DTM of the MHD patients compared with the non-CKD patients. Further outcome studies with larger sample size are needed to definitively demonstrate the prognostic importance of these measures in the MHD population. (ii) The study did not include various stages of renal dysfunction; it only included ESRD patients undergoing MHD. The reason we selected only MHD patients is because of the amount of cardiovascular burden and mortality in this group and we were clearly able to show the high prevalence of CAC score and lower DTM in each CAC score category compared with the control non-CKD population. Also, MHD patients were found to be at much higher risk of significant CAC scores (100–400 and >1000), with relative risks of 7.5 and 14, respectively. (iii) Systemic markers of inflammation like CRP and homocysteine measurements were not included in the study. (iv) The design of the study was cross-sectional; no cause-effect relationship can be derived from this. However, this study clearly gives an idea of the higher burden of coronary atherosclerosis and more vascular dysfunction in MHD patients compared with the control non-CKD patients.

CONCLUSIONS

Long-term MHD patients have significantly worse vascular dysfunction as reflected by the novel DTM metrics when compared with their age- and gender-matched non-CKD subjects. The DTM has a gradient and incremental association with CAC score. The per standard deviation decrease of DTM measured vascular dysfunction was significantly higher in long-term MHD patients compared with age- and gender-matched non-CKD control subjects, independent of traditional cardiovascular risk factors. The novel operator-independent, radiation-free, automated technique of DTM vascular function may provide a very useful tool for risk assessment and follow-up of therapeutic treatments in at-risk long-term MHD patients.

DISCLOSURE

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