Chapter 13

Site and Size of Vascular Calcifications Are Different in Dialysis Patients with Various Underlying Diseases

H. Suzuki, T. Inoue, H. Okada, T. Takenaka, Kunihiko Hayashi, Jyunnichi Nishiyama, Takashi Yamazaki, Yuji Nishiyama and Keiko Kaneko

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52004

1. Introduction

Computed tomography (CT) constitutes the gold standard for quantification of vascular calcification (VC) and, being the most effective and widely available with reproducible measurements, is also useful for monitoring progression as well as assessing the effect of therapeutic strategies to modify progression [1] [2]. VC has a significant effect in cardiovascular diseases on dialysis patients. Tanne et al. [3] focused on calcification of the thoracic aorta and found that it associated with coronary and valvular calcification in hypertensive patients. In the Calcification Outcome in Renal Disease (CORD) study, abdominal aortic calcification was found to have the predictive value for the occurrence of cardiovascular events and mortality in dialysis patients [4]. Coll et al. [5] reported that VC in large, conduit arteries was prevalent in patients on dialysis patients, and that age, dialysis vintage, past medical history of cardiovascular disease, atherosclerosis and inflammation were variable significantly influencing VC. From these studies, it is suggested that VC occurs in vessels of various diameters. However, no definitive studies have determined the significance of VC in different vessels in patients receiving dialysis therapy until the present time. Moreover, there have been few studies examining a relation between semi-quantitative measures of VC and their contributing factors. The aim of this work presented here is to examine a relation between semi quantitatively measured calcification of three major vessels, the thoracic aorta, the abdominal aorta and the iliac arteries and several known contributing factors to VC such as underlying diseases, age, gender, vintage of dialysis, values of serum calcium and phosphate, use of calcium-based phosphate binders and so on.

2. Methods

All HD patients received three dialysis sessions of at least 4 h duration per week. HD was performed using low flux polysalphose dialyhsers (1.5-2.0 m2 APS Asahi Medical R Tokyo, Japan). All HD patients were dialyzed using bicarbonate-bound 1.25 mmol/L, calcium and 134 mmol/sodium containing dialysate. Patients were all dialysed at the Dialysis Unit of Irumadai Hospital.

This was an observational and cross-sectional study that included 79 hemodialysis patients at the Dialysis Unit of Irumadai Hospital, who gave their informed consent to enroll in this study. The inclusion criteria were patient providing informed consent, age ≥ 40 years and duration of dialysis ≥ 1 year. Exclusion criteria were significant fetal diseases that were estimated to reduce life expectancy to < 6 months and patients in whom it was impossible to measure CT scan.

The recorded cardiovascular history and smoking status were obtained. The following baseline biochemical data were obtained; serum calcium, phosphorus, intact parathyroid hormone, albumin, total cholesterol, low-density lipoprotein cholesterol. Data on weight, height, body mass index and duration of dialysis and use of medications: phosphate binders, vitamin D, statins, erythropoietin and antihypertensive agents. Clinical characteristics and laboratory variables including dual-energy x-ray absorptiometry and pulse wave velocity. This study complies with the Declaration of Helsinki and was in agreement with the guidelines approved by the ethics committee at the institution.

2.1. Computed tomography

CT scan of the aorta and arteries was performed with a 16-detector CT scan {Prime Purpose MDCT (GE Healthcare, Milwaukee, WI USA)}. Scanning time was 0.5 s for two contiguous 1.25 mm sections and 20±5 seconds for the entire zone of interest. Examination was performed during a single, unforced, withheld inspiration. During scanning with the tube rotating at 2 rotation/second and the table moving at 55 mm/s with a 1:1.375 scanning pitch, images were obtained with an effective section thickness of 10 mm. Scanning was performed with 120 kVp and 350 mAs, standard resolution, and a 28-36 cm field of view. The total duration of the procedure was 5min. The range of CT scan was illustrated in Fig. 1.

2.2. Evaluation of thoracic and abdominal aorta and iliac artery

Volume acquisitions were analyzed using Volume Viewer software (GE Healthcare). The thoracic and abdominal aorta were segmented manually. In order to reduce errors due to noise, a cut-off of 130 Housefield Unit (HU) was applied. The total calcification volume was calculated as the sum of all voxels in the remaining volume.

2.3. Biochemistry

Blood samples were collected at monthly intervals. The results presented here were time-averaged results from the preceding 6 months prior to the CT scan.

http://dx.doi.org/10.5772/52004

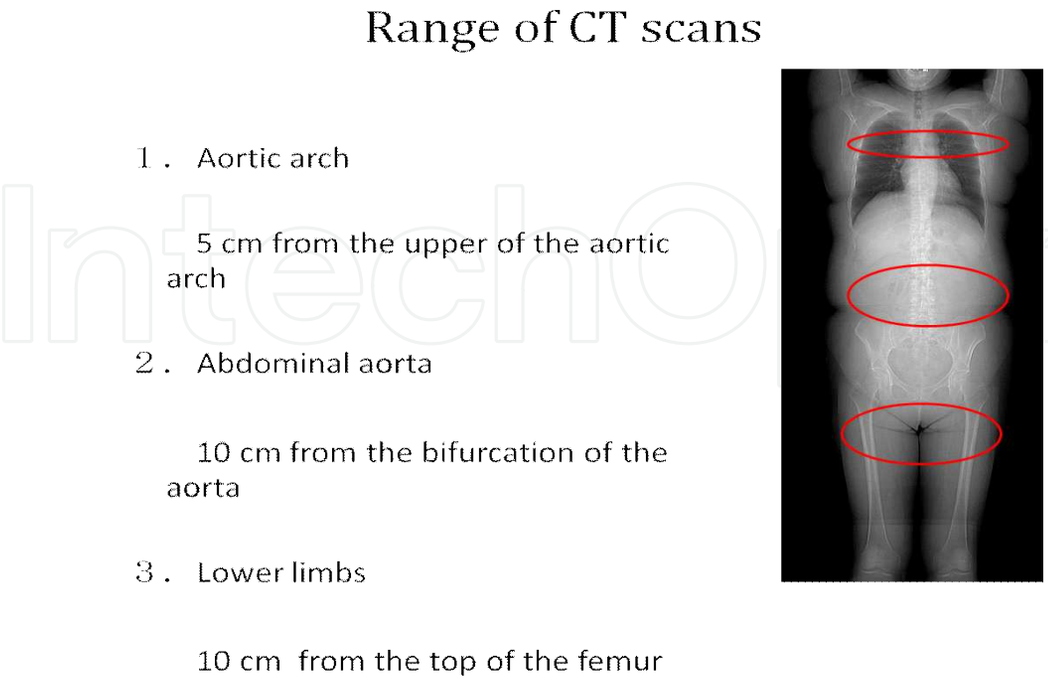

Figure 1. A range of computed tomography (CT) scan is illustrated.

2.4. Blood pressure

Three blood pressure (BP) recording were taken suing automated device.

2.5. Statistics

Data are expressed as means ± SD. Using variables found to be significant in the univariate analysis and potential confounders, we applied forward stepwise logistic regressions, in order to determine which of these variables were most significantly associated with calcification of the thoracic and abdominal aorta and the arteries of the lower limbs. F-to-Remove was set at 2.9. $P<0.05$ was considered as significance.

3. Results

3.1. Patients characteristics

The underlying kidney diseases were diabetic nephropathy [32], chronic glomerulonephritis (23), nephrosclerosis, polycystic kidney disease (3) and others (12).

Baseline demographics and laboratory and hemodynamic values of the study population are shown in Tables 1, 2 and 3 and current medications used are listed in Table 4.

Age （years）	62.3±12.8
Dialysis duration （months）	76.6±83.8
Gender （male/female）	52/27
Diabetes/non diabetes	32/47
Smoking/non smoking	36/43
Body mass index (kg/m^2)	21.9±1.6

Table 1. Characteristics of patients

Systolic Blood Pressure (mmHg)	154±122
Diastolic Blood Pressure (mmHg)	79±13
Heart Rate (beats/min)	74±12

Table 2. Hemodynamic markers

Calcium (mg/dL)	8.9±0.8
Phosphate (mg/dL)	5.6±1.2
Intact PTH (ng/mL)	125.5±65.4
Creatinine (mg/dL)	12.5±1.1
Blood urea nitrogen (mg/dL)	98.4±12.2
Uric acid (mg/dL)	6.3±0.5
Hemoglobin (g/dL)	10.7±0.6
Low density lipoprotein (mg/dL)	84.2±27.0
Albumin (g/dL)	3.7±0.4

Table 3. Serum markers

Agent	Percentage of patients
Phosphate binders	
Calcium containing	86
Sevelamer	65
Vitamin D analogues	59
Cinacalcet	72
Statins	12
Antihypertensives	96
Erythropoiesis stimulating agents	98

Table 4. Current medications of the study population

http://dx.doi.org/10.5772/52004

3.2. Calcification of vessels

In Table 5, the average of calcification scores is shown.

All three lesions correlated significantly with each other. Stepwise regression was applied in which the independent variables were identified from the univariate analyses. Significant associations were seen for the following: the prevalence of calcification; the thoracic aorta with period of dialysis, elevations of both systolic and diastolic blood pressure and levels of serum albumin (Table 6); in the abdominal aorta with age, presence of diabetes, and calcium supplement (Table 7); arteries of the lower limbs with presence of diabetes mellitus, use of sevelamer and cinacalcet and serum levels of intact parathyroid hormone and albumin (Table 8).

Vessels	
Thoracic aorta	3.49 + 4.65
Abdominal aorta	5.21 + 7.21
Iliac artery	1.18 + 1.92

Table 5. Calcification scores of thoracic aorta, abdominal aorta and iliac artery

Constant	Coefficient	Standard Error	F	*P*
Dialysis vintage (months)	0.011	0.006	3.401	0.050
SBP (mmHg)	0.090	0.029	9.336	0.003
DBP (mmHg)	-0.210	0.054	15.071	0.001
Albumin (g/dL)	-2.181	1.206	3.270	0.045

SBP: systolic blood pressuer, DBP: diastolic blood pressure

Table 6. Significant correlations with calcification of thoracic aorta

Constant	Coefficient	Standard Error	F	*P*
Age (years)	0.2445	0.68	13.156	0.001
Presence of DM	3.997	1.715	5.431	0.002
$CaCO_3$	0.001		4.066	0.048
Vitamin D	-4.89	2.231	4.802	0.032
Ca (mg/dL)	2.32	1.224	3.595	0.043

DM: diabetes mellitus, $CaCO_3$: oral administration (g/day), Vitamin D: oral administration (μg/day)

Table 7. Significant correlations with calcification of abdominal aorta

Constant	Coefficient	Standard Error	F	P
Presence of DM	1.346	0.416	10.469	0.002
Savelamer	1.403	0.430	10.632	0.002
Cinacalcet	0.882	0.482	3.353	0.072
Intact PTH	-0.006	0.003	3.446	0.048
Albumin (g/dL)	-1.414	0.473	8.944	0.004

DM: diabetes mellitus, Savelamer: oral administration (g/day), Cinacalcet: oral administration (mg/day)

Table 8. Significant correlations with calcification of lower limb

4. Discussion

In the present study, we found that the contributing factors to VC were different in the different vessels. The development and progression of VC is a multifactorial process. Potentially differing factors may exert their maximum influence at either the predisposition, initiation and continuation phases of the process. The multivariate analysis performed on these data attempt to elucidate which factors might be most significant to the development of VC. In the present study, age, duration of HD, systolic and diastolic BP, presence of DM serum levels of Ca, intact PTH, calcium modulating drugs and albumin contributed differently in the different vessels. Albumin was negatively correlated with the severity of VC. This suggests that a characteristic state of low albumin as seen in malnutrition, inflammation or atherosclerosis complex is most important, as suggested by Wang et al. [6]. Factors shown to predict VC in the current study included older age, longer dialysis vintage, diabetes, higher concentrations of serum phosphorus and calcium are associated with more extensive VC among patients on HD and result partially consistent with those reported previously [7] [8] [9] [10].

Adler et al [11] demonstrated a strong association of coronary calcification and calcification of the thoracic aorta on spiral CT. The aortic calcification signifies a higher probability of coronary atherosclerosis and ischemic stroke (Cerebrovascular disease). Also, Tanne et al. [3] found that severe calcification in descending aorta is a predictor of ischemic cerebrovascular events. Calcification of the thoracic aorta is not a direct causative factor for embolic stroke, but rather a marker of increased burden of vascular (atherosclerotic disease) disease [12]. However, Honkanen et al. [4] reported that although the duration of HD correlates with calcification in coronary [1], carotid and peripheral arteries [7], the association is less clear in the thoracic arteries [8].

In the present study, calcification of the thoracic aorta had a strong association with dialysis vintage, systolic and diastolic BP and albumin, which are a major factors contributing to cardiovascular diseases. From these data, it is possible that severe calcification of the thoracic aorta is produced by hemodynamic, malnutrition and uremia in combination.

http://dx.doi.org/10.5772/52004

Abdominal aorta calcification has been well studied, has been associated with an increase risk of cardiovascular morbidity and mortality in patients with HD [13]. Hanada et al. [14] proposed that the section of the aorta chosen for measuring the semiquantitative calcification score is suitable for evaluation of the severity of VC because the site is associated with turbulent flow and is susceptible to development of atheroma. The chosen site is also simple to investigate radiologically since it is in a significant part of the aorta and is vertical to the transverse section. In the present study, VC of the abdominal aorta was correlated with the presence of diabetes, which is a well-known atherosclerotic risk factor. In addition, the factors relating with calcium-phsophate modulation, such as concentrations of calcium, PTH and so on are frequently evoked as the principal causes associated with vascular remodeling and/or arterial calcifications [15] [16]. Guerin et al. [17] reported that in HD patients, there is an association between the presence of aortic calcification and increased Ca x P products. In contrast, Arad et al. did not find the serum concentrations of calcium, 1,25-Vit D, and PTH to be associated with the presence of arterial calcifications [18]. Besides, the amount of CaO_3 prescribed as a phosphate binder was independently associated with the score of vascular calcifications. One of the adverse effects of calcium based phosphate binders is hypercalcemia, which may in turn result in arterial calcification. It is therefore likely that development of VC of the abdominal aorta is associated with calcium and phosphorus regulation in HD patients. Moreover, mineral bone disease-related factors such as serum calcium, phosphorus and PTH are thought to be strongly associated with the severity of VC in dialysis patients [19] [20].

Sigrist et al. [21] described a simple, sensitive low radiation dose technique as an alternative to coronary artery and aortic measurements to quantify a calcification score for the superficial femoral artery (SFA). The sector of artery chosen for this study is ideal as it avoids major bifurcations and arterial branching, and therefore, obvious site for turbulent flow and the development of atheroma. In the present study, factors contributing to VC of the iliac arteries are similar with those of the abdominal aorta.

In the Calcification Outcome in Renal Disease (CORD) study, 19% of patients had no visible calcification in their abdominal aorta [4]. These findings are partially in line with certain previous observations and it has been suggested that these individuals rarely develop calcification at follow-up [22] [8] [23]. In the present study, we did not find these individuals. Recently, further reports from CORD study provided a new evidence that no coronary [24] or thoracic aortic calcification at baseline, but their calcification developed during 2 years of observation and was most prevalent in those receiving calcium-containing binders. Besides, retrospective and cross-sectional data have given contradicting results with some publication showing a contribution of Vit D to VC [15], whereas others do not support this contention [25]. It is therefore unlikely that HD patients receiving calcium-containing binders and Vitamin D analogues have no VC of the vessels.

Recently Allison et al. [26] demonstrated that in terms of extent of calcification, the iliac arteries showed the strongest association for all mortality and end points, consistent with the well-known association between the severity of peripheral artery disease and both CVD and total mortality [27].

In addition, they concluded [26] that higher levels of calcium in different vascular beds are associated not only with CVD mortality but also with non-CVD and total mortality and that location of the arterial calcification appears to be relevant to the strength of the association with mortality, and the CVD risk factors appear to mediate some of this association.

4.1. Study limitations

First, the imaging methods used in this study did not distinguish the two types of VC (pathy calcification of the intima and calcification of the media). As is known, mineral metabolism disturbances link specifically with medial rather than intimal V and intima calcification associates with atherosclerosis. Second, our studies was cross-sectional, it does not directly show how detection of VC in various vessels predict incident cardiovascular events in the dialysis patients. Third, VC represents the result of long-standing atherosclerotic and calcification processes. It is unclear whether the steady-state of serum chemistry such as calcium, phosphate, intact PTH concentrations measured in this study accurately represents pathological process that occurred when VC was developing.

5. Conclusion

Presence and extension of VC in thoracic and abdominal aortas and lower limbs might be regulated in complex manner and caution should be needed to use these variables as a marker of the burden of vascular disease. The associations between calcified atherosclerosis and mortality differ by vascular bed, suggesting that the location and severity of calcification in different vascular beds provide unique information for mortality.

Author details

H. Suzuki[1], T. Inoue[1], H. Okada[1], T. Takenaka[1], Kunihiko Hayashi[2], Jyunnichi Nishiyama[2], Takashi Yamazaki[2], Yuji Nishiyama[2] and Keiko Kaneko[2]

1 Department of Nephrology, Saitama Medical University Saitama, Japan

2 Department of Internal Medicine, Irumadai Clinic, Saitama, Japan

References

[1] Moe SM, O'Neill KD, Fineberg N, Persohn S, Ahmed S, Garrett P, et al. Assessment of vascular calcification in ESRD patients using spiral CT. Nephrol Dial Transplant. 2003;18(6):1152-8.

[2] Raggi P, Giachelli C, Bellasi A. Interaction of vascular and bone disease in patients with normal renal function and patients undergoing dialysis. Nat Clin Pract Cardiovasc Med. 2007;4(1):26-33.

[3] Tanne D, Tenenbaum A, Shemesh J, Schwammenthal Y, Fisman EZ, Schwammenthal E, et al. Calcification of the thoracic aorta by spiral computed tomography among hypertensive patients: associations and risk of ischemic cerebrovascular events. Int J Cardiol. 2007;120(1):32-7.

[4] Honkanen E, Kauppila L, Wikstrom B, Rensma PL, Krzesinski JM, Aasarod K, et al. Abdominal aortic calcification in dialysis patients: results of the CORD study. Nephrol Dial Transplant. 2008;23(12):4009-15.

[5] Coll B, Betriu A, Martinez-Alonso M, Amoedo ML, Arcidiacono MV, Borras M, et al. Large artery calcification on dialysis patients is located in the intima and related to atherosclerosis. Clin J Am Soc Nephrol. 2011;6(2):303-10.

[6] Wang AY, Woo J, Lam CW, Wang M, Chan IH, Gao P, et al. Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant. 2005;20(8):1676-85.

[7] 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(9):1731-40.

[8] Hujairi NM, Afzali B, Goldsmith DJ. Cardiac calcification in renal patients: what we do and don't know. Am J Kidney Dis. 2004;43(2):234-43.

[9] Raggi P, Bellasi A. Clinical assessment of vascular calcification. Adv Chronic Kidney Dis. 2007;14(1):37-43.

[10] Floege J, Raggi P, Block GA, Torres PU, Csiky B, Naso A, et al. Study design and subject baseline characteristics in the ADVANCE Study: effects of cinacalcet on vascular calcification in haemodialysis patients. Nephrol Dial Transplant. 2010;25(6):1916-23.

[11] Adler Y, Fisman EZ, Shemesh J, Tanne D, Hovav B, Motro M, et al. Usefulness of helical computed tomography in detection of mitral annular calcification as a marker of coronary artery disease. Int J Cardiol. 2005;101(3):371-6.

[12] Jayalath RW, Mangan SH, Golledge J. Aortic Calcification. European Journal of Vascular and Endovascular Surgery. 2005;30(5):476-88.

[13] Okuno S, Ishimura E, Kitatani K, Fujino Y, Kohno K, Maeno Y, et al. Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2007;49(3): 417-25.

[14] Hanada S, Ando R, Naito S, Kobayashi N, Wakabayashi M, Hata T, et al. Assessment and significance of abdominal aortic calcification in chronic kidney disease. Nephrol Dial Transplant. 2010;25(6):1888-95.

[15] Milliner DS, Zinsmeister AR, Lieberman E, Landing B. Soft tissue calcification in pediatric patients with end-stage renal disease. Kidney Int. 1990;38(5):931-6.

[16] 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(1): 37-43.

[17] Guerin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant. 2000;15(7):1014-21.

[18] Arad Y, Spadaro LA, Roth M, Scordo J, Goodman K, Sherman S, et al. Serum concentration of calcium, 1,25 vitamin D and parathyroid hormone are not correlated with coronary calcifications. An electron beam computed tomography study. Coron Artery Dis. 1998;9(8):513-8.

[19] Cozzolino M, Dusso AS, Slatopolsky E. Role of calcium-phosphate product and bone-associated proteins on vascular calcification in renal failure. J Am Soc Nephrol. 2001;12(11):2511-6.

[20] Floege J, Ketteler M. Vascular calcification in patients with end-stage renal disease. Nephrol Dial Transplant. 2004;19 Suppl 5:V59-66.

[21] Spiegel DM, Raggi P, Mehta R, Lindberg JS, Chonchol M, Ehrlich J, et al. Coronary and aortic calcifications in patients new to dialysis. Hemodial Int. 2004;8(3):265-72.

[22] Goodman WG, London G, Amann K, Block GA, Giachelli C, Hruska KA, et al. Vascular calcification in chronic kidney disease. Am J Kidney Dis. 2004;43(3):572-9.

[23] Qunibi WY. Reducing the burden of cardiovascular calcification in patients with chronic kidney disease. J Am Soc Nephrol. 2005;16 Suppl 2:S95-102.

[24] Asmus HG, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, et al. Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. Nephrol Dial Transplant. 2005;20(8):1653-61.

[25] London GM, Guerin AP, Verbeke FH, Pannier B, Boutouyrie P, Marchais SJ, et al. Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. J Am Soc Nephrol. 2007;18(2):613-20.

[26] Allison MA, Hsi S, Wassel CL, Morgan C, Ix JH, Wright CM, et al. Calcified atherosclerosis in different vascular beds and the risk of mortality. Arterioscler Thromb Vasc Biol. 2012;32(1):140-6.

[27] Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300(2):197-208.