Int Urol Nephrol (2014) 46:993–998
DOI 10.1007/s11255-013-0620-y

NEPHROLOGY - ORIGINAL PAPER

Calcification of the thoracic aorta determined by three-dimensional computed tomography predicts cardiovascular complications in patients undergoing hemodialysis

Nozomu Kamiura · Kiyoko Yamamoto · Shioko Okada · Makoto Sakai · Akira Fujimori

Received: 12 August 2013 / Accepted: 26 November 2013 / Published online: 7 December 2013

Abstract
Purpose In patients on dialysis, the most common cause of death is cardiovascular disease. This is caused, at least in part, by excessive vascular calcification. Studies that have examined coronary calcification have been published, but these measurements require expensive equipment. Here, we used computed tomography to determine aortic calcification and evaluated these data as prognostic markers for cardiovascular disease.
Methods Computed tomography with contrast medium was performed on 49 patients undergoing hemodialysis (29 males and 20 females; average age, 68.9 ± 11.0 years). A calcification score (CS) was defined as the ratio of the volume of vascular calcification to the volume of the thoracic aorta. All patients were monitored for cardiovascular end points, which included cerebral infarction or hemorrhage, myocardial infarction, electrocardiographic, or echocardiographic abnormalities that suggested myocardial ischemia, cardiac surgery, leg amputation, and hospitalization or death due to heart failure.
Results Patients were followed for 3 years, with 12 patients reaching the end point. Both high CS ($p = 0.007$) and male gender ($p = 0.009$) were significantly associated with cardiovascular events. In contrast, events were not related to age, dialysis duration, diabetes mellitus, smoking status, low-density lipoprotein cholesterol level, pulse-wave velocity, maximum intima-media thickness of the carotid artery wall, systolic blood pressure, or left ventricular hypertrophy. Multiple logistic regression analysis revealed that a high baseline CS was a significant predictor for cardiovascular events ($p < 0.05$).
Conclusions Calcification of the thoracic aorta determined by three-dimensional computed tomography predicts cardiovascular complications in patients on hemodialysis.

Keywords Cardiovascular disease · Chronic kidney disease · Hemodialysis · Vascular calcification

Introduction

Cardiovascular (CV) disease is extremely common in patients with chronic kidney disease (CKD), and roughly 50 % of patients on hemodialysis (HD) die from CV diseases [1]. Whereas CV deaths are declining within the general population, this trend does not hold true for patients undergoing HD [1]. Uremia is generally associated with accelerated atherosclerosis, and hallmark features of this condition include both medial- and intimal-artery calcification. Vascular calcification is frequently found in patients undergoing HD [2], and its association with CV events is of great interest [3]. Vascular calcification is progressive and associated with both arterial stiffness and increased CV mortality in patients receiving HD [4]. Disorders of mineral metabolism contribute to vascular calcification, leading to CV diseases [5] and lower survival rates [6].

In the evaluation of the relationship between calcification and vascular risk, recent meta-analyses have focused exclusively on coronary artery calcification [7]. Indeed, patients with coronary artery calcification have an elevated

N. Kamiura · M. Sakai
Department of Internal Medicine, Konan Hospital, Kobe, Japan

K. Yamamoto · S. Okada · A. Fujimori (✉)
Blood Purification and Kidney Center, Konan Hospital, 1-5-16 Kamokogahara, Higashinada-ku, Kobe 6580064, Japan
e-mail: louie@kcc.zaq.ne.jp

risk for CV events [8]. Calcium deposits within extra-coronary arterial beds induce loss of arterial elasticity and increase in pulse-wave velocity and may therefore serve as a marker for subclinical CV disease in patients with chronic kidney disease [9]. In a population-based cohort, calcification of the aortic arch evaluated by chest radiographs could identify risk of coronary heart disease [10]. However, other methods to assess coronary artery calcification, such as electron beam computed tomography or multi-detector-row computed tomography, require expensive technical equipment, which limits their routine use in dialysis centers.

Recently, Raggi et al. [11] reported that cinacalcet plus low-dose vitamin D sterols may attenuate the progression of vascular and cardiac valve calcification. However, there is no current effective therapeutic method to reduce pre-existing or advanced aortic calcification. Given the lack of potent treatment, early detection and prevention of progression of vascular calcification is essential for good outcomes, especially in CKD patients on HD. While it is established that aortic calcification determined by thoracic radiograph predicts cardiovascular events [10], early and micro-calcification of the aorta occurs prior to detection by chest radiographs. Furthermore, once detected, calcification could not be readily treated. Approximately, 73 % of patients undergoing HD, who were positive for medial micro-calcification of the iliac arteries via von Kossa staining, showed calcification on a plain pelvic X-ray [12]. The use of multi-detector-row computed tomography (MDCT) to detect micro-calcification in the aorta seems to be promising. Aortic calcification can be measured using prevalent and earlier generations of MDCT, and it is relatively inexpensive compared to coronary CT angiography. Kimura et al. [13] reported a method using MDCT to quantitatively evaluate abdominal aortic calcification in HD patients. Abdominal aortic calcification may also be detected in non-uremic patients and is not associated with CV disease [14–16].

To search for a more practical and sensitive test to detect and quantify vascular calcification in patients undergoing HD, an MDCT was utilized. The relationship between calcification score and the incidence of CV disease was then analyzed.

Materials and methods

Subjects

All patients 18 years or older who had undergone hemodialysis for ≥3 months at Konan Hospital were invited to participate in this prospective cohort study. Patients unable to provide consent, with HIV infection or active malignancy, those who had recent chemotherapy or organ transplantation were excluded. Forty-nine patients with end-stage renal disease (29 males and 20 females) on HD for 9.7 ± 7.7 years, treated at our dialysis center, were enrolled in the study. The mean age was 68.9 ± 11.0 years. Seventeen patients had diabetes mellitus. All patients on HD received the treatment using high-flux dialysis membranes. Blood and dialysate flow rates were 200 and 500 mL/min, respectively. Most patients received 4-h dialysis sessions three times each week. All patients were followed until the time of a CV event, which included cerebral infarction or hemorrhage, myocardial infarction, electro- or echocardiographic abnormalities suggestive of myocardial ischemia, cardiac surgery, leg amputation, and hospitalization or death due to heart failure.

At the 3rd year of follow-up, relationships between CV events and age, gender, dialysis vintage (i.e., the duration of dialysis), diabetes mellitus, smoking status, systolic blood pressure, low-density lipoprotein (LDL) cholesterol levels, pulse-wave velocity, left ventricular hypertrophy (LVH), maximal intima-media thickness (IMT) of the carotid artery, serum calcium and phosphate, calcium-phosphate product, bone mineral density, whole parathyroid hormone (PTH), and calcification of the thoracic aorta were evaluated. LVH was defined as an increase in wall thickness of more than 1.2 cm measured by echocardiography.

Since low bone mineral density may be a high-risk indicator for cardiovascular events in patients on HD [17] and cortical bone deteriorates more readily than trabecular bone [18], bone mineral density of the radial cortical bone was evaluated by peripheral quantitative computed tomography (pQCT; XCT-960, Norland-Stratec, Pforzheim, Germany), as reported previously [19]. Serum whole PTH levels were measured using immunoradiometric assay (SRL Inc. Osaka, Japan). To assess pulse-wave velocity, pressure waveform recordings were carried out simultaneously from the radial artery on the wrist without arteriovenous fistula and at the posterior tibial artery on the ankle using form PWV/ABI (Omron Colin Co., Ltd., Kyoto, Japan). All patients provided informed consent. Study protocol was approved by the Ethics Committee of Konan Hospital and was in accordance with the Declaration of Helsinki.

Imaging procedure

Light Speed 16-slice computed tomography (GE Healthcare, Milwaukee, WI, USA), with Iohexol contrast medium (2 mL/s; 80 mL total; Omnipaque, Daiichi Sankyo Co., Ltd., Tokyo, Japan), was used. Volume of the thoracic aorta was automatically measured from a 10-cm segment immediately caudal to the bifurcation of the trachea. Regions with ≥400 Hounsfield units were considered to

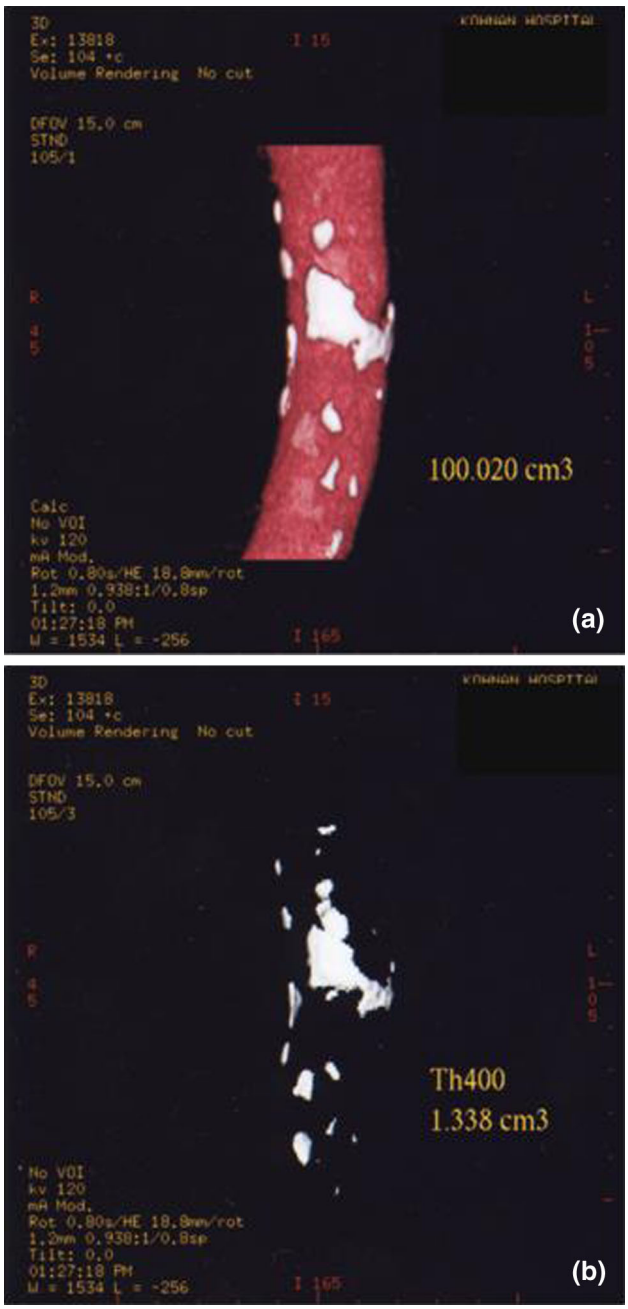

Fig. 1 Three-dimensional images of the thoracic aorta (**a**) and calcification (**b**)

have vascular calcification. Volume was automatically calculated using the Advantage Workstation 4.2 software (GE Healthcare). The calcification score (CS) was defined as the ratio of the volume of vascular calcification to the volume of the thoracic aorta (Fig. 1).

Statistical analysis

Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented as percentages.

Table 1 Characteristics of the patients at baseline

Variable	Measurement[a]
Age (year)	68.9 ± 11.0
Male gender (%)	59.2
Diabetes mellitus (%)	34.7
Dialysis duration (year)	9.7 ± 7.7
Smoking (%)	16.3
Systolic blood pressure (mmHg)	152.8 ± 14.2
LDL cholesterol (mg/dL)	89.3 ± 23.4
Left ventricular hypertrophy (%)	12.2
Pulse-wave velocity (cm/s)	1,953 ± 598
Max-IMT (mm)	2.1 ± 0.8
CS	0.0113 ± 0.0145
Serum calcium (mg/dL)	9.2 ± 0.6
Serum phosphate (mg/dL)	5.3 ± 0.7
Calcium-phosphate product	49.0 ± 6.8
Whole PTH (pg/mL)	95.4 ± 101.1
Radial cortical bone density (mg/ccm)	1,040.9 ± 94.2

CS calcification score, *PTH* parathyroid hormone, *BP* blood pressure, *LDL* low-density lipoprotein, *IMT* intima-media thickness

[a] Data presented as mean ± standard deviation (SD) for continuous variables

The data were analyzed with the Mann–Whitney *U* test for continuous variables. Chi-square analyses were used to investigate associations between different categorical variables. Logistic regression analysis was performed to determine the factors related to CV events. Differences were considered significant at $p < 0.05$. All analyses were performed using StatView statistical software package, version 5.0 (SAS, Inc., Cary, NC).

Results

Patient characteristics

A total of 49 patients on HD were enrolled in the study. Table 1 summarizes the patient clinical characteristics. Participants were more likely to be male and over the age of 70.

Parameters affecting incidence of cardiovascular event

A total of 49 patients were followed for 3 years. Twelve patients experienced a subsequent CV event (Table 2). The events did not occur in the same patient and were entirely independent. Patients who experienced a CV event had a significantly higher baseline CS than those without a CV event ($p < 0.01$). This result suggests that the CS had predictive value concerning subsequent CV events (Fig. 2).

Table 2 Incidence of cardiovascular events

Outcome	No. of patients (%)
Hospitalization and death due to heart failure	5 (10.2)
ECG or echocardiographic abnormalities suggestive of myocardial ischemia	3 (6.1)
Cardiac surgery	1 (2.0)
Cerebral infarction and hemorrhage	2 (4.1)
Leg amputation	1 (2.0)

ECG electrocardiograph

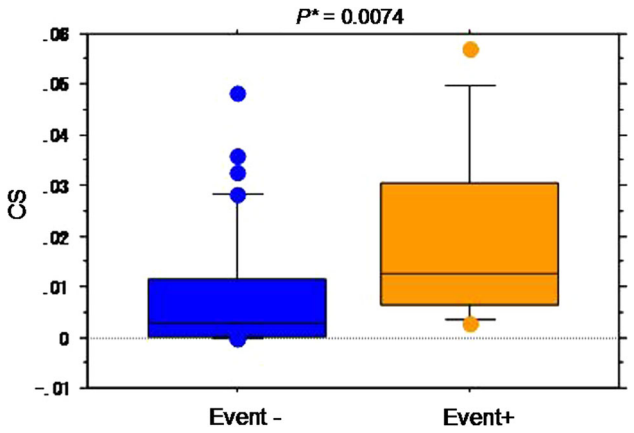

Fig. 2 Relationship between calcification of thoracic aorta and CV events. *CS* calcification score

CV events were also more prevalent in male than in female patients (Table 3). Diabetes mellitus and LVH were not a significant factor in the incidence of a CV event. No significant differences in dialysis vintage, pulse-wave velocity, maximal IMT, systolic blood pressure, LDL cholesterol levels, serum calcium and phosphate, calcium-phosphate product, whole PTH, and radial cortical bone density were detected in patients with and without a CV event (Table 3). A higher age and a history of smoking correlated with a CV event, although the differences were not statistically significant (Table 3).

Regression analyses

Logistic regression analysis using gender, age, CS, and smoking status as independent parameters was performed. Results showed that the male gender and CS were independent predictors for the incidence of a CV event (Table 4).

Discussion

In this study, calcification of the thoracic aorta in CKD patients on HD was evaluated with multi-detector-row computed tomography. Patients who had a subsequent CV event had a significantly higher CS. This suggests that the CS provides predictive value concerning CV complications in CKD patients on HD. These results are consistent, at least in part, with previous studies, where thoracic aortic plaques identified by transesophageal echocardiography were reportedly associated with vascular events such as ischemic stroke [20, 21]. Several established risk factors for CV disease, such as elevated systolic blood pressure, high serum LDL cholesterol levels, and diabetes mellitus, were not associated with CV events in this study. This pattern has also been observed in a previous study [22]. This implies that vascular calcification may be the strongest risk for CV events in CKD patients on HD.

In addition to the classical risk factors mentioned above, disorders that affect the metabolism of minerals (e.g.,

Table 3 Differences between patients with and without cardiovascular events

Variable	CV event[a]	No CV event[a]	*p*
Age (year)	73.8 ± 8.5	67.4 ± 11.3	0.07
Male gender (%)	91.7	48.6	0.008
Diabetes mellitus (%)	41.7	32.4	0.56
Dialysis duration (year)	7.6 ± 8.8	10.4 ± 7.3	0.14
Smoking (%)	33.3	10.8	0.07
Systolic blood pressure (mmHg)	156.9 ± 8.0	151.8 ± 15.3	0.45
LDL cholesterol (mg/dL)	79.4 ± 17.9	92.5 ± 29.3	0.19
Left ventricular hypertrophy (%)	16.7	10.8	0.60
Pulse-wave velocity (cm/s)	1,818 ± 343	1,997 ± 658	0.74
Max-IMT (mm)	2.2 ± 0.9	2.1 ± 0.8	0.67
Serum calcium (mg/dL)	9.3 ± 0.5	9.2 ± 0.6	0.96
Serum phosphate (mg/dL)	5.4 ± 0.8	5.3 ± 0.6	0.94
Calcium-phosphate product	50.0 ± 7.2	48.7 ± 6.8	0.66
PTH (pg/mL)	111.8 ± 108.7	90.0 ± 95.6	0.36
Radial cortical bone density (mg/ccm)	1,039.7 ± 97.9	1,041.2 ± 94.4	0.78

CV cardiovascular, *PTH* parathyroid hormone, *BP* blood pressure, *LDL* low-density lipoprotein, *IMT* intima-media thickness

[a] Data presented as mean ± SD for continuous variables

Table 4 Predictive variables related to cardiovascular events

Variable	*p*	Odds ratio (95 % CI)
Age	0.1149	1.079 (0.982–1.187)
Male gender	0.0261	23.194 (1.452–370.372)
CS	0.0421	9.975×10^{30} ($12.528–7.942 \times 10^{60}$)
Smoking	0.1595	4.311 (0.563–33.022)

CS calcification score, *CI* confidence interval

chronic hyperphosphatemia and hypercalcemia) may contribute toward progressive calcification over time. Calcification occurs both through passive precipitation and active induction of osteoblast-like phenotypes in vascular smooth muscles [23, 24]. Moreover, in patients who develop chronic kidney disease, intravascular ultrasonography revealed that coronary lesions change from necrotic-rich plaques to calcium-rich plaques [25]. We previously demonstrated that annual changes in CS correlate with whole PTH levels, maximal IMT, and serum levels of calcium-phosphorus product. Although disturbances in bone mineral metabolism, such as hypercalcemia and hyperphosphatemia, were related to significantly lower survival rates in patients on HD in Japan [6], serum levels of calcium, phosphate, and calcium-phosphorus products were not predictive of CV events in this study. It would probably take years, even decades, for elevated levels of calcium, phosphate, and calcium-phosphorus products to lead to CV events via the progression of vascular calcification. These factors might be related to CV events if the observation period of the current study would be extended further.

LVH is often a key component of CV disease since LVH may lead to diastolic dysfunction, congestive heart failure, arrhythmia, and sudden death in dialysis patients [26]. High blood pressure, over-hydration, anemia, and arteriovenous shunts are known factors that contribute to LVH via pressure and flow/volume overload [27]. In addition, vascular calcification causes arterial stiffness, which in turn increases left ventricular load resulting in hypertrophy [28]. Although calcification of the thoracic aorta may be predictive of future CV events, baseline LVH was not significant in this study. The reason for this lies in the fact that good blood pressure and fluid management in this study patients reflected low prevalence of severe LVH. Similarly, PWV was not related to CV events in this current study. Low precision and reproducibility of PWV could be the reason for the lower correlation.

Currently, there are no therapeutic strategies to effectively reduce pre-existing or advanced arterial calcification. There is little evidence to support the hypothesis that reduced calcification yields better CV outcomes. However, there are promising therapies that aim to prevent progression of vascular calcification. These include the use of sevelamer, lanthanum carbonate, and cinacalcet, as demonstrated in human studies [11, 29, 30], and matrix Gla protein as a calcification inhibitor in both animal models and human cells [31, 32]. Although statins may reduce the likelihood of a CV event, whether these drugs inhibit calcification remains controversial [33, 34]. Hence, early detection of aortic calcification by MDCT, with good maintenance of normal levels of serum calcium, phosphorus, and calcium-phosphorus product levels, in combination with the above-mentioned therapies would lead to better management and outcomes for CKD patients on hemodialysis.

The limitations of this current study include small number of studied patients, short observation period, and the lack of data in other segments of the aorta. Future studies with larger sample sizes would be necessary to confirm our findings. Moreover, further studies are required to clarify whether management of calcium, phosphate, and PTH levels can inhibit the progression of vascular calcification and lower the risk of CV disease in CKD patients receiving maintenance HD.

In conclusion, calcification of the thoracic aorta determined by three-dimensional computed tomography can predict subsequent CV events in CKD patients on chronic hemodialysis. As vascular calcification is a prognostic factor for patients undergoing HD, it should be assessed and monitored appropriately. Three-dimensional computed tomography might be a suitable method since early and micro-calcifications could be detected and quantified.

Acknowledgments No commercial funding sources were involved in this study. The authors wish to thank Dr. Michael Teraoka for English editing.

Conflict of interest The authors had no conflict of interest to declare in relation to this article.

References

1. Collins AJ, Foley RN, Herzog C et al (2010) Excerpts from the US renal data system 2009 annual data report. Am J Kidney Dis 55(1 Suppl 1):S1–420, A426–427
2. Goodman WG, Goldin J, Kuizon BD et al (2000) Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 342(20):1478–1483
3. Blacher J, Guerin AP, Pannier B et al (2001) Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 38(4):938–942
4. Okuno S, Ishimura E, Kitatani K et al (2007) Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. Am J Kidney Dis 49(3):417–425
5. KDIGO Clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) (2009) Kidney Int Suppl (113):S1–130
6. Nakai S, Akiba T, Kazama J et al (2008) Effects of serum calcium, phosphorous, and intact parathyroid hormone levels on survival in chronic hemodialysis patients in Japan. Ther Apher Dial 12(1):49–54
7. Pletcher MJ, Tice JA, Pignone M et al (2004) Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. Arch Intern Med 164(12):1285–1292
8. Kondos GT, Hoff JA, Sevrukov A et al (2003) Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation 107(20):2571–2576

9. Temmar M, Liabeuf S, Renard C et al (2010) Pulse wave velocity and vascular calcification at different stages of chronic kidney disease. J Hypertens 28(1):163–169
10. Iribarren C, Sidney S, Sternfeld B et al (2000) Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. JAMA 283(21): 2810–2815
11. Raggi P, Chertow GM, Torres PU et al (2011) The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transpl 26(4):1327–1339
12. Schlieper G, Aretz A, Verberckmoes SC et al (2010) Ultrastructural analysis of vascular calcifications in uremia. J Am Soc Nephrol 21(4):689–696
13. Kimura K, Saika Y, Otani H et al (1999) Factors associated with calcification of the abdominal aorta in hemodialysis patients. Kidney Int Suppl 71:S238–S241
14. Honkanen E, Kauppila L, Wikstrom B et al (2008) Abdominal aortic calcification in dialysis patients: results of the CORD study. Nephrol Dial Transpl 23(12):4009–4015
15. Iwamoto J, Matsumoto H, Takeda T et al (2010) A radiographic study on the associations of age and prevalence of vertebral fractures with abdominal aortic calcification in Japanese postmenopausal women and men. J Osteoporos 2010:748380
16. Rodondi N, Taylor BC, Bauer DC et al (2007) Association between aortic calcification and total and cardiovascular mortality in older women. J Intern Med 261(3):238–244
17. Ambrus C, Marton A, Nemeth ZK et al (2010) Bone mineral density in patients on maintenance dialysis. Int Urol Nephrol 42(3):723–739
18. Jamal SA, Gilbert J, Gordon C et al (2006) Cortical pQCT measures are associated with fractures in dialysis patients. J Bone Miner Res 21(4):543–548
19. Fujimori A, Okada S, Sakai M et al (2011) Relationship between biochemical markers and radial cortical bone changes in hemodialysis patients. Nephron Clin Pract 118(4):c375–c379
20. Cohen A, Tzourio C, Bertrand B et al (1997) Aortic plaque morphology and vascular events: a follow-up study in patients with ischemic stroke. FAPS investigators. French study of aortic plaques in stroke. Circulation 96(11):3838–3841
21. Blackshear JL, Pearce LA, Hart RG et al (1999) Aortic plaque in atrial fibrillation: prevalence, predictors, and thromboembolic implications. Stroke 30(4):834–840
22. Iijima K, Hashimoto H, Hashimoto M et al (2010) Aortic arch calcification detectable on chest X-ray is a strong independent predictor of cardiovascular events beyond traditional risk factors. Atherosclerosis 210(1):137–144
23. Chertow GM, Raggi P, Chasan-Taber S et al (2004) Determinants of progressive vascular calcification in haemodialysis patients. Nephrol Dial Transpl 19(6):1489–1496
24. Ketteler M, Westenfeld R, Schlieper G et al (2005) Pathogenesis of vascular calcification in dialysis patients. Clin Exp Nephrol 9(4):265–270
25. Kono K, Fujii H, Nakai K et al (2012) Composition and plaque patterns of coronary culprit lesions and clinical characteristics of patients with chronic kidney disease. Kidney Int 82(3):344–351
26. Zoccali C, Benedetto FA, Mallamaci F et al (2004) Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. J Am Soc Nephrol 15(4):1029–1037
27. Parfrey PS, Foley RN (1999) The clinical epidemiology of cardiac disease in chronic renal failure. J Am Soc Nephrol 10(7): 1606–1615
28. Rabkin SW, Chan SH (2012) Correlation of pulse wave velocity with left ventricular mass in patients with hypertension once blood pressure has been normalized. Heart Int 7(1):e5
29. Takei T, Otsubo S, Uchida K et al (2008) Effects of sevelamer on the progression of vascular calcification in patients on chronic haemodialysis. Nephron Clin Pract 108(4):c278–c283
30. Toussaint ND, Lau KK, Polkinghorne KR et al (2011) Attenuation of aortic calcification with lanthanum carbonate versus calcium-based phosphate binders in haemodialysis: a pilot randomized controlled trial. Nephrology (Carlton) 16(3):290–298
31. Proudfoot D, Skepper JN, Shanahan CM et al (1998) Calcification of human vascular cells in vitro is correlated with high levels of matrix Gla protein and low levels of osteopontin expression. Arter Thromb Vasc Biol 18(3):379–388
32. Luo G, Ducy P, McKee MD et al (1997) Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature 386(6620):78–81
33. Budoff MJ, Yu D, Nasir K et al (2005) Diabetes and progression of coronary calcium under the influence of statin therapy. Am Heart J 149(4):695–700
34. Schmermund A, Achenbach S, Budde T et al (2006) Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation 113(3):427–437