NEPHROLOGY

Nephrology **19** (2014) 251–256

Original Article

Vascular calcification in long-term kidney transplantation

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KEY WORDS:
aortic calcification, atherosclerosis, coronary calcification, dialysis, pelvic calcification.

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Accepted for publication 14 January 2014.
Accepted manuscript online 22 January 2014.

doi:10.1111/nep.12210

ClinicalTrials.gov Identifier: NCT01293786

SUMMARY AT A GLANCE

This study assesses vascular calcification (VC) in kidney transplant recipients and matched patients on dialysis. Not surprisingly, prevalence and determinants of VC were similar for both groups. Of interest, VC severity was greater in transplant patients than in patients on dialysis. Longitudinal studies are required to confirm these data.

ABSTRACT:

Aim: **Vascular calcification (VC) is common among patients with chronic kidney disease (CKD) due to the strong prevalence of cardiovascular and CKD-related risk factors such as diabetes mellitus (DM), hypertension and phosphate retention. Kidney transplantation improves kidney function and abnormal mineral metabolism at the same time. It remains unclear whether kidney transplantation favourably impacts VC in the long-term.**

Methods: **The present study examined VC in 132 kidney transplant (KT) recipients who had been transplanted for longer than one year. The severity of VC was compared to 129 CKD stages 5-5D patients on a kidney transplant (KT) waiting list.**

Results: **The median KT vintage was 88 months. The prevalence of VC among KT and CKD patients were 54.5% and 62.8%, respectively, ($P = 0.2$). There were no differences in age, gender, body mass index (BMI), the prevalence of DM or CVD between the two groups. Among patients with calcification, a more severe degree was observed in KT recipients ($P = 0.01$). Aging, DM, CVD and dialysis vintage were associated with significant VC in both groups. The degree of VC in KT recipients was more pronounced than that in CKD patients among those who experienced prolonged dialysis vintage (>2 years) ($P = 0.04$). Among KT recipients, the severity of VC increased with the length of time after transplantation and became more substantial after 5 years.**

Conclusions: **Long-term KT recipients demonstrated a more severe degree of VC compared to matched CKD stages 5-5D patients. The severity of VC became more pronounced among those with longer transplant vintage and was in part influenced by past dialysis experience.**

Atherosclerosis and vascular calcification (VC) are prevalent among patients with chronic kidney disease (CKD) as a result of uraemia, inflammation, and abnormal mineral metabolism. The extent of VC predicts cardiovascular events and mortality in the entire spectrum of CKD, starting from early stages until end-stage renal disease, and even after kidney transplantation.[1–3] Traditional cardiovascular as well as CKD-related risk factors including aging, smoking, diabetes mellitus (DM), phosphate retention, calcium intake and dialysis vintage are associated with the severity VC.[4]

Pathogenesis of VC is an active cellular process of vascular smooth muscle cell transformation into osteoblast-like cells. This programmed cellular transformation can be induced by high calcium and high phosphate environment and made worse by the reduction of calcification inhibitors.[5] Generally in CKD, VC can occur in the intimal and medial layers of the arterial wall.[6] Intimal calcification is mostly localized in a large artery such as the aorta, whereas medial calcification is found predominantly in peripheral muscular arteries including iliac and femoral arteries.[7] The extent of VC increased with the progression of CKD as a result of continued exposure to mineral derangements and uremic milieu. By the time CKD patients reached end-stage renal disease, the prevalence and magnitude of VC multiplied.[8] Kidney transplantation offers a mean to improve both kidney function and abnormal mineral metabolism at the same time. Follow-

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ing kidney transplant (KT) recipients for 1–2 years post-transplantation revealed a stabilization of VC in most patients.[9] Longer follow-up duration up to 4 years seemed to suggest an overall progression.[10,11] The data on VC in long-term KT recipients are lacking. The present study examined VC in long-term KT recipients with a median transplant vintage of over 7 years. CKD stages 5-5D patients on KT waiting list served as controls. VC data were obtained from plain radiographs of lumbar spine and pelvis, which identified VC in abdominal aorta, iliac and femoral arteries.[7,12] To account for the presence of VC from all sites as well as both intimal and medial calcifications, the combined VC scores were used in analyses. Important factors associated with significant VC were also determined.

METHODS

Patients

This study was approved by the Ethical Committee on Human Rights Related to Researche Involving Human Subjects of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University and conducted according to the Declaration of Helsinki. Informed consent was obtained from all participants. KT recipients who were at least one year post-transplantation and chronic dialysis patients (CKD stage 5D) who were eligible for KT waiting list, all between 18–75 years of age, were recruited consecutively during the routine follow-up visits to the outpatient nephrology clinic of Ramathibodi hospital. An additional 21 non-dialysis CKD stage 5 patients were recruited to match KT recipients who received pre-emptive kidney transplantation or were on dialysis for less than 3 months. Patients with acute illnesses were excluded. The kidney transplant was the first transplant in all KT recipients. A second kidney transplantation in Thailand was uncommon. Only KT recipients who had been transplanted for at least one year were enrolled because the stabilization of mineral metabolites and hormones may take up to 12 months in most patients.[13] Six CKD stage 5D patients received lanthanum carbonate. None of the KT recipients received non-calcium containing phosphate binders or bisphosphonates post-transplantation. Prescribed active vitamin D were calcitriol or alfacalcidol. Prescribed nutritional vitamin D was ergocalciferol. Vitamin D analogues and calcimimetics were not available in Thailand at the time of enrolment. For the KT population, 54% were living-related and 46% were deceased donor transplantations. The maintenance immunosuppressive regimens included corticosteroid in all patients. Eighty-eight percent received a calcineurin-based regimen and 12% received a mammalian target of rapamycin inhibitors-based regimen. The third drug was either mycophenolate mofetil or azathioprine.

Biochemical data

Medical chart review was performed to collect the data on baseline demographics and characteristics. CVD was defined by a history of coronary artery disease (myocardial infarction, unstable angina, positive coronary angiography or abnormal myocardial perfusion scan), cerebrovascular disease and/or peripheral arterial disease. DM was defined according to World Health Organization (WHO) criteria or the use of hypoglycaemic agents. Dyslipidaemia was defined as total cholesterol ≥6.2, LDL ≥3.4, triglycerides ≥2.3 mmol/L, or the use of statin. Hypertension was defined as systolic and diastolic blood pressure ≥140 and ≥90 mmHg, respectively, or the use of anti-hypertensive medication. Smoking was defined as former or current smokers. Laboratory data including serum calcium, phosphate, albumin, cholesterol and alkaline phosphatase (ALP) were calculated as an average of two values obtained at the time of enrolment and within the past 12 months. Intact parathyroid hormone (PTH) level was obtained once at the time of enrolment. Blood samples were analyzed using a Dade Behring Dimension RxL analyzer (Siemens, Germany). Intact PTH was determined by an immunoradiometric assay (ELISA-PTH, Cisbio International, France). Serum calcium was corrected based on the following equation: Corrected Ca (mmol/L) = serum Ca (mmol/L) + [(40 − serum albumin (g/L)/10 × 0.2]. Estimated glomerular filtration rate (eGFR) was calculated using an MDRD formula: EGFR = (186.3 × serum Cr (mg/dL) − 1.154 × age − 0.203) × 0.742 if female.

Vascular calcification

Vascular calcification data were examined by plain radiographs obtained at the time of enrolment. Abdominal aortic calcification was determined using a lateral lumbar spine radiograph and the amount of VC was scored according to the method described previously by Kauppila *et al*. (Total score 0–24).[12] This method has been validated in dialysis patients which demonstrated a high correlation with coronary artery calcification (CAC) scores obtained by computed tomography (CT) and the presence of CVD.[14,15] Lateral lumbar spine radiograph is recommended by KDIGO (Kidney Disease Improving Global Outcome) as an alternative to CT for the detection of VC.[16] Iliac and femoral arterial calcifications were examined using a pelvic radiograph and scored according to Adragao *et al*. method (Total score 0–4).[7] Simple VC scores obtained by lateral lumbar spine and pelvic radiographs have been shown to predict cardiovascular events and mortality in dialysis patients.[17] In order to weight the amount of VC from all sites and the contribution of both intimal and medial calcifications equally, total VC scores in the present study were calculated as follows: Total VC score (maximum score of 48) = aortic calcification score (maximum score of 24) + (pelvic calcification score × 6) (maximum score of 24). Plain radiographs were reviewed by two observers who were blinded to clinical data. The correlation between two observers was 0.938. The data from one observer were used in analyses.

Statistical analysis

Two continuous variables were compared using Student's *t*-test or non-parametric test. Differences between two categorical variables were analyzed by χ^2 test. Important factors associated with significant VC were determined by logistic regression analyses. Total VC score of 6 or greater was selected as the cut off for significant VC because previous studies have shown an improved sensitivity and specificity of aortic calcification score greater than 6 for the prediction of significant CAC and the presence of calcification in at least one of the iliac or femoral arteries (which gave the score of at least 6 in the present study's scoring system) could predict future mortality.[7,14] Variables with *P*-value less than 0.1 in univariate analyses in either group were selected as covariates in multivariate analyses.

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Table 1 Baseline demographics and characteristics of all patients

Parameters	Mean ± SD or Median (IQR)	
	KT (n = 132)	CKD 5-5D (n = 129)
Age (years)	47.9 ± 11.7	48.5 ± 13.8
Male gender†	81 (61.4)	65 (50.4)
Body mass Index (kg/m^2)	23.7 ± 4.5	22.6 ± 4
Smoker†	14 (10.6)*	26 (20.2)
Hypertension†	104 (78.8)	97 (76.4)
Dyslipidaemia†	85 (64.4)*	63 (49.2)
Diabetes mellitus†	33 (25)	33 (25.8)
Cardiovascular disease†	8 (6.1)	17 (13.3)
Dialysis vintage (months)	24 (9–48)*	35 (9–54)
Peritoneal Dialysis†	10 (7.6)	13 (10.3)
KT vintage (months)	88 (41–138)	–
Calcium-based binders†	39 (29.5)*	87 (67.4)
Active vitamin D†	9 (6.8)*	47 (36.4)
Nutritional vitamin D†	1 (0.8)*	40 (31)
Statin use†	79 (59.8)	67 (51.9)
Laboratory data		
Calcium (mmol/L)	2.4 ± 0.1	2.4 ± 0.3
Phosphate (mmol/L)	1.1 ± 0.2*	1.6 ± 0.5
Albumin (g/L)	40 ± 4.4*	36.4 ± 4.5
Cholesterol (mmol/L)	5 ± 0.9*	4.3 ± 1.3
LDL (mmol/L)	2.0 ± 0.8*	2.6 ± 0.9
Triglyceride (mmol/L)	1.5 ± 1.1*	1.6 ± 1.6
ALP (U/L)	74 (57–98)*	94 (72–129)
PTH (pmol/L)	8 (6–12)*	27 (12–59)
eGFR (mL/min/1.73 m^2)	56 ± 21.1	–

*P < 0.05 *versus* CKD. †Number (%). ALP, alkaline phosphatase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KT, kidney transplant; LDL, low density lipoprotein; PTH, parathyroid hormone.

P-value less than 0.05 was considered statistically significant. All computations were performed using SPSS 17.0 software (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics

Baseline demographics and characteristics of all patients are shown in Table 1. There were no significant differences in age, gender, body mass index (BMI), the prevalence of hypertension, DM and CVD and the mode of renal replacement therapy between KT recipients and CKD stages 5-5D patients. KT recipients were less likely to smoke but more likely to have dyslipidaemia. Overall the median dialysis vintage was shorter in KT recipients. The median KT vintage was 88 months. Higher percentage of CKD stages 5-5D patients received calcium-based binders, active vitamin D and nutritional vitamin D. Serum phosphate, triglyceride, ALP and PTH were lower, whereas serum albumin, cholesterol and LDL were higher in KT recipients.

Table 2 Prevalence and severity of vascular calcification

	n (%)	Vascular calcification scores (mean ± SD)	
		All patients	Patients with score > 0
Aortic Calcification			
KT	60 (45.5)	3.9 ± 6.2	8.6 ± 6.7*
CKD 5-5D	68 (52.7)	3.2 ± 5	6 ± 5.5
Pelvic Calcification			
KT	51 (38.6)	5.6 ± 8.5	14.6 ± 7.4
CKD 5-5D	46 (35.7)	4.9 ± 8.1	13.5 ± 8
Total Calcification			
KT	72 (54.5)	9.5 ± 12.9	17.4 ± 12.9*
CKD 5-5D	81 (62.8)	8.1 ± 11.2	12.9 ± 11.8

*P < 0.05 *versus* CKD. CKD, chronic kidney disease; KT, kidney transplant; n (%), number and percentage of patients.

Vascular calcification

The prevalence of aortic, pelvic and total calcifications was similar between CKD stages 5-5D patients and KT recipients (Table 2). Overall there were no significant differences in the average VC scores between the two groups at all regions. However, when analyzing the data only in patients with VC (VC score > 0), aortic and total calcification scores were significantly higher in KT recipients compared to CKD stages 5-5D patients. Factors associated with significant VC (total VC score ≥ 6) in each group are shown in Table 3. In univariate logistic regression analyses, age, DM and CVD were associated with VC in all patients. Male gender, smoking, dialysis vintage and increased serum calcium were associated with VC in KT recipients. There were no relationships between VC and BMI, hypertension, dyslipidaemia, KT vintage, calcium or active vitamin D intake, serum phosphate, albumin, cholesterol ALP, PTH or eGFR in all patients. In multivariate logistic regression analyses, increasing age and dialysis vintage were independently associated with VC in both groups. Since dialysis vintage appeared to influence the severity of VC in both groups and the median dialysis vintage in KT recipients was shorter than CKD patients, VC data were next categorized according to intervals of dialysis vintage (≤2 or >2 years) (Fig. 1). Although KT recipients exhibited higher total VC scores compared to CKD patients at all intervals of dialysis vintage, the differences did not reach statistical significance (Fig. 1a). However, if only patients with calcification (total VC score > 0) were included in analyses, a significant increase in the severity of VC in KT recipients was observed especially among those with dialysis vintage longer than 2 years (Fig. 1b). There were no significant differences in age or the prevalence of DM or CVD between KT recipients and CKD patients in any of the subgroups. In order to determine the influence of time after kidney transplantation on the severity of VC, KT recipients with dialysis vintage longer than 2 years were categorized according to intervals of KT vintage (between 1–5 years or >5 years) and the severity of VC was compared to CKD stages

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Table 3 Logistic regression analyses of factors associated with significant vascular calcification

Parameters	Kidney Transplant				Chronic Kidney Disease 5-5D			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (10 years)	2.79 (1.85–4.23)	<0.001*	3.12 (1.82–5.33)	<0.001*	2.17 (1.56–3.01)	<0.001*	2.54 (1.63–3.94)	<0.001*
Body mass index	1 (0.98–1.02)	0.9	–	–	0.99 (0.97–1.03)	0.95	–	–
Male gender	2.36 (1.13–4.91)	0.02*	2.49 (0.87–7.14)	0.09	1.44 (0.71–2.91)	0.32	2.02 (0.71–5.78)	0.19
Smoker	3.65 (1.08–12.3)	0.04*	3.15 (0.56–17.6)	0.19	0.93 (0.38–2.25)	0.87	0.93 (0.26–3.23)	0.91
Hypertension	1.54 (0.65–3.66)	0.33	–	–	1.46 (0.62–3.46)	0.38	–	–
Dyslipidaemia	1.25 (0.61–2.57)	0.55	0.52 (0.18–1.52)	0.23	1.91 (0.93–3.9)	0.08	1.13 (0.44–2.86)	0.8
Diabetes mellitus	3.5 (1.52–8.04)	0.003*	2.73 (0.86–8.66)	0.09	6.72 (4.15–29.6)	<0.001*	4.46 (1.43–13.9)	0.01*
Cardiovascular disease	10.2 (1.22–85.7)	0.03*	11 (0.98–123)	0.05	9.33 (2.52–34.5)	0.001*	4.81 (0.91–25.3)	0.06
Dialysis vintage (1 year)	1.23 (1.09–1.45)	0.002*	1.35 (1.11–1.64)	0.003*	1.08 (0.96–1.23)	0.2	1.19 (1.02–1.39)	0.03*
KT vintage (1 year)	1.02 (0.94–1.1)	0.67	–	–	–	–	–	–
Calcium intake (yes/no)	1.52 (0.72–3.23)	0.27	–	–	0.87 (0.38–1.96)	0.73	–	–
Active vitamin D intake (yes/no)	2.73 (0.65–11.4)	0.17	–	–	1.38 (0.66–2.91)	0.39	–	–
Laboratory data			–	–				
Calcium	2.42 (1.19–4.91)	0.01*	2.35 (0.84–6.6)	0.1	1.07 (0.79–1.44)	0.67	1.39 (0.93–2.06)	0.11
Phosphate	1.01 (0.6–1.73)	0.96	0.86 (0.4–1.86)	0.7	0.82 (0.65–1.03)	0.09	1.13 (0.82–1.55)	0.46
Albumin	0.98 (0.9–1.06)	0.59	–	–	0.94 (0.87–1.02)	0.13	–	–
Cholesterol	1 (0.99–1.01)	0.54	–	–	1 (1–1.01)	0.22	–	–
Log-ALP	1.45 (0.19–11.3)	0.72	–	–	1.68 (0.46–6.18)	0.43	–	–
Log-PTH	1.65 (0.45–6.01)	0.45	–	–	0.85 (0.43–1.67)	0.63	–	–
eGFR	1 (0.98–1.02)	0.91	–	–	–	–	–	–

ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone. Factors with *P*-value < 0.1 in univariate analyses in either group were included in multivariate analyses. *$P < 0.05$.

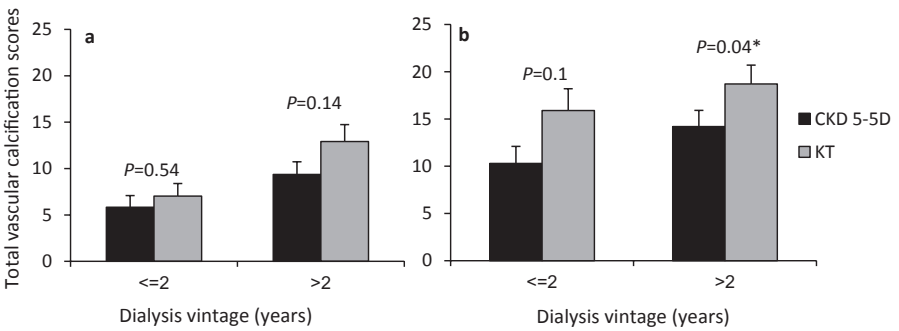

Fig. 1 Total vascular calcification scores (mean ± standard error (SE)) of chronic kidney disease (CKD) stages 5-5D patients and kidney transplant (KT) recipients categorized according to intervals of dialysis vintage. (a) All patients and (b) Patients with total vascular calcification score >0. *$P < 0.05$ *versus* CKD. ■, CKD 5-5D; □, KT.

5-5D patients (Fig. 2). There were no significant differences in age or the prevalence of DM or CVD between CKD patients and KT recipients in either groups. A significant increase in the severity of VC was observed only in the subgroup of KT recipients with a transplant vintage longer than 5 years. Similar results were obtained when only data from patients with VC were analyzed. The prevalence of VC was similar across all groups.

DISCUSSION

The present study examined VC in long-term KT recipients in relation to CKD stages 5-5D patients on a KT waiting list. The two populations were matched for age, gender, BMI, DM and CVD status. Aging and dialysis vintage were the major independent determinants of significant VC in both groups. The prevalence of VC was comparable among the two groups. However, in those with VC, the degree was more severe in KT recipients. More significant VC was observed mostly in KT recipients who experienced prolonged dialysis vintage (>2 years) prior to transplantation. The severity of VC increased with the length of time after transplantation and became more substantial after 5 years.

In the present study, VC was present in 62.8% of CKD stages 5-5D patients and 54.5% of KT population. Previous reported prevalence of VC determined by plain radiographs in CKD stage 5D ranged between 57–81%, which are comparable to the present study.[4,7,18,19] In KT recipients, the previously reported prevalence between 60–70% seemed to be slightly higher than the present study. VC images from these

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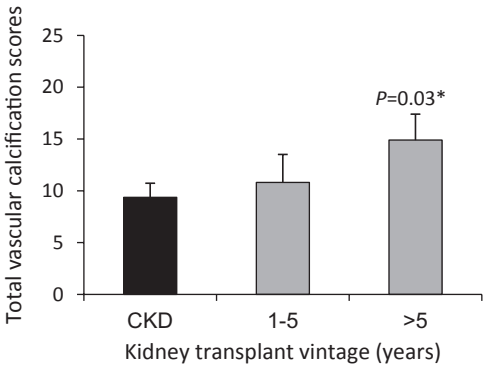

Fig. 2 Total vascular calcification scores (mean ± standard error (SE)) of chronic kidney disease (CKD) stage 5D patients and kidney transplant (KT) recipients with dialysis vintage >2 years categorized according to intervals of KT vintage. *$P < 0.05$ *versus* CKD.

studies were obtained by CT, which is more sensitive than plain radiographs.[9,20] Published studies on VC in KT populations using plain radiographs are lacking.

Due to the diverse nature of KT recipients and CKD stages 5-5D patients, differences in baseline characteristics were observed. Regression analyses revealed increasing age, DM and CVD as predictors of significant VC in most patients. Dialysis vintage emerged as an independent predictor of VC in both KT and CKD populations. Associations between age, DM and CVD with the severity of VC in different CKD populations have been described previously.[4,19–21] In CKD stage 5D patients, the relationship between dialysis vintage and the severity of VC has been documented.[4,15,19,21] In KT recipients, dialysis vintage has been shown to predict the progression of VC in the early post-transplantation period.[22] There has been no report on the relationship between dialysis vintage and the severity of VC in long-term-KT recipients until the present study. The extent of past dialysis experience appears to have a significant impact on the severity of VC long after kidney transplantation. Increasing serum calcium was associated with VC in long-term KT recipients. A number of evidence supported the role of calcium load in the development of VC. Higher serum calcium was associated with the presence of calcified coronary atherosclerotic plaque in subjects with normal renal function.[23] An increase in serum calcium after haemodialysis was related to the progression of aortic calcification.[24]

The overall prevalence of VC was comparable between KT recipients and CKD stages 5-5D patients despite the fact that KT recipients appeared to have less cardiovascular and CKD-related risk factors for VC. Moreover, among patients with VC, a more severe degree of calcification was observed in the KT group. The similar prevalence of VC among the two populations suggested that, in KT recipients who had no calcification at baseline, the likelihood of developing VC after kidney transplantation was small. This observation has been reported by previous small longitudinal studies in incident KT recipients.[25,26] On the other hand, our data also suggested that, in those with VC at the time of transplantation, progression was likely to occur in long-term despite the prolonged period of improvement of kidney function and mineral metabolism. As mentioned earlier, the pathogenesis of VC involves cellular transformation of vascular smooth muscle cells into osteoblast-like cells; therefore, the transformation process may not be reversible. However, to confirm this hypothesis, a prospective study with adequate follow-up time is required. Longer dialysis vintage was the major factor associated with a more substantial degree of VC after kidney transplantation. Previous study has demonstrated the relationship between past dialysis experience and the progression of VC.[22] Others have described the importance of baseline VC on future progression.[9–11] Among patients with dialysis vintage longer than 2 years, only KT recipients who had been transplanted for longer than 5 years demonstrated a greater magnitude of VC compared to CKD stage 5D patients. Previous studies that followed KT recipients for 1–2 years after transplantation revealed a stabilization of VC in most patients.[9,22,25] Two studies that compared the rate of progression of VC after 2 years of follow-up revealed a significant progression in CKD stage 5D but a stabilization in KT.[25,26] However, with a longer follow-up duration up to 3–4 years after transplantation, a progression became more evident.[10,11] It appears that an improvement of renal function and mineral metabolism attenuates the rate of progression of VC in KT recipients compared to patients who remained on dialysis and a significant progression can only be appreciated after a longer follow-up period. In the present study, only those who had been transplanted for longer than 5 years showed a substantial increase in the degree of VC compared to matched CKD stage 5D patients. The presence of common cardiovascular risk factors, for example, hypertension and dyslipidaemia are likely to contribute to the progression of VC in the long-term.[10,11]

Limitations of the study

Plain radiograph is less accurate and less sensitive than CT in the detection of VC. The measurement of VC is also semi-quantitative at best. Nevertheless, significant changes detected by plain radiographs are likely to be of a greater magnitude compared to CT and probably more clinically relevant. The magnitude of VC obtained by plain radiographs correlated with CAC scores and demonstrated the ability to predict important outcomes in CKD patients.[14,17,18,27] Despite the fact that important baseline characteristics were matched between KT and CKD groups, differences in other factors might still be unaccounted for, which limited the comparisons of VC between the two populations. However, in spite of less cardiovascular and CKD-related risk factors for VC, for example, KT recipients were less likely to smoke and the average dialysis vintage and serum phosphate were significantly lower compared to CKD patients, the data still

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suggested a more severe degree of VC among the KT population. The present study is a cross-sectional study and therefore cannot be used to evaluate the progression of VC in the long-term.

In conclusion, long-term KT recipients demonstrated a more severe degree of VC compared to matched CKD stages 5-5D patients. The severity of VC became more pronounced among KT recipients with longer transplant vintage and was at least in part influenced by past dialysis experience.

ACKNOWLEDGEMENTS

This work was supported by the Kidney Foundation of Thailand.

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