International Urology and Nephrology (2019) 51:527–534
https://doi.org/10.1007/s11255-019-02080-x

NEPHROLOGY - ORIGINAL PAPER

Associations of vitamin K status with mortality and cardiovascular events in peritoneal dialysis patients

Qingdong Xu[1] · Huankai Guo[1] · Shirong Cao[2] · Qian Zhou[3] · Jiexin Chen[1] · Ming Su[1] · Siying Chen[1] · Songqin Jiang[1] · Xiaofeng Shi[1] · Yueqiang Wen[4]

Received: 20 July 2018 / Accepted: 7 January 2019 / Published online: 28 January 2019

Abstract

Purpose Vitamin K deficiency, expressed by a high level of desphospho-uncarboxylated matrix GLA protein (dp-ucMGP), is highly prevalent in dialysis patients. However, the predictive ability of the vitamin K status remains unclear in continuous ambulatory peritoneal dialysis (CAPD) patients.

Methods 158 prevalent CAPD patients with a median level of dp-ucMGP of 1093 (752, 1485) pmol/L were enrolled. Patient outcomes including all-cause mortality and cardiovascular events (CVEs) were recorded during follow-up. Survival curves were performed using Kaplan–Meier method, and the influences of dp-ucMGP on outcomes were analyzed by Cox regression models.

Results A total of 59 deaths and 82 new episodes of CVEs occurred during median follow-up of 31.4 ± 13.1 months (range: 3.8–48.0 months). Kaplan–Meier analysis revealed patients with higher dp-ucMGP levels (≥ 1093 pmol/L) had an increased risk for both mortality ($P = 0.005$) and CVEs ($P < 0.001$). Multivariable Cox regression confirmed that higher dp-ucMGP levels increase the mortality risk [hazard ratio (HR), 1.763; 95% CI 1.045–3.291] and CVEs (HR, 1.846; 95% CI 1.074–3.172). For every 100 pmol/L increase in serum dp-ucMGP, the adjusted HRs for mortality and CVEs were 1.054 (95% CI 1.008–1.106) and 1.034 (95% CI 1.012–1.089), respectively.

Conclusions Vitamin K deficiency, as expressed by high dp-ucMGP levels, showed independently associations with mortality and CVEs in CAPD patients.

Keywords Vitamin K status · Desphospho-uncarboxylated matrix GLA protein · Mortality · Peritoneal dialysis

Introduction

Cardiovascular complications are highly prevalent in patients undergoing dialysis with end-stage renal disease (ESRD) [1–3]. The excessive cardiovascular risk is contributed to conventional and novel risk factors including cardiovascular calcification (CVC) [4].

Vitamin K is mainly known as an agent involved in blood coagulation, maintaining the activity of coagulation factors in the liver. Recently, epidemiological studies suggested that vitamin K deficiency is associated with several diseases, including osteoporosis and vascular calcification [5]. Studies both in vitro and in vivo have demonstrated vitamin K as a pivotal regulator of CVC, via carboxylation of vitamin K-dependent proteins such as matrix GLA protein (MGP) [6–9]. Desphospho-uncarboxylated MGP (dp-ucMGP), a fully inactive form of phosphorylated and dephosphorylated MGP, was thought to be associated with the vitamin K status

Qing dong Xu and Huankai Guo have contributed equally to this work.

✉ Qingdong Xu
xqd82@163.com

[1] Department of Nephrology, Jiangmen Central Hospital, Affiliated Jiangmen Hospital of Sun Yat-sen University, Guangdong, People's Republic of China

[2] Department of Nephrology, Central Municipal Hospital of Huizhou, Guangdong, People's Republic of China

[3] Clinical Trials Unit, The First Affiliated Hospital, Sun Yat-sen University, Guangdong, People's Republic of China

[4] Department of Nephrology, the 2nd Affiliated Hospital of Guangzhou Medical University, Guangdong, People's Republic of China

[10–13]. It has been reported that a high vitamin K status resulted in lower dp-ucMGP levels, which in turn reduced CVC [14, 15]. In line with these results, many studies have attempted to investigate the effect of the vitamin K status on clinical outcomes, both in the general population [16] and in high-risk populations such as patients with diabetes [17], chronic vascular diseases [18, 19], or undergoing chronic hemodialysis [20, 21], which showed a potential positive relationship between dp-ucMGP and the risk of all-cause or cardiovascular mortality.

To our knowledge, few reports have investigated the predictive value of the vitamin K status in peritoneal dialysis (PD) patients. We thus evaluated the clinical relevance between the vitamin K status and adverse outcomes in PD patients.

Methods

Study population

This study was approved by the Institutional Review Board of Jiangmen Central Hospital, Affiliated Jiangmen Hospital of Sun Yat-Sen University (June 1, 2012), and informed consent was obtained from all participants before enrollment.

A total of 206 patients who underwent continuous ambulatory peritoneal dialysis (CAPD) for more than 3 months at our center from July 1, 2013 to December 31, 2013 were retrieved from our database. All patients were treated with Dianeal solution (Baxter China Ltd., Guangzhou, China). Exclusion criteria were patients aged < 18 years ($n = 2$); with incomplete data ($n = 27$); on warfarin treatment ($n = 1$); with underlying malignancy ($n = 4$), congenital or chronic rheumatic heart disease ($n = 3$); or with acute infection complications or acute cardiovascular events (CVEs) 1 month before the study ($n = 11$). Ultimately, a total of 158 patients were evaluated in the present study.

Demographic and clinical data

Variables included demographic characteristics (age and gender), body mass index (BMI), etiology of kidney disease, presence of diabetes and cardiovascular disease (CVD; defined as history of either ischemic heart disease, congestive heart failure, ischemic or hemorrhagic stroke, or peripheral vascular disease) [22, 23].

Fasting serum samples were collected for the detection of biochemical data [calcium, phosphate, intact parathyroid hormone (iPTH), hemoglobin, albumin, high-sensitivity CRP (hs-CRP), cholesterol, triglycerides, and dp-ucMGP]. Serum dp-ucMGP, determined with a dual-antibody ("sandwich") ELISA technique, is based on monoclonal antibody detection against the non-carboxylated sequence at amino acids 35 to 49 in human MGP (VitaK BV, Maastricht, The Netherlands). Adequacy of dialysis (total weekly urea clearance, Kt/Vurea) was calculated using a standard method described previously [24]. Residual glomerular filtration rate (rGFR) was measured as the mean of 24-h urinary urea and creatinine clearance [25].

Echocardiography

Echocardiography was performed by a skilled echocardiographist according to the American Society of Echocardiography recommendations [26]. The echocardiographist was blind to all clinical details. Two-dimensional guided M-mode echocardiography images were recorded from standardized views. We defined valvular calcification as bright echoes > 1 mm on one or more cusps of the cardiac valve [27, 28].

Outcomes

The primary outcomes included all-cause mortality and fatal or non-fatal CVEs. Fatal or non-fatal CVEs included electrocardiographically documented myocardial ischemia or infarction, arrhythmia, acute heart failure, ischemic or hemorrhagic stroke, peripheral vascular disease, or sudden death [29]. As non-fatal events can occur repeatedly, the first new episode of event was recorded. All patients were followed up until the occurrence of one of the following events: a primary outcome (death or CVEs), kidney transplantation, transfer to hemodialysis or loss to follow-up, or end of follow-up (June 30, 2017).

Statistical analyses

Summary statistics by median level of serum dp-ucMGP (1093 pmol/L) were expressed as percentages of categorical data, mean ± standard deviation (SD), or median (interquartile range, IQR), according to the distribution. Between-group comparisons were performed using *t* test, Mann–Whitney U, or Chi-Square test when appropriate. The associations of the serum dp-ucMGP level with respect to other variables were carried out by bivariate correlation analysis, with Pearson's correlation coefficients test for quantitative variables and Spearman's correlation coefficients for categorical variables. Multivariable linear regression analysis was further constructed to analyze the independent factors correlated with the serum dp-ucMGP level. Survival estimates for all-cause mortality and CVEs were performed using the Kaplan–Meier and Cox proportional hazards model, with the function of the serum dp-ucMGP level either categorized by the median or as a continuous variable. Factors with $P < 0.05$ in the univariate analysis were included in the multivariable analysis to determine

independent predictors of outcomes. Statistical analyses were performed using SPSS software, version 13.0 (SPSS, Chicago, IL, USA). Statistical significance was defined as a two-side *P* value less than 0.05.

Results

Baseline characteristics of study cohort

A total of 158 patients undergoing CAPD were included in this study. The mean age was 53.17 ± 12.89 years, and 46.8% were female. The median level of dp-ucMGP was 1093 (752, 1485) pmol/L. Table 1 shows the characteristics of the study cohort sorted by the median dp-ucMGP level. Patients with higher serum dp-ucMGP levels were significantly older, with a higher incidence of valvular calcification. They also had lower serum albumin levels and higher hs-CRP levels. No significant difference was observed between the two groups in gender, BMI, etiology of ESRD, presence of diabetes, hypertension or pre-existing CVD, serum level of Ca × P product, iPTH, hemoglobin, cholesterol, and triglycerides. Furthermore, neither prescription use ($CaCO_3$, active vitamin D analog) nor dialysis-specific parameters (dialysis vintage, rGFR, and Kt/Vurea) were significantly different between the two groups.

Univariate analysis showed that the serum dp-ucMGP level positively correlated with age, hs-CRP, and valvular calcification, whereas it negatively correlated with the serum albumin level (Table 2). Multivariate analysis showed that the serum dp-ucMGP level remained positively association with hs-CRP (β = 0.221; *P* = 0.003) and valvular calcification

Table 1 Clinical characteristics of the study cohort stratified by median of dp-ucMGP

	All patients (*n* = 158)	dp-ucMGP < 1093 pmol/L (*n* = 79)	dp-ucMGP ≥ 1093 pmol/L (*n* = 79)	*P* value
Age (years)	53.17 ± 12.89	51.38 ± 12.39	54.96 ± 13.21	0.031
Female (%)	74 (46.8)	33 (41.8)	41 (51.9)	0.202
BMI (kg/m^2)	21.58 ± 2.75	21.82 ± 2.96	21.34 ± 2.51	0.266
Etiology of ESRD (%)				
CGN (%)	73 (46.2)	42 (53.2)	31 (39.2)	0.244
DN (%)	49 (31.0)	22 (27.8)	27 (34.2)	
HN (%)	18 (11.4)	9 (11.4)	9 (11.4)	
Others (%)	18 (11.4)	6 (7.6)	12 (15.2)	
Diabetes (%)	51 (32.3)	20 (25.3)	31 (39.2)	0.063
Pre-existing CVD (%)	46 (29.1)	15 (19.0)	31 (39.2)	0.005
Valvular calcification (%)	53 (33.5)	18 (22.8)	35 (44.3)	0.004
Hypertension (%)	140 (88.6)	68 (86.1)	72 (91.1)	0.317
Prescription (%)				
CCB	104 (65.8)	48 (60.8)	56 (70.9)	0.180
Active vitamin D analog	103 (65.2)	47 (59.5)	56 (70.9)	0.133
Dialysis-specific parameters				
Dialysis vintage (months, IQR)	18.0 (11.8, 25.2)	17.7 (11.0, 24.0)	18.3 (12.0, 26.3)	0.410
rGFR (ml/min/1.73 m^2, IQR)	1.13 (0, 3.14)	0.95 (0, 3.63)	1.20 (0, 3.27)	0.688
Total Kt/Vurea	2.19 ± 0.45	2.20 ± 0.45	2.19 ± 0.45	0.835
Laboratory findings				
Ca × P product (mg^2/dL^2)	54.12 ± 13.66	53.23 ± 14.21	55.01 ± 13.11	0.413
iPTH (pg/Ml, IQR)	320.9 (151.5, 557.6)	324.9 (132.7, 589.9)	320.9 (171.9, 557.4)	0.746
Hemoglobin (g/L)	101. 7 ± 21.2	104.2 ± 21.1	99.2 ± 21.3	0.216
Serum albumin (g/L)	36.36 ± 4.94	37.23 ± 4.73	35.50 ± 5.01	0.021
hs-CRP (mg/L, IQR)	2.88 (0.92, 7.82)	2.21 (0.78, 6.04)	5.80 (1.29, 9.17)	0.006
Cholesterol (mmol/L)	4.73 ± 1.29	4.78 ± 1.43	4.69 ± 1.14	0.648
Triglycerides (mmol/L, IQR)	1.32 (0.95, 1.81)	1.33 (0.95, 1.97)	1.30 (0.92, 1.70)	0.593
dp-ucMGP (pmol/L, IQR)	1093 (752, 1485)	756 (586, 888)	1484 (1286, 1938)	< 0.001

Values expressed as mean ± SD, percent, or median (interquartile range), or the number (percentage) for binary variables

dp-ucMGP desphospho-uncarboxylated MGP; *BMI* body mass index; *ESRD* end-stage renal disease; *CGN* chronic glomerulonephritis; *DN* diabetic nephropathy; *HN* hypertensive nephrosclerosis; *CVD* cardiovascular disease; *CCB* calcium-containing phosphate binder; *IQR* interquartile range; *rGFR* residual glomerular filtration rate; *iPTH* intact parathyroid hormone; *hs-CRP* high-sensitivity C-reactive protein

Table 2 Variables correlation with baseline serum dp-ucMGP levels

Variables	*r*	*P* value
Age (years)	0.234	0.003
Female	0.066	0.410
BMI (kg/m^2)	−0.129	0.106
Diabetes	0.101	0.151
Previous CVD	0.061	0.319
Valvular calcification	0.345	< 0.001
Hypertension	0.039	0.628
Prescription of CCB	0.094	0.241
Prescription of active vitamin D analog	0.129	0.105
Dialysis vintage (months)	0.099	0.217
rGFR (ml/min/1.73 m^2)	0.015	0.852
Total Kt/Vurea	−0.050	0.537
Ca × P product (mg^2/dL^2)	0.006	0.941
iPTH (pg/mL)	−0.049	0.545
Hemoglobin (g/L)	−0.056	0.487
Serum albumin (g/L)	−0.176	0.007
hs-CRP (mg/L)	0.317	< 0.001
Cholesterol (mmol/L)	0.029	0.714
Triglycerides (mmol/L)	0.008	0.925

Abbreviations and definitions as listed in Table 1

Table 3 Multivariate analysis of clinical measures associated with baseline serum dp-ucMGP levels

Variables	Standard error	Standardized β	*t*	*P* value
Age (years)	3.725	0.057	0.709	0.480
Valvular calcification	97.92	0.271	3.472	0.001
Serum albumin (g/L)	9.055	−0.179	−2.267	0.019
hs-CRP (mg/L)	10.31	0.221	2.967	0.003

Abbreviations and definitions as listed in Table 1

(β = 0.271; *P* = 0.001), and negatively association with serum albumin (β = − 0.179; *P* = 0.019; Table 3).

Relation to clinical outcomes

During the median follow-up of 31.4 ± 13.1 months (range: 3.8–48.0 months), 59 patients (37.3%) died, 36 (61.0%) of which were attributed to CVEs, and 82 patients developed one or more fatal or non-fatal CVEs (Table 4). A significant higher incidence of all-cause mortality (48.1% vs. 26.6%, p = 0.005) and CVEs (64.6% vs. 39.2%, p = 0.001) were observed in patients with dp-ucMGP levels ≥ 1093 pmol/L. Also, patients with higher dp-ucMGP levels had a significant higher incidence of stroke (21.5% vs. 10.1%, p = 0.05), and a borderline significant association of high dp-ucMGP levels with ischemic stroke was observed (16.5% vs. 7.6%, p = 0.087). Kaplan–Meier analysis revealed that high dp-ucMGP levels (≥ 1093 pmol/L) were associated with an increased risk for both all-cause mortality and CVEs (Fig. 1; log-rank test: *P* = 0.005 and *P* < 0.001, respectively). The univariate Cox regression analysis showed a hazard ration (HR) of 2.116 (95% CI: 1.239–3.615) for all-cause mortality and a HR of 2.786 (95% CI: 1.758–4.359) for CVEs (Table 5). Regardless of the adjustment method used, the high serum dp-ucMGP level was significantly associated with higher all-cause mortality and CVEs. In model 3, which is a maximally adjusted model including age, gender, BMI, diabetes, previous CVD, hypertension, prescription of CCB, active vitamin D analog, dialysis vintage, rGFR, total Kt/Vurea, Ca × P product, iPTH, hemoglobin, cholesterol, triglycerides, and MICS components (serum albumin, hs-CRP, and valvular calcification), the adjusted HRs for all-cause mortality and CVEs were 1.763 (95% CI: 1.045–3.291) and 1.846 (95% CI: 1.074–3.172), respectively. Similar results were observed when the dp-ucMGP level was used as continuous variable, for every 100 pmol/L increase in the serum level of dp-ucMGP, the adjusted HRs for mortality and CVEs were 1.054 (95% CI: 1.008–1.106) and 1.034 (95% CI: 1.012–1.089), respectively.

Discussion

The current study revealed that among patients undergoing CAPD, a poor vitamin K status, as expressed by high dp-ucMGP levels, correlated with malnutrition, inflammation, and valvular calcification, and thereby conferred to an increased risk of mortality and CVEs, which is independent of traditional CVD risk factors.

Recently, vitamin K deficiency has been considered as a novel risk factor in CKD population [21, 30]. A significant amount of evidence has revealed a high prevalence of vitamin K deficiency as high as 60–90% in patients at all stages of CKD [31], with a robust inverse association between eGFR and serum dp-ucMGP levels. Our data confirmed high plasma dp-ucMGP levels in CAPD patients when compared with that in healthy subjects (448 ± 167 pmol/L) [32, 33]. The factors associated with vitamin K deficiency in CKD patients are complex as many factors are involved, among which a reduced dietary intake may be a vital factor. Generally, CKD patients are recommended a dietary regimen with potassium-rich foods, which are usually rich in vitamin K [34, 35]. Moreover, anorexia and poor appetite are common in these patients, resulting in a compromised overall energy intake and subsequent malnutrition. Indeed, our results showed a robust association between low serum albumin levels and high dp-ucMGP, which is consistent with

Table 4 All-cause mortality, CV mortality, and CVE in patients with different serum dp-ucMGP levels

	All patients ($n=158$)	dp-ucMGP < 1093 pmol/L ($n=79$)	dp-ucMGP ≥ 1093 pmol/L ($n=79$)	P value[a]
All-cause mortality	59 (37.3)	21 (26.6)	38 (48.1)	0.005
Cardiovascular mortality	36 (22.8)	16 (20.3)	20 (25.3)	0.448
Cardiovascular events (fatal and unfatal)	82 (51.9)	31 (39.2)	51 (64.6)	0.001
Angina pectoris	5 (3.2)	2 (2.5)	3 (3.8)	1.0
Acute myocardial infarction	13 (8.2)	5 (6.3)	8 (10.1)	0.564
Acute heart failure	31 (19.6)	12 (15.2)	19 (24.1)	0.229
Arrhythmia	6 (3.8)	3 (3.8)	3 (3.8)	1.0
Stroke	25 (15.8)	8 (10.1)	17 (21.5)	0.05
Ischemic stroke	19 (12.0)	6 (7.6)	13 (16.5)	0.087
Hemorrhagic stroke	6 (3.8)	2 (2.5)	4 (5.0)	0.681
Peripheral vascular accident	2 (1.3)	1 (1.3)	1 (1.3)	1.0

Expressed as number (%)

[a]Chi-Square test was performed between patients with dp-ucMGP < 1093 pmol/L and dp-ucMGP ≥ 1093 pmol/L

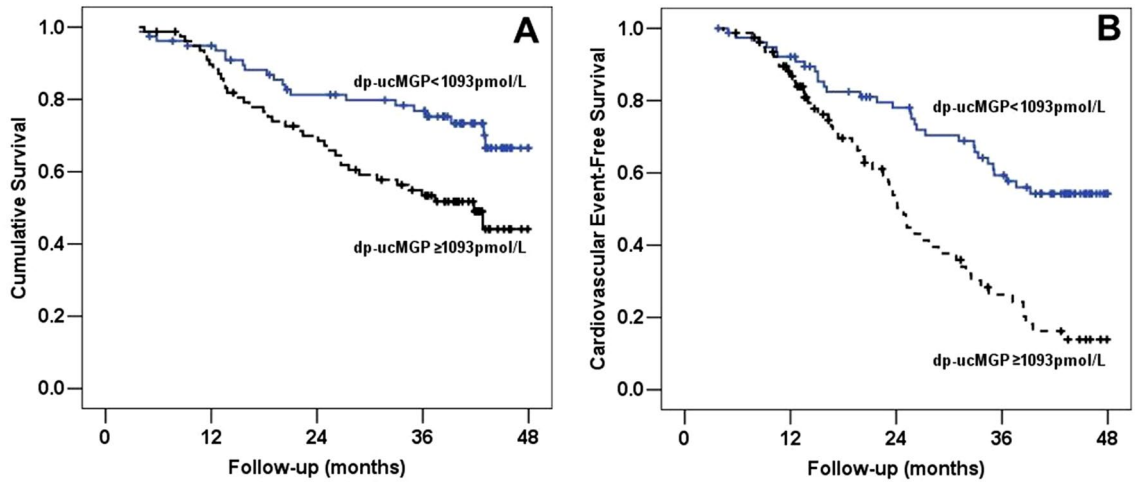

Fig. 1 High dp-ucMGP levels predict all-cause mortality and cardiovascular events in peritoneal dialysis patients. Kaplan–Meier analysis of all-cause (**a**) and cardiovascular events (**b**) in patients with low and high levels of dp-ucMGP (grouped according to median), log-rank test: $P=0.005$ and $P<0.001$, respectively

the study of Delanaye et al., emphasizing the correlation between malnutrition and vitamin K deficiency [36].

Intriguingly, our findings also showed an independent association between vitamin K status and inflammatory marker (hs-CRP) in multivariate analysis, a relationship that has also been found in previous studies in a general population cohort [37] and kidney transplant recipients [38]. A potential anti-inflammatory effect of vitamin K has previously been shown through inhibition of interleukin-6 in lipopolysaccharide-treated fibroblasts [39]. Furthermore, an in vitro study has shown an increment in expression of inflammatory genes with a vitamin K-deficient diet, and this inflammatory response was reversed by vitamin K1-supplemented diets [40].

Other than malnutrition and inflammation, a reduced renal function may also facilitate the poor vitamin K status in CKD patients [30]. However, no association between residual renal function and dp-ucMGP was seen in our patients. Also, we found no relationship between serum dp-ucMGP and dialysis indexes, including dialysis vintage and Kt/Vurea, suggesting the poor renal function of our prevalent PD patients or PD itself is insufficient for developing a significant discrepancy in the clearance or production of serum dp-ucMGP, which needed to be verified in future prospective study.

Cardiovascular disease remains exceedingly common in dialysis patients [1–3]. Despite the progress in the understanding of CVD in these populations, its pathophysiology

Table 5 Crude and adjusted Hazard ratios (95%CI) for the association of dp-ucMGP with all-cause and incident cardiovascular events among PD patients

	Crude	Adjusted		
		Model 1	Model 2	Model 3
All-cause mortality				
Continuous model (per 100 pmol/L increase)	1.067 (1.027–1.108)	1.040 (1.001–1.081)	1.058 (1.013–1.106)	1.054 (1.008–1.106)
dp-ucMGP < 1093 pmol/L	1.00	1.00	1.00	1.00
dp-ucMGP ≥ 1093 pmol/L	2.116 (1.239–3.615)	1.775 (1.024–3.076)	1.845 (1.062–3.494)	1.763 (1.045–3.291)
Cardiovascular events				
Continuous model (per 100 pmol/L increase)	1.084 (1.039–1.215)	1.061 (1.032–1.178)	1.042 (1.026–1.124)	1.034 (1.012–1.089)
dp-ucMGP < 1093 pmol/L	1.00	1.00	1.00	1.00
dp-ucMGP ≥ 1093 pmol/L	2.786 (1.758–4.359)	2.506 (1.575–3.988)	1.780 (1.064–2.978)	1.846 (1.074–3.172)

Model 1 adjusted for epidemiologic parameters including age, gender

Model 2 adjusted for all model 1 parameters plus BMI, diabetes, previous CVD, hypertension, *prescription* of CCB, active vitamin D analog, dialysis vintage, rGFR, total Kt/Vurea, Ca × P product, iPTH, hemoglobin, cholesterol, triglycerides

Model 3 adjusted for all model 2 parameters plus serum albumin, hs-CRP, valvular calcification

has not been fully elucidated. Recently, CVC has been increasingly recognized as a key player in this devastating clinical outcome [3, 4]. In addition, emerging evidence has suggested vitamin K deficiency as a link between vascular calcification and CKD [36, 41]. In this regard, studies both in vitro and in vivo have demonstrated that high dp-ucMGP levels, as a sensitive marker of vitamin K deficiency, correlated with more ectopic calcification [10, 12, 42]. Accordingly, several epidemiological studies have attempted to investigate the effect of the vitamin K status on clinical outcomes, both in the general population [16] and in high-risk populations such as patients with diabetes [17], chronic vascular disease [18, 19], or chronic hemodialysis [20, 21]. These studies showed potential positive clinical relevance between dp-ucMGP and higher mortality risk, especially cardiovascular mortality. Likewise, our study confirmed a robust positive relationship between dp-ucMGP and a higher rate of all-cause mortality in PD patients. Compared with patients with low dp-ucMGP, patients with dp-ucMGP levels above the median level had more than 70% increment in mortality risk independently of conventional risk profiles. Importantly, we extended these results by establishing that high dp-ucMGP levels, beyond conventional risk factors, are also associated with incremental subsequent CVEs risk. In particular, this association was pronounced for the subtype of stroke, especially in terms of ischemic stroke. We speculate this association between vitamin K status and stroke might have something to do with ectopic calcification. Actually, numerous population-based studies have reported a significant higher risk of ischemic stroke in patients with ectopic calcification [43–45]. However, a recent study in general population found no association between vitamin K (dp-ucMGP) and stroke [46], which seemed to differ from our study. The discrepancy in results might be attributable to different populations. As mentioned above, our patients had markedly elevated dp-ucMGP levels as compared with healthy subjects [32, 33]. Also, the relatively small variation in dp-ucMGP levels in healthy subjects may limit the ability of detecting an association between dp-ucMGP levels and stroke. Additionally, inconsistent with a relatively few prevalence of CVC in healthy population, a markedly higher prevalence of CVC in our high-risk patients may contribute to stroke, as was in line with previous studies [44, 45]. Concerning our findings and previous reports, we concluded that a poor vitamin K status, expressed by a high level of dp-ucMGP, could be a pivotal risk factor for CVD, especially ischemic stroke, in PD patients.

Though this study is the first to explore the association between dp-ucMGP and mortality and CVEs in PD patients, there are some limitations to it. First, the nature of cross-sectional design does not allow causal inferences. Second, a single measurement may not reflect the time-average or time-variation in exposure of serum dp-ucMGP. Furthermore, our study included only prevalent but not incident patients and may introduce selection bias. Finally, as a result of the relatively small sample size and limited numbers of events, we may have had limited power to detect a somewhat weaker association, especially in terms of the associations between dp-ucMGP and CVE subtype. Further studies with larger sample sizes should thus be conducted to clarify this issue widely and deeply.

In conclusion, our results showed that dp-ucMGP, a vitamin K status marker, was associated with higher mortality and CVD risk in CAPD patients. Further studies are needed to determine whether vitamin K supplementation, to increase the rate of MGP carboxylation, and thus decrease dp-ucMGP levels, leads to a regression in ectopic

calcification, and subsequently to a reduction in the mortality/CVD risk of patients on CAPD.

Acknowledgements We express our deepest gratitude to all patients who participated in the study and all nephrologists and nurses in our PD center for their helpful assistance.

Funding This research was funded by Medical Scientific Research Foundation of Guangdong Province, China (Grant No. 2015122194432203-A201563).

Compliance with ethical standards

Conflict of interest The authors have no financial conflicts of interest to declare.

References

1. Ortiz A, Covic A, Fliser D, Fouque D, Goldsmith D, Kanbay M, Mallamaci F, Massy ZA, Rossignol P, Vanholder R, Wiecek A, Zoccali C, London GM (2014) Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. Lancet 383:1831–1843
2. Sarnak MJ, Foley RN (2011) Cardiovascular mortality in the general population versus dialysis: a glass half full or empty? Am J Kidney Dis 58:4–6
3. Mavrakanas TA, Charytan DM (2016) Cardiovascular complications in chronic dialysis patients. Curr Opin Nephrol Hypertens 25:536–544
4. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H (2003) Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant 18:1731–1740
5. Fusaro M, Mereu MC, Aghi A, Iervasi G, Gallieni M (2017) Vitamin K and bone. Clin Cases Miner Bone Metab 14:200–206
6. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, Karsenty G (1997) Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature 386:78–81
7. Munroe PB, Olgunturk RO, Fryns JP, Van Maldergem L, Ziereisen F, Yuksel B, Gardiner RM, Chung E (1999) Mutations in the gene encoding the human matrix Gla protein cause keutel syndrome. Nat Genet 21:142–144
8. Murshed M, Schinke T, McKee MD, Karsenty G (2004) Extracellular matrix mineralization is regulated locally; different roles of two Gla-containing proteins. J Cell Biol 165:625–630
9. Schurgers LJ, Spronk HM, Skepper JN, Hackeng TM, Shanahan CM, Vermeer C, Weissberg PL, Proudfoot D (2007) Post-translational modifications regulate matrix Gla protein function: importance for inhibition of vascular smooth muscle cell calcification. J Thromb Haemost 5:2503–2511
10. Rennenberg RJ, de Leeuw PW, Kessels AG, Schurgers LJ, Vermeer C, van Engelshoven JM, Kemerink GJ, Kroon AA (2010) Calcium scores and matrix Gla protein levels: association with vitamin K status. Eur J Clin Invest 40:344–349
11. Shea MK, O'Donnell CJ, Vermeer C, Magdeleyns EJ, Crosier MD, Gundberg CM, Ordovas JM, Kritchevsky SB, Booth SL (2011) Circulating uncarboxylated matrix Gla protein is associated with vitamin K nutritional status, but not coronary artery calcium, in older adults. J Nutr 141:1529–1534
12. Dalmeijer GW, van der Schouw YT, Vermeer C, Magdeleyns EJ, Schurgers LJ, Beulens JW (2013) Circulating matrix Gla protein is associated with coronary artery calcification and vitamin K status in healthy women. J Nutr Biochem 24:624–628
13. Cranenburg EC, Koos R, Schurgers LJ, Magdeleyns EJ, Schoonbrood TH, Landewe RB, Brandenburg VM, Bekers O, Vermeer C (2010) Characterisation and potential diagnostic value of circulating matrix Gla protein (MGP) species. Thromb Haemost 104:811–822
14. Westenfeld R, Krueger T, Schlieper G, Cranenburg EC, Magdeleyns EJ, Heidenreich S, Holzmann S, Vermeer C, Jahnen-Dechent W, Ketteler M, Floege J, Schurgers LJ (2012) Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. Am J Kidney Dis 59:186–195
15. Theuwissen E, Cranenburg EC, Knapen MH, Magdeleyns EJ, Teunissen KJ, Schurgers LJ, Smit E, Vermeer C (2012) Low-dose menaquinone-7 supplementation improved extra-hepatic vitamin K status, but had no effect on thrombin generation in healthy subjects. Br J Nutr 108:1652–1657
16. Nimptsch K, Rohrmann S, Kaaks R, Linseisen J (2010) Dietary vitamin K intake in relation to cancer incidence and mortality: results from the heidelberg cohort of the european prospective investigation into cancer and nutrition (EPIC-Heidelberg). Am J Clin Nutr 91:1348–1358
17. Dalmeijer GW, van der Schouw YT, Magdeleyns EJ, Vermeer C, Verschuren WM, Boer JM, Beulens JW (2013) Matrix Gla protein species and risk of cardiovascular events in type 2 diabetic patients. Diabetes Care 36:3766–3771
18. Ueland T, Gullestad L, Dahl CP, Aukrust P, Aakhus S, Solberg OG, Vermeer C, Schurgers LJ (2010) Undercarboxylated matrix Gla protein is associated with indices of heart failure and mortality in symptomatic aortic stenosis. J Intern Med 268:483–492
19. Mayer OJ, Seidlerova J, Bruthans J, Filipovsky J, Timoracka K, Vanek J, Cerna L, Wohlfahrt P, Cifkova R, Theuwissen E, Vermeer C (2014) Desphospho-uncarboxylated matrix Gla-protein is associated with mortality risk in patients with chronic stable vascular disease. Atherosclerosis 235:162–168
20. Schlieper G, Westenfeld R, Kruger T, Cranenburg EC, Magdeleyns EJ, Brandenburg VM, Djuric Z, Damjanovic T, Ketteler M, Vermeer C, Dimkovic N, Floege J, Schurgers LJ (2011) Circulating nonphosphorylated carboxylated matrix Gla protein predicts survival in ESRD. J Am Soc Nephrol 22:387–395
21. Elliott MJ, Booth SL, Hopman WM, Holden RM (2014) Assessment of potential biomarkers of subclinical vitamin K deficiency in patients with end-stage kidney disease. Can J Kidney Health Dis 1:13
22. Weiner DE, Tighiouart H, Vlagopoulos PT, Griffith JL, Salem DN, Levey AS, Sarnak MJ (2005) Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. J Am Soc Nephrol 16:1803–1810
23. Xu Q, Xiong L, Fan L, Xu F, Yang Y, Li H, Peng X, Cao S, Zheng Z, Yang X, Yu X, Mao H (2015) Association of pulmonary hypertension with mortality in incident peritoneal dialysis patients. Perit Dial Int 35:537–544
24. Rocco MV, Jordan JR, Burkart JM (1994) Determination of peritoneal transport characteristics with 24-hour dialysate collections: dialysis adequacy and transport test. J Am Soc Nephrol 5:1333–1338
25. van Olden RW, Krediet RT, Struijk DG, Arisz L (1996) Measurement of residual renal function in patients treated with continuous ambulatory peritoneal dialysis. J Am Soc Nephrol 7:745–750
26. Sahn DJ, DeMaria A, Kisslo J, Weyman A (1978) Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 58:1072–1083
27. Tarrass F, Benjelloun M, Zamd M, Medkouri G, Hachim K, Benghanem MG, Ramdani B (2006) Heart valve calcifications

in patients with end-stage renal disease: analysis for risk factors. Nephrology (Carlton) 11:494–496
28. Choi MJ, Kim JK, Kim SG, Kim SE, Kim SJ, Kim HJ, Song YR (2013) Association between cardiac valvular calcification and myocardial ischemia in asymptomatic high-risk patients with end-stage renal disease. Atherosclerosis 229:369–373
29. Wang AY, Woo J, Lam CW, Wang M, Chan IH, Gao P, Lui SF, Li PK, Sanderson JE (2005) Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant 20:1676–1685
30. Kurnatowska I, Grzelak P, Masajtis-Zagajewska A, Kaczmarska M, Stefanczyk L, Vermeer C, Maresz K, Nowicki M (2016) Plasma desphospho-uncarboxylated matrix Gla protein as a marker of kidney damage and cardiovascular risk in advanced stage of chronic kidney disease. Kidney Blood Press Res 41:231–239
31. Fusaro M, Plebani M, Iervasi G, Gallieni M (2017) Vitamin K deficiency in chronic kidney disease: evidence is building up. Am J Nephrol 45:1–3
32. Dalmeijer GW, van der Schouw YT, Magdeleyns E, Ahmed N, Vermeer C, Beulens JW (2012) The effect of menaquinone-7 supplementation on circulating species of matrix Gla protein. Atherosclerosis 225:397–402
33. Dam V, Dalmeijer GW, Vermeer C, Drummen NE, Knapen MH, van der Schouw YT, Beulens JW (2015) Association between vitamin K and the metabolic syndrome: a 10-year follow-up study in adults. J Clin Endocrinol Metab 100:2472–2479
34. Caluwe R, Vandecasteele S, Van Vlem B, Vermeer C, De Vriese AS (2014) Vitamin K2 supplementation in haemodialysis patients: a randomized dose-finding study. Nephrol Dial Transplant 29:1385–1390
35. Fusaro M, D'Alessandro C, Noale M, Tripepi G, Plebani M, Veronese N, Iervasi G, Giannini S, Rossini M, Tarroni G, Lucatello S, Vianello A, Santinello I, Bonfante L, Fabris F, Sella S, Piccoli A, Naso A, Ciurlino D, Aghi A, Gallieni M, Cupisti A (2017) Low vitamin K1 intake in haemodialysis patients. Clin Nutr 36:601–607
36. Delanaye P, Krzesinski JM, Warling X, Moonen M, Smelten N, Medart L, Pottel H, Cavalier E (2014) Dephosphorylated-uncarboxylated matrix Gla protein concentration is predictive of vitamin K status and is correlated with vascular calcification in a cohort of hemodialysis patients. BMC Nephrol 15:145
37. Shea MK, Booth SL, Massaro JM, Jacques PF, D'Agostino RS, Dawson-Hughes B, Ordovas JM, O'Donnell CJ, Kathiresan S, Keaney JJ, Vasan RS, Benjamin EJ (2008) Vitamin K and vitamin D status: associations with inflammatory markers in the framingham offspring study. Am J Epidemiol 167:313–320
38. Boxma PY, van den Berg E, Geleijnse JM, Laverman GD, Schurgers LJ, Vermeer C, Kema IP, Muskiet FA, Navis G, Bakker SJ, de Borst MH (2012) Vitamin K intake and plasma desphospho-uncarboxylated matrix Gla-protein levels in kidney transplant recipients. PLoS ONE 7:e47991
39. Reddi K, Henderson B, Meghji S, Wilson M, Poole S, Hopper C, Harris M, Hodges SJ (1995) Interleukin 6 production by lipopolysaccharide-stimulated human fibroblasts is potently inhibited by naphthoquinone (Vitamin K) compounds. Cytokine 7:287–290
40. Ohsaki Y, Shirakawa H, Hiwatashi K, Furukawa Y, Mizutani T, Komai M (2006) Vitamin K suppresses lipopolysaccharide-induced inflammation in the rat. Biosci Biotechnol Biochem 70:926–932
41. Schurgers LJ Vitamin K (2013) Key vitamin in controlling vascular calcification in chronic kidney disease. Kidney Int 83:782–784
42. Schurgers LJ, Barreto DV, Barreto FC, Liabeuf S, Renard C, Magdeleyns EJ, Vermeer C, Choukroun G, Massy ZA (2010) The circulating inactive form of matrix Gla protein is a surrogate marker for vascular calcification in chronic kidney disease: a preliminary report. Clin J Am Soc Nephrol 5:568–575
43. Vliegenthart R, Hollander M, Breteler MM, van der Kuip DA, Hofman A, Oudkerk M, Witteman JC (2002) Stroke is associated with coronary calcification as detected by electron-beam CT: the rotterdam coronary calcification study. Stroke 33:462–465
44. Benjamin EJ, Plehn JF, D'Agostino RB, Belanger AJ, Comai K, Fuller DL, Wolf PA, Levy D (1992) Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 327:374–379
45. De Marco M, Gerdts E, Casalnuovo G, Migliore T, Wachtell K, Boman K, Dahlof B, Olsen MH, Kizer JR, Devereux RB, de Simone G (2013) Mitral annular calcification and incident ischemic stroke in treated hypertensive patients: the life study. Am J Hypertens 26:567–573
46. Dalmeijer GW, van der Schouw YT, Magdeleyns EJ, Vermeer C, Verschuren WM, Boer JM, Beulens JW (2014) Circulating desphospho-uncarboxylated matrix gamma-carboxyglutamate protein and the risk of coronary heart disease and stroke. J Thromb Haemost 12:1028–1034