Vitamin K intake and status are low in hemodialysis patients

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Vitamin K is essential for the activity of γ-carboxyglutamate (Gla)-proteins including matrix Gla28 protein and osteocalcin; an inhibitor of vascular calcification and a bone matrix protein, respectively. Insufficient vitamin K intake leads to the production of non-carboxylated, inactive proteins and this could contribute to the high risk of vascular calcification in hemodialysis patients. To help resolve this, we measured vitamin K_1 and K_2 intake (4-day food record), and the vitamin K status in 40 hemodialysis patients. The intake was low in these patients (median 140 μg/day), especially on days of dialysis and the weekend as compared to intakes reported in a reference population of healthy adults (mean K_1 and K_2 intake 200 μg/day and 31 μg/day, respectively). Non-carboxylated bone and coagulation proteins were found to be elevated in 33 hemodialysis patients, indicating subclinical hepatic vitamin K deficiency. Additionally, very high non-carboxylated matrix Gla28 protein levels, endemic to all patients, suggest vascular vitamin K deficiency. Thus, compared to healthy individuals, hemodialysis patients have a poor overall vitamin K status due to low intake. A randomized controlled trial is needed to test whether vitamin K supplementation reduces the risk of arterial calcification and mortality in hemodialysis patients.

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Vitamin K is necessary for the function of proteins containing γ-carboxyglutamate (Gla) residues. Well-known vitamin K–dependent proteins (Gla proteins) are vitamin K–dependent coagulation factorsthat are mainly synthesized in the liver. Extrahepatic Gla proteins are osteocalcin (OC), synthesized in bone, and matrix Gla protein (MGP), synthesized in the vasculature and cartilage. Gla residues are formed during a vitamin K–dependent posttranslational carboxylation reaction and are essential for the activity of Gla proteins.[1] Insufficient dietary intake of vitamin K will lead to the production of uncarboxylated (i.e., inactive) proteins.[2]

MGP synthesized by vascular smooth muscle cells is the strongest physiological inhibitor of vascular calcification currently known. Deficiency of carboxylated MGP may contribute substantially to the development and progression of arterial calcification. Vascular calcifications are found in 60–80% of hemodialysis (HD) patients[3,4] and are associated with a high cardiovascular risk, independent of traditional atherogenic risk factors.[5,6] Areas of calcification in vascular tissue are associated with accumulation of uncarboxylated MGP species, which has also been found to precede the development of clinically overt calcification in children on dialysis.[7]

Vitamin K intake may be differentiated for the intake of vitamin K_1 (phylloquinone) and vitamin K_2 (group name for menaquinones). The estimated daily vitamin K_1 intake is 200 ± 98 μg and for vitamin K_2 it is 31 ± 7 μg in the general population.[8–10] Vitamin K_1 and K_2 content of food products has been extensively studied by our laboratory in the past,[11] resulting in a comprehensive dietary vitamin K_1 and K_2 database. Previous studies using this database demonstrated that intake of vitamin K_2 was inversely associated with cardiovascular calcification and mortality.[12–14]

Systemic vitamin K status can be determined by measuring (1) circulating vitamin K_1 and K_2 levels and (2) circulating inactive forms of vitamin K–dependent proteins. Intake of vitamin K–containing food products will readily influence measurements of circulating vitamin K levels. In contrast, measurements of uncarboxylated prothrombin (known as

protein induced by vitamin K absence/antagonism II (PIVKA-II)), uncarboxylated OC (ucOC), and desphospho-uncarboxylated (dp-uc) MGP will reflect utilization of vitamin K in tissues. We recently developed a new MGP assay to measure the dp-ucMGP species. First results show that this inactive, immature MGP species is suited to assess extrahepatic vitamin K status, particularly in the vasculature.[15]

In the present study, we aimed to investigate vitamin K_1 and K_2 intake as well as vitamin K status in HD patients. Vitamin K intake was estimated using a comprehensive dietary vitamin K database.[12,13] Vitamin K status was evaluated with measurements of circulating vitamin K_1 and K_2 levels, as well as of hepatic and extrahepatic vitamin K–dependent proteins, including PIVKA-II, MGP, and OC. With the present study, we expected to obtain new insights in different aspects of vitamin K metabolism in HD patients, and to increase our knowledge on the risk factors and pathogenesis of arterial calcification in these patients. Additionally, the results of this study will give an indication whether HD patients may benefit from an increased dietary vitamin K intake.

RESULTS

Patient population

Vitamin K intake and status were investigated in the entire cohort of 40 HD patients, consisting of 22 male and 18 female patients with a mean age of 62 ± 16 years. The median (range) dialysis vintage was 40 (4–385) months. All baseline characteristics of the patient population are presented in Table 1. As expected, the prevalence of cardiovascular disease (CVD) and hypertension was high. Control of calcium and phosphorus was quite well.

Table 1 | Characteristics of the 40 HD patients

Age (years)	65 (23-86)
Sex (male/female ratio)	22/18
Dialysis vintage (months)	40 (4–385)
Cause of ESRD	
Glomerular disease	9 (23)
Vascular disease, hypertension	10 (25)
Polycystic kidney disease	9 (23)
Diabetic kidney disease	2 (5)
Miscellaneous	6 (15)
Unknown	4 (10)
Hypertension	27 (67.5)
Diabetes	6 (15.0)
Current smoking	6 (15.0)
BMI (kg/m^2)	24.6 ± 3.7
Cardiovascular disease	15 (37.5)
Coronary artery disease	10 (25.0)
Peripheral artery disease	5 (12.5)
Cerebrovascular disease	4 (10)
History of renal transplantation	7 (17.5)
History of parathyroidectomy	5 (12.5)
Hb (mmol/l)	7.2 ± 0.8
Ca (mmol/l)	2.3 ± 0.2
P (mmol/l)	1.6 ± 0.3
Ca × P (nmol^2/l^2)	3.6 ± 0.8
AP (U/l)	72 ± 23
PTH (pmol/l)	15 (1–94)
Cholesterol (mmol/l)	4.0 ± 1.0
Triglycerides (mmol/l)	1.9 ± 0.8
Vitamin D supplementation	37 (92.5%)
Cinacalcet	4 (10)
Oral PB	35 (87.5)
>1 Oral PB	20 (50)
Ca-containing PB	16 (40)
Non-Ca-containing PB	29 (72.5)
Antihypertensive medication	28 (70)
>1 Medication	10 (25)
Iron supplementation	38 (95)
Darbepoetin alpha	37 (92.5)
Dietary intake	
Total energy (kJ/day)	7502 ± 2119
Total protein (g/day)	66 ± 8.5
Total fat (g/day)	62 ± 9
Monounsaturated fat (g/day)	21 ± 4
Polyunsaturated fat (g/day)	11 ± 3
Saturated fat (g/day)	26 ± 5
Fiber (g/day)	20 ± 12
Ca (mg/day)	814 ± 235
Vitamin C (mg/day)	68 ± 31

Abbreviations: AP, alkaline phosphatase; BMI, body mass index; Ca, calcium; ESRD, end-stage renal disease; Hb, hemoglobin; HD, hemodialysis; P, phosphorus; PB, phosphate binders; PTH, parathyroid hormone.
Data are given as mean ± s.d., median (range), or as absolute numbers with percentage of total between parentheses. Cardiovascular disease was defined as a history of coronary artery disease (myocardial infarction, angina pectoris, or evidence of obstructive disease by angiography), cerebrovascular disease (thrombotic stroke or transient ischemic attack), calcific aortic valve disease, or peripheral artery disease (a history of claudication or lower extremity revascularization).

Vitamin K intake

Total vitamin K intake of patients, registered during 4 days, was 140 (30–546) μg/day, consisting of 118 (18–494) μg/day vitamin K_1 and 21 (2–68) μg/day vitamin K_2 (Table 2). As expected, total vitamin K intake was predominantly determined by the intake of vitamin K_1. One-third of the patients ($n = 13$; 33%) had an average total vitamin K intake of < 100 μg/day. Total vitamin K intake was considerably lower on weekend days and dialysis days (Table 2), as compared with week days ($P = 0.003$ for both comparisons). These differences originated from differences in vitamin K_1 intake between these day-types ($P = 0.003$ for both comparisons), without significant differences in vitamin K_2 intake.

There were no differences in total vitamin K, K_1, or K_2 intake between males and females, or between patients with CVD or diabetes mellitus and patients without these conditions (Table 2). In correlation analysis, total vitamin K intake was not associated with age, body mass index, dialysis vintage, or any of the biochemical characteristics.

Vitamin K status

Serum vitamin K_1 concentration showed a broad range (Table 3). Almost half of the patients ($n = 18$; 45%) had circulating vitamin K_1 levels below the lower limit of normal range. Of the menaquinones (vitamin K_2), only MK-4 was measurable in low quantities in the blood. MK-5 through MK-10 were