Original Article

Bone is more susceptible to vitamin K deficiency than liver in the institutionalized elderly

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In Japan, γ-carboxylation of blood coagulation factors is the basis for determining adequate intake (AI) for vitamin K in Dietary Reference Intakes (DRIs) issued in 2010. Recently, vitamin K is also known to be essential for preventing fracture. In this study, relative susceptibility of liver and bone to vitamin K deficiency was studied. Thirty-seven elderly institutionalized subjects were evaluated for vitamin K status by measuring serum PIVKA (protein induced by vitamin K absence) –II and ucOC (undercarboxylated osteocalcin) levels, as sensitive markers for hepatic and skeletal vitamin K deficiency, respectively. Serum PIVKA-II and ucOC levels, with their cut-off values in the parentheses, were 20.2±8.9 mAUmL (28 mAU/mL) and 4.7±3.0 ng/mL (4.5 ng/mL), respectively. Median vitamin K intake was approximately 200 μg/day, which is more than 3 times higher than the current Japanese AI. Vitamin K intake was significantly correlated with serum PIVKA-II and ucOC/OC levels, but not with serum ucOC level. Although serum ucOC level is generally a good indicator for vitamin K status, multiple regression analysis revealed that elevated bone turnover marker significantly contributed to serum ucOC level. All subjects had vitamin K intake exceeding AI for vitamin K. Nevertheless, serum PIVKA-II and ucOC concentrations exceeded the cut-off value in 14% and 43% of subjects, respectively. The present findings suggest that vitamin K intake greater than the current AI is required for the skeletal health in the institutionalized elderly.

Key Words: vitamin K, adequate intake, γ-carboxylation, ucOC, PIVKA-II

INTRODUCTION

Gamma-glutamyl carboxylase (GGCX) catalyzes the conversion of glutamyl (Glu) residue into γ-carboxyglutamyl (Gla) residue in certain proteins. The most fundamental role of vitamin K is the one as a cofactor of GGCX.[1] Although GGCX is present in various tissues, its role in the liver has received most attention until recently. In the liver, conversion of Glu residue to Gla residue takes place in four of the blood coagulation factors (II, VII, IX, and X), by which they acquire calcium-binding ability and are activated.[1] Recently, attention have been focused on the physiological roles of vitamin K-dependent proteins in extrahepatic tissues such as bone and blood vessel.[2,3] Osteocalcin is produced by osteoblasts, the most abundant non-collagenous protein in the bone matrix. Through γ-carboxylation, osteocalcin gains hydroxyapatite-binding ability, and regulates bone mineralization.[2] Recent evidences strongly suggest that skeletal vitamin K deficiency increases the risk of hip fracture.[4] Matrix Gla protein (MGP); another vitamin K-dependent protein, is an inhibitor of vascular calcification.[5-7]

In the current Japanese Dietary Reference Intakes (DRIs) issued in 2010, Adequate Intake (AI) for vitamin K in the adult is uniformly 75 μg/day for men and 65 μg/day for women. These values however, carries some problems when applied to the study population.[8] First, they are based on data from America or Europe. Since nutrients intake is greatly dependent on nationality or dietary patterns, vitamin K status in the Japanese must be studied. Second, they are from healthy young volunteers, not from the elderly who are likely to have nutrients malabsorption. This is especially the case with fat-soluble vitamins including vitamin K due to various factors such as decreased secretion of bile acids and pancreatic juice, and reduced dietary fat intake.[8] Finally, AI for vitamin K was determined as the dose sufficient to maintain normal blood coagulation with little mentioning to bone.[8] Serum levels of protein induced by vitamin K absence-II (PIVKA-II) and undercarboxylated osteocalcin (ucOC) are sensitive markers for vitamin K deficiency in the liver and bone, respectively. Vitamin K status in the liver and bone

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can be separately evaluated by measuring these markers. By employing such methodology, previous studies have shown that much higher doses of vitamin K are needed for the γ-carboxylation of osteocalcin than for that of blood coagulation factors.[9,10]

Thus it is possible that an elderly judged to be vitamin K sufficient based on the current AI has skeletal vitamin K deficiency and increased fracture risk. In this paper, we have measured serum PIVKA-II and ucOC levels, assessed vitamin K intake, and studied the prevalence of vitamin K deficiency in the liver and bone in the institutionalized elderly.

MATERIALS AND METHODS

Subjects

The study subjects were 37 institutionalized elderly (male 8, female 29) in a nursing home, Kayu-Shirakawa. Exclusion criteria were routine medication that has potential interference with bone metabolism and vitamin K status such as warfarin. None had history of hepatic diseases. Detailed information about this study was given and written consent was obtained from the subject or the proxy. The study protocol was approved by the ethical committee in Kyoto Women's University.

Laboratory data

Blood was obtained after overnight fasting. After centrifugation, serum was kept frozen at –30°C until analysis. Serum PIVKA-II and ucOC levels were measured by electro chemiluminescence immunoassay (ECLIA) (Sanko Junyaku, Co, Ltd, Tokyo, Japan) as the markers of hepatic and skeletal vitamin K deficiency, respectively. Serum intact osteocalcin (intact OC) was measured by enzyme immunoassay (EIA) (Mitsubishi Yuka, Tokyo, Japan). The ucOC/OC was calculated as the ratio of ucOC to intact OC. Serum levels of tartrate-resistant acid phosphatase-5b (TRACP-5b) and bone specific alkaline phosphatase (BAP) were measured by EIA (DS Pharma Biomedical, Osaka, Japan) and chemiluminescence enzyme immunoassay (CLEIA) (Beckman Coulter Inc, Tokyo, Japan), respectively. TRACP-5b and BAP are markers of bone resorption and bone formation, respectively. The reference range of serum TRACP-5b was 170-590 mU/dL in male and 120-420 mU/dL in female, and that of serum BAP was 3.7-20.9 μg/L in male and 3.8-22.6 μg/L in female.

Nutrition intake study

Nutrient intake was assessed by food record method. The intake of vitamin K was calculated by multiplying the amount of vitamin K supplied from the institution with the average percentage intake. Based on these records, their intake of vitamin K was calculated using the software (Healthy Maker Pro 501, Mushroom Software Corp, Okayama, Japan). Vitamin K intake/kg body weight was also calculated, since 1 μg/kg of vitamin K is considered to be sufficient for maintaining normal coagulation in the adult according to the Japanese DRI 2010.[8]

Statistical analyses

Statistical analyses were performed using the SPSS 17.0 J for Windows (SPSS. Japan Inc, Tokyo, Japan). Association between variables was analyzed by Pearson's or Spearman rank correlation coefficient. Multiple regression analyses with stepwise method were performed to determine independent determinants for serum ucOC and ucOC/OC. Chi-square test was employed for categorical data.

RESULTS

Background profiles of the study subjects

The background profiles and biochemical data are shown in Table 1. Care level is a 5-grade score which is commonly used in the long-term care insurance in Japan with higher number indicating more intensive care needed. It was higher than grade 3 in 78% of subjects, indicating that they had low physical activity level. For example, most of the present subjects required wheelchair for transportation. In 27% of subjects, serum albumin level was lower than 3.5 g/dL, which is a generally accepted cut-off for malnutrition. Overall, nutritional parameters including the biochemical indicators and body mass index (BMI) remained within the reference range for most of the subjects. Thus, despite the elderly population and high level of care needed, the subjects' nutritional status was considered to be generally preserved. Although average serum TRACP-5b and BAP levels were within the reference range as a whole, 20% and 32% of subjects had serum BAP and TRACP-5b level above upper reference range, respectively. Serum PIVKA-II and ucOC levels were 20.2±8.9 mAU/mL and 4.7±3.0 ng/mL, respectively. All subjects were on orally consumed their meals. Although energy intakes were lower than estimated energy requirement (EER) of DRI in all men and 93% of women, the intake of macronutrients such as protein, fat and carbohydrates appeared appropriate for their age and sex. Average vitamin K intake was 194±51 (median; 197)

Table 1. Baseline data of the study subjects

	(M/F; 8/29, n=37)
Age (y)	85.1±8.2（87.0）
Care level	Median; 3 (min-max; 1-5)
Body weight (kg)	45.9±6.1（46.1）
Height (cm)	149.3±9.7（145.3）
BMI (kg/m^2)	20.6±2.5（20.0）
Serum Albumin (g/dL)	3.7±0.3（3.8）
Serum triglyceride (mg/dL)	119±41（118）
Serum total cholesterol (mg/dL)	198±49（191）
eGFR (ml/min./1.73m^2)	65.4±15.8（63.3）
Serum BAP (μg/L)	18.4±9.6（17.6）
Serum TRACP-5b (mU/dL)	365.2±124.9（372.0）
Serum ucOC (ng/mL)	4.7±3.0 (3.8)
Serum total OC (ng/mL)	6.1±3.1 (5.4)
ucOC / intact OC	0.81±0.36 (0.80)
Serum PIVKA-II (mAU/mL)	20.2±8.9 (18.0)
Energy intake (kcal)	1346±129 (1401)
Protein intake (g)	53.2±5.2 (55.4)
Fat intake (g)	35.6±3.6 (36.9)
Carbohydrates intake (g)	193.8±18.7 (199.4)
Vitamin K intake (μg/day)	194±51 (197)
Vitamin K intake/BW (μg/BW kg/day)	3.5±1.1 (3.4)

Data are expressed as mean±SD with the values in parentheses showing the median.

μg/day in the study population, 166±50 (median; 159) μg/day in males and 202±49 (median; 224) μg/day in females. It was approximately 220% and 310% of the AI in DRI in male and female subjects, respectively. All subjects had vitamin K intake exceeding AI. In addition, the vitamin K intake/kg body weight was 3.5±1.1 μg/day in the present study subjects, far exceeding 1μg/kg.

Correlations among vitamin K intake and serum PIVKA-II, OCs

Table 2 shows that vitamin K intake was significantly correlated with serum PIVKA-II and ucOC/OC levels, but not with serum ucOC concentrations. (Table 2)

Correlations among serum OCs and bone turnover markers

Serum TRACP-5b and BAP levels were significantly correlated with serum ucOC concentration, but not with ucOC/OC ratio. (Table 3)

Multiple regression analyses for serum OCs levels

Multiple regression analyses revealed that serum TRACP-5b level was a significant determinant of serum ucOC concentration. Vitamin K intake was a significant predictor for ucOC/OC. (Table 4)

Relative susceptibility of liver and bone to vitamin K deficiency

Serum PIVKA-II level exceeded the cut-off level (28 mAU/mL) in only 14% of the subjects, whereas serum ucOC concentration was above the cut-off value (4.5 ng/mL) in 43% of subjects, which was significantly different by chi-square test (p<0.001). (Table 5)

DISCUSSION

Vitamin status could be evaluated by several ways such as measuring its blood concentration or measuring the markers representing the vitamin status. Recently, we have reported that the prevalence of vitamin D- and K-deficiency is quite high in the institutionalized elderly by measuring plasma levels of 25 hydroxy-vitamin D concentration which is the best indicator of vitamin D status, and plasma vitamin K concentration.[11] Plasma vitamin K concentrations, however, only reflect the vitamin K status as a whole, and do not provide us with information regarding the vitamin K status in various tissues individually. Thus, in this study, we have evaluated the subjects' vitamin K status by measuring their serum levels of PIVKA- II and ucOC rather than their plasma vitamin K levels.

First, we have studied the association between serum levels of PIVKA-II and ucOC, and vitamin K intake. Vitamin K intake was significantly correlated with PIVKA-II and ucOC/OC, but not with ucOC. Similar findings were also reported by Booth *et al* that circulating levels of PIVKA-II and ucOC/OC ratio reflected dietary vitamin K intake, whereas serum ucOC levels did not.[9] Two mechanisms were considered to be responsible for these find-

Table 2. The correlation between vitamin K intake and serum levels of PIVKA-II and ucOC

	ucOC		ucOC/OC		PIVKA-II	
	r	*p*-value	r	*p*-value	r	*p*-value
Vitamin K intake	0.092	0.588	-0.416	0.010	-0.362	0.028

Correlations of vitamin K intake with markers for vitamin K deficiency were analyzed by Spearman rank correlation.

Table 3. The correlation of serum ucOC and uc/OC ration and bone turnover markers

	ucOC		ucOC/OC	
	r	*p*-value	r	*p*-value
Serum TRACP-5b	0.425	0.009	0.014	0.935
Serum BAP	0.517	0.001	0.243	0.147

Correlations of serum OCs with bone turnover markers were analyzed by Spearman rank correlation.

Table 4. Multiple regression analyses for serum ucOC level and ucOC/OC ratio

Dependent variable	R^2	Independent variable	β	*p*-value
ucOC	0.206**	Serum TRACP-5b	0.454	0.005
ucOC/OC	0.134*	Vitamin K	-0.366	0.026

The abbreviations are β for β coefficient. Independent predictor(s) for serum OCs levels were analyzed by multiple regression analyses with stepwise method. Sex, serum TRACP-5b, and vitamin K intake (μg) were included in all analyses.
*; p< 0.05, **; p< 0.01

Table 5. Number of subjects with vitamin K sufficiency and deficiency in the liver and bone

	Vitamin K sufficiency	Vitamin K deficiency
In the bone (serum ucOC concentration)	21 (57%)	16 (43%)
In the liver (serum PIVKA-II concentration)	32 (86%)	5 (14%)

Values represent number of subjects, with percentage of subjects in the parentheses. Vitamin K status in the bone and that in the liver were significantly different by chi-square test (p<0.001).

ings. The first is the different bioavailability of phylloquinone (PK; vitamin K_1) and menaquinones (MKs; vitamin K_2). In the present study, PK was the major form of vitamin K taken as in America or Europe,[12,13] since the subjects had no intake of natto which contains large amount of MK-7 during the study.[14] Recent studies have shown that PK can be utilized for γ-carboxylation in the liver, but can only be utilized in extrahepatic tissues after conversion into MK-4.[15,16]

Second issue is the association of serum ucOC level with bone turnover. Serum levels of BAP and TRACP-5b reflect osteoblastic bone formation and osteoclastic bone resorption, respectively, and are elevated in the high turnover state. Since osteocalcin is produced in osteoblasts,[17] it is conceivable that serum concentration of osteocalcin as well as its subfraction, ucOC level is increased with high turnover. Thus, it is currently under debate whether ucOC alone is satisfactory or measurement of ucOC as well as ucOC/OC is a better indicator of vitamin K status. In the present study, vitamin K intake was a significant predictor for ucOC/OC, but not with ucOC. Therefore, there is a possibility that ucOC/OC is a better index for vitamin K status than serum ucOC concentration. Unfortunately, however, there is no cut-off value published regarding ucOC/OC ratio, while the clinical usefulness of serum ucOC measurement is increasingly acknowledged. Thus, analysis using ucOC/OC could not be done as serum ucOC level in Table 5.

The cut-off value of 4.5 ng/mL for serum ucOC was validated by Shiraki by simultaneously evaluating the subjects' dietary intake of vitamin K, blood levels of vitamin K and ucOC.[18] They also reported that serum ucOC concentration exceeding 5.5 ng/mL was associated with increased risk of fracture. The clinical usefulness of ucOC measurement was previously reported, although with different assay procedure of hydroxy-appatite binding assay. In the European epidemiological study, Vergnaud *et al* reported that subjects in the lowest quartile of femoral neck bone mineral density (BMD) and those in the highest quartile of ucOC had increased hip fracture risk with an odds ratio of 2.4 and 1.9, respectively. These two risk factors were independent of each other, and those with both conditions had a even higher odds ratio of 5.5.[19] Thus, serum ucOC concentration is shown to be a good indicator of skeletal vitamin K deficiency, and a predictor of fracture risk.

In the current study subjects with vitamin K intake far exceeding AI, serum concentration of PIVKA-II and ucOC were within the reference range in 86% and 57% of the subjects respectively, which was significantly different. Thus, their vitamin K intake is sufficient for γ-carboxylation in the liver, but not in the bone, and bone is much more susceptible to vitamin K deficiency than liver. Such difference is likely to arise from the anatomical basis that vitamin K absorbed from the intestine is first transported to liver and preferentially used there, then utilized in extrahepatic organs.[9,10]

Booth *et al* in their depletion-repletion studies, reported that the γ-carboxylation of prothrombin was restored at 200 μg/day of PK, whereas that of osteocalcin was not even at 450 μg/day of PK.[9] Schurgers *et al* also reported that undercarboxylated prothrombin concentration was significantly decreased at supplementary intake of 100 μg/day of PK, whereas ucOC level did not decrease below 300 μg/day of PK.[10] Furthermore, Binkley *et al* reported that supplementation with 1,000 μg/day of vitamin K was optimal for the maximal γ-carboxylation of osteocalcin.[20] These results suggest that at least 300-500 μg g/day of vitamin K intake is required for the sufficient γ-carboxylation in the bone. Our results in the Japanese elderly are compatible with these results from Caucasians, and have additionally provided data on the prevalence of hepatic and skeletal vitamin K deficiency.

We believe that this paper is of importance in considering the AI for vitamin K. The current DRI states that the AI for vitamin K was determined based on its requirement for the γ-carboxylation of blood coagulation factors. The present findings suggest that vitamin K intake greater than the current AI is required for the skeletal health in the institutionalized elderly. Further studies with lager number of subjects and intervention studies are necessary to define the amount of vitamin K necessary for the elderly.

AUTHOR DISCLOSURES

None of the authors have any conflicts of interest.

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居住機構老人骨骼比肝臟易受維生素 K 缺乏影響

日本 2010 年發佈的膳食營養素參考攝取量(DRI)中，維生素 K 的足夠攝取量是根據凝血因子的 γ-羧化作用而訂定的。近來，維生素 K 也被視為預防骨折不可或缺的角色。本研究在於比較肝和骨骼對維生素 K 缺乏的敏感性。評估 37 位居住機構的老人之維生素 K 狀況─測量血清 PIVKA–II (因維生素 K 缺乏所產生的蛋白質)和 ucOC (未羧化的骨鈣素)濃度，兩者分別為肝和骨骼在維生素 K 缺乏時的敏感指標。受試者血清 PIVKA-II 和 ucOC 濃度分別為 20.2±8.9 mAU/mL (臨界值 28 mAU/mL)和 4.7±3.0 ng/mL (臨界值 4.5 ng/mL)。維生素 K 攝取量中位數約為 200 μg/day，超過了日本目前所建議的足夠攝取量 3 倍。維生素 K 攝取量與血清 PIVKA-II 和 ucOC/OC 濃度顯著相關，但與血清 ucOC 濃度無相關。雖然血清 ucOC 濃度是體內維生素 K 狀況很好的指標，但複迴歸分析顯示骨骼轉換標記增加，也會影響血清 ucOC 濃度。所有的受試者維生素 K 攝取量皆超過足夠攝取量。然而，分別有 14%和 43%受試者的血清 PIVKA-II 和 ucOC 濃度超過臨界值。本研究結果建議，對於住在機構的老人，為維持骨骼健康，維生素 K 攝取量應超過目前建議的足夠攝取量。

關鍵字：維生素 K、足夠攝取量、γ-羧化作用、未羧化骨鈣素、PIVKA-II