

## Original Article

# High prevalence of hypovitaminosis D and K in patients with hip fracture

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Although hip fracture is considered to be associated with hypovitaminosis D and K, few reports have previously studied both of them. We have studied the vitamin D- and K-status as well as the general nutritional status in ninety-nine patients with hip fracture. Mean serum concentration of 25hydroxy-vitamin D (25OH-D) in female fractured patients was only approximately 9 ng/mL, suggesting severe vitamin D deficiency. There was no significant difference between the two groups in serum concentration of intact parathyroid hormone in both genders and serum 25OH-D levels in the male subjects. Plasma concentrations of phylloquinone (vitamin K<sub>1</sub>; PK) and menaquinone-7 (MK-7) were significantly lower in the fractured group than in the control group in both genders. Logistic regression analysis indicated that circulating concentrations of albumin, PK and 25OH-D were the significant and independent determinants of fracture risk, with their higher concentrations associated with decreased fracture risk. Finally, principal component analysis (PCA) was performed to summarize the clinical parameters into smaller numbers of independent components. Three components were obtained, each representing the overall nutritional status, the vitamin D status, and the vitamin K status. In conclusion, our study has shown that patients with hip fracture have vitamin D and K deficiency independent of general malnutrition.

**Key Words:** hypovitaminosis D, hypovitaminosis K, patients with hip fracture, general malnutrition, principal component analysis

## INTRODUCTION

Hip fracture is the most serious consequence of osteoporosis. In addition to the high mortality rates after fracture, even the survivors suffer from functional impairment and limited daily activities.<sup>1</sup> With increased percentage of the elderly in the society, the incidence of hip fracture is constantly increasing in Japan, as in other countries.<sup>2</sup> Hip fracture is also considered to be a great burden to the society because of costly medical expenditure.<sup>3</sup>

Among the various risk factors of hip fracture so far reported are the nutritional ones including poor vitamin D and K status. "Vitamin deficiency" causes various disorders with phenotypic abnormalities, such as osteomalacia and rickets by vitamin D deficiency, and clotting abnormality by vitamin K deficiency. Recently, however, it is known that inadequate supply of vitamins, even in the milder form, causes increased susceptibility to various diseases, and is called vitamin insufficiency.<sup>4</sup> For example, vitamin D insufficiency, through decreased calcium absorption and negative calcium balance, is associated with decreased bone mineral density (BMD) and increased risk of fracture. The prevalence of hypovitaminosis D has been reported to be quite high in patients with hip fracture in various countries.<sup>5-7</sup>

The most essential role of vitamin K is to act as the coenzyme in the  $\gamma$ -carboxylation of glutamic acid residue

(glu) to  $\gamma$ -carboxyglutamin acid (gla) residue, through which four of the clotting factors acquire calcium binding capacity. It has long been held that the sole physiological action of vitamin K is the  $\gamma$ -carboxylation of these clotting factors in the liver. Recently, however, extrahepatic action of vitamin K has come to receive much attention.<sup>8</sup> For example, mice devoid of the matrix gla protein (MGP) gene, which is a gla-containing protein present in the skeleton and vasculature, died of severe arterial calcification.<sup>9</sup> Although mice lacking the osteocalcin gene had apparently higher bone mineral density than the control ones, they were more susceptible to bone loss after ovariectomy than their normal littermates, suggesting the compromised bone quality in these mice.<sup>10</sup> There also have been clinical observations to show the association between vitamin K inadequacy and hip fracture. For example, high intake of vitamin K was associated with

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decreased risk of hip fracture,<sup>11</sup> and high serum concentration of undercarboxylated osteocalcin (ucOC), which is a sensitive indicator of insufficient vitamin K action in the skeleton, was a significant risk factor of hip fracture independent of BMD.<sup>12</sup>

Despite these observations, there have been few reports to evaluate the status of these two bone-active vitamins in hip fractured patients.<sup>13</sup> Thus in the current study, we have studied the serum concentration of these two bone-active vitamins in patients with hip fracture and age-matched controls.

## MATERIALS AND METHODS

### Subjects

Consecutive patients with hip fracture transferred to Tamana Central Hospital were studied. The duration of the enrollment was 6 months. Written informed consent was obtained in 99 cases from the patients or a family member when obtaining the patients' approval was practically impossible because of their poor general condition. Age-matched nursing home residents in close proximity to the hospital in Tamana City served as the control. Those without severe liver or kidney dysfunction, or those receiving bone-active drugs or supplementation with vitamin D or K, were encouraged to participate in the study, and the consent was obtained in 48 cases.

Informed consent was similarly obtained in 48 cases. Their background profiles are shown in Table 1. The study protocol was approved by the Ethical Committee of Tamana Central Hospital.

### Laboratory data

Blood was drawn within 24 hours following the fracture. After centrifugation, plasma and serum were stored under dark condition at -30°C until assay. Serum concentration

of 25 hydroxy-vitamin D (25OH-D) was measured by radioimmunoassay (RIA) (DiaSorin, Stillwater, MN, USA). Serum level of intact parathyroid hormone (PTH) was measured by electro chemiluminescent immunoassay (ECLIA) (Roche Diagnostics, Mannheim, Germany). Plasma vitamin K<sub>1</sub> (phylloquinone; PK), and K<sub>2</sub> (menaquinone-7; MK-7) levels were determined by high-performance liquid chromatography-tandem mass-mass spectrometry with atmospheric pressure chemical ionization (LC-APCI-MS/MS) using a HPLC system (Shimadzu, Kyoto, Japan) and API3000 LC-MS/MS System (Applied Biosystems, Foster City, CA) with <sup>18</sup>O-labeled vitamin K as the internal standard.<sup>14</sup>

### Statistical analyses

Statistical analyses were done with SPSS 17.0J. Comparison of two independent groups was done with Student's t-test or Mann-Whitney test depending on normality. The association between vitamin status and the occurrence of hip fracture was analyzed by logistic regression analysis. The relationship between various nutritional indices and circulating vitamin D- and K-levels was analyzed with principal component analysis (PCA) as previously described.<sup>15</sup>

## RESULTS

### Blood tests

Baseline characteristics and data from blood examination are shown in Table 1. Serum albumin concentration was significantly lower in the fractured group in both genders, and serum cholesterol concentration and blood hemoglobin level were significantly lower in female patients with fracture. In Table 2 shows the blood concentrations of vitamin D, vitamin K and related molecules. Mean serum concentration of 25OH-D, which most reliably represents

**Table 1.** Patients' profiles

	Male		Female	
	Control (n=13)	Fracture (n=27)	Control (n=35)	Fracture (n=72)
Age	82.2±9.3	82.6±7.6	84.1±7.8	85.5±7.0
Serum albumin (g/dL)	4.3±0.5	3.5±0.5**	4.4±0.2	3.6±0.4**
Serum cholesterol (mg/dL)	175.4±41.9	156.1±36.6	232.3±37.0	179.4±39.4**
Serum BUN (mg/dL)	24.1±2.2	29.5±26.1	20.6±7.4	20.6±10.2
Hemoglobin (g/dL)	12.4±2.2	11.9±1.9	12.5±1.1	10.8±1.8**
Serum GOT (U/L)	26.2±20.4	32.1±9.4	23.9±7.2	20.9±7.5
Serum GPT (U/L)	19.3±16.2	22.8±21.1	13.7±8.6	14.0±8.4

Data are shown as mean ± SD. The asterisk (\*\*) denotes that the value in fracture group is significantly different from that in control group ( $p<0.01$ ) by Student's t-test. BUN, GOT, and GPT are abbreviations for blood urea nitrogen, glutamyl oxaloacetic transaminase, glutamyl pyruvate transaminase, respectively.

**Table 2.** Serum concentrations of vitamin D, vitamin K and related molecules

	Male		Female	
	Control (n=13)	Fracture (n=27)	Control (n=35)	Fracture (n=72)
Serum 25OH-D (ng/mL)	20.7±7.3	19.0±13.0	18.6±6.3	9.1±4.6**
Serum intact PTH (pg/mL)	64.3±53.7	61.4±34.4	56.0±23.2	67.8±33.9
Plasma PK (ng/mL)	0.55±0.31	0.31±0.24*	0.77±0.36	0.46±0.36**
Plasma MK-7 (ng/mL)	4.28±3.75	1.60±1.60**	10.8±7.01	2.67±4.13**

Data are shown as mean ± SD. The asterisk denotes that the value in fracture group is significantly different from that in control group (\*;  $p<0.05$ ; \*\*;  $p<0.01$ ) by Student's t-test. 25OH-D, PK, and MK-7 are the abbreviations for 25 hydroxy-vitamin D, phylloquinone, and menaquinone-7, respectively.

**Table 3.** Logistic regression analysis

	Odds ratio (95%CI)	p value
Serum 25OH-D (per 10ng/mL increase)	0.246 (0.090-0.673)	<0.001
Plasma PK (per 1ng/mL increase)	0.072 (0.009-0.612)	0.016
Albumin (per 1g/dL increase)	0.003 (0.000-0.054)	<0.001
MK-7 (per 1ng/mL increase)	0.867 (0.747-1.006)	0.061
Hemoglobin (per 1g/dL increase)	1.482 (0.891-2.465)	0.129
Sex (1; Male, 2; Female)	2.464 (0.381-15.95)	0.344

Logistic regression analysis with stepwise method was done. Sex, circulating concentrations of albumin, hemoglobin, 25OH-D, PK, and MK-7 were included for analysis.

**Table 4.** Principal component analysis of nutrition indices

	Component 1	Component 2	Component 3
Serum Albumin	0.744 <sup>†</sup>	0.481 <sup>†</sup>	-0.028
Serum total Cholesterol	0.824 <sup>†</sup>	0.098	0.157
Hemoglobin	0.538 <sup>†</sup>	0.589 <sup>†</sup>	-0.269
Serum 25OH-D	0.035	0.902 <sup>†</sup>	0.228
Plasma PK	0.191	0.109	0.922 <sup>†</sup>
Plasma MK-7	0.773 <sup>†</sup>	0.009	0.210

Factor loadings to three components after varimax rotation are shown. <sup>†</sup>Loadings greater than 0.35

the vitamin D status, was approximately 20 ng/mL in all groups, except for the female fracture group where it was approximately 9 ng/mL. In both genders, serum 25OH-D levels were lower than 20 ng/mL in 90% and 61% of subjects, in the fracture and control groups, respectively. It was below 10 ng/mL in 50% and 7% of subjects in the fracture and control group, respectively. Serum concentration of intact PTH, which is a sensitive indicator of vitamin D insufficiency; hence secondary hyperparathyroidism, was not different between control and fracture groups in males. It was slightly higher in the fractured group than in the control group in female, which, however, did not reach statistical significance ( $p=0.07$ ).

Serum concentrations of PK and MK-7 were significantly lower in the fracture group than in the control group in both genders.

#### **Logistic regression analysis for variables associated with hip fracture**

In order to evaluate whether the above-mentioned vitamin insufficiency is related to the occurrence of hip fracture, logistic regression analysis was performed. Of the factors subjected for analysis, circulating concentrations of albumin, PK and 25OH-D were the significant determinants, whereas MK-7, gender or hemoglobin level was not (Table 3). The odds ratio for fracture markedly decreased in accordance with increased concentrations of albumin, PK and 25OH-D.

#### **Principal component analysis (PCA)**

Since patients with hip fracture are generally malnourished, we considered it to be important whether the low vitamin D- and K-status as described above simply reflects overall malnutrition. Then PCA was performed with parameters included for analysis being: serum albumin and cholesterol concentrations, blood hemoglobin levels, and plasma 25OH-D, PK and MK-7. Three components were

obtained as shown in Table 4. The first component was contributed by high serum albumin, total cholesterol, blood hemoglobin and plasma MK-7. The second component consisted of high serum albumin, blood hemoglobin and serum 25OH-D. The third component was composite of high plasma PK. Each component was interpreted as follows; the first, second, and third component representing overall nutritional status, vitamin D status, and vitamin K<sub>1</sub> status, respectively.

#### **DISCUSSION**

In the present study, we have studied the blood concentration of 25OH-D, PTH, PK, MK-7 and other nutritional indices. In 90% of patients with hip fracture, serum 25OH-D level was lower than 20 ng/mL which is a generally accepted cut-off for hypovitaminosis D. In half of the patients, serum 25OH-D concentration fell into the severe hypovitaminosis D range of below 10 ng/mL. Nurmi *et al.* reported that serum 25OH-D level was lower than 15 ng/mL and 8 ng/mL in 53% and 9%, respectively, of the patients with hip fracture in Finland.<sup>16</sup> In a study on Japanese patients with hip fracture, Sakuma *et al.* reported that 62% of the patients had their serum 25OH-D level below 20 ng/ml.<sup>7</sup> Thus, the prevalence of hypovitaminosis D in the present study was compatible with the previous studies, but was even higher.

Serum concentration of 25OH-D in the fracture group was significantly lower than that in the control group in women, but not in men. There have been some reports to show that elderly women are more prone to vitamin D deficiency than elderly men. Hirani *et al.* reported that hypovitaminosis D was more prevalent in women than men with a odds ratio of 2.1.<sup>17</sup> Maggio *et al.* reported that age-related decline of serum 25OH-D was already evident shortly after age 50 in women, whereas in men it started only after age 70.<sup>18</sup> Thus there seems to be a gender dif-

ference that women are more prone to vitamin D inadequacy, for which there is no clear explanation at present.

Lack of significant difference in serum PTH level between fracture and control groups is most likely due to the large standard deviation in serum PTH concentration. However, there still can be alternative explanations. There have been some reports describing the absence of PTH elevation in face of hypovitaminosis D in patients with hip fracture.<sup>19-22</sup> Sahota *et al.* studied the vitamin D status in the post-hip fracture patients. They found that only half of them had elevated serum PTH levels, the rest had normal to low serum PTH levels in face of hypovitaminosis D.<sup>19</sup> As an explanation for this apparently paradoxical observation, they postulated magnesium deficiency as the underlying cause since magnesium deficiency is known to be associated with impaired PTH secretion.<sup>20</sup> Thus the question has now come to our attention whether skeletal impairment in hypovitaminosis D can be explained by secondary hyperparathyroidism alone. A recent paper from Finland also reported that serum PTH level was within the reference range despite hypovitaminosis D in 74.8% of the bedridden geriatric patients.<sup>21</sup> Patients in the lowest quartile of serum PTH level were associated with the history of hip fracture (odds ratio 2.9). Thus it is obvious that hypovitaminosis D is associated with increased risk of hip fracture, although further studies are required to determine whether it is mediated by secondary hyperparathyroidism or due to hypovitaminosis per se.

Compared to vitamin D, far smaller number of papers has been published on the relationship of vitamin K with hip fracture. Epidemiological studies have shown that higher intake of vitamin K is associated with lower risk of hip fracture.<sup>11,23</sup> Among the two vitamin K analogs studied here, PK seems to best represent the vitamin K status of these subjects. Kaneki *et al.* reported that there is a large geographic difference in serum MK-7 concentration in Japan, which could be accounted for by the frequency of consuming natto, which contains extraordinary amount of MK-7.<sup>24</sup> Blood concentrations of PK and MK-7 were consistently lower in fractured patients than control subjects in both genders.

Kawana *et al.* reported that there was no significant alteration in the circulating concentrations of PK and MK-7 in hip fractured patients.<sup>25</sup> In their paper, these concentrations were below the detection limit in the substantial number of subjects. Blood vitamin K levels were reported to be below the detection limit in other papers also.<sup>24,26</sup> In our data using newly developed LC-APCI-MS/MS method for the determination of circulating vitamin K levels, serum concentrations of PK and MK-7 were detectable in almost all subjects.<sup>14</sup> Thus, previous reports using less sensitive assay methods should be interpreted with caution.

In fractured subjects, serum albumin concentration was significantly lower in both genders, and hemoglobin level and serum cholesterol concentration was significantly lower in the females. Thus patients with hip fracture are malnourished. Then it was considered mandatory to analyze the relationship between the overall malnutrition and decreased levels of circulating these vitamins. We have studied it with two analytical procedures; logistic regression analysis and principal component analysis (PCA). Logistic regression analysis revealed that serum

concentrations of 25OH-D, PK and albumin were significant contributing factors for fracture risk, and suggested that circulating 25OH-D and PK levels contributed to the increased risk of fracture independent of general malnutrition.

Finally PCA was done. Three components were obtained, representing overall nutritional status, vitamin D status, and vitamin K status, respectively. Since these components are, by their definition, independent of each other, these results strongly suggest that hypovitaminosis D and K in patients with hip fracture is not merely a manifestation of general malnutrition. At present, the reason for the association of MK-7 with the first component, representing the overall nutritional status is not known. We have also recently reported that institutionalized elderly subjects had high prevalence of hypovitaminosis D and K, which is independent of general malnutrition by PCA.<sup>15</sup>

One of the limitations of the current work is that it is a case control study, but not a prospective one. Since the association of hip fracture with the insufficiency of two bone-active vitamins; vitamin D and vitamin K has been scarce, we have done this study as the initial step.

Another limitation is that the nursing home residents adjacent to the hospital were the control subjects. It is unclear whether the control subjects represent the average Japanese elderly population or not. However, it is quite unlikely the nursing home residents have nutritional status far better than the average Japanese elderly. Rather, they are likely to be equal to or worse than the average. Thus, we believe that our finding that the blood levels of these vitamins in fractured patients were even lower than that in nursing home residents has clinical implications.

In summary, patients with hip fracture had lower serum concentration of vitamin K in both genders, and lower serum concentration of vitamin D in female subjects. Since blood samples were obtained within 24 hours after fracture, these data is likely to represent the patients' status before fracture. Lower serum albumin concentration in fractured patients suggests that these subjects are also generally malnourished. Insufficiency of these vitamins as well as the overall malnutrition is likely to predispose elderly people to hip fracture, and intervention study to correct these abnormalities is needed.

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#### AUTHOR DISCLOSURES

None of the authors have any conflicts of interest.

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# High prevalence of hypovitaminosis D and K in patients with hip fracture

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## 髋部骨折病患維生素 D 與 K 不足之高盛行率

過去研究顯示髋部骨折與維生素 D 及維生素 K 不足有關，但較少研究將兩者共同納入探討。本研究之對象為 99 位有髋部骨折的病患，檢測其整體營養及體內維生素 D 與維生素 K 的狀態。女性患者血清 25-羥化維生素 D(25OH-D)濃度平均只有約 9 ng/mL，顯示女性患者有嚴重維生素 D 缺乏。男女性患者血清中副甲狀腺素及男性血清 25OH-D 平均濃度與對照組皆沒有顯著差異。然而在男女性髋部骨折患者，其血漿維生素 K<sub>1</sub> 及維生素 K<sub>2</sub> 濃度都顯著較對照組低。以羅吉斯回歸分析發現，體內白蛋白、維生素 K<sub>1</sub> 及 25OH-D 濃度皆為骨折發生風險之顯著獨立預測因子，具呈負相關。最後以主成份分析進行臨床參數統整後，獲得三項代表參數，分別代表整體營養狀態、維生素 D 營養狀態及維生素 K 狀態。總而言之，本研究顯示髋部骨折患者易出現維生素 D 及維生素 K 缺乏，且與整體營養不良無關。

**關鍵字：**維生素 D 缺乏、維生素 K 缺乏、髋部骨折病患、整體營養不良、主成分分析