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Serum Fat-Soluble Vitamin Levels in Patients with Hip Fracture in Central China

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Abstract

Background: To investigate the relationship between fat-soluble vitamins and hip fracture, which is significant for the prevention and treatment of hip fracture.

Method: The present study was a case-control analysis of hip-fracture patients (n=25) and non-fracture patients (n=32). The associations of fat-soluble vitamin (vitamin A, D, E and K) and other variables (such as Bone Mineral Density (BMD), disease status, BMI, age, sex, drinking, smoking) with hip fracture were investigated. Subgroup analysis based on vitamin D status were further emphatically investigated.

Results: The mean serum level of 25(OH)D3 (10.9 ± 4.62 ng/mL) and 25(OH)D (12.5 ± 4.91 ng/mL) for the hip fracture group was significantly lower than that of 25(OH)D3 (17.6 ± 7.63 ng/mL, P<0.001) and 25(OH)D (19.5 ± 7.71 ng/mL, P<0.001) for the controls. A low vitamin A level (P<0.001) was also demonstrated in hip fracture patients (309 ± 115 ng/mL) in comparison with the controls (468 ± 138 ng/mL), but no significant differences were found in vitamin E and vitamin K1. It was found that BMD and 25(OH)D level were final high-risk factors of hip fracture. In subgroup analysis of vitamin D status, 92.0% of the hip-fracture group has deficient or insufficient serum 25(OH)D concentrations, significantly higher than the control group. Besides 25(OH)D3, significant differences in vitamin A (P<0.001) and vitamin K1 (P=0.01) were found among subgroups.

Conclusion: It is found that although insufficiency or deficiency of 25(OH)D and a decrease BMD with osteopenia or osteoporosis are high risk factors of hip fracture, the insufficiency of other fat-soluble vitamins likely plays a role in hip fracture. The proper supplement is favor for reduced risk of hip-fracture.

Keywords: Vitamin D; Fat-soluble vitamin; Bone mineral density; Hip fracture

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Background

Hip fracture is common in the older population and is associated with devastating consequences [1]. Nearly 12% to 17% of patients with a hip fracture die within the first year, and the risk of death is long-term increase two-fold [2]. It is expected that absolute number of hip fracture would reach 4.5 million by the year 2050 [3]. Around 30% of the worldwide hip fractures occurring in Asian population, mostly notably that of China, making this a public health concern [4]. As a result, further studies in risk factors of hip fractures are needed to better their prevention and treatment.

Malnutrition is very prevalent in patients with hip-fracture, especially in older adults [5]. Vitamins, as a kind of famous nutrients, are essential to physiological functions in human body [6]. Vitamins could be classified as fat-soluble or water-soluble vitamins. Among them, the fat-soluble vitamins including vitamin A, D, E, and K paly integral roles in multitude of physiological processes, and these deficiencies are associated with serious health problems. Vitamin D plays an important role in bone metabolism. Its actives the calcium channels and stimulates the formation of calcium binding protein which could promote the uptake of calcium and phosphate and further impact on bone health. Always, vitamin D, comprising vitamin D2 and D3, from the skin and the diet would convert to 25-hydroxyvitamin D [25(OH) D] which is the major circulating form of vitamin D and usually used to evaluate vitamin D status [7]. Vitamin A with beta-ionone structure is important to vision, growth, cell division, reproduction and immunity [8]. Vitamin E is important in the maintenance of health famous for its antioxidant functions or non-antioxidant property [9]. Vitamin K plays a leading role in the blood coagulation cycle [10]. Although the association of 25(OHD) with hip fracture is well-documented and some literatures indicated that other fat-soluble vitamins might also pose greatly impact on bone health [11-14], a few studies systematically

investigated the relationship between fat-soluble vitamins and hip fracture. In this study, we evaluate the association between fat-soluble vitamins and hip fracture.

Method

Study design and participants

Twenty-five patients who presented to General Hospital of the Yangtze River Shipping with a hip fracture requiring fracture surgery were enrolled consecutively over last four months in 2019. Thirty-two subjects undergoing nonfracture procedures-soft tissue injury, osteoarthritis, foot mass and benign osseous tumor excision were enrolled as the contemporaneous control population in the same period. All subjects reside in Wuhan from central China. Variables collected for each patients included as follows: Gender, age, BMI, blood pressure, smoking status, drinking status, bone mineral density, admission time, discharge time, chronic disease status. This work was approved by the ethics committee of General Hospital of the Yangtze River Shipping.

Fat-soluble vitamin assessment

Overnight fasting blood samples were obtained by venipuncture for vitamin detection at initial admission. Sera were obtained by centrifugation of coagulated blood samples at 3,000 rpm for 5 min at room temperature. These sera were frozen and stored at –80°C until analysis. Vitamins including 25-Hydroxyvitamin D2 (25(OH)D2), 25-Hydroxyvitamin D3 (25(OH)D3), vitamin E, vitamin K1 were measured by Liquid Chromatography coupled with tandem Mass Spectrometry (LC-MS/MS) on a AB-SCIEX Qtrap 5500 coupled to an Exion LC system (Applied Biosystems, Foster City, CA, USA). Vitamin D status was evaluated by the concentration of 25(OH) D which was the sum of 25(OH)D2 and 25(OH)D3. Circulating vitamin D concentration cut-offs for the risk of vitamin D deficiency, insufficiency, sufficiency and toxicity levels identified by the U.S. Institute of Medicine are <12 ng/mL, 12-20 ng/mL, >20 ng/mL and >50 ng/mL [15].

Bone measurement

All patients underwent Dual energy X-ray Absorptiometry (DXA) scan to measure spine and hip Bone Mineral Density (BMD). Expression of these scores based on patient age and menopausal. The T-score is accepted for BMD in postmenopausal women and men ≥ 50 years, while Z-scores are the preferred method for reporting BMD in children, adolescents, young adults and men up to the age of 49 years. For T-scores, adults are considered as being normal (T-score ≥ -1.0), low bone mass or osteopenia (-2.5< T-score < -1.0) or osteoporosis (T-score ≤ -2.5). Meanwhile, it is expressed as being normal (Z-score > -2.0) or indicating low BMD (Z-score ≤ -2.0) for Z-scores. The definition of osteopenia and osteoporosis is on the basis of BMD measurement [16].

Statistical analysis

We present the distribution of concentrations of vitamins for all participants. Data normality was analyzed using the Kolmogorov-Smirnov test. Normally-distributed Data were expressed as mean ± SD while non-normally distributed data were presented as median and Interquartile Range (IQR). Student's t test or Mann-Whitney U test based on data distribution were applied to compare the serum concentrations of vitamins in different groups. Pearson's Chi-square test or Fisher's exact test was performed to analyze the categorical data. Spearman's correlation test was used to identify relationships among all variables of interest.

A multivariate logistic regression was performed to assess Odds Ratios (ORs) regarding hip fracture-associated factors. Variable with a global value P<0.05 in the univariate analysis were entered into multivariate analyses. A P-value below 0.05 was considered statistically significant. Analyses were all done using SPSS (version 20.0; SPSS, Isnc., Chicago, Ill, USA), and the Correlation analysis heatmap was plotted by R language.

Results

Demographic characteristics

The demographic characteristics of subjects were demonstrated in Table 1. The fractured and nonfractured groups were similar in most demographic categories, such as BMI, blood pressure status, drinking status, smoking status, disease status and hospitalization time. However, significant differences were found between cases and controls about sex, age and BMD. Hip fractures were seen more commonly in females (68.0%) [2]. The age of patients with hip fractures ranged from 30 to102 years with a mean age of 73 ± 17, while that of nonfractured ranged from 24 to 78 years with an average age of 54 ± 14. In addition, it was found that patients with hip fractures were nearly all in company with osteopenia or osteoporosis (Figure 1), but the disease status posed no significant impact.

Comparison of fat-soluble vitamins between hip fracture patients and non-hip fracture patients

Overall, all fat-soluble vitamins within groups were normally distributed except for 25(OH)D2. The mean serum level of 25(OH) D3 (10.9 ± 4.62 ng/mL) and 25(OH)D (12.5 ± 4.91 ng/mL) for the fracture group was significantly lower than that of 25(OH)D3 (17.6 ± 7.63 ng/mL, P<0.001) and 25(OH)D (19.5 ± 7.71 ng/mL, P<0.001) for the controls. Meanwhile, a low vitamin A level (P<0.001) was demonstrated in hip fracture patients (309 ± 115 ng/mL) in comparison with the controls (468 ± 138 ng/mL). For 25(OH)D2, vitamin E and vitamin K1, no significant differences were found between cases and controls. To study hip-fracture associated factors, logistic regressions were performed. Variables with a global value P<0.05 in the univariate analysis were entered into multivariate analyses, and only BMD and 25(OH)D were found to be significantly associated with increased fracture risk in final multivariate regression analysis as shown in Table 2. Thus, decreased BMD was associated with an increase hip-fracture risk while increase 25(OH)D level decrease the hip-fracture risk.

Subgroup analysis based on vitamin D status

In categorical univariate analysis, 92.0% of the hip-fracture group

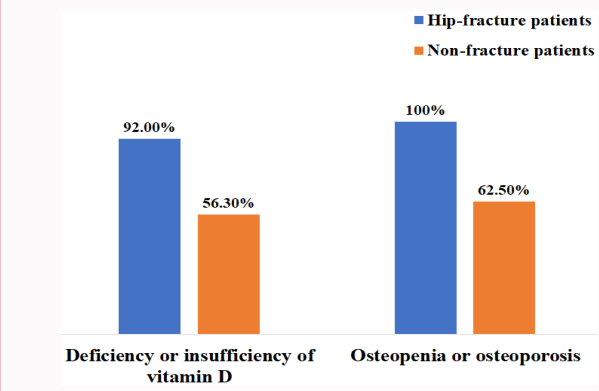

Figure 1: The proportion of patients about deficiency or insufficiency of vitamin D and osteopenia or osteoporosis in case-control study.

Table 1: Baseline characteristics of hip-fracture and non-fracture groups.

	All	Hip-fracture patients	Non-fracture patients	*P*
N	57	25	32	
Female, n (%)	31 (54.4)	17 (68.0)	14 (43.8)	0.026[a]
Age	63 ± 18	74 (59-89)	54 ± 14	<0.001[c]
BMI (kg/m^2)	22.9 (21.4-25.0)	23.4 (21.2-26.8)	23.0 ± 2.36	0.515[c]
Blood pressure				0.384[a]
Normal, n (%)	14 (24.5)	8 (32.0)	6 (18.8)	
Hypertension, n (%)	39 (68.4)	17 (68.0)	22 (68.8)	
Drinking				0.572[a]
Non-drinker, n (%)	49 (86.0)	23 (92.0)	26 (81.2)	
Drinker, n (%)	5 (8.77)	2 (8.00)	3 (9.37)	
Smoking				0.127[a]
Non-smoker, n (%)	38 (66.6)	20 (80.0)	18 (56.2)	
Smoker, n (%)	16 (28.1)	5 (20.0)	11 (34.4)	
BMD				0.013[a]
osteopenia or osteoporosis, n (%)	45 (79.0)	25 (100)	20 (62.5)	
Normal, n (%)	12 (21.0)	0 (0.00)	12 (37.5)	
Diabetes, n (%)	12 (21.1)	7 (28)	5 (15.6)	0.290[a]
Liver disease, n (%)	2 (3.50)	2 (8.00)	0 (0.00)	0.218[a]
Kidney disease, n (%)	1 (1.75)	1 (4.00)	0(0.00)	0.472[a]
cardiovascular disease, n (%)	11 (19.3)	8 (32.0)	3 (9.38)	0.058[a]
Pulmonary disease, n (%)	7 (12.3)	5 (20.0)	2 (6.25)	0.166[a]
25(OH)D$_2$ (ng/ml)	0.80 (0.52-1.01)	0.91 (0.68-1.40)	0.77 (0.45-0.92)	0.111[c]
25(OH)D$_3$ (ng/ml)	14.7 ± 7.26	10.9 ± 4.62	17.6 ± 7.63	<0.001[b]
25(OH)D (ng/ml)	16.4 ± 7.46	12.5 ± 4.91	19.5 ± 7.71	<0.001[b]
Vitamin A (ng/ml)	398 ± 150	309 ± 115	468 ± 138	<0.001[b]
Vitamin E (μg/ml)	16.6 ± 4.36	16.2 ± 4.53	16.9 ± 4.26	0.524[b]
Vitamin K1 (ng/ml)	1.96 (0.88-3.01)	1.60 (0.61-2.74)	2.15 (1.13-3.47)	0.058[c]
Hospitalization time (d)	15.5 (7.00-24.2)	18.6 ± 10.3	13.0 (6.00-26.0)	0.255[c]

Note: Normal distribution data are expressed as mean ± standard deviation; non-normal distribution data are expressed as median (IQR). [a]Chi-squared test; [b]Student's t-test; [c]Mann-Whitney U test

Table 2: Results of logistic regression model for hip-fracture occurrence [a].

Covariates	OR (95% CI)	*P*
BMD		0.04
Normal	1	
Osteopenia or osteoporosis	12.673 (1.119-143.492)	
25(OH)D	0.806 (0.667-0.973)	0.025

[a]The modeling approach-based Logistic Regression (LR)

has deficient or insufficient serum 25(OH)D concentrations, while only 56.3% of the control group exhibited deficient or insufficient 25(OH)D levels (Figure 1). In detail, 11 (44.0%) were deficient and 12 (48.0%) were insufficient for hip-fracture group. Of non-fracture population, 4 (12.5%) were deficient and 14 (43.8%) were insufficient. After controlling for confounders, insufficient or deficient serum 25(OH)D level (≤ 20 ng/mL) significantly increase the risk for hip fracture (OR=8.944; 95% CI, 1.78-44.52; P=0.007). As well, the subjects with insufficient or deficient 25(OH)D concentration were apt to occur osteopenia or osteoporosis. In addition, except for 25(OH)D3 (P<0.001), 25(OH)D (P<0.001), vitamin A (P<0.001) and vitamin K1 (P=0.01), no significant differences were found in other variables among subgroup analysis of vitamin D status (Table 3).

Discussion

Hip-fractures often cause significant morbidity and are related with increased mortality. Thus, learning about factors associated with hip fractures is significant for prevention and treatment of hip fractures. In addition to fully investigate variables, such as sex, age, BMI, blood pressure status, drinking status, smoking status, disease status and hospitalization time, the associations between fat-soluble vitamin levels and hip- fractures were studied in detail. It was found that hip-fractures were more common among females (68.0%, P=0.026). In the literature, it was reported about 80% of hip-fractures occurred in females [2,17]. Besides, the medium age (IQR) of hip-fracture patients was 74 (59-89) years old that significantly older than non-fracture patients (54 ± 14 years old) (P<0.001), which was in accordance with the fact that about 87% to 96% of hip-fracture patients are 65 years of age or older [18]. As well-known, hip-fractures are a serious complication of osteoporosis [19], and thus patients with hip-fracture are apt to present osteopenia or osteoporosis (P=0.013).

Vitamins are a broad group of organic compounds that are important for human healthy. Based on their solubility, vitamins could be grouped into water-soluble vitamins and fat-soluble

Table 3: Categorization of subjects based on serum 25(OH)D levels.

	>20 ng/mL (Sufficient)	12-20 ng/mL (Insufficient)	<12 ng/mL (Deficient)	*P*
N, n (%)	16 (28.1)	25 (43.8)	16 (28.1)	
Age	58 ± 14	62 ± 20	74 (52-85)	0.102[c]
Female, n (%)	7 (43.7)	12 (48.0)	12 (75.0)	0.086[a]
BMI (kg/m^2)	23.1 ± 2.63	22.2 ± 1.57	23.7 (22.9-31.8)	0.144[c]
Blood pressure				0.130[a]
Normal, n (%)	4 (25.0)	3 (12.0)	7 (43.8)	
Hypertension, n (%)	12 (75.0)	18 (72.0)	9 (56.2)	
Drinking				0.143[a]
Non-drinker, n (%)	15 (93.8)	18 (72.0)	16 (100)	
Drinker, n (%)	1 (6.20)	4 (16.0)	0 (0.00)	
Smoking				0.495[a]
Non-smoker, n (%)	11 (68.8)	14 (56.0)	13 (81.2)	
Smoker, n (%)	5 (31.2)	8 (32.0)	3 (18.8)	
BMD				0.032[a]
osteopenia or osteoporosis, n (%)	9 (56.2)	22 (88.0)	14 (87.5)	
Normal, n (%)	7 (43.8)	3 (12.0)	2 (12.5)	
Diabetes, n (%)	3 (18.8)	4 (16.0)	5 (31.2)	0.488[a]
Liver disease, n (%)	0 (0.00)	2 (8.00)	0 (0.00)	0.265[a]
Kidney disease, n (%)	0 (0.00)	0 (0.00)	1 (6.25)	0.271[a]
cardiovascular disease, n (%)	2 (12.5)	3 (12.0)	6 (37.5)	0.094[a]
Pulmonary disease, n (%)	2 (12.5)	2 (8.00)	3 (18.8)	0.592[a]
25(OH)D$_2$ (ng/ml)	0.82 (0.45-1.71)	0.78 (0.54-0.94)	0.88 (0.53-0.95)	0.897[c]
25(OH)D$_3$ (ng/ml)	22.8 ± 7.63	14.1 (12.9-15.7)	7.55 ± 2.10	<0.001[c]
25(OH)D (ng/ml)	24.2 (20.6-29.6)	15.6 ± 1.80	8.51 ± 2.43	<0.001[c]
Vitamin A (ng/ml)	510 ± 134	402 ± 131	281 ± 102	<0.001[b]
Vitamin E (μg/ml)	18.7 ± 4.40	15.8 (12.9-18.8)	15.8 ± 4.84	0.184[c]
Vitamin K1 (ng/ml)	2.64 ± 1.28	2.03 (1.01-2.95)	0.89 (0.52-2.37)	0.010[c]
Hospitalization time (d)	15.0 (6.25-23.5)	19.1 ± 14.0	16.5 (10.3-24.5)	0.838[c]

Note: Normal distribution data are expressed as mean ± standard deviation; non-normal distribution data are expressed as median (IQR). [a]Chi-squared test; [b]Student's t-test; [c]Mann-Whitney U test

vitamins. Fat-soluble vitamins, including vitamin A, D, E and K1, play essential roles in body development and homeostasis [20]. Among these, vitamin D, as a key player in calcium homeostasis, is essential for normal bone turnover, and most studies investigation its relationship with fractures [21-23]. Always, total 25(OH)D were positively correlated with 25(OH)D3 levels [24]. It is easy to know that patients with hip-fracture exhibited both lower levels of 25(OH) D3 and 25(OH)D (Table 1). Up to now, it is controversial about the risk of hip fracture with vitamin A intake or its blood level [25-27]. In our study, we found that patients with hip-fracture had significantly low vitamin A level (P<0.001) (Table 1), which were comparable with Barker's study [28].

In present study, osteopenia or osteoporosis was greatly associated with hip-fracture. It also demonstrated that decreasing 25(OH)D level were significant risk factors of hip-fracture (Table 2). All these results were in line with the findings of other similar studies [29-31]. 25(OH)D is recognized as the main circulating form of vitamin D; it accurately indicates the vitamin D concentration in the body. Patients with hip-fracture are apt to suffer from vitamin D deficiency or insufficiency, and so as well osteopenia or osteoporosis (Figure 1). Meanwhile, it was reported that 25(OH)D levels posed an effect on BMD, and low serum 25(OH)D accounted for a considerable proportion of patients with osteoporotic or osteopenic fracture [30], which also be evidently by our study (Table 3). Thus, the occurrence of hip fractures is the result of a combination of vitamin D content and BMD. In addition, it was found that patients with decreased serum 25(OH)D level also showed decrease level of vitamin A and vitamin K1 (Table 3). Great evidence has already shown associations between poor vitamin D or vitamin A and bone loss [28,30]. Vitamin K1, as a cofactor for metabolic of glutamic acid in osteocalcin which has been thought to act as a regulator of bone mineralization, is thought to be associated with bone turnover [32], in consideration that fat-soluble vitamins, especially vitamin D, A and K1, pose in-negligible effect on bone health, it is easily understood that the decrease in one fat-soluble vitamin is always in company with the similar change tendency in others.

This study also has several limitations. Firstly, the cross-section design limited our ability to identify a causal relationship between fat-soluble vitamins and hip fracture. Secondly, more sample size should be included for further validation.

Conclusion

Our study shows that insufficiency or deficiency of 25(OH)D and a decrease BMD with osteopenia or osteoporosis are high risk factors of hip fracture. Other fat-soluble vitamins, such as vitamin A, might also pose great influence on hip-fracture. Although we cannot definitively conclude that fat-soluble vitamin testing or supplementation would change health outcomes, the insufficiency of in fat-soluble vitamins level likely play a role in hip fracture from low-energy mechanisms and consideration should be taken to routine serum fat-soluble vitamins testing, especially 25(OH)D and vitamin A, and possible supplementation in patients with hip-fracture, which is favorable for reduced risk of surgery.

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