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Randomized Controlled Trial

Effects of nutritional intervention upon bone turnover in elderly hip fracture patients. Randomized controlled trial

Anne C. Torbergsen [a, b, *], Leiv O. Watne [a, c, d], Frede Frihagen [e], Torgeir B. Wyller [a, c], Morten Mowè [a, b]

[a] Institute of Clinical Medicine, University of Oslo, Norway
[b] Department of General Internal Medicine, Oslo University Hospital, Norway
[c] Oslo Delirium Research Group, Department of Geriatric Medicine, Oslo University Hospital, Norway
[d] Institute of Basic Medical Sciences, University of Oslo, Norway
[e] Orthopaedic Department, Oslo University Hospital, Norway

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SUMMARY

Background and aim: Hip fracture patients are at great risk of malnutrition, but documentation of the effect of nutrition supplementation in this group is sparse and inconclusive. The aim of this study was to examine if personalized nutrition advice combined with vitamin K1, Ca and vitamin D could improve bone turnover 4 months after hip fracture.

Design: This is a preplanned sub study of a randomized controlled trial of orthogeriatric care. The intervention group received orthogeriatric care, including nutrition advice and supplementation. The control group received usual care at the orthopedic ward. Blood was drawn for measurements of a number of vitamins and of bone turnover markers upon admission and at four months follow up.

Results: 71 patients (31 in the intervention group and 40 controls) had available data at 4 months as well as at baseline. After four months, vitamin K1 and 25(OH)D were higher in the intervention group compared with controls; vitamin K1: 1.0 ± 1.2 vs 0.6 ± 0.6 ng/ml, $p = 0.09$, 25(OH)D: 60 ± 29 vs 43 ± 22 nmol/L, $p = 0.01$ when adjusted for baseline differences. In a secondary, unadjusted analysis, comprising all patients with available four months data ($n = 136$), the differences were statistically significant for vitamin K1 as well as 25(OH)D ($p = 0.03$ and $p < 0.001$, respectively). There was a non-significant increase in 25(OH)D in the intervention group from baseline to 4 months follow up, and a significant decrease in the control group. There was no difference in bone turnover markers between the two groups at 4 months follow up. A substantial loss of weight and physical function was found in both groups.

Conclusions: The supplementation of 25(OH)D and vitamin K1 improved serum concentrations of these vitamins, but this did not translate into any improvement in the bone turnover markers.

The RCT is registered in ClinicalTrials.gov NCT01009268 and NCT01738776.

1. Introduction

Hip fracture is an important cause of loss of function and loss of independence. The prevalence of hip fracture in Oslo is reported to be amongst the highest in the world [1,2] and bone mineral density (BMD) in elderly men and women in Oslo among the lowest in Europe [2]. Bone turnover markers (BTM) increase with age and elevated BTM are commonly observed in osteoporotic patients [3,4]. We previously reported that vitamins are associated with BTM measured preoperatively in hip fracture patients [5].

List of abbreviations: BALP, Bonespeciffic Alcaline Phosphatase; BADL, Barthel Activity of daily living; BMD, Bone Mineral Density; BTM, Bone turnover markers; CRP, C-Reactive Protein; CV, Coefficient of variance; HGS, Hand Grip Strength; IGF1, Insulin like growth factor 1; IQR, Inter Quartile Range; OC, Osteocalcin; OOT, Oslo Geriatric Trial; PINP, Procollagen Type I N-Terminal Propeptide; PTH, Parathyroid Hormone; RCT, Randomized Controlled Trial; totOC, Total Osteocalcin; ucOC, Undercarboxylated Osteocalcin Effects of vitamin D and K1.

* Corresponding author. Strålsundveien 5, 1672, Kråkerøy, Norway.
E-mail addresses: a.c.torbergsen@medisin.uio.no, actorbergsen@hotmail.com (A.C. Torbergsen).

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Low BMI is common in hip fracture patients, and many of the patients suffer from further weight loss after the fracture. Nutrition interventions in hip fracture patients show varying results. It may have an effect on the fittest patients, but not all [6,7]. Protein intake affects bone in several ways: it provides the structural matrix of bone, it improves IGF-1 levels, and increases intestinal calcium absorption [8]. During low protein intake, the body will use muscle protein to provide energy needed by functional organs, thus compromising muscle mass and subsequently BMD. A beneficial effect on bone is seen for supplementation of vitamin D and Ca [9], and some evidence indicates a beneficial effect also for vitamin K [10].

One of the roles of vitamin K is to retain calcium in bone. An increased risk of hip fracture is seen with low intake of vitamin K1 [11]. We previously reported low vitamin K1 in hip fracture patients compared with healthy controls [5]. Low intake of vitamin K1 rich foods are reported in Norway [12]. However, supplementation trials show conflicting results and to our knowledge no previous trial have tested the effect of vitamin K1, vitamin D and Ca supplements on BTM in hip fracture patients.

Therefore, we designed a randomized controlled trial (RCT) to examine the effect of nutrition supplementation with focus of vitamin K1, vitamin D and Ca on BTM. The RCT was carried out as a sub study of a RCT of orthogeriatric care [13].

2. Patients and methods

2.1. Patients

This study was a preplanned sub study of the Oslo Orthogeriatric Trial, Norway (OOT) [13]. The patients in the OOT were consecutively included and randomized in the emergency room by the orthopaedic surgeon on call to either the orthogeriatric unit (intervention group) or to the standard orthopaedic ward (care as usual) on admission for a hip fracture. The inclusion criteria was that the fracture had to be the result of a low energy trauma, which was defined as a fall from own height or from a level not higher than 1 m and a valid consent. We excluded patients who were regarded as moribund at admittance (as determined by the admitting orthopaedic surgeon based upon their clinical experience).

Inclusion of patients started in September 2009, and patients who were included until April 2011 were eligible for the vitamin substudy. The primary and secondary aims were assessed after 4 months intervention. The Primary aim was to study differences in BTM between the intervention and control group and the secondary aim was to study differences in weight change and physical performance between the groups.

2.2. The nutrition intervention

The supplement consisted of 150 μg vitamin K1, 20 μg vitamin D3 and 1000 mg Ca as well as 250 μg vitamin A, 10 mg vitamin E and 1.2 g ω-3 fatty acids using cod liver oil and a Ca, vitamin D3 and K1 fortification tablet. If the patient was taking vitamin K antagonists, vitamin K1 was omitted from the supplement.

Upon discharge from hospital, the patients in the intervention group had vitamin supplements handed out to them for 4 months usage and the supplements were noted in their medication list. A letter followed every patient to explain their participation in a research project and all patients had an individual plan, made by a clinical nutritionist, on how to improve their food intake. As part of the individualized plan, the patients were advised to take 2 protein enriched nutrition drinks daily.

The control received usual care in the orthopedic ward without any systematic nutritional advice or supplements.

2.3. Data sampling

Baseline characteristics were collected by the same project staff in both intervention patients and controls, but the nutritionist in the orthogeriatric unit never entered the orthopedic ward. Demographic data at baseline is described in [13]. The same chair scale was used in the two treatment groups to record baseline weight. Baseline activities of daily living was measured using the Barthel ADL Index (BADL) [14].

A designated nurse, blinded to treatment allocation, examined all patients at their residence four months following fracture. Weight was measured using a portable standing scale, patients wearing light clothing. Height was measured towards a wall using a tape measure. The chair scale and the portable scale were calibrated before, during and at the end of the 4 months follow up. At 4 months follow up, the same data were recorded using the same instruments for Handgrip strength (HGS, Jamar- Germany), three repetitions per examination in the dominant arm. The best handgrip test was used, and BADL was recorded as baseline.

2.4. Preparation of blood samples

At baseline, blood was collected by venipuncture shortly after admission for the hip fracture and prior to operation. All samples clotted 30 min at room temperature and serum was separated by centrifugation. Aliquots were immediately stored at −80 °C for later analysis. At 4 months follow up, blood was drawn in the patient's home and aliquots were blocked for sunlight and stored at −80 °C within 1 h for assays of vitamins and BTM. The laborites were blinded to treatment allocation.

2.5. Laboratory analysis

Vitamins examined both preoperatively and at 4 months follow up were: vitamin K1, 25(OH)D, vitamin B1, B6, C, E and A. BTM examined both preoperatively and postoperatively were: Total osteocalcin (total OC), undercarboxylated osteocalcin (ucOC), bone-specific alkaline phosphatase (BALP), insulin like growth factor 1 (IGF1) and procollagen type I N-terminal propeptide (PINP), all markers of bone formation, and furthermore the bone resorption markers C-telopeptide-cross-linked type I collagen (CTX1) and PTH.

Vitamin K1 and ucOC were analyzed in serum by Vitas AS Norway (www.vitas.no). Vitamin K1 was analyzed by HPLC with on-line electrochemical reduction and fluorescent detection, and ucOC by enzyme ELISA (Japan). The following analyses were performed by the endocrinological laboratory at Oslo University Hospital, Aker: 25(OH)D by radioimmunoassay (RIA, USA), BALP by enzyme activity immune extraction (Ca USA). BALP was quantified in E/Liter, 1E = 1 μmol hydrolyzed p-NPP/minute, where p-NPP is a monoclonal anti-bone-ALP antigene. TotOC and PTH were analyzed by a non-competitive immunoradiometric assay (LIMA USA), IGF-1 and CTX1 was analyzed by ELISA, Finland and Denmark respectively. PINP was analyzed by radioimmunoassay (RIA, Finland).

The analysis of vitamin C was performed according to Zannoni V et al. [15]. Vitamin E was assayed by radioimmunoassay (RIA, Germany). High pressure liquid chromatography (HPLC) was used for assays of blood thiamine diphosphate (vitamin B-1), and blood Pyridoxal-5′-phosphate (vitamin B6) by Chromsystems, (Munich, Germany).

2.6. Statistical analysis

Pre specified analyses comprised comparison of BTM between the intervention and the control group four months after the fracture, adjusted for the baseline values. As a supplementary analysis, we also compared BTM between all intervention and control patients having available data at four months, not adjusting for baseline values.

No studies have previously reported the effect of supplementation of vitamin K1, vitamin D3 and Ca on BTM in the subacute phase after a hip fracture. This trial is therefore of explorative nature. Data are presented as means or medians ± SD or numbers (percentages). Student's *t* test or Mann–Whitney *U* test were used to compare continuous data between groups, Chi-square test to compare categorical data and Spearman's rho or Pearson correlation coefficients were calculated to explore correlations between continuous variables. The level of significance was $P < 0.05$, and all *P* values are 2-tailed.

Statistical analyses were performed in SPSS 18 (SPSS Inc, Chicago, IL) for Windows.

2.7. Ethics

The Regional Committee for Medical Research Ethics, the Data Inspectorate and the Directorate for Health and Social Affairs approved the study protocol. Most patients, or the nearest next of kin, gave informed written consent before enrollment; some patients were included on presumed consent, confirmed by next of kin shortly after enrolment. The study was performed according to the Helsinki declaration. ClinicalTrials.gov NCT01009268 and NCT01738776.

3. Results

Patient flow is shown in Fig. 1. In total, 216 patients were randomized in OOT during the inclusion period for the nutrition sub analysis, whereof 103 for technical or logistic reasons did not have a baseline blood analysis performed. A further 24 patients withdrew from the study before the four moths follow up, of these 13 were dead (Fig. 1). From 18 we did not obtain blood samples at 4 months because the patient did not cooperate in blood sampling or because an insufficient amount of blood was drawn. This left 71 patients (31 intervention patients and 40 controls) for the primary analysis. There was no significant difference in the number of missing patients between the intervention and the control group. 65 patients without baseline values had blood drawn at four months, contributing to the supplementary, unadjusted analyses thus comprising 136 patients (66 intervention patients and 70 controls).

In total 79 percent were women. There were no statistically significant difference in vitamin K1, 25(OH)D or in any of the BTM between males and females measured at 4 months. Neither was there any difference in our findings when analyzing the population as one group or stratified by gender. The results are therefore presented as one group.

At 4 months, 25(OH)D was statistically significantly higher in the intervention group than in the control group, whereas there was a marginally significant trend for vitamin K1 (Table 1). The patients in both groups had lost weight, and there was no difference in weight change between the groups (Table 1). No differences between groups were found in BTM or IGF1 when adjusting for baseline data (Table 1).

In a secondary, unadjusted analysis comprising all patients with available data at four months (n = 136), vitamin K1 as well as 25(OH)D was significantly higher in the intervention group, but there were no differences for the other vitamins, the BTM, nor for body weight (Table 2). Neither was there any difference in BADL or HGS between the intervention and the control group at 4 months follow up.

Vitamin K1 correlated negatively with totOC, ucOC and CTX1. 25(OH)D correlated negatively with ucOC, BALP, PINP, PTH and CTX1. Vitamin A and E correlated negatively with BALP. Vitamin E correlated negatively with totOC and CTX1. A strong positive correlation was seen between vitamin A and IGF1, $p < 0.001$ (Table 3). Vitamins correlated with hand muscle strength and with activities of daily living as measured by HGS and BADL, respectively (Table 3).

In the 24 patients who were lost between baseline and 4 moths follow up (Fig. 1), baseline values of vitamins K1, C and B6 were significantly lower than in patients with complete 4 months data. Although not statistically significant, the same trend was seen for BMI and thiamine. There was also a trend towards a higher PTH and ucOC in the patients lost to follow up compared to those with complete data. There were no differences in age, BADL or in Charlson Comorbidity Index (Table 4). For the 18 patients who were followed up at four months but lacked blood samples (Fig. 1), we observed no differences in baseline vitamins, age, BMI, Charlson Comorbidity Index, BADL or BTM from those with a blood sample available at four months (data not shown).

4. Discussion

We found a statistically significantly effect of vitamin supplementation on 25(OH)D and a borderline significant effect on vitamin K1. Both differences were statistically significant in secondary analyses utilizing all available four months data, most likely due to better statistical power in this analysis. Vitamin K1 increased in both groups, whereas there was a clear reduction in 25(OH)D in the control group. However, there was no difference in BTM between the two groups.

There are several possible explanations why there was no effect on BTM. The effect of nutrition supplementation might have been masked by the strong increase in BTM signal after fracture, and a follow-up of four months may be too short. The dosage may have been too low, the supplementation of energy and protein might have been insufficient, and some controls may have taken supplement.

The reported positive effect of vitamin D, Ca and vitamin K upon bone tissue has been demonstrated in healthy, pre- and postmenopausal as well as osteoporotic elderly populations [9,16–18]. To the best of our knowledge, the effect of Vitamin D, Ca and vitamin K1 on BTM in hip fracture patients has not previously been studied. However, elevated BTM after hip fracture have been described to last for several months, up to a year [19]. The increased BTM signal due to fracture may be stronger than a possible decrease due to supplementation and may mask any change in BTM as the duration of our supplementation may have been too short.

We used supplements commonly used in elderly (cod liver oil) combined with a Ca, vitamin K1 and D3 containing tablet due to a possible positive interaction between vitamin D and vitamin K on bone [5]. The recommended daily dosage of vitamin K1 in the USA is 95 μg. The literature suggests, however, that 200–500 mg is required to achieve an optimal carboxylation of osteocalcin [20]. It has been suggested that pharmacological doses of vitamin D rather than physiological doses is required to enhance 25(OH)D from a deficient state at 50 nmol/L to an adequate state at 75 nmol/L [9]. Lower ucOC and improved BMD has been found after 1 year supplementation using physiological doses of vitamin D3, vitamin K1 and B6 in a healthy elderly population [21]. In a post fracture state, higher dosages may be necessary.

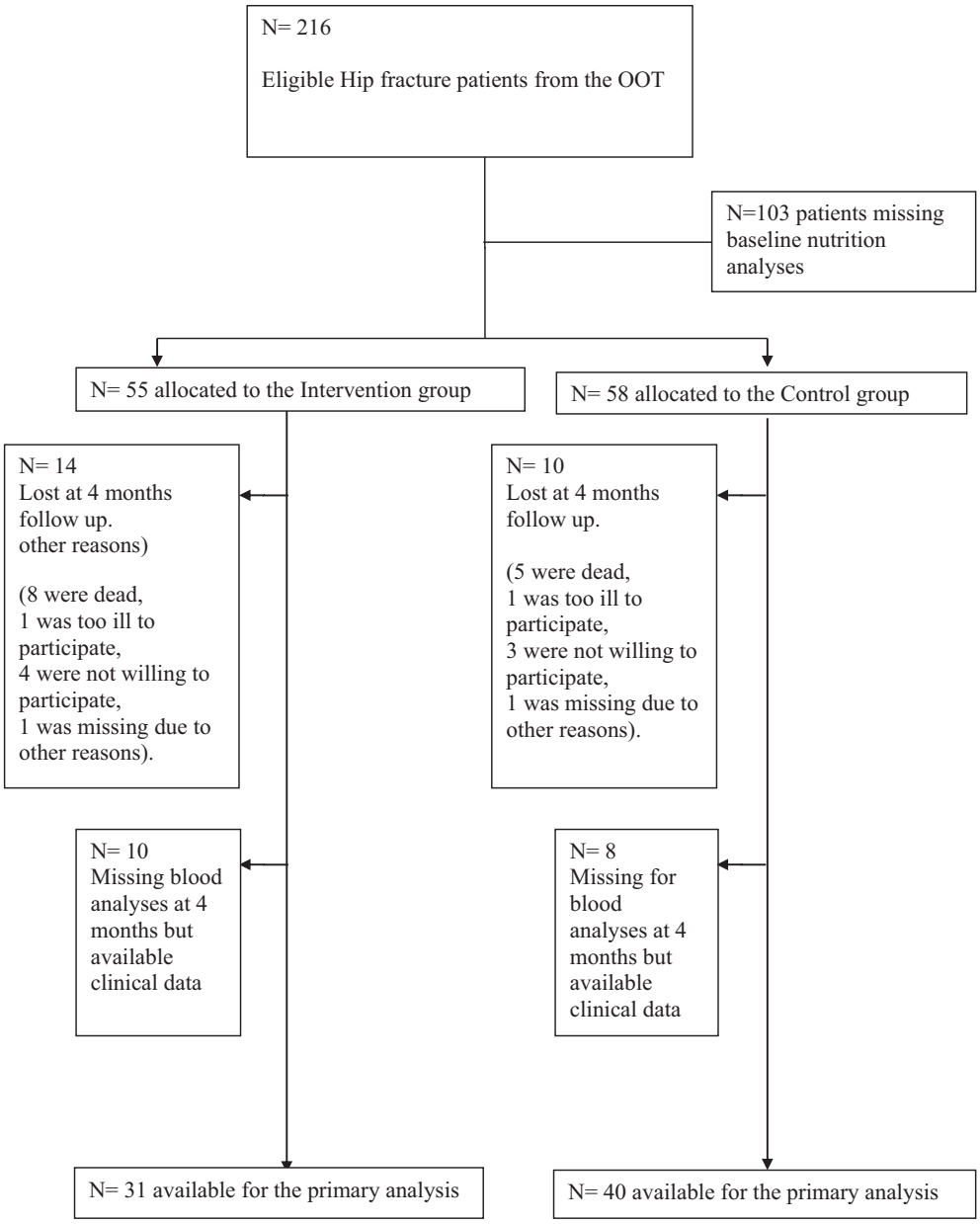

Fig. 1. Patient flow.

Most nutritional interventions after fracture have focused on increasing protein and caloric intake through nutrition drinks with mixed results [7,22]. We encouraged oral nutrition drinks and gave individual advice on how to improve protein and energy. However, we were not able to prevent weight loss, commonly reported after hip fracture [23]. A negative energy and protein balance may have counteracted any beneficial effect of the micronutrients.

At 4 months follow up, vitamin K1 status had improved in the control group as well as in the intervention group. Some patients in the control group may have received supplement since control patients for ethical reasons were not told not to take supplements.

There was an inverse correlation between 25(OH)D and vitamin K1 and BTM, indicating that patients higher in these two vitamins have lower BTM and improved recovery in bone metabolism after hip fracture, independent of treatment group. Other vitamins also showed inverse correlations with BTM, possibly indicating that future nutrition supplementation trials in hip fracture patients should aim to optimize these vitamins as well as protein and energy.

A further decrease in 25(OH)D seems to be prevented in the supplementation group. A low 25(OH)D after fracture may increase the risk of recurrent falls and thus a second fracture [16]. It has also been suggested that inflammation contributes to prolonged rehabilitation after hip fracture [24], and a low 25(OH)D has recently been associated with increased inflammation [25]. We have previously reported better mobility in home dwelling patients admitted to the intervention group in the OOT 4 months after fracture compared with home dwelling patients in the control group [13]. The improved 25(OH)D status in the intervention group may have contributed to this.

Table 1
Change in primary and secondary effect variables during the treatment period[a].

	Intervention group (n = 31)			Control group (n = 40)			Adjusted mean difference between groups[b] (95% CI) ANCOVA
	Baseline	4 months follow up	Mean change (95% CI)	Baseline	4 months follow up	Mean change (95% CI)	
Vitamin K1, ng/ml[c]	0.3 ± 0.2	1.0 ± 1.2	0.7 (0.2,1.1)	0.4 ± 0.3	0.6 ± 0.6	0.3 (0.1,0.4)	0.4 (−0.06,0.89)
25(OH)D, nmol/L	53 ± 26	60 ± 29	7 (−2,16)	49 ± 21	43 ± 22	−6 (−11,−0.6)	14 (5,23)
Bone formation:							
TotOC, nmol/L	1.0 ± 0.8	1.9 ± 1.1	1.0 (0.6,1.3)	0.8 ± 0.6	1.8 ± 0.9	1.1 (0.8,1.3)	−0.1 (−0.5,0.3)
UcOC, ng/ml	2.9 ± 3.4	5.9 ± 5.4	2.9 (0.8,5.0)	3.2 ± 3.9	5.7 ± 3.6	2.5 (0.9,4.1)	0.3 (−2.0,2.5)
BALP, E/L[a]	27 ± 11	32 ± 13	5 (−0.6,11)	29 ± 14	36 ± 15	8 (4,12)	−3 (−9,3)
PINP, μg/L	41 ± 22	111 ± 87	70 (41,99)	43 ± 25	115 ± 45	72 (58,86)	−2 (−31,28)
IGF1, nmol/L	12 ± 5	16 ± 8	4 (1,7)	13 ± 6	17 ± 6	4 (2,6)	−0.1 (−3.2,3.0)
Bone resorption:							
PTH, pmol/L	6.2 ± 3.5	6.8 ± 6.0	0.6 (−1.8,2.9)	7.0 ± 5.1	5.9 ± 2.9	−1.1 (−2.8,0.6)	1.0 (−1.1,3.2)
CTX1, μg/L	0.48 ± 0.23	0.51 ± 0.22	0.03 (−0.04,0.10)	0.47 ± 0.22	0.47 ± 0.16	0.00 (−0.06,0.06)	0.04 (−0.04,0.11)
Weight, kg	60 ± 5	56 ± 15	−4 (−6,−3)	66 ± 16	61 ± 16	−5 (−8,−2)	−0.1 (−2.9,3.1)

1E = 1 μmol hydrolysed p-NPP/minute, where p-NPP is a monoclonal anti-bone-ALP antigene. BALP = Bone specific Alcaline Phosphatase, CTX1 = C-Telopeptide-Cross-Linked Type I Collagen, IGF1 = Insulin like growth factor 1, PTH= Parathyroid Hormone, PINP = Procollagen Type I N-Terminal Propeptide, TotOC = total Osteocalcin, UcOC = Undercarboxylated Osteocalcin.

[a] Only patients with baseline as well as 4 months data for the respective variables are included in the analyses. In the intervention group 1 patient was missing for 25(OH)D and CTX1, 2 patients were missing for totOC and weight was missing in 4 patients. In the control group 1 patient was missing for PTH, CTX1 and BALP, 2 patients were missing for totOC and PINP, 3 patients for IGF1, 7 patients for vitamin K1 and ucOC and weight was missing in 18 patients.

[b] Intervention group − control group.

[c] Numbers are mean ± SD.

Table 2
Secondary, unadjusted analysis of outcome variables at 4 months (all patients with available data at that time).

	Intervention group N = 66	Control group N = 70	P
Vitamin K1, ng/ml[a]	0.7 (0.3,1.1)	0.5 (0.3,0.8)	0.03
25(OH)D, nmol/L[b]	61 ± 26	45 ± 21	<0.001
Vitamin C, μmol/L	45 ± 27	43 ± 25	0.76
Vitamin E, μmol/L	28 ± 7	30 ± 8	0.21
Vitamin B6, nmol/L	77 (49,147)	61 (50,122)	0.64
Thiamin, nmol/L	174 ± 41	169 ± 42	0.47
Vitamin A, μmol/L	2.1 ± 0.7	1.9 ± 0.5	0.17
Weight change, Kg	−4.2 ± 4.6	−4.7 ± 6.3	0.77
Bone formation			
TotOC, nmol/L	1.5 (0.9,2.1)	1.6 (1.2,2.2)	0.44
UcOC, ng/ml	4.2 (2.5,8.4)	4.6 (3.7,7.8)	0.50
BALP, E/L[c]	29 (23,37)	30 (24,44)	0.23
PINP, μg/L	88 (66,129)	106 (77,156)	0.13
IGF1, nmol/L	16 ± 7	15 ± 6	0.47
Bone resorption			
PTH, pmol/L	4.4 (3.0,6.2)	5.0 (3.6,6.9)	0.36
CTX1, μg/L	0.45 (0.29,0.61)	0.45 (0.35,0.55)	0.94

BALP = Bone specific Alcaline Phosphatase, CTX1 = C-Telopeptide-Cross-Linked Type I Collagen, IGF1 = Insulin like growth factor 1, Parathyroidea Hormone, PINP = Procollagen Type I N-Terminal Propeptide, TotOC = total Osteocalcin, UcOC = Undercarboxylated Osteocalcin.

Measurements are missing for some variables. In the intervention group: Weight change in 35, Vitamin C in 26, Vitamin E and A in 15, Vitamin B6 and Thiamin in 9, TotOC in 6, CTX1 in 4, 25(OH)D, ucOC, BALP, PINP, IGF1 and PTH in 3 and Vitamin K1 in 2 patients. In the control group: Weight change in 48, Vitamin C in 26, Thiamin, Vitamin E and A in 15, Vitamin B6 in 9, Vitamin K1 in 8, ucOC in 7, TotOC and IGF1 in 4, BALP, PINP, 25(OH)D, PTH and CTX1 in 1.

[a] Numbers are median (IQR), all such data. Tested using Mann Whitney U-test.

[b] Numbers are mean ± sd, all such data. Tested using Students T-test unless otherwise stated.

[c] 1E = 1 μmol hydrolysed p-NPP/minute, where p-NPP is a monoclonal anti-bone-ALP antigene.

Out of 216 eligible patients from the OOT, only 71 participated in the primary analysis adjusted for baseline data. In an attempt to rule out selection bias and to increase statistical power, we performed a secondary analysis comprising all participants at 4 months follow up, but without baseline data, n = 136 patients. The result of this secondary analysis was in principle identical.

Table 3
Correlations between vitamins and bone turnover markers as well as physical function.

	Vitamin A	Vitamin C	25(OH)D	Vitamin E	Vitamin K1	Thiamin	Vitamin B6
TotOC				−0.29*[a]	−0.19*[b]		
UcOC		−0.27**[a]	−0.18*[a]		−0.23**[a]		
BALP	−0.24**[a]		−0.22**[a]	−0.25**[b]			
PINP			−0.29***[a]				−0.19*[a]
IGF1	0.49***[b]						
PTH			−0.32***[a]				
CTX1			−0.27**[a]	−0.20*[b]	−0.20*[a]		
Hand grip strength, kg		0.25*[a]	0.22*[a]	0.22*[a]		0.28**[b]	
BADL		0.26*[a]	0.39***[a]			0.31***[a]	0.30***[a]

*p= 0.05, **p = 0.01, ***p ≤ 0.001.

BALP = Bone specific Alcaline Phosphatase, CTX1 = C-Telopeptide-Cross-Linked Type I Collagen, IGF1 = Insulin like growth factor 1, Parathyroidea Hormone, PINP = Procollagen Type I N-Terminal Propeptide, TotOC = total Osteocalcin, UcOC = Undercarboxylated Osteocalcin.

Only statistically significant correlations are displayed.

[a] Spearmans correlation.

[b] Pearson correlation.

The primary aim of the OOT was to study the outcome of treatment in the orthogeriatric ward compared with traditional treatment in the orthopedic ward, and the intervention was therefore not prolonged beyond the acute stay. Varying compliance is a well known challenge in nutrition supplementation studies, and if we had followed up the intervention group, compliance may have been better inducing larger differences in 25(OH)D and vitamin K1 between cases and controls, prevented weight loss and the results on BTM may have been different.

Patients who were missing at 4 months follow up in the OOT due, primarily, to mortality and morbidity had lower vitamin K1, vitamin C and thiamine at baseline compared with patients with complete data, indicating that the poorest nourished patients prior to fracture has the poorest outcome 4 months after fracture. Furthermore, 25(OH)D status worsened in the control group. Nutritional efforts in the care and rehabilitation of hip fracture

Table 4
Baseline characteristics in lost patients (n = 24) versus patients with 4 months follow up data (n = 74).

	Participants N = 74	Missing at 4 months N = 24	P
Patient characteristics			
Age, years[a]	83 ± 9	83 ± 8	0.92
BMI, kg/m	25 ± 6	23 ± 3	0.17
Charlson index[b]	1 (0,2)	1 (0,2)	0.38
Albumin, g/L	40 ± 4	40 ± 3	0.79
CRP, mg/L[b]	6 (2,30)	6 (1,14)	0.83
Vitamin analyses			
Vitamin K1, ng/ml[b]	0.25 (0.18,0.39)	0.16 (0.10,0.20)	0.01
25(OH)D, nmol/L	51 ± 23	47 ± 26	0.50
Vitamin C, μmol/L	35 ± 20	24 ± 12	0.01
Vitamin E, μmol/L	23 ± 9	2 ± 7	0.31
Vitamin B6, nmol/L[b]	76 (57,117)	60 (43,78)	0.01
Thiamin, nmol/L	179 ± 48	151 ± 54	0.06
Vitamin A, μmol/L	1.2 ± 0.6	1.2 ± 0.4	0.66
Bone formation			
TotOC nmol/L	0.5 (0.4,1.1)	0.8 (0.4,1.1)	0.24
ucOC, ng/ml[b]	1.8 (1.0,3.8)	3.1 (1.3,5.5)	0.12
BALP E/L	24 (20,31)	25 (21,31)	0.57
PINP μg/L[b]	35 (26,54)	42 (26,64)	0.36
IGF1, nmol/L	12 ± 6	12 ± 5	0.68
Bone resorption:			
PTH pmol/L[b]	6 (4,9)	8 (4,12)	0.09
CTX1 μg/L[b]	0.42 (0.35,0.60)	0.48 (0.34,0.71)	0.25

BALP = Bone specific Alcaline Phosphatase, CTX1 = C-Telopeptide-Cross-Linked Type I Collagen, Parathyroidea Hormone, PINP = Procollagen Type I N-Terminal Propeptide, TotOC = total Osteocalcin, Baseline data are missing for some patients. Participating patients: BMI 26, vitamin C 20, thiamin 15, vitamin B6 12, vitamin A 8, vitamin E 6, K1 4, 25(OH)D 3, totOC 13, ucOC and PINP 6, IGF1, BALP, PTH and CTX1 5 patients. In the missing patients: BMI 15, Thiamin 4, vitamin C and B6 3, vitamin K1 CRP and albumin 1.
1E = 1 μmol hydrolyzed p-NPP/minute, where p-NPP is a monoclonal anti-bone-ALP Antigen.
[a] Numbers are mean ± sd, all such data. Tested using Students T-test unless otherwise stated.
[b] Numbers are median (IQR), tested using Mann Whitney U-test.

patients may be important even though we were unable to find differences in BTM 4 months after fracture.

5. Conclusion

The supplementation of 25(OH)D and vitamin K1 improved the serum concentration of these vitamins, but this did not translate into any improvement in the bone turnover markers.

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TBW, FF and MM designed the research. FF were the principal orthopedic surgeons in charge of including hip fracture patients. ACT and LOW conducted the research. ACT analyzed the data and wrote the manuscript. MM had primary responsibility for final content. All authors read and approved the final manuscript.

The full trial protocol can be read in (27)

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Conflict of interest statement

There are no conflicts of interest related to the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnesp.2017.11.012.

References

[1] Lofthus CM, Osnes EK, Falch JA, Kaastad TS, Kristiansen IS, Nordsletten L, et al. Epidemiology of hip fractures in Oslo, Norway. Bone 2001;29:413–8.
[2] O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ. The prevalence of vertebral deformity in european men and women: the European Vertebral Osteoporosis Study. J Bone Miner Res 1996;11:1010–8.
[3] Burtis CA, Ashwood ER, Bruns DE. Tietz textbook of clinical chemistry and molecular diagnostics. 2011. p. 1733–93.
[4] Gossiel F, Finigan J, Jacques R, Reid D, Felsenberg D, Roux C, et al. Establishing reference intervals for bone turnover markers in healthy postmenopausal women in a nonfasting state. Bonekey Rep 2014;3:573.
[5] Torbergsen AC, Watne LO, Wyller TB, Frihagen F, Stromsoe K, Bohmer T, et al. Vitamin K1 and 25(OH)D are independently and synergistically associated with a risk for hip fracture in an elderly population: a case control study. Clin Nutr 2015;34:101–6.
[6] Espaulella J, Guyer H, az-Escriu F, Mellado-Navas JA, Castells M, Pladevall M. Nutritional supplementation of elderly hip fracture patients. A randomized, double-blind, placebo-controlled trial. Age Ageing 2000;29:425–31.
[7] Avenell A, Handoll HH. Nutritional supplementation for hip fracture aftercare in older people. Cochrane Database Syst Rev 2010, CD001880.
[8] Heaney RP, Layman DK. Amount and type of protein influences bone health. Am J Clin Nutr 2008;87:1567S–70S.
[9] Brincat M, Gambin J, Brincat M, Calleja-Agius J. The role of vitamin D in osteoporosis. Maturitas 2015;80:329–32.
[10] Vermeer C, Theuwissen E, Vitamin K. Osteoporosis and degenerative diseases of ageing. Menopause Int 2011;17:19–23.
[11] Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. Am J Clin Nutr 1999;69:74–9.
[12] Askim M. Vitamin K in the Norwegian diet and osteoporosis. Tidsskr Nor Laegeforen 2001;121:2614–6.
[13] Watne LO, Torbergsen AC, Conroy S, Engedal K, Frihagen F, Hjorthaug GA, et al. The effect of a pre- and postoperative orthogeriatric service on cognitive function in patients with hip fracture: randomized controlled trial (Oslo Orthogeriatric Trial). BMC Med 2014;12:63.
[14] Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J 1965;14:61–5.
[15] Zannoni V, Lynch M, Goldstein S, Sato P. A rapid micromethod for the determination of ascorbic acid in plasma and tissues. Biochem Med 1974;11:41–8.
[16] Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692.
[17] Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. Lancet Diabetes Endocrinol 2014;2:307–20.
[18] Stevenson M, Lloyd-Jones M, Papaioannou D. Vitamin K to prevent fractures in older women: systematic review and economic evaluation. Health Technol Assess 2009. 13:iii-134.
[19] Ivaska KK, Gerdhem P, Akesson K, Garnero P, Obrant KJ. Effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women. J Bone Miner Res 2007;22:1155–64.
[20] Guralp O, Erel CT. Effects of vitamin K in postmenopausal women: mini review. Maturitas 2014;77:294–9.
[21] Mazzanti L, Battino M, Nanetti L, Raffaelli F, Alidori A, Sforza G, et al. Effect of 1-year dietary supplementation with vitaminized olive oil on markers of bone turnover and oxidative stress in healthy post-menopausal women. Endocrine 2015;50(2):326–34.

[22] Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998;128:801–9.
[23] Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritional supplementation and resistance training in nutritionally at risk older adults following lower limb fracture: a randomized controlled trial. Clin Rehabil 2006;20:311–23.
[24] Miller RR, Cappola AR, Shardell MD, Hawkes WG, Yu-Yahiro JA, Hebel JR, et al. Persistent changes in interleukin-6 and lower extremity function following hip fracture. J Gerontol A Biol Sci Med Sci 2006;61:1053–8.
[25] Kroner JC, Sommer A, Fabri M. Vitamin D every day to keep the infection away? Nutrients 2015;7:4170–88.