Original article

Vitamin D status and adult fracture healing

E.A. Gorter*, P. Krijnen, I.B. Schipper

Department of Surgery and Traumatology, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

Introduction: The effect of vitamin D on maintaining bone health is well researched and its role in the various metabolic stages of fracture healing has become evident, the clinical effects of a vitamin D deficiency in human fracture healing are less well described. Considering today's high prevalence of vitamin D deficiency, the aim of this present study was to investigate the effect of vitamin D status on human adult fracture healing.

Methods: The serum calcidiol concentration was measured in a cohort of adult patients with a fracture in the upper or lower extremity between September 2012 and October 2013. Deficient patients (serum calcidiol <50 nmol/L) were treated with vitamin D. Clinical and radiological consolidation was determined.

Results: Vitamin D concentration was measured in 617 patients; 249 (40%) were vitamin D deficient, they subsequently received vitamin D supplements. In 141 patients with a deficiency vitamin D was measured again after 4 months; 111 patients (78.7%) were no longer vitamin D deficient, and 30 remained vitamin D deficient. In six patients of the entire cohort, a clinical delayed union was described. The incidence of delayed union was higher in the group that remained vitamin D deficient (9.7%) compared to the patients who were not initially deficient (0.3%) and those who were no longer deficient after supplementation (1.7%; $p < 0.001$). The incidence of radiological delayed union did not differ between these three groups ($p = 0.67$).

Conclusion: The results of this research suggest that the vitamin D status at time of fracture affects fracture healing. Further research is needed to confirm these results.

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1. Introduction

Vitamin D is synthesised in the skin under influence of UV irradiation. It is hydroxylated in the liver, forming calcidiol (25(OH)D), and later in the kidneys to its most biochemically active form: 1,25(OH)₂D₃. The active form binds to receptors in the intestine, kidney, parathyroid glands and bone, regulating plasma levels of calcium and phosphorus and subsequently bone mineralisation and bone quality.¹ The high prevalence of vitamin D deficiency is considered a global problem.^{2,3} Vitamin D deficiency is known to cause osteopenia, and osteomalacia, and to worsen osteoporosis.⁴ It also weakens the muscles and may subsequently increase the risk of falls and fractures.⁵

The effect of vitamin D on maintaining bone health is well researched on a cellular level and its role in the various metabolic stages of fracture healing has become evident.⁶ However, the

clinical effects of a vitamin D deficiency and of supplementation on human fracture healing are less well described and published results remain inconclusive.⁶ In two retrospective studies, no difference in vitamin D concentrations was found between fracture patients with delayed or non-union and matched healthy controls.^{7,8} Two case-control studies found significantly lower serum concentrations of vitamin D in patients with a non-union.^{9,10} Two human studies reported the effect of supplementation of vitamin D on fracture healing, one found a positive effect on bone mineral density¹¹ and one found increased fracture callus area at the fracture site.¹²

Considering today's high prevalence of vitamin D deficiency, it is relevant to address the potentially adverse clinical effect of vitamin D deficiency on fracture healing. The aim of the present study was to investigate whether complications in fracture consolidation occur more frequently in continued vitamin D deficient patients even after vitamin D supplementation, compared to patients who are no longer vitamin D deficient after vitamin D supplementation and patients who had adequate vitamin D levels at time of trauma.

* Corresponding author at: Leiden University Medical Center, Department of Surgery and Traumatology, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
E-mail address: e.a.gorter@lumc.nl (E.A. Gorter).

2. Methods

2.1. Patients

All adult patients (≥ 18 years) with a fracture of the upper or lower extremity, treated between September 2012 and October 2013 in the outpatient clinic of the Leiden University Medical Centre, a level 1 trauma centre, were eligible for inclusion in the study. No exclusion criteria were applied. Within one week after fracture patients were asked to participate and to provide written informed consent. After the patient's consent was obtained, blood was taken and a questionnaire was filled out covering medical history and prior medication use. Demographics and fracture characteristics were also documented. The study was approved by the institutional Medical Ethics Review Board (protocol 12.058).

2.2. Vitamin D status

The serum calcidiol (25-(OH)D) concentration was measured by means of Roche Diagnostics' Electro Chemo Luminescence Immuno Assay (ECLIA, Modular E170). The vitamin D serum concentration was defined as sufficient if the serum calcidiol level was ≥ 75 nmol/L (30 ng/ml); insufficient if the level was between 50 and 75 nmol/L; deficient if the serum calcidiol level was < 50 nmol/L (20 ng/ml), and severely deficient if the serum level was < 25 nmol/L (10 ng/ml).^{4,13–16} Patients who were vitamin D deficient (< 50 nmol/L) received a prescription for cholecalciferol supplementation (1200 IU per os once daily) for a duration of 4 months, without verification of daily intake during this period. After four months, all initially deficient patients were asked to have their vitamin D serum concentration measured again either by the general practitioner or in the outpatient clinic if they had not been discharged.

2.3. Fracture consolidation

Both clinical and radiological delayed union were registered retrospectively from the electronic hospital records. Clinical delayed union was registered when this was appointed in the hospital records as such. Radiological delayed union was defined as incomplete union/consolidation on radiography after 16 weeks or more, i.e. no complete bridging bone growth between the two fracture fragments.

2.4. Statistical analysis

Patient characteristics are presented as mean and standard deviation (SD) or as number and percentage. Categorical variables

were compared between patient groups using the Chi-square test, and the student *t*-test was used for group comparisons of continuous variables. *P* values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS software version 20 (SPSS, Inc. Chicago, IL, USA).

3. Results

3.1. Patients and vitamin D status

The vitamin D concentration of 617 patients was measured. Patients' characteristics are shown in Table 1. The study population were generally healthy with slightly more women around the age of 50. At the time of trauma, the serum calcidiol levels ranged between 7 and 175 nmol/L, with a mean of 59.2 nmol/L (SD = 29.0). Vitamin D deficiency was detected in 249 patients (40%), including 67 (11%) patients with severe deficiency. Only 173 patients (28%) had sufficient vitamin D levels (Fig. 1). In 141 deficient patients (57%), the vitamin D serum concentration was determined again after four months of supplementation. Thirty (21%) of these patients still had insufficient vitamin D levels at that time. Eighteen of the 30 patients with persistent deficiency had a severe deficiency at the time of trauma.

3.2. Fracture consolidation

Together these 617 patients were treated for 643 fractures. In 6 patients a clinical delayed union was described in the patient record; three patient were treated for a midshaft humerus fracture, one for a proximal humerus fracture, one for a metatarsal fracture and one for an ankle fracture. In patients who remained vitamin D deficient despite supplementation, significantly more clinical delayed unions ($n = 3$; 9.7%) were registered compared to patients who were not initially vitamin D deficient (0.3%) and initially deficient patients who were no longer vitamin D deficient after supplementation (1.7%; $p < 0.001$; Table 2).

Most (87%) of the 643 fractures healed within 16 weeks. These patients were discharged from follow-up at the outpatient clinic. Of the remaining 84 (13%) fractures radiological imaging was available to assess consolidation after 16 weeks. In this group of fractures, 39 (46%) fractures did not show complete radiological consolidation at 16 weeks and were considered to have radiological delayed union. No statistically significant difference was found for the incidence of radiological delayed union between the patients presenting with initially no vitamin D deficiency, the patients who were no longer vitamin D deficient after supplementations and the patients who remained vitamin D deficient after supplementation ($p = 0.67$; Table 2).

Table 1

Characteristics of patients with an extremity fracture, by vitamin D status.

Characteristic	Initially not vitamin D deficient ($n = 368$)	Initially vitamin D deficient status after supplementation			Vitamin D status unknown ($n = 108$)
		Not vitamin D deficient ($n = 111$)	Still vitamin D deficient ($n = 30$)	<i>p</i> ^a	
Female gender, <i>n</i> (%)	229 (62)	79 (71)	14 (47)	0.04	39 (36)
Age in years, mean (SD)	48.7 (19.1)	58.5 (16.5)	50.3 (18.3)	0.00	41.6 (20.3)
No medical history, <i>n</i> (%)	232 (63)	85 (77)	26 (87)	0.002	69 (64)
No use of medication, <i>n</i> (%)	150 (40)	35 (32)	11 (37)	0.21	61 (57)
Conservative treatment, <i>n</i> (%)	316 (86)	93 (85)	27 (90)	0.68	90 (83)
Fracture location, <i>n</i> (%)					
- Distal forearm	123 (32)	46 (40)	7 (23)		24 (21)
- Metacarpalia	51 (13)	12 (10)	1 (3)		17 (15)
- Metatarsalia	39 (10)	7 (6)	8 (26)		21 (18)
- Ankle	38 (10)	17 (15)	3 (10)		11 (10)

^a Comparison of 3 groups: patients who were initially not vitamin D deficient, patients who were no longer vitamin D deficient after supplementation, and patients who were still vitamin D deficient after supplementation.

Fig. 1. Flowchart vitamin D status fracture population.

4. Discussion

A high prevalence of vitamin D deficiency (40%) or severe deficiency (11%) was found in a general adult outpatient fracture population. In patients with a vitamin D deficiency more delayed union were described clinically, although the incidence of radiological delayed union did not depend on vitamin D status.

Up until now, a few studies have been performed that explored the effect of vitamin D on fracture healing, all with inconclusive results. This study investigated the effect of the initial vitamin D status and supplementation on fracture healing in a large cohort. Two case-control studies found more vitamin D deficiency in patients with delayed or non-union compared to patients with normal fracture healing.^{9,10} A possible detrimental effect of vitamin D deficiency on clinical fracture healing has been suggested by Brinker et al.¹⁷ Tauber et al.⁹ suggested that a deficiency might be the result of increased consumption of vitamin D metabolites during the process of delayed union. In our large cohort of patients with an extremity fracture, we found only 5 cases of clinical and radiological delayed union that resulted in secondary surgery. We did not find any indication that the initial vitamin D status or supplementation influenced the incidence of radiological delayed union. This result is supported by two other case-control studies, that both did not find a significant difference in serum vitamin D concentration in patients with a delayed or non-union compared to patients with normal a fracture healing.^{7,8}

In contrast to the studies of Doetsch et al.,¹¹ Kolb et al.¹² and Hoikka et al.,¹⁸ our study did not show a positive influence of vitamin D supplementation on radiological fracture healing. Doetsch et al.¹¹ found a significant positive effect of calcium and vitamin D supplementation on callus formation after 6 weeks in a placebo randomised controlled trial in female osteoporotic or osteopenic patients with a mean age 78 years and a humerus fracture. Kolb et al.¹² who studied postmenopausal women of 50 years or older with a single distal radius fracture, found that supplementation of calcium and vitamin D in case of a vitamin D deficiency resulted in normal fracture callus area parameters. Hoikka et al.¹⁸ postulated that vitamin D may have a positive effect on callus formation, based on the alkaline phosphatase and

calcium serum concentration after vitamin D and calcium supplementation in patients with an osteoporotic hip fracture. Lee et al.¹⁹ found that vitamin D supplementation was associated with better grip strength recovery after 6 months in postmenopausal women with a distal radius fracture. The studies mentioned above that showed a positive effect of vitamin D supplementation in case of vitamin D deficiency on fracture healing, were performed in elderly postmenopausal female patients, patients with osteoporotic fractures or patients with one single type of fracture. Not only were the patient populations rather specific, but in three studies also the effect of vitamin D in combination with calcium was measured, as opposed to the effect of isolated vitamin D supplementation. Because inclusion into our study population was not limited to gender, age group, type or location of the fracture, our results are likely to reflect the effect of vitamin D in a general adult outpatient fracture population.

This study has some notable limitations. Due to the retrospective and non-protocolled data collection and radiological imaging, information about vitamin D serum concentration and radiological parameters during fracture treatment was incomplete. Using clinical notes by different physicians invariably leads to inter-observer bias. Additionally, treatment was completed within four months after fracture for the majority of patients. Considering that discharged patients would have returned if they had encountered complications, we assume that further fracture healing occurred without any problems, although patients may have consulted a different hospital and were therefore missed. For this reason, the incidence of radiological delayed union could be determined in a small subgroup (14%) of the patients. These patients were slightly older (mean 54 vs 49 years, $p = 0.03$), but had a similar initial vitamin D serum level and a similar male/female ratio compared to the group without radiological follow-up after 16 weeks. They can therefore be considered as a fairly accurate representation of the average patient population.

Altogether, the results of this research suggest that the initial vitamin D status of adult patients with an extremity fracture does affect fracture healing. Further research is needed to confirm these results. Considering the high prevalence of vitamin D deficiency, the clinical implications of such an effect may be substantial and

Table 2

Incidence of clinical and radiological delayed union in patients with extremity fractures, by vitamin D status.

Delayed union ^a	Initially not vitamin D deficient	Initially vitamin D deficient status after supplementation			
		Not vitamin D deficient	Still vitamin D deficient	p^b	Vitamin D status unknown
Clinical	1/382 (0.3%)	2/117 (1.7%)	3/30 (9.7%)	<0.001	0/114 (0%)
Radiological	20/42 (48%)	11/21 (52%)	4/6 (67%)	0.67	4/15 (27%)

^a The incidence of clinical delayed union was determined in 643 fractures, and of radiological delayed union in 84 fractures.

^b Comparison of 3 groups: patients who were initially not vitamin D deficient, patients who were no longer vitamin D deficient after supplementation, and patients who were still vitamin D deficient after supplementation.

improved fracture healing could possibly be gained by vitamin D supplementation in deficient patients.

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Conflicts of interest

The authors have none to declare.

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