REVIEW

How can the orthopedic surgeon ensure optimal vitamin D status in patients operated for an osteoporotic fracture?

T. Chevalley[1] · M.L. Brandi[2] · E. Cavalier[3] · N.C. Harvey[4] · G. Iolascon[5] · C. Cooper[4,6] · D. Hannouche[7] · J.-F. Kaux[8] · A. Kurth[9] · S. Maggi[10] · G. Maier[11] · K. Papavasiliou[12] · N. Al-Daghri[13] · M. Sosa-Henríquez[14,15] · N. Suhm[16] · U. Tarantino[17] · J.-Y. Reginster[18] · R. Rizzoli[1]

Abstract

In this narrative review, the role of vitamin D deficiency in the pathophysiology, healing of fragility fractures, and rehabilitation is discussed. Vitamin D status can be assessed by measuring serum 25(OH)-vitamin D level with standardized assays. There is a high prevalence of vitamin D insufficiency (25(OH)D < 50 nmol/l (i.e., 20 ng/mL)) or deficiency (25(OH)D < 25 nmol/l (i.e., 10 ng/mL)) in patients with fragility fractures and especially in those with a hip fracture. The evidence on the effects of vitamin D deficiency and/or vitamin D supplementation on fracture healing and material osseointegration is still limited. However, it appears that vitamin D have a rather positive influence on these processes. The fracture liaison service (FLS) model can help to inform orthopedic surgeons, all caregivers, and fractured patients about the importance of optimal vitamin D status in the management of patients with fragility fractures. Therefore, vitamin D status should be included in Capture the Fracture® program as an outcome of FLS in addition to dual-energy X-ray absorptiometry (DXA) and specific antiosteoporosis medication. Vitamin D plays a significant role in the pathophysiology and healing of fragility fractures and in rehabilitation after fracture. Correction of vitamin D deficiency should be one of the main outcomes in fracture liaison services.

Keywords Fragility fracture · Fracture healing · Fracture liaison service · Rehabilitation · Vitamin D

✉ T. Chevalley
Thierry.chevalley@hcuge.ch

1 Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

2 Metabolic Bone Diseases Unit, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy

3 Department of Clinical Chemistry, University of Liege, CHU de Liege, Liege, Belgium

4 MRC Lifecourse Epidemiology Unit, NIHR Southampton Biomedical Research Centre, University of Southampton, University Hospital Southampton NHS Foundation Trust, Southampton, UK

5 Department of Medical and Surgical Specialties and Dentistry, University of Campania "Luigi Vanvitelli", Naples, Italy

6 UKNIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

7 Service of Orthopaedics and Trauma Surgery, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

8 Department of Physical Medicine and Rehabilitation, University and University Hospital of Liège, Liège, Belgium

9 Department of Orthopaedic and Trauma Surgery, Campus Kemperhof, Community Clinics Middle Rhine, Koblenz, Germany

10 CNR Aging Branch-IN, Padua, Italy

11 Department of Orthopaedic and Rheumatological Rehabilitation, Rehazentrum am Meer, Bad Zwischenahn, Germany

12 3rd Orthopaedic Department, Aristotle University of Thessaloniki Medical School, Papageorgiou General Hospital, Thessaloniki, Greece

13 Chair for Biomarkers of Chronic Diseases, Biochemistry Department, College of Science King Saud University, Riyadh 11451, Saudi Arabia

14 University Institute of Investigation on Biomedical Sciences (IUIBMS), University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Canary Islands, Spain

15 Bone Metabolic Unit, Hospital University Insular, Las Palmas de Gran Canaria, Canary Islands, Spain

16 Department of Orthopaedic and Trauma Surgery, University Hospital Basel, Spitalstrasse 21, 4031 Basel, Switzerland

17 Department of Clinical Sciences and Translational Medicine, Faculty of Medicine and Surgery, Tor Vergata University of Rome, Via Montpellier 1, 00133 Rome, Italy

18 Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

Ⓢ Springer

Introduction

With the aging of the population, osteoporosis and fragility fractures represent a dramatic challenge for health burden and medical professionals. Hip fractures in particular with a 1-year excess mortality of at least 20% account for the high burden of osteoporosis in terms of morbidity and costs [1–3]. Thirty percent of these patients become permanently disabled, while 40% of them loose the ability to walk independently and 80% become dependent for the activities of daily living after the fracture [4, 5]. Total fragility fractures in the largest five European Union (EU) countries and Sweden (EU6) are estimated to increase by 23% from 2.7 million in 2017 to 3.3 million on 2030 [5]. In EU6, an estimated 1.0 million quality-adjusted life years (QALYs) were lost in 2017 due to fragility fractures, and a 27% increase of the resulting annual fracture-related costs of 37.5 billion euros in 2017 is expected by 2030 [5].

Among the various risk factors for fragility fractures, vitamin D deficiency appears to play a significant role [6, 7]. Vitamin D is a pleiotropic substance, with receptors and effects in a large variety of tissues [8]. Vitamin D deficiency is implicated in impaired muscle function and risk of falling [9, 10] and in calcium and phosphorus homeostasis [11]. Low calcifediol levels, hence vitamin D deficiency, are consistently found in patients with fragility fractures, including hip fractures [12, 13]. In addition, vitamin D deficiency is associated with reduced mobility after hip fracture surgical repair [14].

In the present narrative review, the role of vitamin D deficiency in the pathophysiology and the recovery of fragility fractures is addressed, and the ways to detect and correct it, as available to the orthopedic surgeon, who is at the forefront of the problem, are discussed. Depending on the local structure, other specialties such as geriatrician in the frame of orthogeriatric units and metabolic bone diseases specialists are essential complements for the orthopedic surgeon in the early management of fractured patients.

Methods

An expert working group was convened in September 2020 under the auspices of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). This group, comprising expert clinicians of different medical specialties (orthopedic surgeons, physical and rehabilitation medicine (PRM) specialists, rheumatologists, endocrinologists, and geriatricians) and researchers, reviewed the literature and presented the current state of the art on the followings topics : (1) assessment of vitamin D status and the need for appropriate 25(OH)-vitamin D [25(OH)D] measurements (when and how); (2) prevalence of vitamin D insufficiency/deficiency in patients admitted to

the orthopedic ward; (3) role of vitamin D in fracture healing and material osseointegration; (4) supplementation with vitamin D during rehabilitation; (5) fracture liaison service for the optimal management of the vitamin D deficiency in patients with fragility fracture. This paper reflects the presentations and the discussions of the working group that reviewed the current evidence of vitamin D in the management of patients in the orthopedic ward for a fragility fracture. It is based on an extensive narrative literature review, focusing on the most robust evidence such as a series of recent meta-analyses of post fracture care, i.e., fracture repair, rehabilitation in relation with vitamin D status, which constituted the search criteria in PubMed. A special emphasis was given to the prevalence of vitamin D deficiency in the fractured people population and to the approach to correct it, as well as the critical role of Fracture Liaison Services in achieving this goal.

Assessment of vitamin D status and the need for appropriate 25(OH)-vitamin D measurements

Vitamin D metabolism

Vitamin D3 (cholecalciferol) and D2 (ergocalciferol) are the two major forms of vitamin D and differ in the structure of their side chains. Vitamin D3 is the form of the vitamin synthesized by mammals. Both vitamin D3 and D2 may be obtained in small amounts from the diet, or in more significant quantities from fortified foods or vitamin supplements [15]. Dietary sources usually represent only 10–20% of total vitamin D [16, 17]. Fatty fish, fish liver oil, and egg yolk naturally contain the highest concentrations of vitamin D [18, 19]. Synthesis of vitamin D in the skin commences when 7-dehydrocholesterol absorbs UVB radiation with a wave length between 290 and 315 nm leading first to the formation of previtamin D3 which is further transformed in a more stable isomer, vitamin D3 [20] (Fig. 1). In the liver, vitamin D is hydroxylated by the enzyme CYP2R1 to 25-hydroxy-vitamin D (25(OH)D, calcifediol), which has a half-life of 3 weeks and circulates in the nanomolar range bound to vitamin D binding protein (VDBP) and albumin and as a free form. Subsequently, 25(OH)D is hydroxylated to bioactive 1,25-dihydroxy-vitamin D (1,25-$(OH)_2$D,calcitriol) by the enzyme CYP27B1. This hydroxylation in the kidney (1alpha hydroxylase) is stimulated by PTH, IGF-I, a low calcium diet, low circulating calcium, or phosphate levels and inhibited by FGF23, 1,25-$(OH)_2$D, and glucocorticoids. 1,25-$(OH)_2$D has a shorter half-live of about 4h and circulates in the picomolar range bound to VDBP with 10- to 100-fold lower affinity than 25(OH)D. It interacts with vitamin D receptor (VDR) with genomic and non-genomic effects.
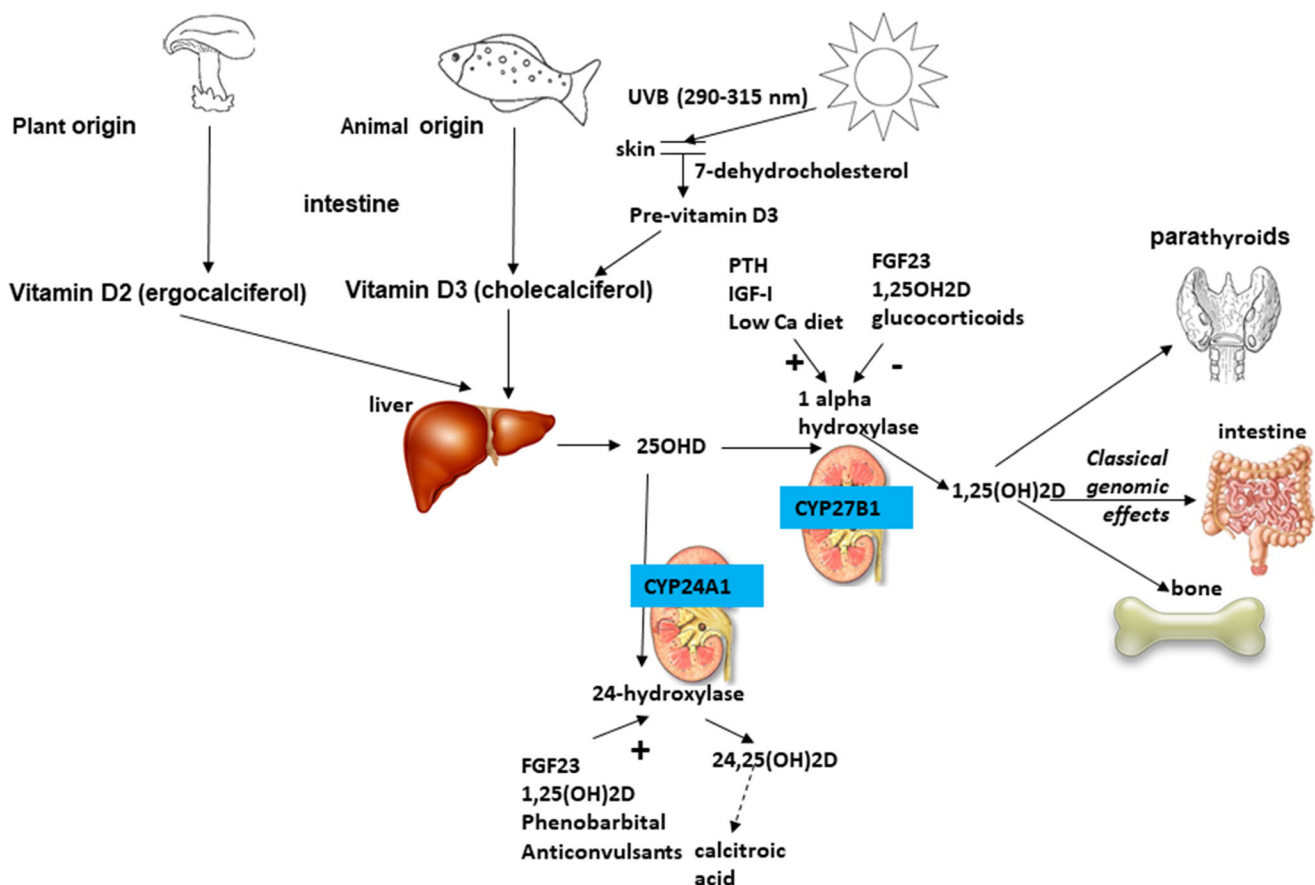
Fig. 1 Vitamin D metabolism

Assays variability for vitamin D status assessment

Measurement of serum circulating 25(OH)D level to evaluate vitamin D status in patients who are at risk of vitamin D deficiency should be performed using a reliable and standardized assay. Substantial variability in 25(OH)D measurement exists between the different assays available, whatever the methodology used [21]. Without standardization, the bias observed between the methods renders impossible the integration of the different studies in meta-analyses allowing valid recommendations. In this context, the vitamin D standardization program (VDSP) developed a reference measurement system including gold standard reference method procedures (RMPs from NIST, CDC, and the University of Ghent), NIST Standard Reference Materials, and a Standardization Certification Program (VDSCP) aiming at standardization of 25(OH)D measurement [22]. Its objective is that laboratories using standardized 25(OH)D assays report not only the same value but most importantly the true 25(OH)D concentration. The list of the certified assays is hosted on the CDC website (https://www.cdc.gov/labstandards/pdf/hs/CDC_Certified_Vitamin_D_Assays-508.pdf). Serum total 25(OH)D is expressed by the sum of the serum concentrations of 25(OH)D2 and 25(OH)D3. However, 25-OHD2 is not equivalently recognized by all immunoassays [23], and standardization of 25-OHD2 is not achieved yet. In countries where vitamin D2 can be used as a pharmaceutical supplement, LCMS/MS methods or methods equivalently recognizing both moieties should be preferred.

Other vitamin D metabolites as markers of vitamin status?

$1,25\text{-}(OH)_2D$ measurement should not be used to evaluate vitamin D status due to its tight regulation and its short half-life. Indeed, serum $1,25\text{-}(OH)_2D$ levels in vitamin D deficient individuals are often normal and may even be elevated due to secondary hyperparathyroidism. However, $1,25\text{-}(OH)_2D$ may be useful in some specific situations, for example, exploration of non–PTH-mediated hypercalcemia, vitamin D-dependent rickets, tumor-induced osteomalacia, and hypophosphatemic rickets.

Free 25(OH)D, bound to neither vitamin D binding protein (VDBP) nor albumin, can be calculated using a formula that takes into account 25(OH)D, VDBP, and albumin [24, 25] or with an ELISA kit (Diasource, Belgium). The choice of assay for VDBP in the calculation of free 25(OH)D is of importance to correctly capture the VDBP polymorphism variants which are present in white and black individuals [26, 27].

Nevertheless, the very low concentration of free and bioavailable 25(OH)D as well as the lack of a reference method remain clear limitations and support the measurement of total 25(OH)D in the general population as a marker of vitamin D status.

24,25(OH)₂D to replace 25(OH)D as a marker of vitamin D deficiency?

Both concentrations of 25(OH)D and 24,25-(OH)₂D are strongly correlated. Indeed vitamin D catabolism is predominantly due to CYP24A1 which through 24-hydroxylase (stimulated by FGF23, 1,25-(OH)₂D, phenobarbital and anticonvulsants) metabolizes 1,25-(OH)₂D to 1,24,25-(OH)₃D and 25(OH)D to 24,25-(OH)₂D (Fig. 1). Therefore, serum 24,25(OH)₂D concentration depends on the availability of 25(OH)D and the expression of CYP24A1 which is in part regulated by VDR and then 24,25(OH)₂D reflects VDR activity. It also means that when sufficient amounts of biologically active vitamin D are available, CYP24A1 is upregulated, and more 24,25(OH)₂D is formed [28, 29]. This approach could lead to a better personalization of vitamin D supplementation [30]. Nevertheless, measurement of 24,25(OH)₂D and VMR (vitamin D metabolite ratio of serum, 24, 25(OH)₂D to 25(OH)D) values are available only to clinical laboratories equipped with LC-MS capabilities in the absence of available automated immunoassays.

In summary, vitamin D status can be assessed by measuring serum 25(OH)D level with a robust and reliable standardized assay. The other vitamin D metabolites 1,25-(OH)₂D, free 25(OH)D, and even 24,25-(OH)₂D should not be used as a surrogate marker of vitamin D status.

Prevalence of vitamin D insufficiency/deficiency in patients admitted to the orthopedic ward

Interpretation of serum levels of 25(OH)D OHD

Vitamin D deficiency is a potential problem for countries at high latitude and can ranged between 10 and 40% in winter according mainly to regional sunlight exposure and to a lesser degree to dietary vitamin D intake [31–33]. Serum 25(OH)D status varies also according to gender and age as reported among 95,000 Korean men and women [32]. The mean 25(OH)D levels were higher in men than in women for all age groups and were highest in those aged ≥ 70 years and lowest in younger individuals < 30 years in both genders.

Body composition can influence serum levels of 25(OH)D as shown in an elderly cohort of German women in which 25(OH)D levels were affected by total body fat after controlling for age, lifestyle, and serum intact PTH [34]. In a meta-analysis of 21 studies

including up to 42'024 subjects, each unit (kg/m²) increase in BMI was associated with 1.15% lower concentrations of 25(OH)D after adjusting for age, sex, laboratory batch, and month of measurement [35]. BMI and BMI single-nucleotide polymorphisms (SNPs) were associated with 25(OH)D, while 25(OH)D SNPs were not associated with BMI. This study, on the basis of a bi-directional genetic approach, suggested that a higher BMI leads to lower 25(OH)D, while any effects of lower 25(OH)D increasing BMI were likely to be small.

Acute infection may alter vitamin D status. To characterize this deleterious effect of acute infection on vitamin D status, 6 vitamin-replete bull calves were experimentally infected with bovine viral diarrhea virus and compared to 6 sham-inoculated controls [36]. During the last 8 days of the 14-day post-inoculation period, serum 25(OH)D concentrations decreased by 51% in infected calves, and the inverse association between vitamin D status and serum amyloid A suggested that the infection-induced acute phase response contributed to the reduced serum 25(OH)D concentration. Furthermore, during a systemic inflammatory response induced 48 h after elective orthopedic surgery in 30 patients, serum 25(OH)D concentrations as well as VDBP decreased suggesting that serum 25(OH)D as a biomarker of vitamin D status should be interpreted with caution in the context of acute inflammation [37].

Prevalence of vitamin D deficiency in patients with osteoporotic fractures

Among patients with osteoporotic fractures, prevalence of vitamin D deficiency is high. Risk factors for vitamin D deficiency include a lack of sun exposure, dark skin, low intake, liver and gastrointestinal diseases, and some drugs. In a prospective study including Japanese postmenopausal women with osteoporotic fractures and a mean age of 80.7 years, 78% of these patients had 25(OH)D concentrations < 50 nmol/l (20 ng/ml) with lower values in hip fractures than in vertebral or distal radius fractures [38] (Fig. 2). As compared, higher 25(OH)D levels were observed in Japanese postmenopausal women without fracture [39] (Fig. 2). Many studies in patients with hip fractures and an average age of around 80 years and over have reported a prevalence of serum 25(OH)D below 50 nmol/l ranging between 34 and 80%, even if mean values are around 40 to 50 nmol/l [12, 14, 40–48] (Table 1). A high prevalence of vitamin D deficiency was also observed among 219 orthopedic patients presenting with vertebral fragility fractures [49] as well as among 93 patients with pelvic insufficiency fractures [50]. Vitamin D insufficiency or deficiency was also common across all age groups in two cohorts of patients undergoing fracture repair surgery [51]. In a meta-analysis exploring the correlation between serum 25(OH)D

Table 1 Circulating calcifediol levels in patients admitted to orthopedic wards for fragility fractures

Study	Country	Population (% female)	Mean (SD) age, years	Mean (SD) 25(OH)D nmol/l	% 25(OH)D < 50 nmol/l
Awal et al. [40][#]	Australia	313	79.5		34
Hao et al. [14][*]	USA	290 (73)	82 (7)	55 (24)	46
Bischoff-Ferrari et al. [12][*]	Switzerland	222 (77)	86	34.6 (community) 24 (nursing homes)	80
Cher et al. [41][*]	Singapore	801 (71)	77.7 (8)	-	47.4
Niikura et al. [44][*]	Japan	360 878)	84.7 (8.2)	41.3 (18)	71.7
Papaiannou et al. [45][*]	Canada	65 (56)	78.5 (10.3)	52.3	-
Ish-Shalom et al. [46][*]	Israel	48 (100)	81 (89	39.3 (25.3)	-
Mak et al. [47][*]	Australia	218 (77)	83.9 (7.2)	52.7 (23.5)	47
Moo et al. [48][*]	Singapore	796 (71)	77.7 (8)	50.1 (18.5)	53.9

[#] Proximal femur fracture ; [*] Hip fracture

levels and osteoporotic fractures in elderly, high as compared to low serum 25(OH)D levels were associated with reduced risk of hip fracture but had no significant relationship with total fracture risk [52]. Vitamin D deficiency may contribute to the pathogenesis of fragility fracture through altered bone strength and increasing fall risk and indeed may also be relevant for post-fracture recovery (Fig. 3). Indeed, in a recent study among 290 hip fracture patients, those with a vitamin D deficiency (25(OH)D < 25 nmol/l; 12%) had a reduced mobility at 60 days after the fracture [14]. In another study in Singapore among 801 hip fracture patients, 25(OH)D insufficiency and/or deficiency affecting about 92% of patients was a significant predictor of mortality at 2 years but not at 90 days [41]. Despite severe vitamin D deficiency below 30 nmol/l being present in the majority of hip fracture patient, only 10% of hip fracture patients had any vitamin D supplementation on admission [12]. The prevalence of vitamin D deficiency is even higher in patients with previous contralateral hip fractures as compared to those without [44], suggesting that most surgeons do not prescribe vitamin D to fractured patients. Patients with osteoporotic fractures and/or musculoskeletal symptoms, which can be potentially improved by vitamin D treatment or need the correction of vitamin D deficiency prior to specific treatment, should have serum 25(OH)D levels measured [53]. Since there is no daily circadian rhythm, fasting is not needed, and samples should be taken before the next load when monitoring weekly or monthly doses.

In summary, there is a high prevalence of vitamin D insufficiency or deficiency in patients with fragility fractures and especially in those with a hip fracture. Determinants of 25(OH)D concentrations include the seasonality and latitude as well as some conditions such as obesity, malnutrition, acute inflammation, or infection which can lower serum vitamin D levels.

Role of vitamin D in fracture healing and material osseointegration

Vitamin D deficiency can adversely affect fracture healing and conceivably contribute to the development of nonunion [54]. It may account for the concomitant findings of elevated alkaline phosphatase, elevated parathyroid hormone, and low calcium levels observed in some patients [55]. In a case-control study, the prevalence of 25(OH)D levels below 23 nmol/l was 60% in a group of non-union closed tibia fracture, while it was 30% only in those with union by 3 to 6 months of follow-up [56]. In a large database with more than 300,000 fractures, vitamin D deficiency was associated with an odds ratio of 1.14 of non-union, which affected 4.9% of the fractures [57]. As mechanism for non-union, impaired IL-4 and IL-13 production under vitamin D deficiency has been proposed, since these cytokines increase bone formation and fracture bridging [58].

However, a high-dose bolus of vitamin D_3 during the acute recovery period did not impact the rate of union in vitamin D deficient patients with a long bone fracture in a randomized double-blind placebo-controlled trial [59]. Out of 2 trials having tested the effects on fracture healing of proximal humerus [60] or upper and lower limbs fractures [61] of 800 and 1200 IU vitamin D per day, respectively, the former concluded to some improved fracture healing by higher bone content in the callus with vitamin D. In the latter, the incidence of delayed union was 9.7% in the group who remained vitamin D deficient, while it was 0.3% in the vitamin D replete at baseline and 1.7 % in those the deficiency of whom was corrected. In both trials, 1 g calcium supplements were administered as well. The contrasting effects of vitamin D supplementation on fracture healing have been reviewed elsewhere [62, 63].

A few preclinical studies reviewed in [64, 65] have concluded to a lower bone to implant contact and impaired

Fig. 2 Calcifediol (25-OHD) levels by fracture type from Fig. 1 [38] and in postmenopausal women without fracture (adapted from Fig. 1) [39]. Calcifediol levels in 317 fractured women with a mean age of 81 years. Values below 50 nmol/l (20 ng/ml) were found in 78% [38]
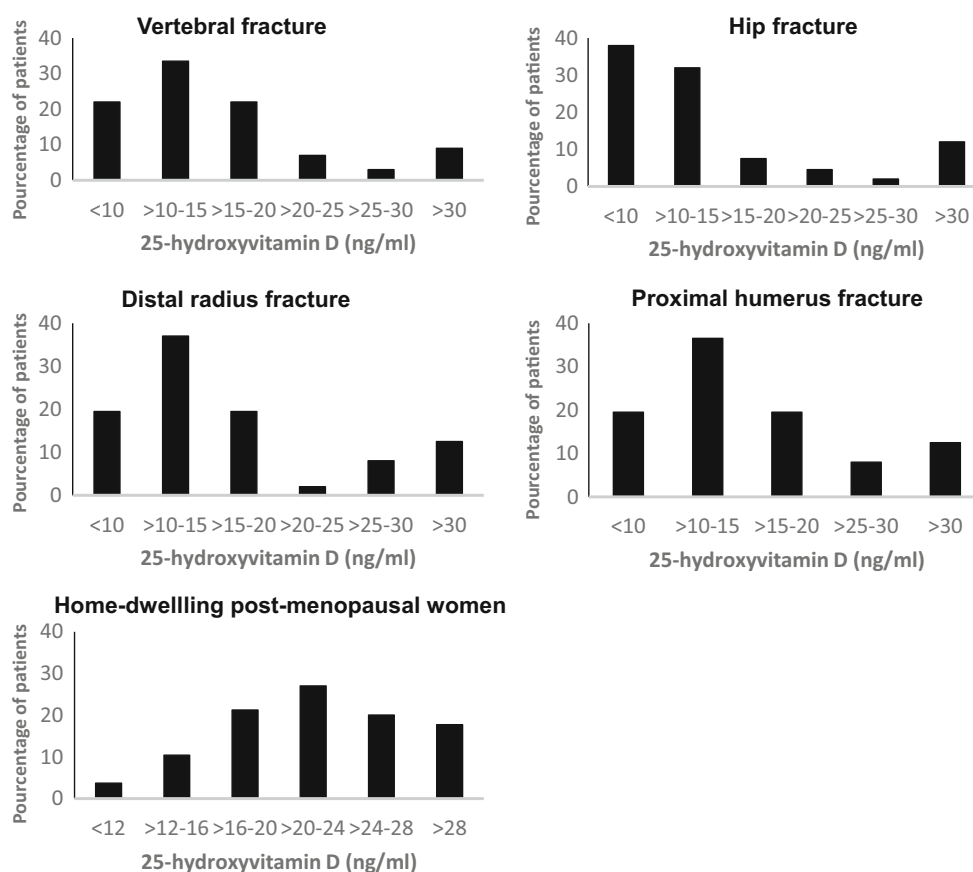
functional osseointegration in vitamin deficient animals. There seems to be a clear association between hypovitaminosis D and an impaired osseointegration, with a higher probability of early implant failure, as reported in both clinical studies and animal models [66, 67]. It seems that bone healing process and bone metabolism are strongly influenced by nutritional aspects and are essential to reach a good bone restoration, enhancing the osseointegration processes. These effects were sustained by vitamin D administration. Both in the frail elderly and in younger patients, with a traumatic fracture, hypovitaminosis D is associated with a worse bone stock and a delay in the formation of callus and healing [68]. Vitamin D promotes mineralization and bone repair processes [69]. In patients who undergo hip and knee prostheses, hypovitaminosis D, favored by the inflammatory reaction, can compromise surgical outcome and functional recovery [70]. In these patients, vitamin D supplementation may be useful to ensure proper osseointegration and, therefore, a better surgical outcome [71]. Low vitamin D levels are also associated with increased exposure to infections [72, 73], a longer length of hospital stay [74], and a higher frequency of post-operative complications. In these patients, supplementation should be considered. Retrospective clinical studies would suggest some trend to early dental implant failure in patients with low circulating 25-OHD [75, 76]. Intervention trials with vitamin D are still missing.

The effects of vitamin D deficiency and/or vitamin D supplementation on fracture healing in clinical studies are rare. However, the overall impression is that vitamin D has a positive influence on this process, but the mechanism and the magnitude of the effect remain to be determined. The role of vitamin D in material osseointegration requires further investigation.
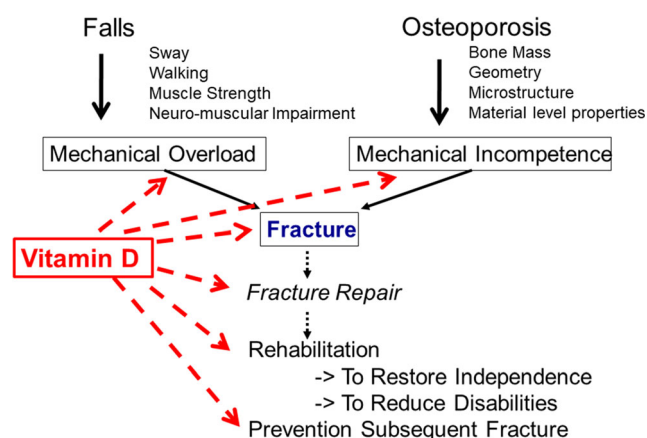

Fig. 3 Role of vitamin D in the pathogenesis and management of osteoporotic fractures (adapted from [7])

Rehabilitation after osteoporotic fracture

Multidimensional approach of rehabilitation

The main goals of fracture management are to recover pre-fracture functional level and to reduce fracture risk (Fig. 3). Rehabilitation of the patient with fragility fracture begins in acute settings within 24 h (possibly within a few hours) after surgery or any conservative treatment [77]. Rehabilitation program of hip fractures include multimodal pain management, intensive post-discharge physical therapy, and an interdisciplinary care program even in patients with mild to moderate dementia to improve functional outcomes [78]. Moderate evidence supports that postoperative nutritional supplementation improves nutritional status and reduces mortality and that supervised occupational and physical therapy across the continuum of care, including home, improves functional outcomes and fall prevention [78]. Some influence on length of stay in rehabilitation ward has been suggested with dietary protein repletion [79]. Complex, multidimensional, m-Health interventions hold promise to health behavior change related to calcium and vitamin D intake, balance, core and leg strength, and physical activity [80].

Care pathway of patient with hip fracture

For patients with hip fracture, an early admission could improve care by an orthopedist and a geriatrician team during both the acute and rehabilitation phases [81], in combination with a physiatrist [82, 83]. Indeed, a recent meta-analysis showed a decrease of, respectively, 27 and 19%, in 30-day and 1-year mortality after initiating an orthogeriatric program in patients with recent hip fractures [84]. In addition, a decrease in complications such as confusion states, urinary tract infections, pressure ulcers, cardiac decompensations, and thromboembolic events was observed in patients with recent hip fracture who underwent a joint orthogeriatric management either in retrospective studies [85], before/after implementation [86], or in a meta-analysis [87]. Functionality in the first 3 months after a hip fracture was also significantly improved thanks to orthogeriatric co-management in three studies including two randomized studies [88–90]. In another recent randomized study in non-institutionalized patients aged 70 years and over and able to walk at least 10 m before their hip fracture, the SPPB (short physical performance battery) score, as well as the Barthel index were better in patients of the co-management group not only during the first weeks but also at 4 and 12 months [91].

Vitamin D and the musculoskeletal system

Vitamin D plays an important role in orthopedic surgery [92]. Low vitamin D levels in patients undergoing total hip replacement have been associated with lower pre- and postoperative Harris hip score [93], increase of postoperative complications, including periprosthetic joint infection [72] as well as longer hospital stays [74]. Severe vitamin D deficiency is causing muscle pain and weakness as well as gait impairment [16]. In a cross-sectional study in adults, serum 25(OH)D level on admission to acute rehabilitation unit was inversely associated with non-specific musculoskeletal pain [94]. Vitamin D deficiency has been associated with proximal muscle weakness, increase in body sway, and an increased risk of falling [9, 95, 96]. In a prospective observational study in inpatients with hip fractures, $25(OH)D_3$ below 30 nmol/l (12 ng/ml) was associated with worse functional recovery (Barthel index) than those between 30 and 50 nmol/l (12–20 ng/ml) that were in turn associated with a worse recovery than those between 50 and 75 nmol/l (20–29 ng/ml), but with no further advantages with serum 25(OH)D above 75 nmol/l (30 ng/ml) [97]. Vitamin D sufficiency may play an important role in lower extremity function 1 year after hip fractures [98]. In a meta-analysis of 11 observational studies bringing together 39,141 participants, an increase in serum 25(OH)D of 10 ng/ml (25 nmol/l) was associated with a risk reduction of 20% for hip fractures and of 7% for any fracture [99].

Vitamin D supplementation

ESCEO recommends a 50 nmol/L (i.e., 20 ng/mL) as the minimal serum 25(OH)D concentration at the population level and 75 nmol/l in patients with osteoporosis to ensure optimal bone health [7]. For vitamin D supplementation, ESCEO maintains its recommendation at a dosage of 800 IU/day [100] which is in line with the majority of current vitamin D recommendations in Europe for women older than 50 years [100–105], as well as those of the Institute of Medicine (IOM)/Endocrine Society [106, 107] and International Osteoporosis Foundation (IOF) [108] (Table 2). Patients with symptomatic deficiency or those requiring treatment prior to receiving a potent antiresorptive agent may receive beforehand a single loading dose of 300,000 IU or 50,000 IU/week over 6 weeks, followed by maintenance doses of 800–1000 UI daily to maintain appropriate vitamin D levels [53, 109]. When vitamin D is co-prescribed with an oral antiresorptive agent, the maintenance dose of 800–1000 IU can be started [53] but may increase to 2000 IU/day in conditions of severe vitamin D deficiency, renal failure, or obesity [110]. In case of important comorbidities, a consultation with a metabolic bone disease specialist may be indicated. On the other hand, in patients with baseline serum 25(OH)D around 50 nmol/l, a randomized study after acute hip fracture has shown no advantage of loading doses over daily supplementation to reach a target therapeutic threshold of 75 nmol/l [45]. Oral cholecalciferol (D3) is generally the recommended form [111]. If only one loading dose is considered, no more than

Table 2 Recommended vitamin D supply in women older than 50 years

Authority and/or country (year)	Recommended intake of vitamin D (IU/d)		
	Age 50–60 years	Age 61–70 years	Age > 70 years
IOF (2010) [108]	800	800	800-1000; up to 2000 IU/day if needed to achieve sufficient vitamin D level
IOM (2011) [106]	600	600	800
Endocrine society (2011) [107]	600	600	800 ; up to 1500–2000 IU/day if needed to achieve sufficient vitamin D level
DACH (2012) [101]	800	800	800
Nordic countries (2012) [102]	400	400	800 (> 75 years)
ESCEO (2013) [100]	800	800	800
EFSA (2016) [103]	600	600	600
UK (SACN 2016) [104]	400	400	400
ESCEO-IOF (2019) [105]	800	800	800

IOF (International Osteoporosis Foundation); IOM (Institute of Medicine) ; DACH (Germany (D), Austria (A) and Switzerland (CH)); ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases); EFSA (European Food Safety Authority); UK SACN (United Kingdom-Scientific Advisory Committee on Nutrition)

100'000 IU should be prescribed since a higher rate of falls and fractures has been described in several studies using higher doses in older participants [112–115]. A systematic review has evaluated the effectiveness of combined exercise training and vitamin D supplementation on musculoskeletal health in older adults and has concluded to an additive effect of resistance exercise and vitamin D supplementation on muscle strength [116]. However, no additional benefit beyond exercise was shown for other functional variables such as short physical performance battery and the timed up and go test.

Adequate vitamin D status is necessary for the functional recovery process. For patients with hip fracture, a co-management by an orthopedist and a geriatrician has demonstrated significant benefits by decreasing medical complications and mortality and improving functional independence.

Fracture liaison service: a need for an optimal management of the vitamin D deficiency in patients with fragility fracture

Fracture liaison service (FLS)

Fracture liaison service started in the late 1990s to address the growing problem of bone fragility [117]. Indeed, following fragility fractures, there is at least a twofold risk of refracture [118, 119], and this risk can even be multiplied by 4 times after initial vertebral fracture [120]. Furthermore, the risk of major osteoporotic fracture (MOF) after a first MOF is increased over the whole duration of follow-up, but the imminent risk for the first 2 years is even higher justifying the rapid introduction of antiosteoporosis treatment after a fracture [121]. Unfortunately, in many instances, diagnosis, evaluation, and treatment of osteoporosis, including correction of

vitamin D deficiency, are not undertaken after a fragility fracture [122–127]. Orthopedic surgeons are well aware of a care gap for patients presenting with a fragility fracture. Indeed, in two surveys, the majority of orthopedic surgeons would prefer to establish a fracture liaison service rather than to pursue a protocol-based approach to address the osteoporosis care gap at their institutions [128]. The goal of an FLS is to ensure a management continuity in patients who sustained a fragility fracture from the time of injury presentation until the transition to the primary care provider through an interdisciplinary team [117, 129–131] [132]. The essential elements of an FLS include identification and assessment of patients with fragility fracture, exercise, and education programs including dietary counselling, falls risk assessment, initiation of osteoporosis medication including vitamin D repletion, and long-term follow-up and/or transition of care through a comprehensive management plan to primary care provider and a fully integrated FLS database system [129]. FLS reduce not only the incidence of subsequent fractures by around 30% [86, 133–136] by improving prescription [137] and adherence to prevention protocols and antiosteoporosis medication [138]. FLS are cost saving [139–141]. Therefore, secondary prevention of fractures with FLS is now considered as a standard of care with the worldwide implementation of FLS [142–144]. Since its launch in 2013, Capture the Fracture®, a global program of IOF, has welcomed a growing number of FLS and continues to facilitate the implementation of FLS worldwide. Until September 2020, this network of FLS has reached 440 from 48 countries, spread across 6 continents.

Impact of FLS on prescription

Drug therapy is an essential component of management of patients with fragility fracture and cannot be limited to vitamin D and calcium supplementation [145]. In a cohort of 3475

osteoporotic patients with a recent vertebral or hip fracture, the risk of re-fracture after a mean follow-up of 3 years was 44.4% lower in patients under anti-osteoporotic treatment compared to untreated ones [146]. This risk of subsequent fracture was 64.4% lower in those receiving calcium/vitamin D supplementation in addition to osteoporosis treatment and 77.2% lower in patients who were adherent to medication. Over this follow-up period, a 64% lower mortality risk was also observed [146]. In another study among patients aged over 85 years with a clinical fracture, a significant lower cumulative mortality was observed over 2 years in the FLS attenders group without a reduced subsequent fracture rate [147].

A spectacular improvement in vitamin D status in elderly women with a fragility fracture has been observed over an 8-year analysis in a dedicated FLS in France since the level of patients with severe hypovitaminosis D fell dramatically from 79.3 to 19.7%, showing that supplementation has been widely integrated into current practice [148]. In a secondary FLS analysis in Taiwan on participants grouped according to fracture types, there were significant differences after intervention between baseline and 12-month in calcium/vitamin D supplementation use, adequate protein intake, and exercise rate (except for hip fracture group) [149]. Post-hip fracture use of calcium and vitamin D was shown to be a protective factor on mortality over a minimum of 11-year follow-up in a study performed in Finland [150]. In another small FLS cohort of hip fracture patients in the USA, a higher proportion of patients changed vitamin D intake after the FLS program was instituted and a higher proportion obtained a BMD measurement, but there was no increase in the proportion of patients taking osteoporosis medication [151]. On the other hand, another FLS in the USA increased the percentage of patients under osteoporosis medication from 20 to 54% as well as calcium/vitamin D prescription from 36% at baseline to 93% and the percentage of patients receiving BMD testing from 21 to 93% [152]. Higher prescription of osteoporosis medication is of importance since a 40% lower subsequent fracture risk and 21% lower mortality risk were observed in a prospective FLS cohort study in Glasgow in which 50.7% of patients were recommended for oral bisphosphonates [153]. Since FLS may be less feasible and accessible in rural areas, with limited availability of care services, a centralized E-consult program can effectively and efficiently provide specialty bone health services to patients with recent fracture residing in rural areas [154]. Since the COVID-19 pandemic is also influencing healthcare delivery for osteoporosis outpatients, remote consultations are also applicable to osteoporosis services [155].

The FLS model can help to inform orthopedic surgeons on the importance of vitamin D status in the management of patients with fragility fractures in addition to anti-osteoporotic treatment. Therefore, vitamin D status should be included in Capture the Fracture® program as an outcome of FLS in addition to DXA and specific anti-osteoporotic

medication. However, long-term studies on the impact of FLS on major outcomes are still to be investigated.

Conclusions

- There is a high prevalence of vitamin D insufficiency and/or deficiency in patients with fragility fractures and especially in those with a hip fracture.
- Vitamin D status can be assessed by measuring serum 25(OH)-vitamin D level with standardized assays.
- Vitamin D may have a positive influence on fracture healing, but the mechanism and the magnitude of the effect remain to be determined.
- Adequate vitamin D status which plays an important role in the musculoskeletal system is required for the functional recovery after fracture.
- For vitamin D supplementation, a dosage of 800–1000 IU/day is in line with the majority of current vitamin D recommendations in Europe for women older than 50 years.
- In patients with fragility fracture, a serum 25(OH)D concentration of 75 nmol/l (30ng/ml) should be targeted to ensure optimal musculoskeletal health.
- The FLS model can help to inform orthopedic surgeons and their patients on the importance of vitamin D status in the management of patients with fragility fractures in addition to anti-osteoporotic treatment.

Research agenda

- To further clarify the role of vitamin D levels and supplementation in fracture healing and material osseointegration
- To evaluate the role of a vitamin D loading dose and its regimen on clinical relevant outcomes
- To evaluate whether vitamin D dose should be adapted to the level of renal function
- To test the effects of combined vitamin D and calcium on imminent fracture risk

meetings. NS has received fees for lectures or scientific advisory boards from AgNovos, EliLilly, Amgen, AO Foundation, UCB Pharma, Roche, Labatec. JYR reports consulting fees or advisory board participation for IBSA-Genevrier, Mylan, Radius Health and Pierre Fabre, lecturing fees for IBSA-Genevrier, Mylan, Cniel and Dairy Research Council (DRC) and grant support from IBSA-Genevrier, Mylan, Cniel and Radius Health. RR has received fees for lectures or scientific advisory boards from Abiogen, Danone, Echolight, European Milk Forum, Mithra, ObsEva, Pfizer Consumer Health and Theramex. The Working Group was entirely funded by the ESCEO. The ESCEO receives Unrestricted Educational Grants, to support its educational and scientific activities, from non-governmental organizations, not-for-profit organizations, non-commercial and corporate partners. The choice of topics, participants, content and agenda of the Working Groups, as well as the writing, editing, submission and reviewing of the manuscript are under the sole responsibility of the ESCEO, without any influence from third parties.

Declarations

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