Vitamin D supplementation in fractured patient: how, when and why

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Summary

Vitamin D, through its action on calcium metabolism, is essential for bone physiology. It's also required in a wide range of biological systems to act modulating the proliferation and inducing terminal differentiation of a variety of normal cells. Actually vitamin D deficiency can impact muscle function and increases fall risk in elderly, while severe vitamin D deficiency (< 30 nmol/L) is common in patients with fragility fractures. Vitamin D and calcium supplementation, in addition to antiosteoporosis treatment after surgery or conservative treatment, can ensure optimal recovery and survival, especially in hip fractured patients.

KEY WORDS: vitamin D, fragility fractures, orthopedic surgery.

The role of vitamin D in metabolism

Vitamin D (both D2 and D3) can be obtained through the intake of foods or dietary supplements as Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). However, about 80% of human vitamin D is made through skin exposure to ultraviolet light that converts cutaneous provitamin D3 to previtamin D3, which isomerizes into vitamin D3 and translocates into the circulation. Vitamin D is biologically inert and must undergo two successive hydroxylations in the liver and kidney to become the biologically active 1,25-dihydroxyvitamin D [1,25(OH)2D] (1). Its main biological effect is to maintain the plasma calcium concentrations within the normal range. If the plasma becomes less than saturated with respect to calcium and phosphate, the mineralization fails, which results in rickets among children and osteomalacia among adults (2). The vitamin D increases serum calcium concentrations through three different activities. It induces the synthesis of proteins involved in active intestinal calcium absorption, and furthermore, stimulates active intestinal absorption of phosphate. The second activity of vitamin D consists to make possible the mobilization of calcium in the absence of calcium coming from the environment in a condition of no-calcium diet. Vitamin D stimulates osteoblasts to produce RANKL, that stimulates osteoclastogenesis and activates resting osteoclasts for bone resorption (3). Both vitamin D and parathyroid hormone are required to realize calcium mobilization from bone (4, 5). Vitamin D, finally, interacting with PTH, stimulates the reabsorption of the last 1% of the filtered load of calcium in the distal renal tubule (6) and this represents a major contribution to the calcium pool.
Furthermore, Vitamin D exerts its genomic effects through a nuclear gene transcription factor, the vitamin D receptor (VDR). VDR is, classically, present in the organs involved in calcium homeostasis, including the intestine, bone, kidney, and the parathyroid glands. Recently, VDR was found also in many other non-classical tissues and cell types (7-10). This may explain, the action of 1,25D in these non-classical tissues associated with a diverse range of biological systems such as modulation of immune function, inhibition of cell growth, and induction of cell differentiation.
In addition, 1,25(OH)2D not only regulates calcium metabolism but also is capable of inhibiting the proliferation and inducing terminal differentiation of a variety of normal and cancer cells, modulating the immune system, enhancing insulin secretion, and down regulating the renin/angiotension system. Active vitamin D compounds are used for the treatment of the hyperproliferative skin disease psoriasis and are being developed to treat some cancers and type 1 diabetes (11). Furthermore, vitamin D is reported to be involved in the pathogenesis of many cardiovascular problems (12). Vitamin D has been found to affect cardiac contractility, vascular tone, cardiac collagen content, and cardiac tissue maturation. Also skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function. Receptors for vitamin D on muscle cells decrease with advancing age (13-15) (Figure 1).

Vitamin D supplementation in fractured patient: why

Hip fractures and other non-vertebral fragility fractures represent the most frequent fractures in patients presenting to the trauma center or orthopedic department. After these fractures, patients are at increased risk for subsequent fracture. Patients with a prior hip fracture have a risk to sustain another osteoporotic fracture of 2.5-fold higher than in age-matched people without a previous hip fracture. The increased fracture risk is associated with increased morbidity, mortality and, therefore, social and economic costs (16, 17). All national and international societies guidelines on osteoporosis advocate to evaluate patients presenting with a fracture in order to consider treatment to reduce the risk of subsequent fractures.
In fractured patients we have to analyze the presence of risk factors related to fracture risk, independently of BMD, such as clinical risk factors, fall risks, prevalent morphometric vertebral fractures and secondary osteoporosis (18).
Recently it has been reported that in patients with a hip fracture, the 80% had secondary causes of bone loss, mainly related to disturbed calcium and vitamin D homeostasis. Despite this, only few patients receive evaluation and treatment for osteoporosis following a hip fracture (19).
Vitamin D deficiency can impact on falls and bone mass. Severe vitamin D deficiency (< 30 nmol/L) is common in hip fracture patients (20).
Even if vitamin D hormone system is considered essential for

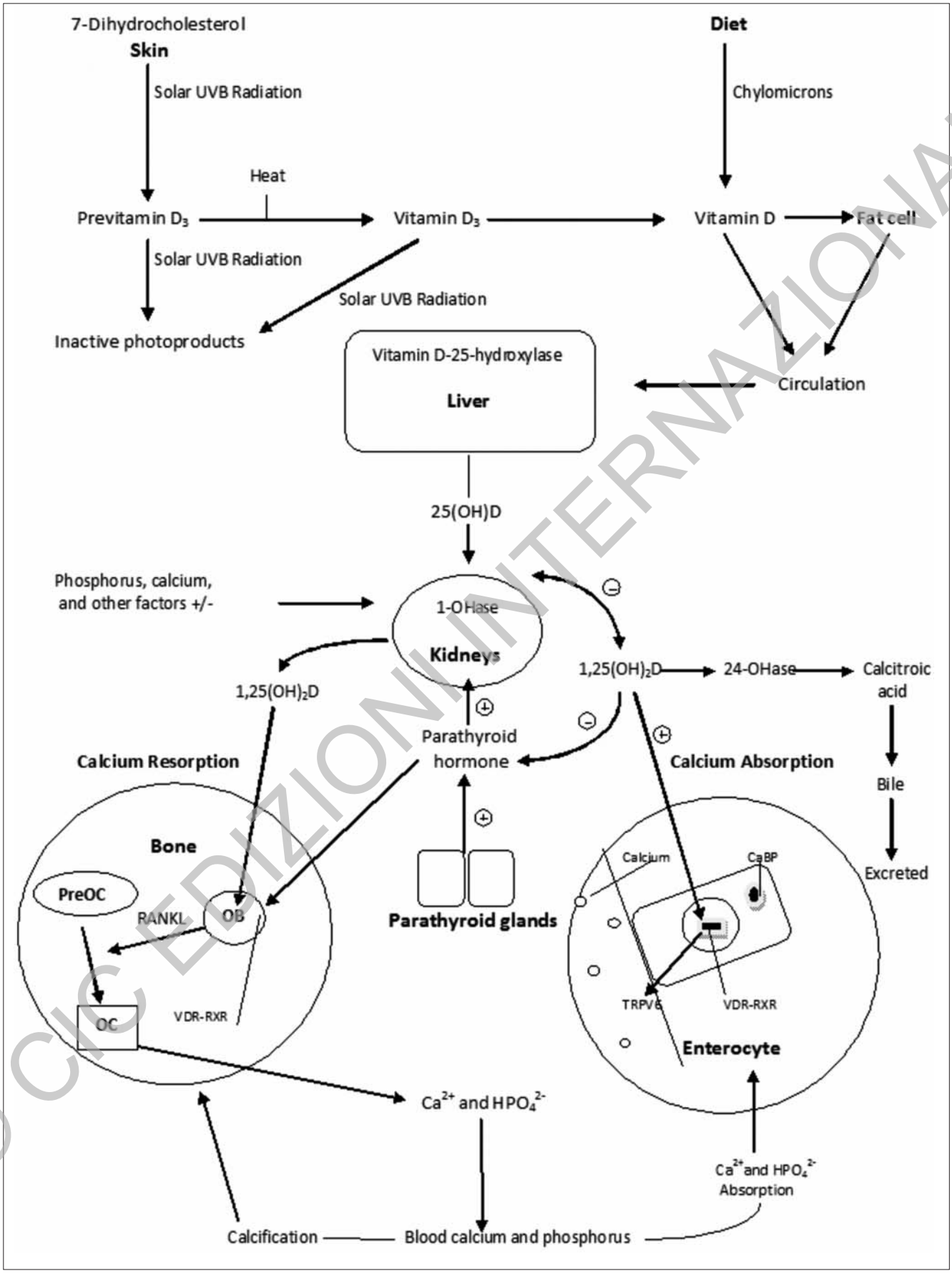

Figure 1 - Physiological pathways of vitamin D activities.

calcium homeostasis there is no general consensus about vitamin D efficacy and safety in relation to bone health. A. Cranney et al. have recently found inconsistent evidence of an association between serum 25(OH)-D concentration (the accepted marker for vitamin D nutritional status) and bone mineral content in infants, and fair evidence of an association with bone mineral content or BMD in older children and older adults (21). Furthermore they have also found inconsistent evidence of an association between serum 25(OH)-D concentration and some clinical outcomes (fractures, performance measures) in postmenopausal women and older men. The author pointed out that there is inaccuracy and imprecision on the different assays for measuring 25(OH)-D, and moreover it is difficult to define an overall 25(OH)-D threshold for vitamin deficiency or insufficiency (21).

Probably the relationship between neuromuscular function and vitamin D plasma concentrations is considered more consistent. Neuromuscular function is sensitive to vitamin D levels and patients with lower vitamin D levels have slower walking times and take longer to stand up (22). In the past, this impairment has been related to a typical myopathy secondary to disturbed calcium and vitamin D homeostasis (osteomalacic myopathy), that is characterized by: proximal muscles weakness, in particular of hip extensors, flexors and abductors and knee flexors and extensors, disabilities in getting up from a chair and climbing stairs, and widespread muscle pain. Muscle biopsies in affected subjects showed selective alterations of type II muscle fibers. Nowadays it has been found that vitamin D directly affects muscle metabolism, by mediating gene transcription, through rapid not genomic pathways, and also by the allelic variant of the VDR (15).

It's been well documented that higher levels of 25-(OH)-D are correlated with the better lower-extremities function in subjects older than 60 years old, whether they are active or not.

Simonelli et al. proved that the 97% of patients with a history of falls and minimal trauma fractures had serum 25(OH)-D levels inferior to 30 ng/ml, and the 72.5% of them had levels even lower to 20 ng/ml (23).

Recently, Leboff et al. have proven that after hip fracture, patients with higher serum vitamin D levels (> 22 nmol/L) show better outcome in terms of lower extremity function and are less likely to fall (24).

Bischoff-Ferrari et al. have demonstrated that Vitamin D supplementation (to serum levels > 60 nmol/L) in hip fracture patients is associated, not only with an increased BMD at femoral site, but also with a significative reduction in falls (25).

Literature data agree that vitamin D is important to obtain a good functional outcome and reduce the risks of new fractures in clinical vertebral and non vertebral fractured patients.

Vitamin D supplementation in fractured patient: when

Vitamin D supplementation is very important if there is a low serum concentration of 25-(OH)-D, which represent a measurable and reliable marker to quantify vitamin D activity.

There is no consensus on optimal levels of plasma concentrations of 25-(OH)-D. Vitamin D deficiency is defined by most experts as a 25-(OH)-D level inferior to 20 ng/ml (50 nmol/L). 25-(OH)-D levels are inversely associated with parathyroid hormone levels until the former reach 30 to 40 ng/ml (75 to 100 nmol/L), at which point parathyroid hormone levels begin to level off (at their nadir) (26-31). Furthermore, intestinal calcium transport increases by 45-65% in women when 25-(OH)-D levels increase from an average of 20 to 32 ng/ml (50 to 80 nmol/L) (32). Therefore a level of 25-(OH)-D of 21 to 29 ng/ml (52 to 72 nmol/L) can be considered indicative of a relative insufficiency of vitamin D, and a level of 30 ng/ml or greater can be considered to indicate sufficient vitamin D concentration (33). According to several studies, 40 to 100% of U.S. and European elderly men and women still living in the community (not in nursing homes) are deficient in vitamin D (34-41). More than 50% of postmenopausal women taking medication for osteoporosis had suboptimal levels of 25-(OH)-D - below 30 ng/ml (75 nmol/L). In Europe, where very few foods are fortified with vitamin D, children and adults would appear to be at especially high risk.

Bischoff-Ferrari et al., in a recent study, have reported that mean serum 25(OH)D levels were low among hip fracture patients admitted from home (34.6 nmol/l), from assisted living (27.7 nmol/l), and from nursing homes (24 nmol/l). Severe vitamin D deficiency below 30 nmol/l was present in 60%, 80% were below 50 nmol/l, and less than 4% reached desirable levels of at least 75 nmol/l. Consistently, only 10% of hip fracture patients had any vitamin D supplementation on admission to acute care with significantly higher 25(OH)D levels among individuals supplemented with 800-880 IU/day (63.5 nmol/l) (42).

The prevalence of vitamin D-deficiency in Italy is high. Isaia et al. reported a prevalence of 80% in subjects older than 79 (43). This percentage increases to about 90% in long term institutionalized patients, who are also the ones at higher risk of hip fractures (44).

The prevalence of this deficit is particularly high in the departments of orthopedics and traumatology whatever the age of patients it is, infact Bogunovic et al., have recently reported percentages of 25-(OH)-D deficiency above 40% in specialistic orthopaedics departments (foot surgery, hand surgery, arthroscopy), and above 90% in the departments of traumatology (45).

Vitamin D supplementation should be always prescribed in several cases, as shown in Table I.

Vitamin D supplementation in fractured patient: how and how much?

The aim of vitamin D supplementation is to bring serum concentration of 25-(OH)-D above 30 ng/ml. A recent Expert Panel identified as the minimum acceptable a concentration of 28-32 ng/ml (70-80 nmol/ml) of 25-(OH)-D. This concentration should be reached with a dietary intake of 800-1000 UI of vitamin D in an elderly people (21).

Table I

Vitamin D supplementation is needed in:

– elderly people (> 65 years old);
– people with a prevalent fragility fracture (vertebral, wrist, hip, pelvis, ribs, humerus, proximal tibia, distal femur, etc.);
– people who are taking anti-osteoporotic drug therapy (clinical studies confirm the efficacy of these drugs only in association with an adequate calcium and vitamin D supplementation);
– people who are at risk of reduced assumption and/or absorption of dietary calcium;
– people who are taking corticosteroids or other drugs which can induce osteoporosis;
– people with a deficit of vitamin D due to liver or kidney severe diseases;
– rickets or osteomalacia.

Table II - Vitamin D formulations available in Italy.

Vitamin D type	Formulation	Biological half-life	Ipercalcemic/ ipercalciuric risk
Calcitriol	Tablets 0,25-0,50 µg	< 24 hrs	+++
1-α-hydroxycholecalciferol	Tablets 0.25-1 µg	< 24 hrs	++
Calcifediol	Gtt (1 gtt= 200 IU)	1-2 weeks	+
Ergocalciferol	Fl os im 400000 IU Fl os im 600000 IU	months	+
Cholecalciferol	Fl os im 10000 IU Fl os im 100000 IU Fl os im 300000 IU	months	+

A certain quantity of vitamin D is present in foods such as salmon, eggs, milk, cheese, and above all in animal fats. Sunlight usually covers 80% of vitamin D needed (11).
When a vitamin D supplementation is needed, it can be prescribed both as ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). In the European countries it is usually given cholecalciferol, while in the United States ergocalciferol is preferred. Some authors report a greater efficacy of cholecalciferol, but there isn't an unanimous agreement about that (46).
In Italy both types of vitamin D are available. In Table II are reported all the types of vitamin D commercialized in our country. It is possible to provide a bolus formulation thanks to the ability of vitamin D to be stored in fat tissue.
In a recent comparative metanalysis of Randomized Controlled Trials (RCT), Boonen suggests that oral vitamin D appears to reduce the risk of hip (and any non-vertebral) fractures only when calcium is added. Thus, to optimize clinical efficacy, vitamin D 700-800 IU/d should be complemented with calcium, using a dose of 1000-1200 mg/d of elemental calcium (47).

Conclusion

Clinical pathways have been developed to support orthopedic surgeons to improve medical management of patients following orthopedic/surgical management of the fracture. The pathways include advising primary care physicians and orthopedic surgeons of diagnostic and therapeutic approaches, promoting their appropriate use without compromising the quality of care, and educating patients about not pharmacological management of their disease (physical therapy, lifestyle habits and nutrition). The data discussed in this paper suggest that vitamin D is important to reach a good functional outcome and to reduce the risks of new fractures. A lot of formulations of vitamin D are nowadays available in Italy to cover different patients' needs and to guarantee at least 800 IU/die. After orthopedic surgery, vitamin D and calcium supplementation, a correct nutrition, physical exercise, and also a rapid and appropriate antiosteoporosis treatment, can ensure the optimal recovery and survival, especially in hip fractured patients.

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