

VITAMIN D

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 Editorial

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of Vitamin D
metabolites

 Native Vitamin D
in chronic kidney
disease

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EDITORIAL

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Dear Readers,

As you will read in this issue, recent studies have confirmed that a deficiency of native vitamin D (cholecalciferol, or D3) plays an important role in the pathogenesis of altered mineral metabolism and perhaps also of some extra-skeletal complications in patients with chronic kidney disease (CKD). On the other hand, for some time now it has been known that the kidney is one of the most important organs in the regulation of vitamin D metabolism and of its endocrine activities.

The best known of these disorders in the course of CKD is the increase of parathormone: even if this increase is also caused by phosphatemia, a typical symptom of CKD, it has always been believed that active vitamin D metabolites (calcitriol and similar analogues) are required to manage this condition. The assumption here is that the activation of vitamin D is an exclusive function of the kidneys, especially of healthy ones. In truth, it has recently been observed that even if renal synthesis of calcitriol is decreased by the progressive reduction of the function of the kidneys, its complete failure occurs only when glomerular filtration is less than 15 mL/min. In addition, 1- α -hydroxylase activity is present in various tissues and organs other than the kidneys, where it carries out important autocrine and paracrine functions, which are related to potentially significant extra mineral effects. In addition, you will read that it has been recently observed that:

- the prevalence of 25OHD deficiency is notable and generally widespread in patients affected by CKD, and cannot be traced to the loss of renal function;
- supplementation with cholecalciferol is able to correct, at least in part, secondary hyperparathyroidism, which often characterizes anamneses of osteomalacia and high-turnover renal osteodystrophy bone disease, which is at the base of increased fracture risk;
- vitamin D deficiency seems to be involved in other CKD complications (proteinuria, cardiovascular risk, anemia and progression of renal dysfunction); in particular it

has been observed in placebo studies that cholecalciferol supplementation reduces proteinuria and improves vascular functions (defined as the variation of the endothelium-dependent flow in the brachial artery and of the carotid-femoral pulse-wave velocity);

- significant side effects have not been reported in the course of cholecalciferol supplementation in patients with CKD, which confirms the good safety profile of native vitamin D for this condition as well.

Indeed, new guidelines [1-3] for the treatment of secondary hyperparathyroidism in patients with non-dialysis stage 3-5 CKD recommend a reduction of the intake of phosphate and a rationing of 25OHD, supplementing them with vitamin D in the case of deficiency, using the same recommended strategies as for the general population. They further warn against the routine use of calcitriol and other active forms of vitamin D in these patients, given the high risk of hypercalcemia; it should only be used in patients with stage 4-5 CKD with severe and progressive hyperparathyroidism.

With regard to the use of various vitamin D metabolites, in this issue you will also find summaries of the pharmacokinetic and pharmacodynamic motivations – and also with regard to evidence-based outcomes – behind the safe and rational use of cholecalciferol, calcifediol or calcitriol in different clinical conditions. In particular, readers will be reminded that even in conditions of severely compromised activity of the renal 1- α -hydroxylase enzyme, levels of 25OHD must be kept in the normal range to guarantee an adequate substrate for extra-renal 1- α -hydroxylase. On the other hand, as far as calcifediol is concerned, the authors write that its most rational use should be in cases of patients with chronic kidney disease and severely reduced liver functions.

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Meanwhile, there is still doubt on a clinical level as to whether an equivalent dose of calcifediol or cholecalciferol has better intestinal absorption. This doubt is warranted because of the different pharmacokinetics of the two substances, a difference which could be compensated by more generous doses of cholecalciferol bio-equivalents. In any case, the doses of calcifediol which are still recommended for postmenopausal osteoporosis in the package insert – 10-25 drops and even more per day– certainly seem excessive; for some time, it has been known [4] (and recently confirmed [5]) that a dose of 20-25 drops of calcifediol a week allows optimal 25OHD serum levels to be reached.
What do you think?

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CLINICAL COMPARISON OF VITAMIN D METABOLITES

VITAMIN D
UpDates

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INTRODUCTION

In the last 20-30 years, increasing awareness of the role of vitamin D in the pathogenesis of some musculoskeletal and extra-skeletal diseases, together with substantial epidemiologic evidence on the prevalence of hypovitaminosis D in the general adult population and in the elderly, have given rise to an ever-growing debate concerning the appropriateness of the strategies for the prevention and treatment of vitamin D deficiency [1-9].

A number of scientific works have investigated the use of cholecalciferol and vitamin D metabolites (calcifediol in particular) for the prevention and treatment of vitamin D deficiency [1-9]. Undoubtedly, the great number of these randomized, controlled trials (RCTs) have produced a significant advance in our knowledge on this topic, highlighting extremely important clinical aspects [1, 3, 5, 6]. However, the quantity, quality (not always high) and heterogeneity of these published studies have also generated some doubts on the issue.

The aim of our narrative review is to describe the main attributes of vitamin D metabolites and to define their role in daily clinical practice, with the aim of aiding physicians in choosing adequate strategies to use in patients with proven vitamin D deficiency or with a risk of hypovitaminosis D.

VITAMIN D PRODUCTION AND METABOLISM

In general, the term vitamin D refers to both vitamin D₃ (cholecalciferol), produced by animals and humans, and vitamin D₂ (ergocalciferol), produced by plants [1]. Endogenous synthesis is the principal source of vitamin D for the organism; it derives from the conversion of 7-dehydrocholesterol after skin exposure to UV rays of a specific wavelength. This mechanism should produce most (approx-

imately 80%) of the vitamin D requirements (vitamin D₃), while lower quantities (approximately 20%) of vitamin D₃ and vitamin D₂ should come from dietary sources [1].

Vitamin D₃ skin production is greatly influenced by seasonal change (lower during winter), latitude, the surface area and thickness of the skin exposed to sunlight (and perhaps also the use of sunscreens), and age (lower in the elderly) [1]. A lower dosage of vitamin D₃ can be obtained from food, in particular from animal fats, while the amount of vitamin D₃ in vegetable fats is totally negligible [1]. Dietary intake of vitamin D is significantly higher in those countries where vitamin D fortified foods with cholecalciferol are allowed [1].

Vitamin D is highly liposoluble, such that upon absorption it is stored in fatty tissues and released in small quantities. This explains why obese subjects are at higher risk of vitamin D deficiency, as it becomes "diluted" in the higher body mass [1]. As vitamin D does not stay in the body for very long, its concentration in the bloodstream is very low (1-2 ng/mL) [1]. In the liver, vitamin D is converted into 25-hydroxyvitamin D [25(OH)D] by the enzyme 25-hydroxylase. This transformation process can also take place in the presence of a significant reduction in the hepatic tissue function, although a high prevalence of hypovitaminosis D is evident in patients with correlated chronic hepatitis HCV [1].

Calcifediol, or 25(OH)D, has a high affinity for the vitamin D binding protein (VDBP) and represents the main vitamin D blood metabolite. Its concentrations are the most reliable representation of the vitamin D status of individuals [1]. Serum 25(OH)D concentrations constitute an accurate indicator of our storage of vitamin D. As a result, the question of vitamin status (deficiency, insufficiency and sufficiency) is exclusively based on serum 25(OH)D levels (Table I).

Abstract

The effects of cholecalciferol and of several vitamin D metabolites have been investigated and are now available for clinical use. The numerous and important differences between vitamin D metabolites, both in pharmacokinetics and for clinical purposes, need to be taken into account when determining the most appropriate drug for the treatment and/or prevention of vitamin D deficiency.

In this context, and based on data from clinical studies, cholecalciferol appears to be the preferred supplement in the prevention and treatment of vitamin D deficiency. In conjunction with other therapies, it is also used in the prevention of primary and secondary fractures associated with bone fragility in patients with osteoporosis receiving antiresorptives or osteoanabolic medication.

Based on current evidence, the use of other metabolites must be limited to specific medical conditions, such as chronic renal insufficiency or hypoparathyroidism (alfacalcidol and calcitriol), malabsorption syndrome, severe obesity or hepatic insufficiency (calcifediol).

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In part, 25(OH)D is a hydrophilic metabolite; it is stored only in the liver and muscles [1]. Its half-life is shorter than that of vitamin D, such that it is able to satisfy the organism's requirements for no more than 12-18 days [1, 4]. 25(OH)D has a low affinity for the specific vitamin D receptor and thus needs to be transformed into calcitriol, or 1,25-dihydroxyvitamin D [1,25(OH)2D], to become metabolically active [1, 4].

The conversion of 25(OH)D into 1,25(OH)2D by the action of the 1-alpha-hydroxylase enzyme takes place predominantly in the kidneys, but it can also occur in other tissues [1]. Most of the production of 1,25(OH)2D, whose most important role is to control mineral metabolism, occurs in the renal proximal tubules. The production of 1,25(OH)2D by the action of the 1-alpha-hydroxylase enzyme involves the presence of the parathyroid hormone (PTH) and is in part modulated by serum calcium and phosphorus levels [1]. 1,25(OH)2D is not stored at tissue level and has a very short half-life [1, 4].

Renal insufficiency progressively reduces 1,25(OH)2D production [1]. Nevertheless, a significant decline in 1-alpha-hydroxylase enzyme activity, such that normal hormone levels are compromised, is only detected when associated to severe renal function impairment (generally 4-5/5D stage) [1, 10]. However, it should be emphasized that even when renal 1-alpha-hydroxylase enzyme activity is severely compromised, 25OHD levels must be kept within the normal range to ensure an adequate substrate for extra-renal 1-alpha-hydroxylase [1, 10].

By binding with a specific receptor (VDR, which is present both in the nucleus and in the cell membrane), 1,25(OH)2D (as

an active metabolite) produces a biological response at the cellular level [1]. Such a response is produced both by triggering gene transcription (genomic mechanism) and through the action of cellular second messengers or the phosphorylation of some proteins (non-genomic mechanism) [1]. Vitamin D receptors are ubiquitous in the body.

CHOLECALCIFEROL, ERGOCALCIFEROL AND VITAMIN D METABOLITES

In addition to the two natural forms of vitamin D – vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) – many other supplements/metabolites with the same vitamin D activity are available for daily clinical practice [1, 4]. Some of them, such as calcifediol, were already clinically synthesized and utilized in the last century. Other forms, meanwhile, have been synthesized and primarily employed in nephrology (for example, paricalcitol) [4].

A comprehensive discussion of all vitamin D metabolites, particularly those which are mainly used in nephrology, is not the intent of our review. Our presentation will therefore focus on the most common types of vitamin D utilized in daily clinical practice; it will aim to describe their properties (Table 2) and to briefly summarize clinical data obtained from RCTs.

Cholecalciferol

Cholecalciferol (vitamin D3) is the natural form of vitamin D of animal and human production. Cholecalciferol (vitamin D3) is a prohormone, the precursor of the two vitamin D hydroxylated forms [25OHD and 1,25(OH)2D]; it therefore needs to undergo two processes of hydroxylation before being transformed into its metabolically active form [1, 4].

Cholecalciferol is normally stored in the adipose tissue, from where it is slowly released [1]. For this reason, its blood half-life is very short (estimated T1/2 = 19-25 hours), while its functional half-life (several weeks) is definitely longer (in correlation with its slow release from the adipose tissue) [4], making it an extremely flexible and adaptable substance to use in daily clinical practice and rendering possible intermittent administration regimes [1, 2].

Cholecalciferol is available on the market for oral and intramuscular use. With the exception of specific clinical conditions (malabsorption syndrome), oral administration is preferable to intramuscular injection because it is more effective in boosting serum 25OHD [11, 12].

Clinical studies have employed many administration regimes and different doses of cholecalciferol, ranging from 400 to 4000 IU/day and 25,000 to 50,000 IU per month [4, 6, 13-18]. Figure 1 illustrates the effect – in terms of mean increase of serum 25OHD (ng/mL) after three months – of different doses and therapeutic treatments with cholecalciferol. The lowest doses (e.g., 400-600 IU/day) have proved to be ineffective in achieving clinical endpoints (e.g., reduction of risk for fractures) [15]. Some RCTs have also investigated the effectiveness of massive doses (boli) of cholecalciferol, with mixed results for clinical outcomes such as falls and fractures [1, 2, 6]. It is therefore recommended not to exceed the bolus dosage of 100,000 IU and to distribute the administration of any higher therapeutic dosage (aiming to attain the optimal serum value of less than 30 ng/mL) over the course of two weeks [1, 2]. Recently, the Italian society SIOMMMS proposed a strategy for the prevention and treatment of vitamin D deficiency with cholecalciferol (Table 3), based on basal vitamin D status (25OHD) [2]. The cholecalciferol doses shown in Table 3 must be considered standard, although they are susceptible to variations in relation, for example, to the existence of risk factors (such as obesity) that could reduce the effect of cholecalciferol in increasing serum 25OHD values [16].

In the context of vitamin D metabolites correlated to vitamin D deficiency, cholecalciferol has by far been the one to attract most attention, both in clinical studies for the prevention and treatment of hypovitaminosis D and in RCTs evaluating its effectiveness on skeletal (falls and fractures) and extraskeletal

TABLE I.

Interpretation of blood levels of 25(OH)D (Adami et al. 2011, mod.; Rossini et al. 2016, mod.) [1, 2]

DEFINITION	25OHD Units	
	nmol/l	ng/ml
Severe deficiency	< 25	< 10
Deficiency	25-50	10-20
Insufficiency	50-75	20-30
Optimal Range	75-125	30-50
Excess	> 250	> 100
Intoxication	> 375	> 150

(e.g., pneumonia and neoplasia) endpoints [1-3, 6]. A systematic discussion of RCTs on cholecalciferol falls outside the aims of our review, which is limited to describing the most important findings in the field of osteo metabolic disorders.

Numerous RCTs have evaluated the efficacy of cholecalciferol in normalizing and maintaining the optimal level of serum 25OHD (> 30 ng/ml) [1, 2, 11-18]. These studies have shown that when used at appropriate doses and in suitable therapeutic regimes cholecalciferol was able to efficiently normalize 25OHD and keep it within the de-

sired range (30-50 ng/ml) [1, 2, 13, 14, 16-18]. The definition of an appropriate dose must take into account both the basal serum 25OHD value and other clinical factors that may influence treatment response (e.g., body mass index, age, pathologies and pharmacological therapies) [1, 2, 16]. The prevention and treatment strategies described in Table III summarize a part of the evidence from these RCTs [2]. Cholecalciferol has noticeably been the focus of the greatest number of RCTs that aim to evaluate the efficiency of this metabolite in reducing the risk of fracture [6]. These

RCTs and their meta-analyses have shown that cholecalciferol, when administered in appropriate doses and therapeutic regimes and when associated with adequate calcium supplementation – either through foods (only dietary calcium) or supplements – is able to produce a significant reduction in the risk of femur and non-vertebral fractures in at-risk populations (such as the elderly and adults with low 25OHD levels) [1, 2, 5, 6]. Reduced fracture risk was in part attributed to a significant reduction in the risk of falls. Even if the findings of these RCTs are not completely consistent, reports of higher scientific

TABLE II.

Half-life and commonly used doses of vitamin D and its metabolites in clinical practice (Mazzaferro, et al. 2014, mod.) [4].

	CHOLECALCIFEROL	ERGOCALCIFEROL	CALCIFEDIOL	ALFACALCIDOL	CALCITRIOL
Half-life	Blood: 19-25 hours Functional: many weeks	Blood: 48 hours Functional: 2 months or less	10-22 days	12 hours	5-8 hours
Dose Range (most commonly evaluated in clinical studies)	400-4,000 IU/day 5,000-10,000 IU/week 25,000-50,000 IU/month	800-2,000 IU/day 50,000 IU/week	5-20 µg/day	0.5-5 µg/day	0.25-1 µg/day

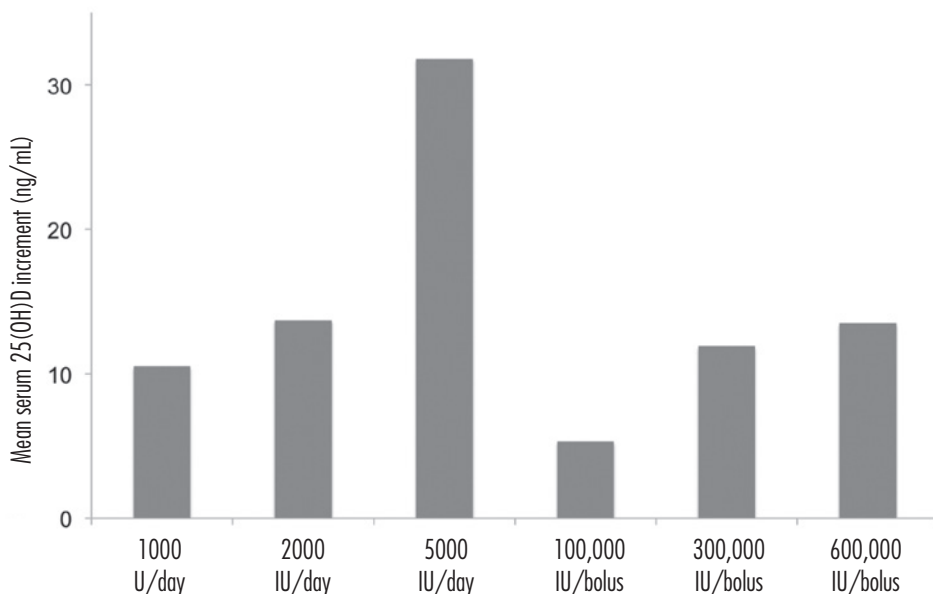


FIGURE 1.

Mean increment of absolute serum 25(OH)D level (ng/mL) at 3 months with different doses and therapeutic regimes of cholecalciferol (1000 IU/day, 2000 IU/day, 5000 IU/day, 100,000 IU bolus, 300,000 IU bolus, 600,000 IU bolus). For clinical indications, see text (from Rossini et al., 2012, mod.; Diamond et al., 2013, mod.; Giusti et al., 2010, mod.) [13, 14, 16].

quality allow us to estimate a risk reduction in subjects treated with cholecalciferol of 16-30% for femur fracture and of ca. 14% for non-vertebral fracture [5, 6]. It should be emphasized that these findings derive from trials in which cholecalciferol was administered to appropriate patients (with, that is, vitamin D deficiency), and above all in suitable doses (between 800 IU and 2,000 IU/day) [5, 6, 15]. In the clinical studies, the administration of bolus less than 100,000 IU turned out to be safe and free of side effects, including hypercalcemia and hypercalciuria [1, 2, 4, 6].

Finally, to provide a comprehensible framework for the use of cholecalciferol in clinical practice, we should highlight several points of undeniable importance:

- cholecalciferol has proven to be effective in reducing the risk of femur and non-vertebral fracture when it is used in doses that allow an appropriate level of 25OHD to be reached (> 30 ng/ml). In patients with osteoporosis at risk for fracture, treatment with cholecalciferol only is not sufficient to produce a significant reduction of this risk; it must be associated with anti-fracture pharmaco-

TABLE III.

Estimate of therapeutic dose (to be distributed over several weeks) and of maintenance dose of cholecalciferol based on basal 25 (OH) D concentrations (from Rossini, et al. 2016, mod.) [2].

BASAL 25OHD LEVEL	CUMULATIVE THERAPEUTIC DOSE (IU)	DAILY MAINTENANCE DOSE (IU)
< 10 ng/mL (25 nmol/L)	600.000	2.000
10 to 20 ng/mL (25-50 nmol/L)	400.000	1.000
20 to 30 ng/mL (50-75 nmol/L)	100.000	800

logical therapy, such as antiresorptive or osteoanabolic therapy;

- in all phase III pivotal RCTs, the active substance (bisphosphonate, denosumab or teriparatide) proved to be effective in reducing the risk of osteoporotic fracture in association with cholecalciferol;
- vitamin D deficiency (defined as a lack of cholecalciferol intake or reduced serum 25OHD) is probably the main cause of a lack of clinical response to pharmacological therapy for osteoporosis (particularly in the case of antiresorptive).

Ergocalciferol

Ergocalciferol is natural vitamin D₂ of plant origin. It is a prohormone that requires double hydroxylation to be transformed into its active form [1,25(OH)₂D] [1].

It has been calculated that the T_{1/2} of circulating ergocalciferol is ca. 48 hours, while its functional half-life may be less than two months [4]. Ergocalciferol is available on the market in oral and intramuscular form. For years it was believed that ergocalciferol and cholecalciferol were equally effective and were therefore interchangeable [4]. Recently, however, several studies have shown that ergocalciferol is less effective in increasing serum 25OHD levels than cholecalciferol, with an estimated ratio of 3 to 1 (ergo- vs. cholecalciferol) [4, 11, 12].

Few RCTs have been conducted to evaluate the anti-fracture effectiveness of ergocalciferol, either in the general population or in at-risk groups, such as elderly persons in institutions. Overall, on the basis of the results of these RCTs, we can affirm that ergocalciferol – in the experimented doses – has proved to be substantially ineffective in reducing the risk of vertebral, non-vertebral and femur fracture [4, 6, 15].

Based on what has been described above, the use of ergocalciferol in daily clinical practice does seem justifiable.

Calcifediol

Calcifediol (25OHD) is the hepatic metabolite of vitamin D. Compared to calcitriol (a biologically active metabolite), calcifediol has a higher affinity for VDBP, but a lower affinity for VDR [4]. For this reason, calcifediol must hydroxylate into its active form (calcitriol) in order to become biologically effective. Calcifediol is partially hydrophilic and is stored only in the liver and muscles [1]. It is thus unable to cause repletion of vitamin D storage (unlike cholecalciferol). The half-life of 25OHD is shorter than that of vitamin D₃ and has been calculated to be ca. 10-22 days [4]. This shorter half-life (with respect to that of cholecalciferol, which is believed to be of many weeks) certainly makes calcifediol a less flexible and adaptable product in clinical practice. Its administration/intake must in fact follow more rigid therapeutic regimes, as its shorter half-life reduces the margins between one administration and another. It is indeed believed that a single dose is able to supply the body's requirements for no more than 12-18 days (depending on the quantity of the dose) [1, 4]. For this reason, daily or weekly protocols are usually followed, even if it has been proposed that monthly administration regimes (of high doses) are also effective [4, 6-9, 19, 20]. In this context, treatment which is not regularly followed over long periods of time may make patients more susceptible to the risk of hypovitaminosis D or to a lesser response to serum 25OHD.

Recent pharmacokinetic studies have shown that calcifediol produces a more rapid increase in serum 25OHD than cholecalciferol in subjects with vitamin D deficiency [7-9, 19, 20]. In these studies, calcifediol was typically administered in doses of 20 µg/day [19, 20]. Even if higher doses were also used, in daily clinical practice calcifediol is normally prescribed at doses between 5 and 20 µg/day [4, 6-9, 19, 20]. This suggests that in the pharmacokinetic studies cited above calcifediol was used in medi-

um to high doses, while cholecalciferol was administered in relatively low ones (800 IU/day, which, as we have seen, was described in the RCTs as the minimum effective dose for fracture risk reduction) [5-9, 15, 20]. This critical difference obviously complicates the interpretation of the findings of these pharmacokinetic studies on calcifediol (vs. cholecalciferol) and reduces their value on a clinical level.

Compared to the significant number of RCTs conducted on cholecalciferol to evaluate its effectiveness in reducing the risk of fracture, there have been decidedly fewer RCTs on calcifediol [4, 6]. A recent meta-analysis by Cochrane reviewed therapeutic RCTs (investigating fracture risk reduction) conducted with vitamin D and its metabolites: the analysis identified only two studies on calcifediol which were deemed acceptable based on the quality of their experimental design [6]. It should be pointed out that in both of these studies the risk of bias was not measurable [6]. On the basis of the findings of these two studies, we can affirm that at present there is not sufficient scientific evidence to warrant the anti-fracture effectiveness of calcifediol [6, 21]. In a more recent RCT published by Peacock et al., for example, the incidence of new vertebral and nonvertebral fracture turned out to be similar in subjects treated over four years with calcium (750 mg/day), calcifediol (15 µg/day) or a placebo [21]. On the whole, if we wish to summarize the available evidence, we can state that in clinical practice calcifediol has a single advantage compared to cholecalciferol: the greater rapidity at which the serum 25OHD level increases. In which situations this different pharmacokinetics is able to provide greater benefits on a clinical level (e.g., reduction of the risk of fracture) has not, however, been clearly defined, in part given the lack of clinical data from RCTs which have persuasively demonstrated its effectiveness in achieving primary endpoints.

As has been recently emphasized in a liter-

ature review, we must, finally, keep in mind the potential risk of toxicity with higher doses of calcifediol (Table I) [4], even if pharmacokinetic studies (20 µg/day) have not shown significant adverse events [20]. As indicated in the guidelines, it therefore does not seem appropriate to consider calcifediol a preferred drug for the prevention and treatment of hypovitaminosis D or in the prevention of fragility fractures in patients with osteoporosis, in association with antiresorptive or osteoanabolic medication. [1, 2]. It is, by contrast, necessary to emphasize that calcifediol represents the chosen vitamin D metabolite in treating patients with chronic liver disease and severe reduction of the hepatic function.

Calcitriol

Calcitriol [1,25(OH)2D] is the active metabolite of vitamin D and the natural ligand of VDR. It has a short half-life, calculated at ca. 5-8 hours [4]. For this reason it must be administered daily (in some studies it is also used with intermittent regimes) and sometimes in lower doses distributed over a 24-hour period [4, 6, 20]. Administered doses usually range from 0.25 to 1 µg/day [4, 6].

Since its discovery in the 1970's, calcitriol has been successfully used in treating secondary hyperparathyroidism in patients affected with chronic renal insufficiency, or in the prevention of hypocalcemia in patients suffering from hyperparathyroidism [4, 20]. More recently, calcitriol has been used and studied in RCTs aimed at evaluating its effectiveness in reducing fracture risk [6, 20]. In some – though not all – of these RCTs, calcitriol has been shown to reduce the risk of fracture [4, 6, 20]. Nonetheless, these same RCTs have also reported a greater and more significant incidence of adverse events, such as hypercalcemia, hypercalciuria and nephrolithiasis in subjects treated with calcitriol [4, 6, 20].

Because of the lesser degree of safety and clinical practicality of calcitriol, the international scientific community agrees that its use should be limited to patients suffering from chronic renal insufficiency or to patients affected by hypoparathyroidism [2, 4, 20].

In the context of treating patients suffering from chronic renal insufficiency, two other aspects of the use of calcitriol should be mentioned [4, 10]:

numerous writers and opinion leaders propose the contemporary administration of cholecalciferol in patients affected by chron-

ic renal insufficiency who are being treated with calcitriol: this recommendation is motivated by the activity of extra-renal 1- α -hydroxylase, which is not linked to feedback mechanisms and is not compromised by the reduced renal function;

it has recently been suggested that the use of calcitriol be limited to patients suffering from chronic renal insufficiency with low cardiovascular risk profiles.

Alfacalcidol

Alfacalcidol, or 1- α -hydroxy-vitamin D, is a prodrug which requires 25-hydroxylation in the liver to become metabolically active [1,25(OH)2D]. It was first synthesized in the early 1970's and used clinically beginning in 1973, with the aim of administering a prohormone that was able to bypass renal 1- α -hydroxylation and that would thus be usable even in the presence of reduced renal function [4, 20]. Alfacalcidol therefore represents an alternative to calcitriol.

For a certain period, the use of alfacalcidol in clinical practice was strongly encouraged. It was indeed believed that because alfacalcidol needs to be activated (25-hydroxylation) its pharmacokinetics was preferable to that of calcitriol, as its action is more enduring (because of its longer half-life) and it creates less exposure to the risk of hypercalcemia [4, 20]. This theoretical advantage, however, has not been realized in clinical practice.

Although slightly longer than that of calcitriol, the half-life of alfacalcidol is ca. 12 hours (the time necessary for its total metabolic conversion) [4]. For this reason, alfacalcidol must also be administered daily. It has been calculated that a daily dose of 1 µg of alfacalcidol is the bioequivalent of 0.5 µg of calcitriol [20]. Administered doses typically range from 1 to 5 µg/day [4, 6].

As in the case of calcitriol, alfacalcidol is generally recommended for use in patients affected by chronic renal insufficiency [4, 20].

In some RCTs (and meta-analyses), alfacalcidol has been shown to significantly reduce the incidence of new fractures [4, 6, 20]. As with calcitriol, though, prolonged treatment with alfacalcidol can expose patients to a heightened risk of adverse events linked to its hypercalcemizing action. For this reason, the use of alfacalcidol in clinical contexts should be subject to the same guidelines and limitations as those for calcitriol [4].

CONCLUSIONS

In daily clinical practice, cholecalciferol should be considered the preferred supplement for preventing and treating vitamin D deficiency and for the primary and secondary prevention of fragility fractures in patients with osteoporosis, in association with antiresorptive or osteoanabolic therapy. The use of other vitamin D metabolites – calcifediol, alfalcidol and calcitriol in particular – should be limited to specific situations, such as conditions of chronic renal insufficiency or hypoparathyroidism (alfalcidol and calcitriol), malabsorption syndrome, severe obesity or hepatic insufficiency (calcifediol). These recommended restrictions concerning the use of vitamin D metabolites are mainly due to the limited evidence proving their effectiveness in reducing the risk of fracture, the lack of appropriate studies that directly “pit” them against cholecalciferol, and the potential risk of adverse events linked to their hypercalcemizing action (especially for 1- α -hydroxylated metabolites).

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NATIVE VITAMIN D IN CHRONIC KIDNEY DISEASE

VITAMIN D
UpDates

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VITAMIN D AND KIDNEYS

Kidneys are certainly among the most important organs with regard to the metabolism of the vitamin D endocrine system. It is known that 1,25 (OH)₂ vitamin D (or calcitriol) – the system's most active metabolite in terms of function – is indeed produced within kidney tissue, where cytochrome CYP27B1 is maximally expressed. This gene is responsible for synthesizing the 1-alpha-hydroxylase enzyme, which is able to convert 25 (OH) vitamin D – which mostly comes from the liver – into calcitriol (Fig. 1). Calcitriol is the most powerful stimulator of the vitamin D receptor (VDR) (Fig. 2), whose activity generates the most important functions of this hormonal system within the human body [1].

For this reason, it has always been believed – and still is today – that the progressive loss of renal function can reduce calcitriol synthesis. This, in turn, triggers complex metabolic and clinical alterations which lead to the onset of the condition known as CKD - MBD (Chronic Kidney Disease - Mineral and Bone Disorder): this disorder is largely responsible for skeletal and vascular complications, which quite frequently afflict those with CKD [2]. The most notable of the complications caused by an impaired function of the vitamin D endocrine system is the increase in parathyroid hormone (PTH). Although also plays a significant role in the increase of phosphatemia, a typical symptom of CKD, it has always been held that treatment of secondary hyperparathyroidism, which is characteristic of CKD, should be effected with active vitamin D metabolites (calcitriol and analogs) [3].

In recent years, however, new scientific evidence has been collected that has led scientists to reconsider this idea, at least in part. If it is indeed true that renal synthesis of calcitriol decreases with a reduction of kidney function, today it is known that the nearly total cessation of 1-alpha-hydroxylase activity of the

kidney occurs when the glomerular filtration rate (GFR, mL/min) is less than 15. In previous stages of CKD, this activity is present and efficient, at least in part (Table I). It then became increasingly clear that expression of cytochrome CYP27B1 and the resulting activity of 1-alpha-hydroxylase enzyme is actually present in tissues and organs other than the kidneys [4], thus rendering possible a significant degree of extra-renal calcitriol synthesis. This synthesis is largely carried out through the local actions, autocrine and paracrine, rather than the systemic ones, of this metabolite (Table II). Nonetheless, the most relevant fact is certainly an increasingly evident prevalence of reduced levels – sometimes markedly reduced – of 25 (OH) vitamin D, which is surely not attributable to the loss of renal function.

This observation has given rise to a long series of studies which aim to assess the importance of “pre-renal” hypovitaminosis D in the genesis of various complications related to chronic kidney disease (CKD) and the possible role of native vitamin D in the treatment of this condition [5].

HYPOVITAMINOSIS D IN CHRONIC KIDNEY DISEASE: PREVALENCE, POSSIBLE COMPLICATIONS AND THERAPY

As we have seen, in the last ten years many studies have focused on the role of 25 (OH) D status in patients with CKD. Most of these show that serum levels of this hormone tend to decrease, in parallel with what takes place with calcitriol, with a progressive deterioration of renal function [6]. Already in patients with stage 1-2 CKD, it is estimated that the prevalence of 25 (OH) vitamin D serum values < 30 ng/mL is close to 80% [6], reaching almost 85% in patients with terminal stage CKD. In particular, it has been shown that 25 (OH) vitamin D levels below 15 ng/mL are found in ca. 50% of patients with stage 4-5 CKD. Quite similar data indicate that low

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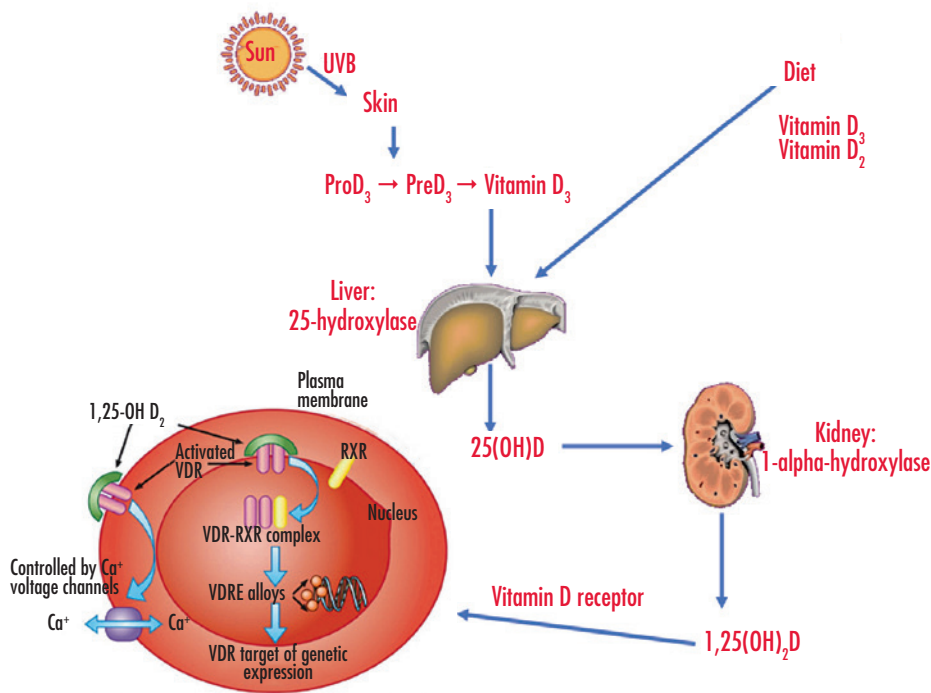


FIGURE 1.
Vitamin D endocrine system.

vitamin D levels are also present following kidney transplants, with a prevalent tendency toward 25 (OH) vitamin D deficiency. The reason for this very high prevalence of hypovitaminosis D is not completely clear. One possibility is that, as in the general population, insufficient exposure to sunlight could in part explain this phenomenon. It

has in fact been demonstrated that exposure to UVB rays in terminal stage CKD patients is able to significantly raise 25 (OH) D serum levels [8]. On the other hand, it is also clear that the seasonal boost of these blood levels is, on the whole, rather modest in these patients. Indeed, one study has shown that a prevalence of severe vitamin D deficiency of

96% during winter months dropped to only 86% in summer months in subjects undergoing hemodialysis [9]. This datum should not surprise us, given that these patients suffer from significant morbidity, which is little compatible with adequate exposure to sunlight during the warm months.

The complications of this widespread condition are still not clear today. There are still very few studies which aim to show the cause-effect relationship between hypovitaminosis 25 (OH) D and morbidity in CKD patients. Nonetheless, a number of interesting suggestions backed by sound scientific evidence have been produced in the last few years. Bone fragility and subsequent fractures are quite common conditions in CKD. They result from a series of impairments of bone tissue, which constitute the basis of renal osteodystrophy and which frequently include the concomitance of various stages of osteomalacia, high turnover bone disease and adynamic bone disease. Secondary hyperparathyroidism is certainly a distinctive characteristic of the first two forms; it is therefore not surprising that a significant portion of scientific work has focused on the role of low 25 (OH) vitamin D levels in the genesis of this condition. Although no sound studies are available to show the ability of therapy with native vitamin D to reduce the risk of fractures in the course of CDK, recent data indicate that it plays a clear role in the pathogenesis and correction of the main metabolic alterations related to them.

In subjects with kidney transplants, 25(OH) D serum levels were quite low in the majority of evaluated individuals and represented the greatest predictive factor for high parathormone levels, as the latter were correlated to a high risk of vertebral fracture in these patients [7]. Indeed, several studies regarding this category of patients have shown that therapy with cholecalciferol – even if different doses were used – was able to broadly and significantly reduce serum parathormone levels [10]. Even more interesting results come from a randomized double-blind controlled study which involved stage 3-4 CKD patients with 25 (OH) vitamin D serum levels < 20 ng/mL. These subjects were administered either 300,000 IU of cholecalciferol on two occasions at a distance of 8 weeks, or a placebo. At the end of the study, after a follow-up conducted at 16 weeks, researchers found that those treated with cholecalciferol had fully normal 25 (OH) vitamin D serum levels.

Activation of the vitamin D receptor produces:

- genomic actions
- non-genomic actions – rapid intestinal absorption
- endocrine function – systemic
- paracrine and autocrine functions – local

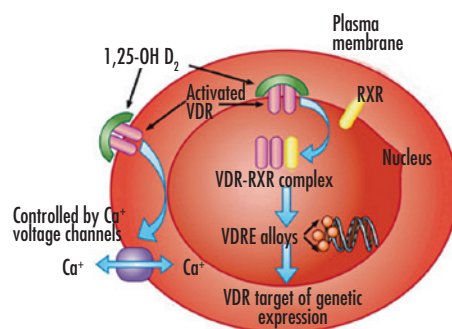


FIGURE 2.
Vitamin D receptor and its activation.

TABLE I.
Stages of chronic kidney disease (CKD).

STAGE	DESCRIPTION	GFR (ML/MIN)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with slight GFR reduction	60-89
3	Kidney damage with moderate GFR reduction	30-59
4	Kidney damage with severe GFR reduction	15-29
5-5D	Kidney failure (D = Dialysis)	< 15

TABLE II.
Main organs and tissues that express mRNA for CYP27B1 in (1-alpha-hydroxylase synthesis).

Adrenal Gland	Mammary Gland
Bone	Muscle
Bone Marrow	Neoplastic Cells
Brain	Ovary
Cartilage	Pancreas
Fat	Parathyroid Glands
Heart	Placenta
Intestine	Prostate
Kidney	Skin
Liver	Testicle
Lung	Thyroid
Lymphocyte	Uterus

Nonetheless, the most relevant finding of this study was certainly that of a reduction of ca. 25% in PTH values, which are high at basal conditions, and of 30% and ca. 18% of bone alkaline phosphatase and of the Cross-Laps of the pyridinium, respectively, which are known to be reliable bone-remodeling markers. These results allow us to postulate a positive effect of cholecalciferol in terms of bone morbidity in CKD patients [11].

In both of the studies cited above, as in others that we are forced to omit, no significant or clinically relevant modification of serum calcium values or renal function was observed, indicating that this therapy has safety characteristics that are completely reassuring. Vitamin D insufficiency has, moreover, been associated with the genesis of other possible CKD complications. Even though, in this context, we still lack sufficiently solid evidence to confidently recommend the use of native vitamin D in the course of CKD,

some interesting scientific data are already available. In these patients, it is known that residual proteinuria following maximum therapy with angiotensin-converting enzyme inhibitors constitutes an independent risk factor for the progression of CKD and for the onset of cardiovascular events.

A recent prospective and controlled study of pre-dialysis CKD patients with hypovitaminosis D found a significant (41%) reduction in proteinuria in subjects treated with cholecalciferol (666 IU/day for 6 months), while no variation was observed in untreated subjects. In this study, stage 3-4 CKD patients with 25 (OH) vitamin D serum levels < 20 ng/mL were given either 300,000 IU of cholecalciferol on two occasions at a distance of 8 weeks, or a placebo: it was observed that vascular function – defined as the variation of the endothelium-dependent flow in the brachial artery and of the carotid-femoral pulse-wave velocity – improved significantly in the treated subjects, but not in the placebo group [12].

It is clear that sufficient data are lacking in order to draw realistic conclusions and that further studies are still necessary; even so, the available literature seems to suggest that low levels of 25 (OH) vitamin D can be correlated to a worsening of anemia and a progression of renal dysfunction in patients with CKD [5].

CONCLUSIONS

Solid evidence from different studies provides increasingly convincing indications that insufficiency of 25 (OH) vitamin D (and not only of calcitriol) may be responsible for many clinical consequences of CKD. Undoubtedly, the challenge over the next few years will be to definitively show the importance and the wide range of potential applications of therapy with native vitamin D, including in this complex and common clinical condition.

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