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Cholecalciferol or calcifediol? A question of narrative!

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Abstract

Over the last decade, significant progress has been made in strategies for the prevention and treatment of vitamin D deficiency thanks to clinical trials and pharmaco-kinetic studies, which have also made it possible to define the pharmacological properties of cholecalciferol and calcifediol.
Although cholecalciferol and calcifediol are often considered and used equally in clinical practice, there are a number of significant differences between them, both pharmacologically and clinically, that need to be taken into account when choosing the most appropriate strategy for treating/preventing vitamin D deficiency and for the prevention of fragility fractures.
In particular, calcifediol has recently been proposed as the drug of choice as an alternative to cholecalciferol in treating vitamin D deficiency, due to a greater potency and rapidity in normalising 25-hydroxy-vitamin D serum concentration. However, a thorough evaluation of the available evidence and in particular of randomised controlled clinical trials, confirms the primacy of cholecalciferol in the prevention and treatment of vitamin D deficiency and in the primary and secondary prevention of fragility fractures in osteoporotic individuals in combination with an antiresorptive or osteoanabolic drug. Therefore, based on current evidence, the use of calcifediol should be limited to particular situations, such as malabsorption syndromes, severe obesity or liver failure.

INTRODUCTION

Epidemiological studies describe a high prevalence of hypovitaminosis D in the general adult and elderly population that is not appropriately integrated with vitamin D supplements, particularly in at-risk sub-populations such as frail or chronically ill individuals, patients suffering from malabsorption syndrome and institutionalised subjects [1-3].
Vitamin D, and in particular its deficiency, plays a significant role in the pathogenesis of fragility fractures, falls and numerous acute and chronic 'extra-skeletal' clinical conditions (for example, COVID-19 and infectious diseases, rheumatological diseases, neoplasms, diabetes and cardiovascular diseases) [1-7]. In this clinical-epidemiological context, as expected, growing international debate has arisen on the most appropriate therapeutic strategies for the prevention and treatment of vitamin D deficiency [7-12].
In particular, talk has recently focused on a specific question, namely whether it is more appropriate to use calcifediol instead of the traditionally-used cholecalciferol in the treatment of hypovitaminosis D [9-12]. Numerous Randomised Controlled Trials (RCTs) and pharmaco-kinetic studies have attempted to answer this question, having broadened knowledge of the pharmacological and clinical effects of these two molecules. Although the results of the most recent studies have rendered it possible to generate significant evidence with clinical impact, the numerous limitations of the published studies (such as the choice of surrogate outcomes and the extreme heterogeneity of the dosages used) have resulted in significant confusion on the subject, resulting in a narrative that is not always appropriate.
The aim of our narrative review is to summarise some of the pharmacological and non-pharmacological characteristics of cholecalciferol and calcifediol, bringing the

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narrative back to a clinical level in order to define their role in daily clinical practice.

VITAMIN D PRODUCTION AND METABOLISM

A thorough knowledge of the physiology and metabolism of vitamin D is the essential foundation and "condicio sine qua non" for settling the question of whether it is more appropriate to use cholecalciferol or calcifediol in clinical practice.

The term vitamin D normally loosely refers to both animal- and human-produced vitamin D_3 (cholecalciferol) and plant-produced vitamin D_2 (ergocalciferol)[1,10-12].

The main source of vitamin D for the body should be endogenous vitamin D derived from the conversion of 7-dehydrocholesterol following exposure of the skin to ultraviolet rays of a specific wavelength. This mechanism should produce the preponderant quota (approximately 80%) of vitamin D (vitamin D_3) for the body's needs, whilst smaller amounts (approximately 20%) of vitamin D_3 and vitamine D_2 can be taken in through diet [1].

The skin's production of cholecalciferol is strongly influenced by the seasons, latitude, the characteristics of the skin exposed to the sun, the use of sunscreen and by age 1. A smaller quota of vitamin D_3 can be taken from food, in particular animal fats, whilst the quota of vitamin D_2 in vegetable fats is absolutely negligible [1]. In some countries, the liberal fortification of food with cholecalciferol is stored in the adipose tissue, which releases small amounts. This is also one of the reasons why obese subjects are at a higher risk of deficiency as a result of 'dilution' in a larger adipose mass [1,11-14]. Finally, the high fat-solubility of vitamin D also results in a prolonged functional half-life, estimated to be around 2 months [12]. Vitamin D remains in the bloodstream for a short time so its blood concentrations are very low (1-2 ng/ml) [1].

To become metabolically active, vitamin D must undergo two enzymatic hydroxylation processes, which occur mainly in the liver and kidney [1,12]. During hepatic transit, vitamin D is converted to 25-hydroxy-vitamin D [25(OH)D] by the enzyme 25-hydroxylase. The process of transformation of vitamin D into 25(OH)D can occur even in the presence of a significant reduction in functioning liver tissue, although a higher prevalence of hypovitaminosis D is evident in patients with HCV-related chronic hepatitis [1].

25(OH)D, also known as calcifediol, has a high affinity for *Vitamin D Binding Protein* (VDBP) and is the main blood metabolite of vitamin D. By far, its concentrations are the most reliable index of a subject's vitamin D status [1]. Serum 25(OH)D dosage is an accurate indicator of our vitamin D deposits. Therefore, the definition of a subject's vitamin D status (deficiency, insufficiency and sufficiency) is currently based exclusively on the interpretation of serum 25(OH)D levels (Tab. I).

25(OH)D (or calcifediol) is a partially hydrophilic metabolite and is only deposited in liver and muscle [1]. The half-life of 25(OH)D is shorter than that of vitamin D, such that requirements are met for no more than 12-18 days [1,8]. 25(OH)D has a low affinity for the specific Vitamin D Receptor (VDR) and thus needs to be converted into calcitriol or 1,25-dihydroxy-vitamin D [$1,25(OH)_2D$], in order to become metabolically active [1,8]. It has been estimated that calcifediol, or 25(OH)D, possesses approximately 50 times less affinity for the VDR than calcitriol or $1,25(OH)_2D$ [15]. Despite the lower affinity for the VDR, recent experimental studies have shown that calcifediol can produce genomic (stimulation of gene transcription) and non-genomic (formation of cellular second messengers, phosphorylation of certain proteins) cellular effects through binding to nuclear and/or membrane receptors [15].

Conversion to $1,25(OH)_2D$ by 1-α-hydroxylase occurs mainly in the kidney, but also can be actuated in other tissues [1]. The largest share of $1,25(OH)_2D$, and that which is most relevant in the control of mineral metabolism, is produced in the renal proximal tubules. The production of $1,25(OH)_2D$ by 1-α-hydroxylase requires the presence of Parathyroid Hormone (PTH) and is modulated by serum levels of calcium, phosphorus and FGF23 [1,12]. $1,25(OH)_2D$ is not deposited in the tissue and has a very short half-life [1,8].

Renal insufficiency progressively reduces the production of $1,25(OH)_2D$ [1]. However, a significant deterioration in 1-α-hydroxylase activity, such as to permitted an increased dietary vitamin D intake, facilitated increased dietary vitamin D intake, although this strategy does not always optimise vitamin D intake [1].

Vitamin D is highly fat-soluble and this fat-solubility significantly influences its pharmacological characteristics. Its absorption in the gastrointestinal tract requires the presence of bile acids and takes place via the lymphatic system [1-12]. After entering the bloodstream, vitamin D no longer be able to ensure normal hormone levels, is only detectable in the presence of significant impairment of renal function (usually stage 4–5/5D) [1,16]. It must be emphasised, however, that even under conditions of severe compromise of renal 1-α-hydroxylase activity, 25(OH)D levels must be kept in the normal range to ensure an adequate substrate for extra-renal 1-α-hydroxylases [1,16].

The $1,25(OH)_2D$ (active metabolite) binding to a specific receptor (VDR, which is present both in the nucleus and in the cell membrane), produces the final effect of vitamin D at a cellular level [1]. This effect occurs either through the stimulation of gene transcription (genomic mechanism) or through the formation of cellular second messengers or the phosphorylation of certain proteins (non-genomic mechanism) [1]. Receptors for vitamin D are ubiquitous in the body.

TABLE I.
Interpretation of serum 25(OH)D levels (from Adami et al., 2011 and Rossini et al., 2016, mod.) [1,2].

Definition	Unit of measurement of 25(OH)D	
	nmol/L	ng/ml
Severe deficiency	< 25	< 10
Deficiency	25-50	10 -20
Insufficiency	50-75	20-30
Optimum range	75 -125	30-50
Excess	> 250	> 100
Intoxication	> 375	> 150

CHOLECALCIFEROL, CALCIFEDIOL AND THE LONG-STANDING ISSUE OF NORMALISING 25(OH)D CONCENTRATION

In addition to the two natural forms of vitamin D, vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol, in disuse), numerous pharmaceuticals/metabolites with vitamin D activity have become available in daily clinical practice [1,2,8]. Some have been synthesised and used prevalently in specific areas, such as the treatment of systemic disorders of mineral metabolism in chronic kidney disease or hypoparathyroidism, and thus have no relevance to the question under review. Yet, cholecalciferol and calcifediol, as already explained, are by far the two molecules most investigated and used for correcting hypovitaminosis D and for the prevention of fragility fractures in the non-nephropathic population.

Cholecalciferol

Cholecalciferol (D_3) is the natural vitamin D compound of animal/human origin. As described, cholecalciferol is a prohormone, precursor of the two hydroxylated forms [25(OH)D and 1,25$(OH)_2$D] of vitamin D and thus needs to undergo two natural hydroxylation processes to be transformed into its metabolically active form [1,8].

Cholecalciferol is strongly lipophilic. In connection with this characteristic, gastrointestinal absorption is influenced by the presence of bile acids, occurring via the lymphatic system and can be significantly impaired in the case of malabsorption.[12] Also by virtue of its lipophilicity, cholecalciferol is normally stored in adipose tissue, where it creates deposits from which it is slowly release 1. Precisely for this reason, it has a rather short blood half-life (estimated T1/2 of 19–25 hours) but a much longer functional half-life (several weeks) [8]. The high functional half-life of cholecalciferol is one of its main strengths in clinical use, making it an extremely flexible and adaptable product in practice, allowing for intermittent administration regimes [1,2]. Therefore, if on the one hand, high lipophilicity represents an advantage in relation to the functional half-life, on the other it can constitute a disadvantage – as mentioned – in obese subjects (high dilution) and in patients suffering from malabsorption (reduced intestinal absorption).

Cholecalciferol is available in formulations for oral and intramuscular use. With the exception of particular clinical conditions (malabsorption syndromes), oral administration is preferable due to being superior in terms of efficacy in raising serum 25(OH)D concentration compared to the intramuscular formulation [17,18].

In the RCTs designed to identify the most appropriate dosage and treatment regimen for normalising and maintaining optimal 25(OH)D concentration (30-50 ng/ml), cholecalciferol has been used in broadly varying dosages and administration regimens, going from doses of 400-4,000 IU per day to doses of 25,000-50,000 IU per month, also utilising therapeutic "bolus" doses of up to 600,000 IU (not recommended). In terms of increased 25(OH)D concentration, the RCTs have generally shown great heterogeneity in the response to supplementation with standard doses of cholecalciferol. This significant heterogeneity, which makes the dose-response to treatment less predictable, would appear to be linked to numerous factors (some of which are not fully elucidated), such as the basal 25(OH)D value, the Body Mass Index and factors affecting intestinal absorption and metabolism [12-14,19,20].

Taking into account the interfering factors illustrated and considering the results of the main RCTs, however, it can be stated that when used at appropriate dosages and treatment regimens, cholecalciferol is able to effectively normalise and maintain concentrations of 25(OH)D within the optimal/desirable range (30-50 ng/ml). For severe hypovitaminosis D (<10 ng/ml), the most appropriate approach, being broadly supported by the Italian guidelines, requires the administration of a therapeutic dose of 3,000-10,000 IU per day for 1-2 months, followed by a maintenance dose of approximately 2,000 IU per day [1,2,21]. In subjects with less severe hypovitaminosis D and in patients who are candidates for remineralising therapy (anti-resorptive or osteoanabolic), the most recent Italian guidelines suggest daily doses (or cumulative equivalents) of between 800 IU and 2,000 IU per day (with a single maximum dose not exceeding 100,000 IU) [21].

The main concern raised with respect to the use of cholecalciferol and the treatment regimes illustrated is the "relative slowness" of cholecalciferol in normalising 25(OH)D concentration in absolute terms and with respect to calcifediol [11-14]. As we shall see, this aspect is one of the main battle horses for advocates of the use of calcifediol in clinical practice. In this context, we thus feel it is important to emphasise the results of a recent RCT, published by Fassio et al., which challenged the aforementioned assumption [22]. The drug-kinetics study by Fassio et al. [22], investigating the effect of three different cholecalciferol treatment regimens (10,000 IU per day for 8 weeks followed by 1,000 IU per day for 4 weeks; 50,000 IU per week for 12 weeks; 100,000 IU every 2 weeks for 12 weeks), showed that supplementation with 10,000 IU cholecalciferol per day for 8 weeks, followed by 1,000 IU per day for 4 weeks in healthy subjects with hypovitaminosis (baseline 25(OH)D value averaging 14 ng/ml), was able to result in achieving the target concentration of 25(OH)D >20 ng/ml in all subjects in just two weeks. Similar results have been described for the other two treatment regimens. Furthermore, after four weeks of treatment, almost all subjects had achieved a value of 25(OH)D >30 ng/ml. This treatment regimen proved to be safe since there were no cases in which the concentration of serum 25(OH)D exceeded the safety limit of 100 ng/ml (Tab. I).

In conclusion, based on the evidence described, cholecalciferol must be considered as the therapy of choice in the treatment and prevention of hypovitaminosis D.

Calcifediol

Calcifediol [25(OH)D] is the hepatic metabolite of vitamin D and can roughly be said to differ from cholecalciferol due to the presence of a hydroxyl group at position C-25 [12]. Thus, along the vitamin D metabolism pathway, calcifediol is a step up from cholecalciferol to the biologically-active form (calcitriol) [12].

25-hydroxylation confers certain properties to calcifediol that underlie its different pharmacokinetics and pharmacodynamics, being the prerequisite for proposing it as an alternative to cholecalciferol. Being more hydrophilic, calcifediol is absorbed directly into the portal system and not through the lymphatic system, so does not undergo 'dilution' in adipose tissue. Furthermore, although with less affinity than calcitriol, it is able to bind to the VDR and potentially have cellular effects that are genomic (stimulation of gene transcription) and non-genomic (formation of cellular

second messengers, phosphorylation of certain proteins) [15].

Therefore, calcifediol would present some strongly emphasised pharmacological and clinical advantages, which can be summed up in five points: 1) Greater rapidity and potency (compared to cholecalciferol) in increasing serum 25(OH)D concentration; 2) More linear and predictable dose-response curve compared to cholecalciferol, independent of basal 25(OH)D concentration and other factors; 3) Efficacy even in the presence of liver function impairment, due to not requiring hepatic hydroxylation; 4) Greater efficacy (compared to cholecalciferol) in obese subjects, not being sequestered from adipose tissue; 5) Greater efficacy in subjects suffering from malabsorption syndrome, in relation to the different intestinal absorption mechanism (compared to cholecalciferol) [12]. Overall, these aspects – which can be summarised as the greater potency and speed of calcifediol – have been corroborated by the results of several RCTs comparing the efficacy of cholecalciferol and calcifediol in normalising serum 25(OH)D concentration in subjects with hypovitaminosis D [9-14,23-25].

As a whole, the studies would demonstrate that at "defined comparable" doses, calcifediol would be able to produce a faster and greater increase in 25(OH)D concentration than cholecalciferol. What's more, calcifediol would have a relative potency compared to cholecalciferol that is around 2–8 times greater. The extreme variability in the estimate of relative potency would be attributable to the doses used, the basal value of the serum 25(OH)D concentration (which can influence the cholecalciferol response) and the non-linear dose-response curve of cholecalciferol (higher 25(OH)D increase for very low basal 25(OH)D values and vice-versa) [11,12]. Therefore, when observing the growth curves of 25(OH)D concentration during therapy with cholecalciferol and calcifediol, the greater speed and potency of calcifediol is evident. These findings were also confirmed in studies conducted in elderly or overweight/obese subjects and in patients suffering from malabsorption syndrome [13-14,26].

Based on these results, recent Italian guidelines have included calcifediol in therapeutic strategies for the management of hypovitaminosis D [21]. In particular, in subjects with osteomalacia or with a serum concentration of 25(OH)D <10 ng/ml, calcifediol (as an alternative to cholecalciferol) has been suggested at a dose of 20-40 mcg per day for 20-30 days, before switching to a maintenance dose [21]. This recommendation has been proposed limited to specific conditions where a rapid normalisation of serum 25(OH)D concentration is deemed necessary. From the time of Aesop through to "The Canterbury Tales" and "The Merchant of Venice", the proverb "*all that glitters is not gold*" has been a well-known expression that takes on particular relevance in this context.

Indeed, the interpretation of comparative studies between cholecalciferol and calcifediol deserves to be supplemented with some considerations aimed at correcting the narrative, as is also emphasised by the Italian guidelines and some literature reviews [10,11,21]. The limited half-life of calcifediol (12-18 days as opposed to several weeks for cholecalciferol) and the fact that it is not able to lead to a repletion of vitamin D stores (depositing only in liver and muscle) may be a problem in the event of reduced adherence or persistence to treatment [1,8]. Although there are few published studies on the negative effects of reduced adherence/persistence to treatment, a very recent study conducted in patients initially hypovitaminous with calcifediol supplementation showed that after discontinuation of calcifediol treatment, there was already evidence of a progressive and significant reduction in serum 25(OH)D concentration in the first few weeks, which restabilised to within the deficiency range between 8 and 12 months [23]. In relation to hydroxylation, calcifediol is a step up from cholecalciferol towards the biologically-active form and is thus partially released from the physiological control mechanisms of vitamin D metabolism [10,21]. Although reports of intoxication (hypercalcaemia) are relatively few and mostly related to inappropriately high dosages due to intake errors, the use of calcifediol is strictly limited to defined doses and may in some circumstances require frequent monitoring of serum 25(OH)D and calcium values in order to identify intoxication and hypercalcaemia at an early stage [10,21,27]. Based on literature data, this risk is inexistent with cholecalciferol, just as no serological monitoring is deemed necessary during treatment with vitamin D_3 [10,21].

At a pharmaco-dynamic level, few studies have investigated the effect of cholecalciferol and calcifediol on vitamin D metabolites, regulators of calcium and phosphorus homeostasis, markers of bone removal and inhibitors of the Wnt system [28]. Without going into too much detail, it should be pointed out that with respect to the effects on parathyroid hormone (decrease) or bone remodelling markers, the results of the comparison studies are not univocal in establishing a superiority of calcifediol over cholecalciferol (Fig. 1) [23,24,26]. In this context, however, the most critical issue with respect to the use of calcifediol is the absence of evidence in terms of antifracture efficacy [10,11,21].

CHOLECALCIFEROL AND CALCIFEDIOL IN FRACTURE PREVENTION

In the introduction to our review, we mentioned the importance of narrative in settling the matter of whether cholecalciferol is superior to calcifediol or vice-versa. Indeed, reviewing the literature makes it extremely clear that the RCTs have only focused on the certainly important outcome of normalising the serum concentration of 25(OH)D, whilst systematically failing to investigate one of the most important endpoints of vitamin D treatment, namely a reduction in the incidence of fragility fractures, not to mention the effect on falls and potential extra-skeletal impacts.

No extensive literature research is required to support the anti-fracture efficacy of cholecalciferol in at-risk, vitamin D-deficient populations when used in appropriate doses (and in combination with calcium supplementation) [10,11,29].

In view of overwhelming evidence in support of the anti-fracture efficacy of cholecalciferol supplementation, the contribution of the RCTs conducted with calcifediol is decidedly limited. A recent Cochrane meta-analysis, which reviewed RCTs of therapeutic intervention (fracture risk reduction) conducted with vitamin D and its metabolites, identified only two studies with calcifediol, which were deemed pertinent on the basis of the quality of the experimental design [29]. It should be noted that in both studies, the risk of 'bias' could not be assessed. On the basis of the results of these two studies, it can be said that there is currently insufficient scientific evidence to support the anti-fracture efficacy of calcifediol [29,30]. In the most recent RCT published by Peacock et al., for example, the incidence

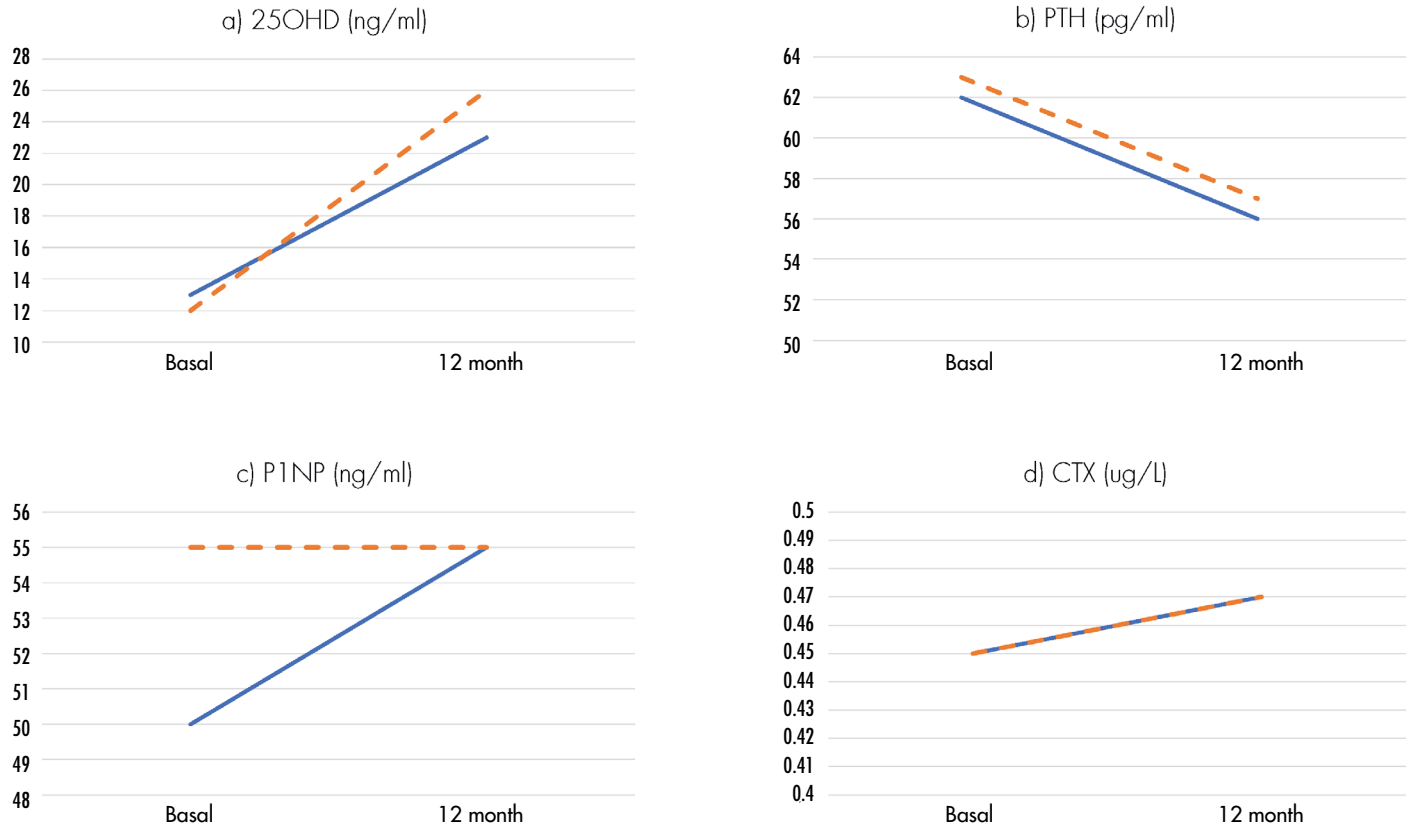

FIGURE 1.
The baseline and 12-month mean value of 25(OH)D (a), PTH (b), P1NP (c) and CTX (d) concentrations in patients treated with cholecalciferol (blue solid line) or calcifediol (orange dashed line) (Pérez-Castrillón et al., 2023, mod.) [23].

of new vertebral and non-vertebral fractures was similar in subjects treated for 4 years with calcium (750 mg daily), calcifediol (15 ug daily) or a placebo [30].

To support the correct narrative referring to a reduction in fracture risk, what is perhaps the most relevant aspect of this narrative, namely the fact that in all of the most successful RCTs registering pharmaceuticals for fracture prevention, it should be noted that patients were supplemented with cholecalciferol (and calcium) in varying dosages. Therefore, the anti-fracturing efficacy of bisphosphonates, teriparatide, denosumab and romosozumab has been demonstrated in the presence of supplementation with cholecalciferol and calcium [10,11,21]. It can be concluded, therefore, that robust evidence unequivocally demonstrating an effect of calcifediol on fracture reduction is lacking.

CONCLUSIONS

In conclusion, in daily clinical practice, cholecalciferol should be considered the therapy of choice in the prevention and treatment of vitamin D deficiency, as well as in the primary and secondary prevention of fragility fractures in osteoporotic individuals in combination with an anti-resorptive or osteoanabolic drug. Calcifediol may offer some advantages in terms of its possible increased speed and potency in raising and normalising serum 25(OH)D concentration, although this claim needs further investigation in view of the recent work published by Fassio et al. [22]. In this regard, it is also worth emphasising that the extent that this different drug-kinetics may lead to greater clinical benefits (such as a reduction in the risk of fracture) has not been clarified, in view of a lack of clinical data from RCTs.

It thus seems inappropriate, as is also stated in the Italian guidelines, to recommend calcifediol, a drug of choice and alternative to cholecalciferol in the prevention/treatment of hypovitaminosis D and/or in the prevention of fragility fractures in osteoporotic patients in combination with an antiresorptive or osteoanabolic [1,2,21]. As recently suggested, calcifediol may be considered as a therapy of choice in particular clinical situations such as obesity, advanced chronic hepatopathy and malabsorption syndrome [1,2,21].

Randomised, controlled clinical trials will be necessary to define the efficacy of calcifediol in different clinical settings, in terms of skeletal and extra-skeletal benefits.

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