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Vitamin D supplementation for osteoporosis in older adults: can we make it help better?

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Abstract. – With the increase of the average age of our population, the incidence of diseases specific for older adults has been increasing. One of such diseases is osteoporosis. The true incidence of osteoporosis is unknown. But the estimates indicate that this disease affects wide proportions of the population, ranging in millions or even ten millions in large countries like the United States. As this poses a significant burden on the health care system, interventions that could prevent or treat this condition are in the focus of clinical research. Vitamin D, the determinant of bone health, has been tested in clinical studies as the agent to treat osteoporosis. Despite the progress, there is still some controversy about the targeted blood levels of vitamin D, most efficient way to supplement this vitamin, and clinical efficacy of this supplementation in the elderly.

In the present review, we will highlight the metabolism of vitamin D and the aforementioned unresolved issues, as well as review the recent interventional studies on vitamin D supplementation.

Key Words:
Elderly, Osteoporosis, Vitamin D, Supplementation, Guidelines, Analysis, Biochemistry, Metabolism, Clinical efficacy.

Introduction

With industrialization and urbanization of increasing number of countries in the world, life expectancy increases, and so does the relative proportion of older adults. The definition of "older adults", or the "elderly", differs depending on the country (http://www.who.int/healthinfo/survey/ageingdefnolder/en/), and most industrialized countries consider the population at the age of 65 years or older as "older adults". Our longer life expectancy has also brought about several age-related diseases and conditions that had been relatively rare in pre-industrialized ages. One of such diseases is osteoporosis. The true incidence of osteoporosis, the disease of weakened bones that causes heightened risk of bone fractures, is unknown. But the estimates indicate that this disease affects wide proportions of the population, ranging in millions or even ten millions in large countries like the United States. As this poses a significant burden on the health care system, interventions that could prevent or treat this condition are in the focus of clinical research. Vitamin D, the determinant of bone health, has been tested in clinical studies as the agent to treat osteoporosis. Despite the progress, there is still some controversy about the targeted blood levels of vitamin D, most efficient way to supplement this vitamin, and clinical efficacy of this supplementation in the elderly. In the present review, we will highlight the metabolism of vitamin D and the aforementioned unresolved issues, as well as review the recent interventional studies on vitamin D supplementation.

The Metabolism of Vitamin D

Vitamin D is classified as a fat-soluble vitamin, although the chemical structure of its biologically active metabolite is actually close to steroid hormones. Another similarity between the biologically active metabolite and steroid hormones is that both these compounds bind to specialized receptors to exert their biological effects. We will address this metabolite in a few paragraphs below.

Humans maintain the circulating levels of vitamin D mainly through exposure of our skin to the ultraviolet light during sunny days. At higher latitudes, vitamin D production occurs mostly during warm seasons, probably due to the quantity and quality of sun's ultraviolet light reaching the surface[1]. Minor contributors to circulating levels of vitamin D are dietary sources (such as cod liver oil, fish, and milk supplemented with vitamin

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D). Recommendations have been introduced that vitamin D supplements should also be recognized as one of the sources, especially for populations at increased risk for osteoporosis, including the elderly[2]. Therefore, pharmaceutical supplements have become another determinant of the circulating vitamin D levels.

When our skin is exposed to the sun, some of the ultraviolet light is absorbed by melanin, the skin pigment. Therefore, people with darker skin need longer exposure to the sun than people with fair skin to achieve similar levels of the circulating vitamin D[3]. The ultraviolet light catalyzes a chemical reaction in the skin that produces vitamin D from 7-dehydrocholesterol[4]. The form of vitamin D produced in our skin or in animals is referred to as vitamin D_3 (or cholecalciferol; Figure 1), whereas its counterpart produced in plants is called vitamin D_2 (ergocalciferol). Both D_3 and D_2 forms of vitamin D can be equally well metabolized in our body[4]. The experts often use the term "vitamin D" interchangeably, referring to D_3 or D_2[4,5]. Oral supplementation can be done with either plant-based or animal metabolites of vitamin D.

After it is produced in the skin, vitamin D_3 (or D_2) is further metabolized in the liver, or can be stored in the fat tissue[5] to be released into the blood stream when needed, thereby repleting the levels. In the liver, vitamin D_3 passes through hydroxylation[5]. This process yields the circulating vitamin D metabolite called 25-hydroxyvitamin D_3 (Figure 1). It will be highlighted in the subsequent text that 25-hydroxyvitamin D_3 is the current indicator of our body's vitamin D status quantified in hospital labs. Notably, clinical rec-

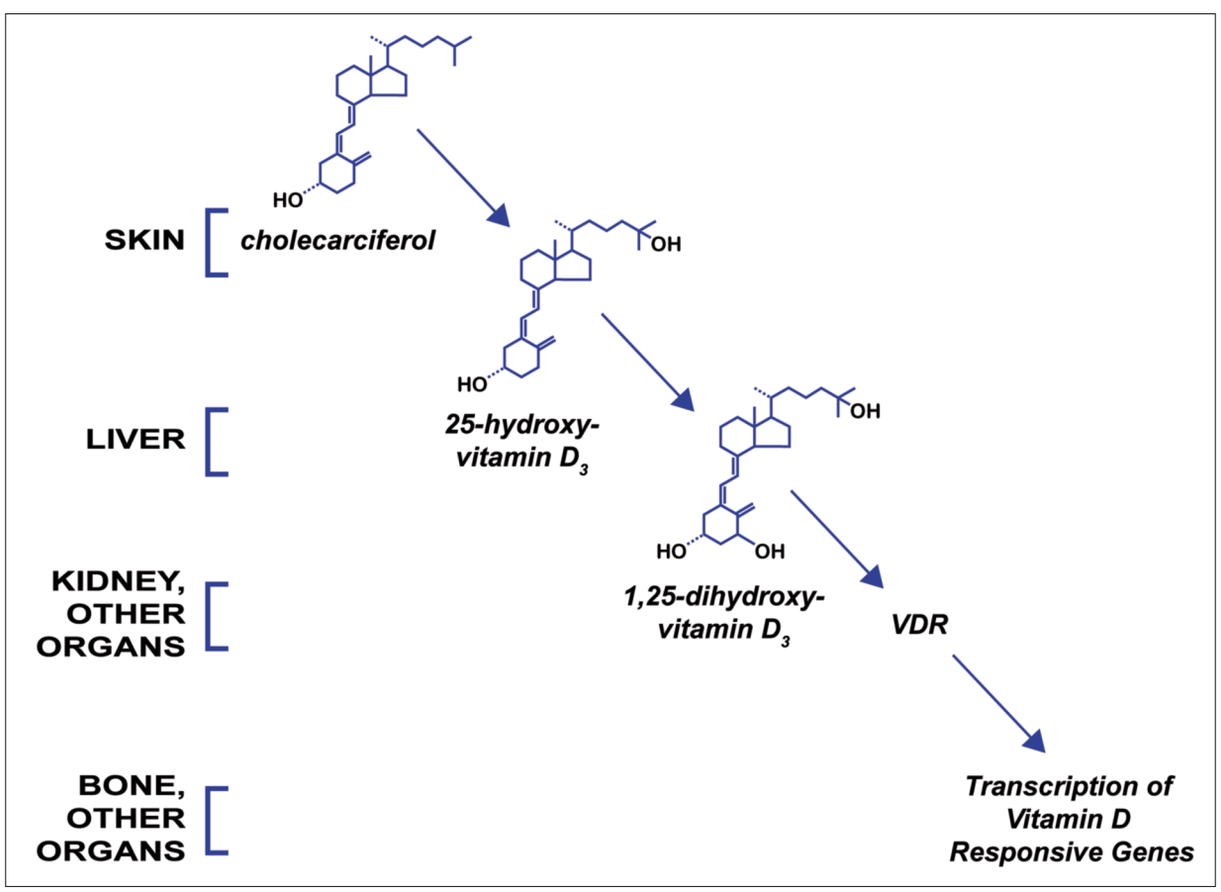

Figure 1. Metabolism of vitamin D. The skin produces the preform of vitamin D (cholecalciferol) from 7-dehydrocholesterol. After it is produced in the skin, cholecalciferol is hydroxylated in the liver to yield 25-hydroxyvitamin D3. 25-hydroxyvitamin D3 is the most abundant circulating form of vitamin D in the human body. 25-hydroxyvitamin D3 circulates in blood mostly bound to the transporting protein (vitamin D binding protein). A very small fraction of 25-hydroxyvitamin D3 is bound to serum albumin or is free. In kidney and other organs, 25-hydroxyvitamin D3 is further hydroxylated to produce the biologically active 1,25-dihydroxyvitamin D3. The latter vitamin D metabolite in the target organs activates the vitamin D receptor (VDR) which up-regulates transcription of a large group of genes, called "vitamin D-responsive genes".

ommendations for healthy and diseased bone metabolism have been developed around this metabolite.

First, the circulating levels of 25-hydroxyvitamin D_3 are considered stable, with a half-life of about two weeks[6] or even longer[7]. Thus, these levels are not the subject to diurnal or between-days variations, and newest reports suggest that muscle tissue can be the body's storage site for 25-hydroxyvitamin D_3[8]. Thereby, our body appears to have at least two storage tissues: fat tissue to store vitamin D_3 and muscle tissue for 25-hydroxyvitamin D_3 storage. It is possible that for this reason, our body maintains healthy levels of 25-hydroxyvitamin D_3 long after begin of the cold season.

25-hydroxyvitamin D_3 circulates in blood mostly bound to the transporting protein (vitamin D binding protein). A very small fraction of 25-hydroxyvitamin D_3 is bound to serum albumin or is free[9]. In the kidney, 25-hydroxyvitamin D_3 is further metabolized to produce the biologically active 1,25-dihydroxyvitamin D_3 (Figure 1). While the kidney is considered the major conversion site from 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3[5], this conversion is also thought to occur in other tissues[4]. The latter vitamin D metabolite activates the vitamin D receptor (Figure 1) which modulates transcription of a large group of genes, called "vitamin D-responsive genes" (or "vitamin D-sensitive genes") (Figure 1). In addition to this transcriptional mechanism, 1,25-dihydroxyvitamin D_3 also exerts non-transcriptional (also called "non-genomic") effects[10]. The transcriptional effects of 1,25-dihydroxyvitamin D_3 seem to be more important for bone health[11].

Transcriptional and non-transcriptional effects of 1,25-dihydroxyvitamin D_3 are limited by its catabolism. Moreover, the aforementioned vitamin D-responsive genes include the enzymes that catabolize 1,25-dihydroxyvitamin D_3, meaning that vitamin D up-regulates the enzymes that curb its biological activity. This represents an important mechanism to prevent excessive accumulation of 1,25-dihydroxyvitamin D_3. Furthermore, the existence of this negative feedback mechanism is the mechanism explaining short lifespan of 1,25-dihydroxyvitamin D_3. Since circulating levels of 25-hydroxyvitamin D_3 exceed the circulating levels of 1,25-dihydroxyvitamin D_3 by the factor of 1000, the levels of the latter metabolite are likely to be repleted very easily. Nonetheless, this requires healthy circulating levels of 25-hydroxyvitamin D_3 to maintain sufficient circulating and intracellular levels of 1,25-dihydroxyvitamin D_3. This is why it is important that the levels of 25-hydroxyvitamin D_3 are sufficiently high, and this will be addressed in the subsequent text.

Analytical Issues

There are several reasons why 25-hydroxyvitamin D_3 is still considered the indicator of the body's vitamin D status.

First, the serum concentration of 25-hydroxyvitamin D_3 is much higher than that of 1,25-dihydroxyvitamin D_3, which makes it less challenging to develop an analytical assay. The second reason is the much shorter lifespan 1,25-dihydroxyvitamin D_3 and fluctuation of its levels. Obviously, an indicator should be stable under similar bodily conditions, and this is not the case with 1,25-dihydroxyvitamin D_3.

However, this does not mean that the analytical tests for 25-hydroxyvitamin D_3 are problem-free. There is a discrepancy between analytical assays from different suppliers. Furthermore, some assays report total 25-hydroxyvitamin D (i.e. the sum of 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2), whereas other assays provide information on these two metabolites separately. For consistency reasons, the guidelines recommend reporting total 25-hydroxyvitamin D levels, as this will be applicable to the patients taking plant-derived supplements.

Another issue is that many laboratories still continue to utilize radioimmunoassays, or ELISA- / HPL-based assays, while newer labs have begun to phase out these assays and replace them with the mass spectrometry based assays[12]. The mass spectrometry based assays offer unrivaled specificity and sensitivity[13] and are, thus, becoming the gold standard in the diagnostics of the vitamin D status. Conversely, non-mass spectrometry-based assays may inaccurately estimate 25-hydroxyvitamin D_3[12].

Apart from analytical issues, there is no consistent recommendation on what should be considered as healthy circulating levels of 25-hydroxyvitamin D_3.

Normal and Abnormal Vitamin D Levels

In the past, absolute vitamin D deficiency has existed and caused clinical disease (rickets, osteomalacia). These are now very rare in Western countries because of consumption of vitamin D enriched food[5]. Still, despite the infrequency of

absolute vitamin D deficiency, we remain at risk for relative deficiency of this vitamin D[5]. With industrialization and urbanization of developing countries, including China, the population is no longer exposed to the sunlight as frequently as before. Since our skin's exposure to the sun's ultraviolet light is the principal source of vitamin D in our body (Figure 1), modern humans easily develop suboptimal vitamin D levels, and this can be defined as insufficiency or relative vitamin D deficiency (Table I). Since vitamin D is essential for bone health (highlighted in the next subsection), its suboptimal levels predispose to osteoporosis and fall-related fractures.

There are two expert opinions on what to consider the optimal range of circulating vitamin D levels. The first opinion is advocated by the Institute of Medicine. As per this expert opinion, the optimal 25-hydroxyvitamin D_3 levels in blood range between 50 and 100 nM[14]. The reader should be aware that in the USA, non-SI measurement units are utilized to describe vitamin D levels. Thus, for 25-hydroxyvitamin D_3 levels, US literature uses ng/ml, with the conversion factor being approximately 2.5 times lower than the SI-based system. Therefore, their recommendation in the original publication is expressed as "20-40 ng/ml". This review will use SI units throughout. The second expert panel considers the levels between 75 and 125 nM (30-50 ng/ml) as normal blood levels[15].

The Institute of Medicine considers that the lowest level of 50 nM of 25-hydroxyvitamin D_3 is adequate for 97% of people. As the main rationale for settling on the highest recommended range, the Institute of Medicine describes insufficient evidence that higher levels of 25-hydroxyvitamin D_3 actually lead to greater health benefits. Moreover, their experts, using the literature data argue, that adverse effects are very likely to occur at high levels of 25-hydroxyvitamin D_3. Therefore, the debate is still ongoing[16]. At the moment, it can be safely stated that even by the most conservative estimates, the lowest circulating levels of 25-hydroxyvitamin D_3 should be 50 nM, and that the levels lower that this should be considered deficient. Thereby, the lowest level of healthy vitamin D status has been increased from the previous recommendations[17].

The decision of what to consider the normal, insufficient and high level of 25-hydroxyvitamin D_3 is affected by many factors, hence the existence of two major opinions on this matter. As 25-hydroxyvitamin D_3 is the major determinant of bone health, it is obvious that bone-related outcomes have been considered when the respective expert panels have worked out the recommendations. The factors considered included parathyroid hormone, decreased risk to develop fractures, and some other outcomes.

What causes vitamin D relative or absolute deficiency? Multiple factors can be involved, including decreased synthesis due to diminished exposure to the sun, diminished dietary intake, and increased catabolism in the body. Furthermore, there appears to be a non-linear relationship between altered levels of vitamin D and osteoporosis. For example, a very recent review has addressed genetic and non-genetic factors determining propensity to develop osteoporosis following vitamin D deficiency[18]. The importance of genetic predisposition for osteoporosis has been demonstrated by other publications as well[19]. Furthermore, women develop osteoporosis more frequently than men, which underscores the gender-associated character of this disease. Still, there is a consensus in the literature that vitamin D status in the body, reflected by circulated levels of 25-hydroxyvitamin D_3, is the major determinant of osteoporosis development. The effects of vitamin D on bones are highlighted in the next subsection.

Table I. Normal and abnormal levels of circulating 25-hydroxyvitamin D_3.

	Absolute deficiency, (ng/ml)	Insufficient (or also called "Inadequate"), nM (ng/ml)	Normal (or also called "Adequate"), nM (ng/ml)	High (or also called "Toxic"), nM (ng/ml)
The Institute of Medicine recommendations (ref. 25)	< 30 (< 12)	30-< 50 (12-< 20)	≥ 50 (≥ 20)-125 (20)	> 125 (> 20)
The Endocrine Society recommendations (ref. 15)	<5 0 (< 20)	50-75 (20-< 30)	75-250	

Bone Health and Vitamin D

We have mentioned previously that vitamin D-associated effects on bone health are determined by transcriptional up-regulation of vitamin D-responsive genes, that is, by transcriptional mechanisms. The vitamin D-responsive genes relevant to bone health are present both in the gut and in the bone. For example, the gut tissue, exposed to vitamin D, up-regulates expression of proteins increasing absorption of calcium, the mineral vital for bone health. This is a clinically important mechanism as older age is associated with decreased absorption of calcium in the gut[20]. This causes osteomalacia, or inadequate mineralization of the bone tissue. In addition, vitamin D suppresses the parathyroid hormone that removes calcium from the bones.

In the bone, expression of the receptor activator of nuclear factor B ligand (RANKL) is up-regulated. RANKL promotes maturation of bone cells and their functional activity. Also, studies in mice have demonstrated that vitamin D exerts indirect effects on the bone (i.e., not involving bone cells)[21], and that these effects depend on the systemic availability of calcium[21].

An important contributor to bone health is the liver. For example, under certain conditions or in certain diseases, the liver defines the functional efficacy of vitamin D[22,23]. Another contributor is the kidney, and kidney diseases affect the body's vitamin D status[24]. Given these data, it is clear that the mechanism and the end effect of vitamin D effects on bone health is very complex, involving several organs (gut, liver, kidney and bone) and several cell types.

Supplementation With Vitamin D

If the circulating levels of 25-hydroxyvitamin D_3 are deficient, how can we replete them? Luckily, there is a large choice of vitamin D metabolites and their analogs to choose from.

The first objective of vitamin D supplementation is to maintain the healthy circulating levels. The aforementioned recommendation Institute of Medicine provides detailed guidelines on the tentative lower and upper ranges of vitamin D supplementation[14]. Their expert panel considers the healthy levels of 25-hydroxyvitamin D_3 to be between 50 and 100 nM. To achieve these circulating levels, healthy adults are estimated to require approximately 400 to 800 IU of dietary vitamin D (regardless of whether D_3 or D_2) per day. It is thought that each 100 IU of dietary vitamin D will be converted in the body to yield between 1.75 and 2.5 nM. A large glass of fortified milk in North America contains about 100 IU of vitamin D. Dietary supplementation comes on top of endogenous 25-hydroxyvitamin D_3 levels and repletion happens much more efficient if endogenous levels are low. Therefore, the experts believe that the recommended intake is sufficient to maintain healthy levels of 25-hydroxyvitamin D_3.

For older adults, the recommendation is to take slightly higher levels of vitamin D supplement (between 51 and 70 years old: a minimum of 600 IU per day; > 70 years old: at least 800 IU/day; Table II). The recommendation is further extended to individuals with diseases and conditions that may affect the circulating levels of 25-hydroxyvitamin D_3[14]. Importantly, the expert recommendation on vitamin D intake is done in parallel with the recommendation on calcium intake. This is because calcium deficiency modifies the effects of vitamin D supplementation.

For certain, high-risk populations, alternative recommendations exist. For example, Canadian guidelines for preventing fractures in long-term care facilities[2] recommend taking between 800

Table II. Recommended daily intake guidelines on calcium and vitamin D pertinent to older patients (> 65 years).

	Gender	19-70 years		> 70 years	
		Calcium, mg/day	Vitamin D, IU/day	Calcium, mg/day	Vitamin D, IU/day
The Institute of Medicine recommendations (ref. 25)	Men	1000	600 (4000 max)*	1200	800 (4000 max)*
	Women	1200	600 (4000 max)	1200	800
The Endocrine Society recommendations (ref. 15)	Not stratified by gender		1500-2000 (10,000 max)		1500-2000 (10,000 max)

Footnote: Canadian Osteoporosis Society (ref. 2) recommends taking between 800 and 2000 IU/day for preventing fractures in long-term care facilities.

and 2000 IU per day of vitamin D_3. Still, this recommendation does not exceed the upper level of daily supplementation with vitamin D_3 (< 4000 IU/day) given by the Institute of Medicine for people above 51 years old[14].

25-hydroxyvitamin D_3 can be used to replete our endogenous levels of 25-hydroxyvitamin D_3, and this approach appears to be more efficacious and rapid than the use of dietary vitamin D_2/D_3[25]. Direct supplementation of 1,25-dihydroxyvitamin D_3, the biologically active metabolite, can also be done, but is severely limited by the narrow therapeutic window and adverse effects, including hypercalcemia. There thus exist synthetic 1,25-dihydroxyvitamin D_3 analogs with wider therapeutic window and lower calcemic effects (e.g. paricalcitol) [26]. Paricalcitol has been approved in the USA for secondary hyperparathyroidism during kidney disease. The biological effects of paricalcitol are rapid, and this compound is rapidly eliminated from blood (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020819s025lbl.pdf). This is to be expected, since its parent compound, 1,25-dihydroxyvitamin D_3, is also short-lived. However, this is in contrast to supplementation with dietary vitamin D_2/D_3 or 25-hydroxyvitamin D_3 that have a considerably longer half-life in blood, and are stored in fat or muscle tissue. Therefore, vitamin D_2/D_3 or 25-hydroxyvitamin D_3 supplements can be taken as bolus supplementation. In contrast to 1,25-dihydroxyvitamin D_3, hypercalcemia is only observed at very high doses of 25-hydroxyvitamin D_3 or not seen at all[25].

Efficacy of vitamin D Supplementation to Alleviate Osteoporosis in the Elderly

We have conducted Medline and Google Scholar searches to identify clinical studies that had addressed clinical usefulness of vitamin D supplementation for osteoporosis in the elderly. The searches have been done using the keywords "osteoporosis", "vitamin D", "clinical study", "clinical trial", and "human", and have been limited to English language publications and to the past 10 years because of newest recommendations[14,15]. After the searches have not yielded many publications, we have expanded the searches by adding the "post-menopausal" keyword.

These searches yielded 39 documents in the Medline and 25 documents in Google Scholar. The latter documents have included the 4 documents dated before 2006, which have been excluded from the analysis.

A secondary search with a broader choice of keywords has been conducted in the Medline to ascertain that all relevant publications have been found. The search strategy has included the keywords "elderly [Text word]" OR "Aged" [Mesh] OR old* [Text word] AND "last 10 years" [PDat] AND "Humans" [Mesh] AND "English" [lang] AND "Clinical Trial" [PType]. These searches have revealed 28 documents. Some publications have been found by checking reference lists of the previously found publications, and some publications have been excluded manually after reading the abstracts. Altogether, the searches have revealed 88 publications.

As some publications[27] had tested metabolites of vitamin D in combination with other therapies. These publications have been included in the final analysis if the study design allowed to clearly discern the effects of vitamin D supplementation on osteoporosis (such by testing the markers of bone turnover). A similar approach has been applied if a publication had stated conducting the study in elderly patients with osteoporosis and other, non-osteoporosis chronic diseases (such as Crohn's disease[28]). Cross-sectional studies exploring the use of vitamin D supplements without an active intervention arm or without bone density data[29] have been excluded from the analysis.

The persistence of circulating levels of 25-hydroxyvitamin D_3 may be longer than 2 weeks, as indicated by Mocanu and Vieth[7]. In comparison, the half-life of the biologically active metabolite, 1,25-dihydroxyvitamin D_3, and its analogs is considerably shorter (several hours). Given differing half-lives and transcriptional activities of these two forms of vitamin D (25-hydroxyvitamin D_3 needs to be converted to 1,25-dihydroxyvitamin D3 for biological effects, whereas 1,25-dihydroxyvitamin D_3 is transcriptionally active), we have analyzed the published studies separately for either metabolite.

Out of 5 studies that had dealt with the analogs of 1,25-dihydroxyvitamin D_3, two studies had made a direct comparison of the effects on bone resorption markers between the analogs and placebo [30 31], and the third study has evaluated muscle-based outcomes[32]. We have included the first two studies in the analysis, as well as the third study because of the relevance of muscle strength to fractures in the elderly. The remaining two studies[33,34] have been excluded. These studies had compared different analogs of 1,25-dihydroxyvitamin D_3 and have thus been considered irrelevant for our objective.

Two out of the three included studies had presented evidence of positive effects of the analogs on bone resorption markers[30,31]. Positive effects had also been observed concerning the muscle strength[32].

The following studies had tested the effects of either vitamin D_2 or D_3 supplementation on bone resorption markers or related outcomes[35-48]. Another two studies have been identified, but they had addressed secondary post-corticosteroid osteoporosis[49,50]. The latter two studies have not been included in the analysis. Of the included studies, some[48] had tested oral vitamin or injectable D_2[43] supplementation. The majority of the studies had reported beneficial effects of vitamin D_2 or D_3 supplementation[35-38,40,45,47]. Interestingly, the described effects had sometimes been limited to elevation of 25-hydroxyvitamin D_3[48], but this we have still considered beneficial. The remaining studies had reported either no beneficial effects[39,41 44] or even negative impact of the supplementation on the studied outcomes[42]. Interestingly, one of the studies showing positive effects of the supplementation had also reported heterogeneity of responses[37].

Based on this literature search, we have concluded that the publications generally show positive effects of supplementation with vitamin D_2/D_3 or analogs of 1,25-dihydroxyvitamin D_3, but there is a considerable heterogeneity of the outcomes. This heterogeneity is demonstrated by not all studies yielding positive results. Moreover, patients' response to supplementation demonstrates heterogeneity as well.

Therefore, it can be summarized that there still exists some controversy about beneficial effects of vitamin D supplementation, as some studies had reported ambivalent results. The meta-analysis studies on this topic also confirm our conclusions[51,52].

This controversy could be because of patients' heterogeneity, but could also be caused or aggravated by the wide variation of study designs. Indeed, the studies had utilized different metabolites as supplements, at different doses, and even administered through different routes. The discrepancies could have contributed to negative results observed in some studies. Another important factor is patients' compliance with the supplementation. In the studies in which patients take the supplement on a regular basis, this should have a negligible effect because of the longer life span of 25-hydroxyvitamin D_3. But studies with bolus administration may certainly suffer from insufficient patients' compliance. Other unresolved questions are the range of 25-hydroxyvitamin D_3 concentrations to target in clinical studies and existing lab-to-lab analytical differences. All these should be considered in prospective studies.

Still, despite the existing ambiguity, the published reports seem to support the beneficial role of this vitamin to improve unwanted bone resorption. In addition, vitamin D supplementation shows some extraskeletal effects, such as an increase in muscle power. These extraskeletal effects can also be beneficial to limit osteoporosis.

In addition to vitamin D supplementation, as recommended by international guidelines, osteoporosis management involves other approaches, such as changes in the lifestyle and diet, and the use of medications other than vitamin D[53,54].

We also would like to underscore that the studies analyzed in this subsection represent intervention studies with relatively short-term designs, and some of them had used quite high supplementation doses. Large long-term studies using the recommended daily intake doses[14] for prevention of osteoporosis are also urgently needed. This will help to assess better whether the current recommendations are adequate in preventing osteoporosis in elderly patients.

Conclusions

Vitamin D is an important determinant of bone health, especially in older people. The majority of studies demonstrate its beneficial role as a therapeutic agent to maintain bone density in older patients with osteoporosis. The progress has been somewhat hampered by the lack of uniform analytical assay and expert consensus on targeted circulating levels of this vitamin. Future studies should adjust the study designs to reflect all these issues, as well as potential patient heterogeneity.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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