Potential role of vitamin D in prevention of skeletal and extraskeletal diseases in older people

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ABSTRACT

Vitamin D and calcium are essential for bone health. An adequate calcium-phosphorus product determines a high quality mineralization long lifetime. In older people, both calcium and vitamin D levels may be lower causing osteomalacia and/or osteoporosis with a higher risk of fracture. Epidemiological data have clearly associated serum vitamin D lower levels (deficiency) with bone fracture in older people, however, not univocal data exist in regard to a beneficial effect of vitamin D supplementation in general population. Although not systematic, the present review aims to make a narrative synthesis of the most recent published data on vitamin D effect not only on bone, classical target associated with vitamin D studies, but namely on extraskeletal diseases. In fact, recently, there has been an increasing interest on this latter issue with surprising findings. Vitamin D, and in particular its deficiency, seems to have a role in pathophysiological pathways in several diseases involving cardiovascular, central nervous system and neoplastic process. On the other hand, vitamin D supplementation may modify the outcome of a wide range of illnesses. Up to date the data are conflicting mainly because of difficulty to establish a consensus on the threshold of vitamin D deficit. The US Institute of Medicine recommends to distinguish a level of insufficiency [defined as 30-50 nmol/L or 16-25 ng/mL of 25(OH)D] and another of deficiency identified by 25(OH)D levels lower than 30 nmol/L (or <16 ng/mL). This latter level is considered a minimum level necessary in older adults to minimize the risk of falls, fracture and probably to have some effects of vitamin D supplementation in extraskeletal diseases. Although there are no absolute certainties in such issue, the most recent data suggest that vitamin D deficiency, and its supplementation, may play an important role in a wide range of diseases other than in bone metabolic diseases in older but not in general population. For such reason a widespread measurement of vitamin D levels in general population, and not only in older, seems to be inappropriate and it could induce an overuse of vitamin D supplementation in situations in which its efficacy and cost-effectiveness have not been proven.

Vitamin D insufficiency and deficiency

The intake of two nutrients such as calcium, which is essential for bone health, and vitamin D, which im-

proves the absorption of calcium, is usually taken into account in older population namely in the prevention and treatment of osteoporosis.[1] Dairy products are the main dietary source of calcium, although it is also found in some fruits, vegetables and grain products. On the contrary, very few foods provide concentrated vitamin D, therefore in some countries are used to fortify milk or other foods with vitamin D. It exists an endogenous production of vitamin D that requires physiological liver and kidney function other than a prolonged exposure to the sun (Figure 1). For this latter reason the median of plasma levels of vitamin vary strongly by latitude in Europe and United States. However, it is uncertain how much these differences are related to different ultraviolet B exposure, vitamin D consumption in the diet, and vitamin D fortification habits in the countries or are just artefacts of the different 25(OH)D assays employed.[2] Surprisingly, a recent meta-analysis confirmed that population means of 25(OH)D concentrations are higher in northern than in southern Europe, as it was also reported by Seneca study, a previous important European cohort study.[3] The Authors of this latter study mainly suspected country differences in vitamin D fortification of foods, such as margarine, as possible causes of the large regional differences. The meta-analysis of Schöttker *et al.* confirmed that vitamin D serum levels vary strongly by

age, sex, season, education, obesity, physical activity, and smoking.[2] These data evidence that it is difficult to identify cut-off values for vitamin D deficiency, namely for 25(OH)D variations by geographic region, sex, and season, factors that might need to be taken into account (Table 1). The American Institute of Medicine (IOM) recommends to distinguish a level of insufficiency [defined as 30-50 nmol/L or 16-25 ng/mL of 25(OH)D] and another of deficiency identified by 25(OH)D levels lower than 30 nmol/L (or <16 ng/mL). Vitamin D3 supplementation seems to be able to maintain bone health and reduce fracture risk in population with deficiency, whereas in population with vitamin D insufficiency the evidence would be yet insufficient.[4] Unfortunately, among the main health scientific societies there is not a complete consensus on the real threshold to apply in the definition of deficit of vitamin D. In fact, the IOM emphasizes that 97.5% of the population are ensured bone health when levels of serum 25-hydroxyvitamin D are ≥20 ng/mL and defines vitamin D deficiency as <16 ng/mL,[1] whereas the Endocrine Society defines vitamin D levels as sufficient at >30 ng/mL, insufficient between 21 and 29 ng/mL, and deficient at 20 ng/mL.[5] Other Societies of experts in this field [the *National Osteoporosis Foundation* (NOF), the *International Osteoporosis Foundation* (IOF), the *American Geriatric Society* (AGS)] suggest that a minimum level of 30 ng/mL (75 nmol/L) is necessary in older adults to minimize the risk of falls and fracture.[6,7] On the other hand, while Institute of Medicine suggests a screening of general population with regard to vitamin D serum levels in order to enhance bone health, Endocrine Society considers not fully appropriate a routinely evaluation of vitamin D levels in general population, if anything in older subjects. A further confounding factor in determining a useful threshold for vitamin D, could also be the variety of assay techniques available for the measurement of serum 25(OH)D concentrations. This concern should suggest healthcare providers to be aware. Liquid chromatography-tandem mass spectrometry is considered the gold standard, but a variety of other assay kits are available, including the DiaSorin automated immunoassay test (DiaSorin, Saluggia, Italy), the IDS radioimmunoassay
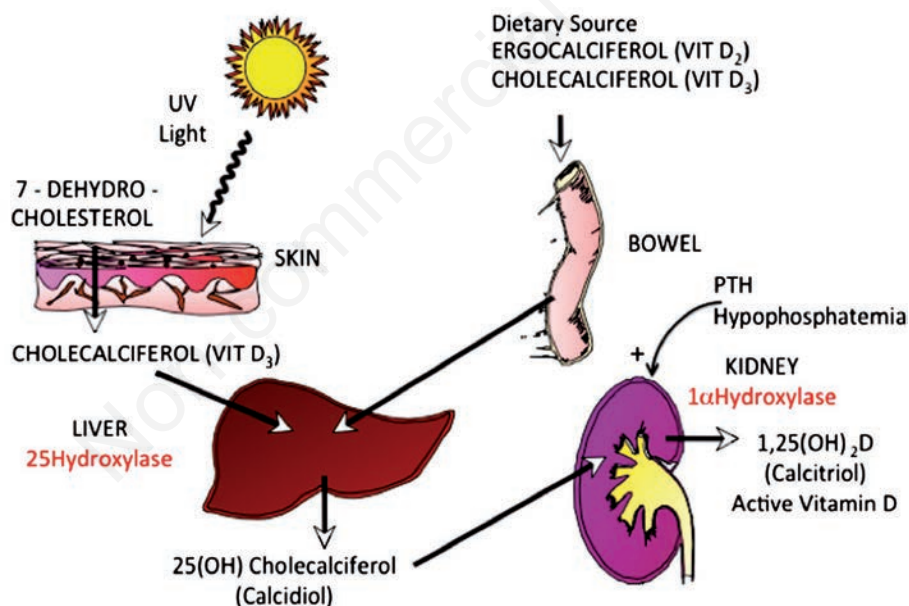
Figure 1. Metabolism of vitamin D.

Table 1. Definition of vitamin D status according to some of the most important International Societies of Medicine.

Society	Sufficiency	Insufficiency	Deficiency
Endocrine Society	≥30 ng/mL	≥21 and <29 ng/mL	<20 ng/mL
Institute of Medicine (IOM)	≥25 ng/mL	>16 and <25 ng/mL	≤16 ng/mL
National Osteoporosis Foundation (NOF) International Osteoporosis Foundation (IOF) American Geriatric Society (AGS)	≥30 ng/mL	>10 and <30 ng/mL	≤10 ng/mL

(IDS Ltd., Tyne and Wear, UK) and enzyme immunoassay, and automated protein binding assays. Compared with the gold standard, other tests can produce variable results and in some cases, systematically undermeasure serum 25(OH)D levels.[8]

The previous information seems to be still more important since vitamin D status seems to be correlated to health status, and not only with regard to bone health, namely in older people. In fact, epidemiologic evidence links vitamin D deficiency to autoimmune disease, cancer, cardiovascular disease, depression, dementia, infectious diseases, musculoskeletal decline, and more.[9]

In the literature a relationship between poor health state and vitamin D deficiency was largely reported. A simple link could be the fact that subjects with poor health spend less time in open space because of their reduced physical activity determining a reduced activation of provitamin D by ultraviolet B radiation on the skin. However, several data in literature seem to suggest a possible relationship between vitamin D deficit and health, and in addition a potential role of vitamin D in prevention of bone and extraskeletal diseases.

Vitamin D and bone fractures

Vitamin D promotes bone health by stimulating parathyroid hormone synthesis and thereby osteoblastic activity and inducing bone mineralization.[10] In older people, both calcium and vitamin D levels may be lower causing osteomalacia and/or osteoporosis with a higher risk of fracture.

Several studies have been carried out to evaluate the effect of vitamin D supplementation on the fracture risk, with some studies showing a significant reduction in the risk of fractures[11,12] while others did not.[13,14] More recently, Reid *et al.* have published a systematic review which provides very little evidence of an overall benefit of vitamin D supplementation on bone density[15] and Balland *et al.* confirmed that vitamin D supplementation with or without calcium does not reduce skeletal or non-skeletal outcomes in unselected community-dwelling individuals by more than 15%.[16] To date, the evidence is not yet sufficient to recommend vitamin D3 supplementation for subjects with vitamin D insufficiency (defined as 30-50 nmol/L 25(OH)D) however it helps to understand that subjects with vitamin D deficiency (<30 nmol/L 25(OH)D) could profit from vitamin D3 supplementation by maintaining bone health and reduction in fracture risk.[2]

Vitamin D and extraskeletal diseases

It is known that vitamin D has a wide range of biological actions (Table 2),[11-25] and that vitamin D receptor is present in most tissues and cells in the body.[26] As a result, it is not unexpected that multiple studies[27] have associated vitamin D deficiency with cardiovascular diseases, type 2 diabetes, hypertension, many types of cancer, rheumatoid arthritis, Crohn's disease, multiple sclerosis, asthma, and infectious diseases.

Cardiovascular effects

Cross-sectional studies have reported consistent associations between lower 25(OH)D concentration or vitamin D intake and prevalent cardiometabolic outcomes.[28] An important prospective study with a large sample of patients revealed that 25(OH)D <15 ng/mL compared to 25(OH)D >30 ng/mL was associated with highly significant increases in the prevalence

Table 2. Main effects of vitamin D on skeletal and extraskeletal target.

Bone	Conflicting data about vitamin D supplementation effects on bone fracture risk[11-14]
	Vitamin D supplementation has little effect on BMD[15,16]
Cardiometabolic	Low vitamin D is associated with hypertension, hyperlipidemia, peripheral vascular disease, coronary artery disease, heart failure, and stroke[17]
	Vitamin D supplementation reduces the incidence of diabetes[18]
Central nervous system	Hypovitaminosis D is predictor for dementia[19]
	No significant associations between lower levels of 25(OH)D and lower cognitive test scores
Immune system	Hypovitaminosis D inhibits maturation of monocyte-derived dendritic cells[20]
	Low 25(OH)D levels are associated with SLE[21]
Oncological diseases	25(OH)D reduces aromatase expression reducing breast cancer growth[22]
	Low 25(OH)D is associated with high incidence of cancers of colon,[23] breast and prostate[24]
	High dosage (1000 IU/d) of vitamin D can reduce the risk for total cancer[25]

BMD, bone mineral density; SLE, systemic lupus erythematosus.

of type 2 diabetes mellitus, hypertension, hyperlipidemia, and peripheral vascular disease, coronary artery disease, myocardial infarction, heart failure, and stroke.[17] Similar but weaker associations have been found in longitudinal study, whereas no evidence for such association has been discovered by trials.[29] Many of these associations are well established; causation, however, is yet to be proven. Several plausible mechanisms may explain how vitamin D plays a role in modifying the risk for cardiometabolic outcomes. The vitamin D receptor (VDR) is present in endothelium, vascular smooth muscle, and cardiomyocytes with potential effects on cardiovascular system.[30] Vitamin D influences the renin-angiotensin system,[31] suppresses proliferation of vascular cell smooth muscle,[32] and endothelial cell-dependent vasodilation,[33] and finally it may modulate macrophage activity and cytokine generation[34] with possible positive consequences on atherosclerotic process. A deficit of vitamin D seems to increase impaired pancreatic cell function and insulin resistance in patients with type 2 diabetes by a direct effect through an activation of vitamin D receptor or indirectly by the regulation of calcium homeostasis.[28] A meta-analysis examining the association between vitamin D status or vitamin D supplementation, and incident type 2 diabetes showed that individuals with 25(OH)D levels >25 ng/mL compared to those with 25(OH)D <14 ng/mL had a 43% lower risk of developing type 2 diabetes and that a vitamin D supplementation with >500 IU/day compared to <200 IU/day reduced the risk by 13%.[18]

Central nervous system effects

Vitamin D is able to enter the cerebrospinal fluid (CSF) and brain by crossing the blood-brain barrier *via* passive diffusion and additional specific carriers in the cerebral capillaries or the blood-CSF barrier in the plexus choroideus.[35] The binding of vitamin D on the VDR triggers neuronal protection against several degenerative processes. Older adults with Alzheimer's disease have lower vitamin D concentrations than others.[36] Prospective longitudinal cohort studies in older adults have also reported that hypovitaminosis D predicted increased incidence of dementia after 7 years of follow-up.[19] The threshold at 10 ng/mL, but not at 20 ng/mL, was associated with degenerative cognition. Since hypovitaminosis D occurs gradually, patients with 25(OH)D concentration lower than 10 ng/mL have cronically low vitamin levels leading to brain dysfunction for a long time. However, two recent important studies query such relationship. A cognitive study of Schneider *et al.* did not find significant associations between lower levels of 25(OH)D and lower cognitive test scores at baseline, change in scores over time, or dementia risk in more than 1500 patients.[37] Moreover, a second important longitudinal study showed that 25(OH)D levels were not associated with white matter hyperintensities or prevalent subclinical infarcts in cross-sectional or prospective analyses.[38]

Muscle weakness and fall

Several randomized control trials (RCTs)[39] have shown positive effects of vitamin D supplementation on muscle function and fall prevention. Two systematic reviews[40,41] concluded that vitamin D supplementation with or without calcium was associated with a reduced risk for falling without showing a dose-response relationship between vitamin D and fall reduction. On the other hand, an opposite relationship was found by Sanders *et al.*[41] who treated a large group of women older than 70 years with very large dose of vitamin D3 (500,000 IU) once yearly. Patients, treated for a period of 5 years, showed a significant increase in the mean 25(OH)D after just 1 month but at the same time they had higher incidence of falls (relative risk: 1.15 and 1.26, respectively). The same effects were not reported in adults receiving vitamin D at doses currently prescribed in clinical practice (no more than 50,000 IU per week for 8-12 weeks, equivalent to 6000 IU per day).

Immunomodulation effect

Among the *non-classical* actions of 1.25(OH)D is possible to include an immunomodulation mediated through the VDR, found in almost all cell types, including macrophages, dendritic cells, B and T lymphocytes and neutrophils. Studies *in vitro* have shown that 1.25(OH)D seems to be able to inhibit maturation of monocyte-derived dendritic cells, impairing their ability to process and present antigen to T lymphocytes.[20] T lymphocyte expression of VDR increases upon antigenic activation and their activation determines a suppression of cell-mediated and promotion of humoral immune process.[42] On these basis 1.25(OH)D appears able to regular and probably to contain autoimmune pathological mechanisms. In particular, as regards systemic lupus erythematosus, several studies have confirmed a relationship between low 25(OH)D levels and enhanced disease activity,[21] however, to date there is no high-level evidence to support that vitamin D supplementation may prevent or influence this disease. Other studies were carried out on possible influence of vitamin D status on rheumatoid arthritis without finding any relationship between 25(OH)D and levels of rheumatoid factor or anti-cyclic citrullinated peptide antibodies,[43] whereas an increased incidence in deficiency was found only in undifferentiated arthritis. In short, many autoimmune rheumatologic disorders appear to be associated with vitamin D deficiency and in some cases this extends to an association with disease activity, however, there are no convincing studies showing de-

crease in disease risk following supplementation with vitamin D.

Anti-carcinogenic effects

Vitamin D may exert anti-carcinogenic effects by promoting various pro-apoptotic mechanisms and controlling the angiogenesis. It also regulates androgen and estrogen receptor signalling, thereby inhibiting the growth of some sex hormone-dependent tumors, such as prostate and breast cancer. Moreover, 25(OH)D seems to reduce the expression of aromatase with negative effect on breast cancer growth.[22] An inverse association between 25(OH)D and the incidence of several cancers and mortality from these cancers has been shown in case-control studies, prospective and retrospective studies, especially for colon breast and prostate cancers.[24] Recently, vitamin D supplementation has been tested in cancer prevention. A population-based, double-blind, randomized placebo-controlled trial of 4 years duration with more than thousand postmenopausal women pointed out that the administration of calcium (1400-1500 mg/day) and vitamin D3 (1100 IU/day) reduced the cancer incidence by 60%. Multiple regression models also shown in which both treatment and serum 25(OH)D concentrations were significant, independent predictors of cancer risk.[44] In an interesting meta-analysis Chung *et al.*[25] reported that direct evidence from RCTs for the effects of vitamin D (with or without calcium) supplementation on cancer outcomes is limited and does not agree with data from observational studies. Limited data from RCTs suggest that a high dosage (1000 IU/d) of vitamin D can reduce the risk of total cancer. Higher blood vitamin D concentrations were associated with a reduced risk for colorectal cancer but not breast or prostate cancer. A recent systematic umbrella review of meta-analyses of observational studies, assessing the association of 25(OH)D levels with site-specific cancer incidences, concluded that there is evidence for an association of 25(OH)D levels with colorectal cancer, whereas there is inconclusive or no evidence for an association of 25(OH)D with other cancer sites.[23] These results, however, are limited by the methodological quality of the included observational studies.

Vitamin D and mortality

A recent meta-analysis has addressed the association between serum 25(OH)D concentrations and mortality in a large consortium of cohort studies, trying to consider any potential confounding factors, such as age, sex, season, and country differences.[2] The pooled effect estimates from this meta-analysis for all-cause mortality and cardiovascular mortality, in subjects without cardiovascular disease at baseline comparing

the lowest and highest quintile of 25(OH)D concentration, showed an increase by 57% and 41%, respectively. Such results were in agreement with previous meta-analyses.[45,46] These associations of low 25(OH)D concentrations with all-cause and cardiovascular mortality outcomes resulted equally significant everywhere they would be tested. A clear difference in the association of 25(OH)D with cancer mortality was found between subjects with a history of cancer and those without, being closer for the first. Moreover, recent systematic reviews[46-48] have outlined that vitamin D could have a role on mortality. Wang *et al.*, reported that in eight prospective cohort studies from Europe and the United States, the lowest quintile of serum 25(OH)D concentration was associated with increased all-cause and cardiovascular mortality, with a curvilinear association between 25(OH)D concentration and these outcomes. A second one is a Cochrane systematic review of 56 randomised trials with 95,286 participants. Most trials included women older than 70 years. Vitamin D decreased mortality when the Authors globally analysed 56 trials. In sub-analysis by type of vitamin D, only vitamin D3 decreased mortality, whereas vitamin D2, alfacalcidol and calcitriol did not significantly affect mortality. To prevent one additional death 150 people should be treated over 5 years.[48] However, in an interesting trial sequential analysis, recently published by Balland *et al.*, the effect estimate showed uncertainty as to whether vitamin D with calcium reduces mortality by 5% or more.[16] Vitamin D supplementation seemed to be significantly effective only for the administration of vitamin D3 in subjects with low 25(OH)D levels at baseline.

Conclusions

Vitamin D with calcium is essential for bone health. It improves the intestinal and renal calcium absorption maintaining an adequate calcium-phosphorus product for a high quality mineralization during the life. In older people, both calcium and vitamin D levels may be lower causing osteomalacia and/or osteoporosis with a higher risk of fracture. Epidemiological data have clearly associated serum vitamin D lower levels (deficiency) with bone fracture in older people, whereas not univocal data exist regarding e beneficial effect of vitamin D supplementation in general population. Probably, trial with a specific end-point could really sweep away the doubts.

As previously reported, vitamin D seems to have a role in pathophysiological pathways of several diseases involving cardiovascular, central nervous system and neoplastic process. On these bases, it has been hypothesised that vitamin D supplementation could modify the outcome of a wide range of illnesses. Un-

fortunately, in face of several positive and encouraging results, other findings seem to suggest caution to consider vitamin D supplementation able to influence mortality and the course of cardiovascular, degenerative and neoplastic diseases.

It seems reasonable to follow the US Institute of Medicine recommendations saying that evidence is not yet sufficient to recommend vitamin D3 supplementation for subjects with vitamin D insufficiency (defined as 30-50 nmol/L 25(OH)D) but that subjects with vitamin D deficiency (<30 nmol/L 25(OH)D) could profit from vitamin D3 supplementation by maintaining bone health and reduction in fracture risk.[4] On the other hand, since most data concerning the relationship vitamin D supplementation and reduction in extraskeletal event derived mostly from meta-analysis studies is reasonable to wait for larger and prospective studies built up namely with such primary end-points. To date, we may assess that in general population vitamin D insufficiency is not frequent as well as in older people who take more advantage by a prevention strategy of measure serum levels of vitamin D and therefore its supplementation when deficiency condition (<30 nmol/L or 10 ng/mL) is observed. However, there is no consensus on the ideal cut-off values for vitamin D deficiency, because they are currently based on the prevention of osteoporotic outcomes, whereas other outcomes might also be more relevant from a public health point view.

Although there are no absolute certainties about this issue, the most recent data suggest that vitamin D deficiency, and its supplementation, may play an important role in a wide range of diseases other than in bone metabolic diseases probably in older but not in general population. For this reason a wide measurement of vitamin D levels in general population seems to be inappropriate whereas a prevention strategy of assessment and supplementation of vitamin D deficiency would result cost-effective in older population.

Take home message

- No solid consensus on the threshold of vitamin D deficit;
- Vitamin D supplementation is effective in reducing bone fracture in older patients with vitamin D deficiency;
- According to epidemiological studies, vitamin D deficit may have a role in pathophysiological pathways of several diseases involving cardiovascular, central nervous systems and neoplastic process;
- Caution to consider vitamin D supplementation able to influence mortality and the course of cardiovascular, degenerative and neoplastic diseases;
- A prevention strategy of assessment and supplementation of vitamin D deficiency would result cost-effective in older population.

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