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IM - REVIEW

Vitamin D and health status in elderly

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Abstract Recently, vitamin D has aroused considerable interest for several reasons. Many epidemiological studies have shown a widespread deficiency of vitamin D at all ages, and the recent finding that many organs and tissues have vitamin D receptors has fostered the clinical and biological relevance of vitamin D. Elderly people are at high risk for vitamin D deficiency if their life style entails few outdoor activities, their skin is thick and they exhibit impairment of renal function. In the elderly, vitamin D deficiency is very important because it can affect the function of many organs such as the muscle–skeletal, cardio-vascular systems and kidney, and may be involved in various diseases and pathological conditions including type II diabetes, cancer and cognitive decline. In the present review, the most relevant features of vitamin D are described as well as the clinical consequences of hypovitaminosis D in the elderly. Finally, the role of an adequate oral supplementation in the geriatric population is stressed.

Keywords Vitamin D Elderly Chronic diseases Vitamin D receptors

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Biomarkers currently available show that vitamin D deficiency is a major public health problem in any part of the world, which requires urgent attention. Symposium: Vitamin D and Health in the 21st Century–update [1]

Introduction

It is now widely recognized that more than 50% of the world population is at risk of vitamin D deficiency. This deficiency is in part due to the misconception that a healthy diet contains an adequate amount of vitamin D. Several epidemiological surveys in Europe, North America and also in Afro-Asian countries have shown a worldwide deficiency of vitamin D at all ages, particularly in the elderly [2]. Moreover, the identification of vitamin D receptors (VDR) in a number of tissues and organs not involved in calcium homeostasis has suggested important functions of vitamin D unrelated to bone health [3]. For these reasons, in the last decade vitamin D has gained a new role in biological and clinical settings, and undoubtedly the old picture of vitamin D has changed. Finally, the 'black-box' warning launched by the international scientific community was effective because today vitamin D is measured everywhere.

Measuring vitamin D: the new standard for efficacy and safety

Vitamin D is present in two different forms: (1) *ergocalciferol* (vitamin D_2), a molecule with 28 atoms of carbon, which originates from a vegetal precursor (ergosterol) under the action of UV light; (2) *cholecalciferol* (vitamin D_3), a

molecule with 27 atoms of carbon, which is derived from 7-dehydrocholesterol and produced in the skin when exposed to UV light. Following exposure to sunlight, both vegetables and animals are able to synthesize vitamin D. Vitamin D_2 is generated in yeast and plants and vitamin D_3 in fishes and mammals with the only exception being the cat, whose skin is virtually lacking 7-dehydrocholesterol. Vitamin D requires two metabolic conversions: 25-hydroxylation in the liver [25(OH)D] and 1-α-hydroxylation in the kidney before obtaining the active form [1,25 di-hydroxy vitamin D or $1,25(OH)_2D$] that can bind VDR to modulate gene transcription and regulate mineral ion homeostasis. The dietary source of vitamin D is extraordinarily low (10%) compared to endogenous production (90%).

Markers of vitamin D state

It is generally believed that circulating 25(OH)D is a reliable indicator for vitamin D status. In fact, serum levels of 25(OH)D reflect nutritional intake and endogenous synthesis, while the serum concentration of $1,25(OH)_2D$ is tightly regulated and not ordinarily dependent on sunlight exposure or diet.

$1,25(OH)_2D$ has a short half-life (4–6 h), and exists at circulating levels amounting to 1/1,000 of 25(OH)D that conversely shows a relatively long life (about 5 weeks). The receptor affinity of 25(OH)D is about 100 times lesser than that of $1,25(OH)_2D$. In the past, investigators have proposed the use of biomarkers or functional end points such as parathyroid hormone (PTH), calcium absorption, bone turnover or bone mineral density to more clearly define the adequacy of circulating 25(OH)D concentration.

In population studies, however, measurement of 25(OH)D has several limits as an index of individual vitamin D adequacy, because (1) a single annual determination is not adequate due to winter–summer variations, (2) the cut-off values can be different according to either physiological requirements (plasma levels of PTH, bone health, optimal calcium absorption) or clinical goals (efficient neuro-muscular function, prevention of fractures and some malignancies, such as prostate or abdominal cancer), (3) the serum concentration of 25(OH)D should be considered in relation to genetically determined changes in proteins linked to the transport or function of vitamin D (i.e. vitamin D binding protein–VDBP and VDR), the relative importance of which is presently unknown in a single individual. However, several recent studies have demonstrated that a common criterion can be shared for both physiological and clinical purposes [4]. Hence, there is a general agreement that serum PTH values remain stable until the vitamin D concentration is greater than 30 ng/mL, starting to increase at lower concentrations (secondary hyper-parathyroidism). Since the response to PTH is determined by baseline PTH levels, changes in vitamin D status and age and mobility of the subject, older adults need more vitamin D to produce higher 25(OH)D concentrations required to overcome the hyperparathyroidism associated with their diminishing renal function.

In addition, the intestinal absorption of calcium is maximal again for a concentration of vitamin D approximately 30 ng/mL, while the achievement of clinical objectives is guaranteed with levels of vitamin D greater than 40 ng/mL. The current normal limits of vitamin D are shown in the Fig. 1 [5].

A new look of "old" vitamin D

Recently, there has been a growing interest in, and evidence for, previously unrecognized roles of vitamin D (and its metabolites) in the physiology of normal health and the patho-physiology of a wide range of clinical disorders [3, 6]. The discovery that several tissues (brain, prostate, breast, colon) and immune cells have VDR and many of those possess the "biochemistry machinery" [CYP27B1: 25(OH)-1-α-hydroxylase] to convert the primary circulating form of vitamin D [25(OH)D] to the active form $[1,25(OH)_2D]$ highlights a potentially relevant role of vitamin D as a factor capable of reducing the risk of many chronic diseases. A paramount contribution to the comprehension of exact mode of action and full spectrum of

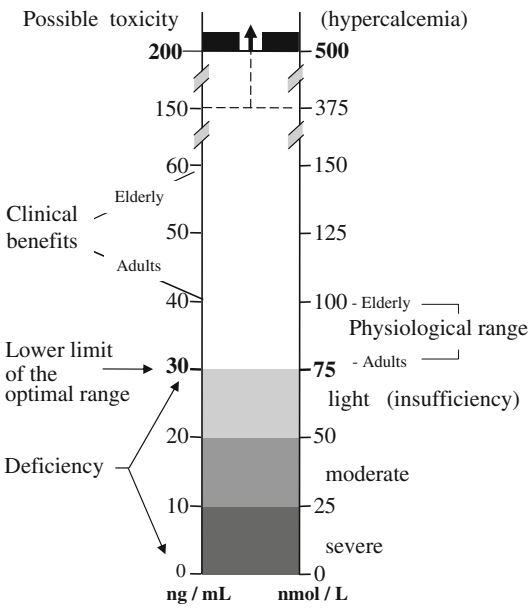

Fig. 1 The new dimensions of vitamin D. More elevated plasma levels of 25(OH)D are needed for elderly people for either physiological purposes (stabilization of PTH levels–optimal calcium intestinal absorption) or clinical benefits. Toxicity: the safety upper level is typically placed at 150 ng/mL; actually, toxic effects have been observed only above 200 ng/mL

activities of vitamin D has been provided by the analysis of mice with engineered deletion of VDR [7]. The non-classic actions of vitamin D can be summarized as follows (Fig. 2):

1. Regulation of hormone secretion: $1,25(OH)_2D$ inhibits the synthesis of PTH and prevents the proliferation of parathyroid gland tissue. VDR are found in pancreatic beta-cells and $1,25(OH)_2D$ stimulates insulin secretion. A number of observational studies have suggested that vitamin D deficiency contributes to increased risk of type I and type II diabetes mellitus [8].
2. Immunomodulatory effects, infections and autoimmune disorders: The $1,25(OH)_2D$ hydroxylating enzyme present in macrophages is identical to the renal form, but its expression is controlled in a completely different manner, because it is significantly up-regulated by immune signals such interferon gamma or viral infections. Neither in macrophages nor in dendritic cells, 1-α-hydroxylase activity is subjected to negative feedback signals deriving from $1,25(OH)_2D$ itself, different from what occurs in the kidney. That can explain the massive local production of $1,25(OH)_2D$ by disease-associated macrophages in patients with granulomatous diseases (sarcoidosis and tuberculosis) [9].
3. Regulation of cellular proliferation and differentiation: For many years, $1,25(OH)_2D$ has been evaluated for its potential anticancer activity, there being quite an extensive list of malignant cells that express VDR. The accepted basis for using the analogues of $1,25(OH)_2D$ in the prevention and treatment of malignancy includes antiproliferative and pro-differentiating effects on several cell types. Most attention has been paid to cancers of the colon and prostate.

Very recently, von Essen and co-workers [10] from Copenhagen University were able to show that vitamin D is an essential trigger for an effective immune system, because it seems to control T cell antigen receptor signaling and T cell activation.

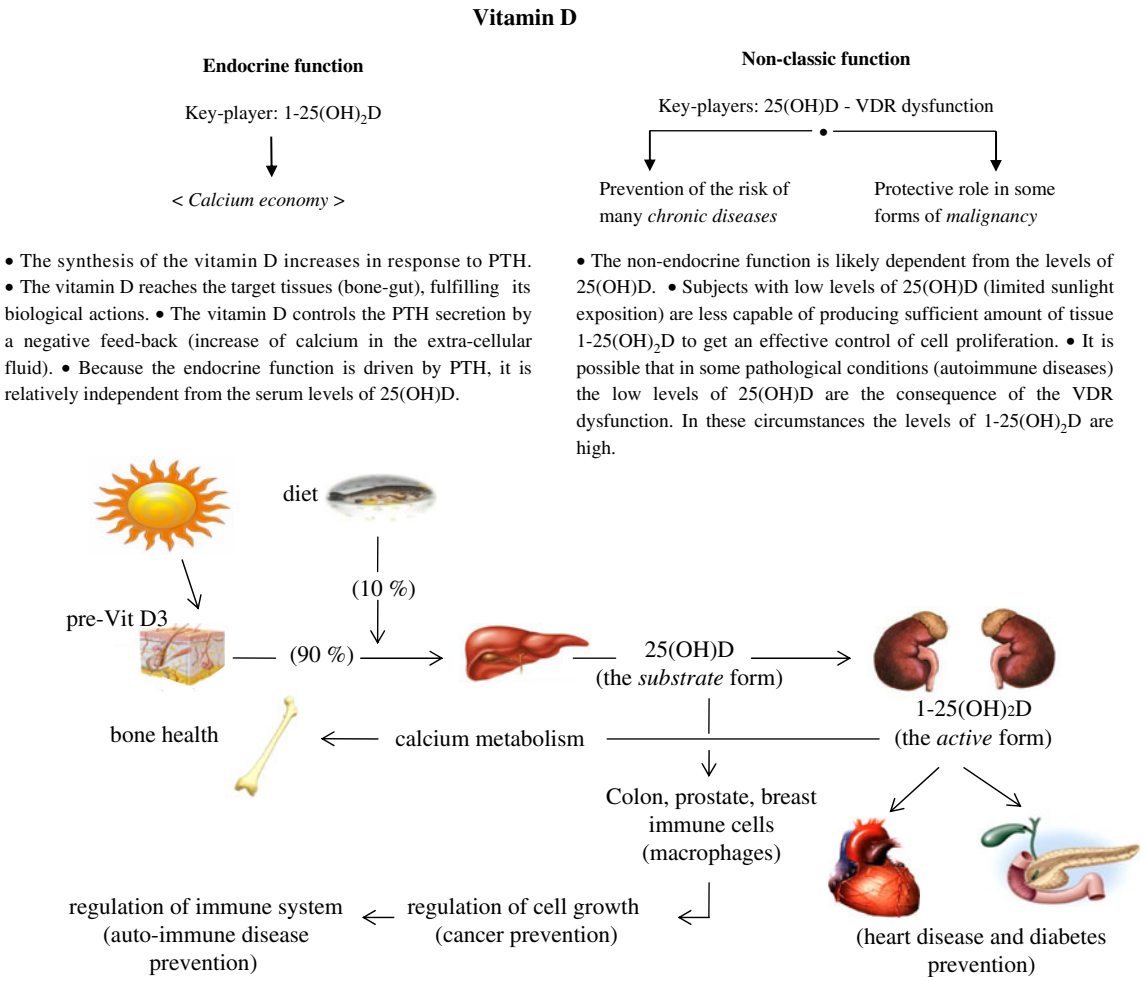

Fig. 2 Vitamin D functions

Vitamin D and aging

Vitamin D deficiency, a worldwide problem, is more prevalent among older people. The high prevalence of vitamin D deficiency in older people may have several causes:

- Cholecalciferol synthesis in the skin after sun exposure is less effective in old age because of a decline in cutaneous levels of 7-dehydrocholesterol;
- The increase in fat mass leads to a larger distribution volume of the fat-soluble 25(OH)D, which decreases the bioavailability of 25(OH)D;
- When vitamin D levels are low, $1,25(OH)_2D$ formation is impaired due to a lack of substrate. Additionally, renal function declines with age and this induces a decline in renal 1-α-hydroxylase activity, thus impairing the conversion of 25(OH)D to $1,25(OH)_2D$.

The active metabolite [$1,25(OH)_2D$] exerts its function via VDR, a nuclear receptor. With aging, a decrease in VDR expression (leading to vitamin resistance) in bone, intestine and muscle tissue has been reported.

PTH

PTH levels exhibit seasonal variation with the highest levels observed during winter season. The most important causes of secondary hyperparathyroidism with aging are: vitamin D deficiency, renal insufficiency and low dietary intake of calcium. Hyperparathyroidism:

- negatively influences bone health,
- stimulates muscle protein breakdown,
- promotes vascular calcification and has been related to cardiovascular events.

Older adults need more vitamin D to produce the higher 25(OH)D concentrations required to overcome the hyperparathyroidism associated with their diminishing renal function. PTH levels of the elderly who have 25(OH)D concentrations > 40 ng/mL matches those of younger adults having 25(OH)D concentrations near 30 ng/mL [11]. These results have been confirmed by a study conducted in the Chianti area (Italy) showing that higher levels of 25(OH)D are required in older compared to younger subjects to avoid the age-associated compensatory hyperparathyroidism [12].

Hypovitaminosis D

For a long time, vitamin D diseases have been rachitism in childhood and osteomalacia in adult age (due to calcium malabsorption), and for those reasons everyone thought that in the absence of those short-latency diseases there was no vitamin D deficiency [13]. Lately, however, it has been discovered that hypovitaminosis D could induce long-latency diseases such as osteoporosis and cancer (Table 1). Furthermore, it has been documented that many tissues have vitamin D receptors and express α-hydroxylase for vitamin D and then are able to produce by themselves vitamin D. In many of those tissues, vitamin D induces "cell differentiation" and controls cell proliferation. Therefore there are two main groups of vitamin D functions (Fig. 2).

Our experience confirms the elevated prevalence of hypovitaminosis D in the elderly (Fig. 3). Two hundred and fifty five old subjects with mean age of 78.5 ± 5.2 years (76% were women) admitted to a geriatric rehabilitation in Gussago (Brescia: latitude 45.4° N) were studied when clinically stable and with a normal hepatic and renal function. 25(OH)D was measured by HPLC [14]. Most of the subjects with plasma levels of 25(OH)D $\geq$ 70 ng/mL (all obtained in the summer time) were taking supplements of vitamin D for different reasons. These values were collected in the period between May 2007 and June 2009.

In a national study looking at the general population performed in 43 osteoporosis centers from all regions of Italy, 700 women aged 60–80 years were evaluated during winter season. In this representative sample of elderly women, the prevalence of hypovitaminosis D as values of 25(OH)D < 5 ng/mL (severe deficiency) was found in 27% and values <12 ng/mL in 76% of women, respectively [15].

Figure 4 gives an overview of vitamin D levels in the elderly (Europe) and in post-menopausal women (worldwide). The highest prevalence of vitamin D deficiency is observed in countries of central and southern Europe. Worldwide, serum 25(OH)D levels are negatively correlated with latitude. Among other established factors, differences in clothing also explain the lower vitamin D levels in overweight and elderly individuals living at low latitude [16, 17].

Elderly

The functions of vitamin D in the elderly are complex and diversified [18–20]. As space constraints prevent a detailed description, a general framing of the issue will be helpful. Types of evidence that are necessary to fully understand the effects of vitamin D include: first, findings must have an appropriate biological plausibility. Secondly, association is not causation: a correlation (although strong) does not necessarily imply a cause–effect relation. Thus, observational studies may be subject to various biases for estimating the effect of vitamin D on disease endpoints.

Table 1 Hypovitaminosis D

Risk factors	
Environment: latitude (higher), season (winter)	Reduced skin synthesis
Individual: black people, aging, clothing, use of sunscreen	
Malabsorption–Obesity	Decreased bioavailability
Liver failure	Decreased synthesis of 25(OH)D
Renal failure	Decreased synthesis of $1,25(OH)_2$ D
Drugs: glucocorticoids, anticonvulsants, barbiturates, rifampicin	Increased catabolism
Chronic diseases associated to low levels of vitamin D	
Muscle-skeletal apparatus: Osteoporosis, increased body sway, increased susceptibility to fall and fractures, proximal myophaty (muscle-skeletal pain).	
Chronic liver disease: cirrhosis, primary biliary cirrhosis	
Chronic kidney disease	
Cardiovascular system: heart failure, ischemic heart disease, hypertension, peripheral arterial disease	
Respiratory system: COPD (chronic obstructive pulmonary disease), asthma	
Autoimmune and chronic inflammatory disease: diabetes (type 1 and 2), multiple schlerosis, psoriasis, Crohn's disease, rheumatoid arthritis.	
Cancer: colorectal, prostate, breast.	
Brain: cognitive function (poorer performance on the cognitive function tests)	
Dental health: periodontal disease (periodontitis, tooth loss).	

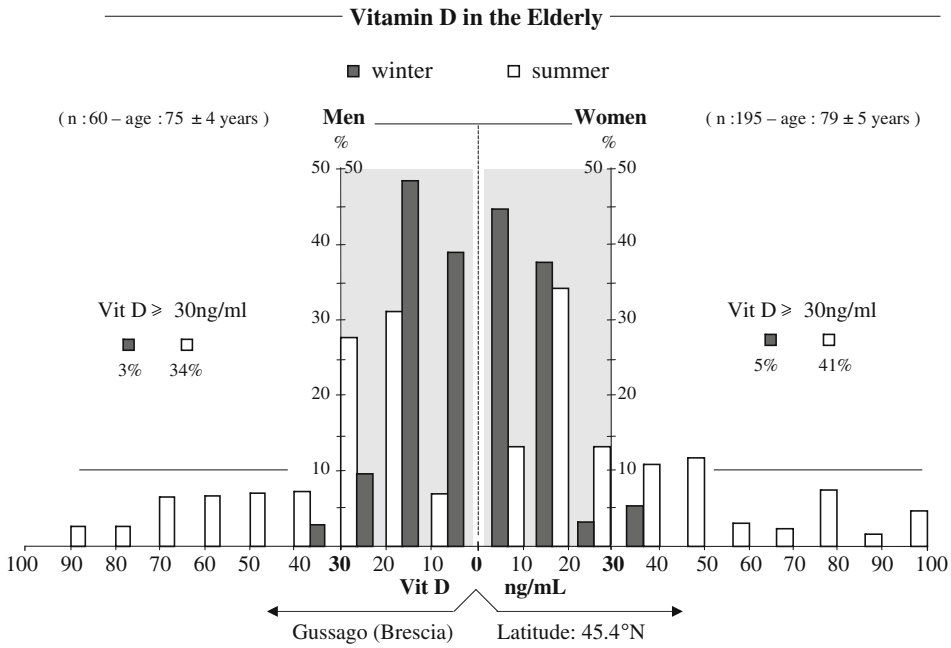

Fig. 3 Vitamin D in the elderly

Randomized, controlled trials are more likely to provide unbiased evidence. Clinical studies aiming at evaluating the effects of vitamin D supplementation (intervention studies) are often useless due to the low dosages employed. To obtain reliable conclusions on this issue, it will be necessary to plan clinical trials evaluating vitamin D supplements able to reach clinically useful serum concentrations (approximately 40 ng/ml). Studies focusing on elderly people will have to draw conclusions based on attained serum concentrations rather than on the administered doses of vitamin D. Such clinical trials are now beginning to be published [21]. An excellent example is the Finnish study aiming to assess the effects of vitamin D supplementation on the risk of type I diabetes in children [8].

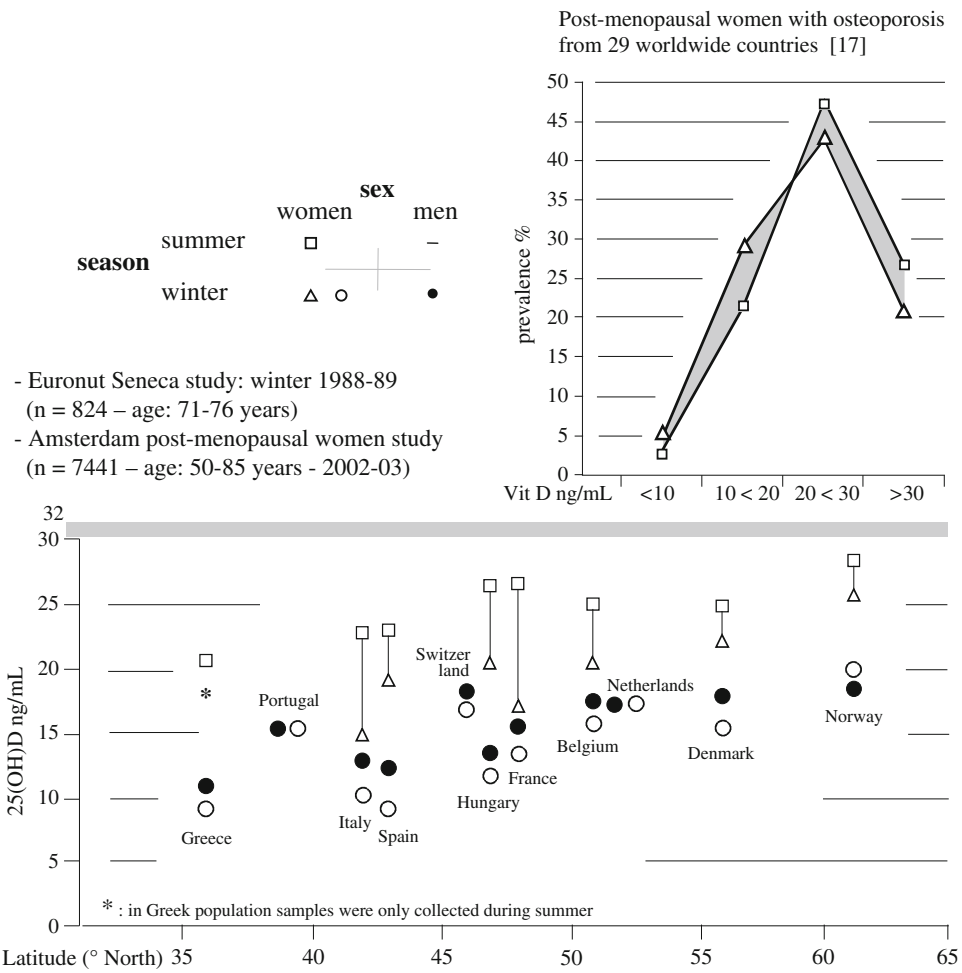

Fig. 4 Geographical distribution of mean 25(OH)D serum concentrations relative to latitude and distinct for sex (Euronut Seneca Study [16]) and season (Amsterdam postmenopausal women study [17])

Muscle–skeletal apparatus

Despite numerous biological effects, it is recognized that the primary function of vitamin D is to facilitate the processes that are necessary to maintain a healthy, mineralized skeleton. In general, the effect of vitamin D on change in bone density and mass is small (1–2%) and unlikely to be sufficient per se to substantially reduce the fracture risk. The role of vitamin D in fracture risk, however, extends beyond bone. Many factors including declining bone mass, muscle loss and reduced muscle strength and increased risk of falls contribute to fracture risk in the elderly. Vitamin D balance is positively associated with physical performance, and the association between muscle weakness and vitamin D deficiency has been recognized for a long time, though now it is better understood. The molecular mechanisms of the vitamin D action on muscle tissue include genomic effects due to the binding of $1,25(OH)_2D$ to its nuclear receptor causing changes in gene transcription of mRNA and subsequent non-genomic effects mediated through synthesis of a cell surface receptor [22].

Many studies have assessed the effects of vitamin D on fracture risk since Trivedi and colleagues [23] demonstrated a reduction of fracture rate in older adults with supplementation of vitamin D. Although these results are controversial, two meta-analyses from Bischoff-Ferrari and colleagues [24] have recently clarified that supplementation of vitamin D in a dose of 700–1,000 IU/day is effective to reduce the fracture risk among elderly people by 29% and that higher doses (≥800 IU/day) of vitamin D decrease non-vertebral fractures in community-dwelling individuals by 29% and institutionalized older individuals by 15%, independent of calcium supplementation [25].

To summarize: (1) vitamin D deficiency is associated with muscle weakness as well as osteomalacia and also falls and fractures among elderly people that are not explained by reduced bone density, (2) supplementation of >800 IU/day of vitamin D is needed to have a positive effect on falls, (3) prevention of non-vertebral fractures with vitamin D is dose dependent and independent of additional calcium intake.

Osteoporosis

Osteoporosis is a worldwide problem (not only in postmenopausal women): the increasing prevalence of osteoporosis has paralleled a pandemic of vitamin D insufficiency. According to a recent survey by the Italian Society of Osteoporosis, about 5 millions of individuals are affected by osteoporosis (two/thirds are women). Postmenopausal women are at higher risk because the 25(OH)D serum levels decline with age earlier in women than in men [12].

The Amsterdam postmenopausal women study [17] shows that the percentage of postmenopausal women suffering from osteoporosis with 25(OH)D serum levels <30 ng/mL in the winter approaches 90% in Europe, and that almost 80% of postmenopausal women with osteoporosis worldwide were affected by hypovitaminosis D in winter, and up to 70% in summer (Fig. 4).

Glucocorticoid (GH)-induced osteoporosis (GIO)

Glucocorticoid (GH)-induced osteoporosis (GIO) is the most common secondary form of osteoporosis, and is a relevant clinical condition. The increase of bone loss associated with the use of GC is an early phenomenon, especially of the vertebral spine. Fractures, which are often asymptomatic, may occur in as many as 30–50% of patients [26]. Reduced osteoblast function is a primary defect in GIO, and is reflected by decreased biochemical markers of bone formation. Risk factors for GIO include old age, high doses and long-term treatment. For bone health, calcium and vitamin D are of utmost importance: each complements the other with respect to various bone health endpoints. Vitamin D should be always included in every therapeutic regimen of osteoporosis. As documented by a recent study [27], the persistence of secondary hyperparathyroidism due to hypovitaminosis D reduces body mass density response to bisphosphonates in older women with osteoporosis. In conclusion, patients being treated for osteoporosis should be adequately supplemented with calcium and vitamin D to maximize the benefit of treatment. The association of vitamin D and bisphosphonates appears to be an effective therapeutic regimen for these patients.

Chronic kidney disease

Vitamin D has an emergent and expanding role in chronic kidney disease (CKD). The kidney is a key organ in the normal metabolism and function of vitamin D.

Renal failure with the reduction of vitamin D activation and subsequent secondary hyperparathyroidism is involved in the disproportionately high burden of cardiovascular morbidity and mortality described in patients with CKD. In fact, observational studies strongly suggest that disturbed bone and mineral metabolism play an important role in the development of vascular calcification and attendant vascular disease in patients affected by CKD. Briefly, 'soft bones and hard arteries' (arterial stiffness) is present in these patients [28]. Moreover, the impairment of the vitamin D hormonal system in CKD is associated with increased renal inflammation, low-grade systemic inflammation, cytokine network dysregulation (IL-10, IL-6, TNF-α) and oxidative stress. All these factors are thought to be implicated in the association between CKD and cardiovascular disease [29].

Malnutrition is prevalent in advanced CKD patients and protein energy wasting is a maladaptive metabolic state, often linked to inflammation, which is common in these patients. Intradialytic loss of amino acids and activation of pro-inflammatory cytokines, mainly IL-6, lead to protein catabolism during hemodialysis. The changes in albumin, fibrinogen and muscle protein kinetics during hemodialysis reflect competing and complementary effects of the availability of amino acids and activation of pro-inflammatory cytokines [30]. Oral cholecalciferol in patients during hemodialysis seems to be an effective therapeutic measure. It allows (1) reduction of vitamin D deficiency, (2) better control of mineral metabolism (with less use of active vitamin D), and (3) attenuation of inflammation.

Cardiovascular system

VDR are present in a large variety of cell types including cardiomyocytes. Several epidemiologic and clinical studies suggest that there is a strong association between hypovitaminosis D and cardiovascular disease. Recently, a study reports that patients with high blood pressure who possess a gene variant affecting an enzyme critical to vitamin D activation are twice as likely as those without the variant prone to have congestive heart failure. This study is the first indication of a genetic link between vitamin D action and heart disease [31].

For a long time, human and animal studies established a connection between vitamin D deficiency and cardiovascular dysfunction including cardiac hypertrophy, fibrosis and hypertension, as well as alterations of renin levels. An interesting clinical study documents that vitamin D (2,000 IU/day) improves cytokine profiles in patients with congestive heart failure, and so it appears to be anti-inflammatory agent for the treatment of the cardiovascular disease [32]. Low levels of 25(OH)D are also associated with myocardial infarction. A sub-study of HPFS (Health Professional Follow-up Study) shows that men deficient in 25(OH)D (<15 ng/mL) are at increased risk for myocardial infarction compared to those with sufficient 25(OH)D

(>30 ng/mL) [33]. Recently, the observation that in a group of 23 male subjects with hypovitaminosis D (mean 25(OH)D levels < 10 ng/mL) the supplementation of 300,000 IU monthly for 3 months has a favorable effect on endothelial function and lipid peroxidation that were basally abnormal compared to controls (mean 25(OH)D levels of 30 ng/mL), suggests that vitamin D deficiency might be an independent risk factor for atherosclerosis [34].

Hyperparathyroidism increases cardiovascular risk

Diseases with elevated levels of parathyroid hormone (PTH), such as primary and secondary hyperparathyroidism, are associated with a high incidence of cardiovascular disease and death. Very recently, the ULSAM study (Uppsala Longitudinal Study of Adult Men) reports that higher plasma PTH levels are associated with a higher risk for cardiovascular mortality [35]. Several mechanisms can explain the link between plasma PTH levels and cardiovascular mortality, such as atherogenesis via vascular calcification and vascular remodeling, left ventricular hypertrophy and cardiac fibrosis.

Deficiency of vitamin D may be associated with cardiac failure because vitamin D has both direct effects on heart cells and indirect effects on the risk factors of the disease. Actually, vitamin D can act on myocardial contractile function, regulation of natriuretic hormone secretion, extracellular matrix remodeling and regulation of inflammatory cytokines and renin gene [32].

Hypertension

Increased activation of the renin–angiotensin–aldosterone (RAA) system, which is the main regulator of electrolyte and volume homeostasis contributing to the development of arterial hypertension, has been reported in VDR and 1-α-hydroxylase knock-out mice. In fact, VDR and 1-α-hydroxylase knock-out mouse develops arterial hypertension and myocardial hypertrophy. Blocking the RAA system with ACE inhibitors normalizes the blood pressure and cardiac abnormalities [36].

The association between 25(OH)D levels and arterial hypertension has been assessed in several cross-sectional studies. The NHANES III shows that systolic blood pressure is inversely correlated with 25(OH)D levels [37]. These results are confirmed by subgroup analyses, in which the age-related increment in systolic blood pressure is significantly lower in individuals with vitamin D sufficiency.

Despite the inconsistent findings from some cross-sectional studies, the majority of large surveys demonstrate that plasma 25(OH)D levels are inversely and independently associated with the risk of developing hypertension.

Respiratory health

Few years ago, the NHANES III study showed a strong correlation between serum concentration of 25(OH)D and the pulmonary function parameters [38]. These initial results, however, were controversial, but in later studies the link between vitamin D and respiratory diseases became more evident. In young people, vitamin D levels are associated with markers of asthma and allergy severity, while in COPD patients they are linked with upper respiratory tract infection. Actually, COPD is characterized by frequent infections, persistent inflammation, muscle–skeletal dysfunction, multiple co-morbidities, all features that vitamin D may affect [39]. Vitamin D deficiency occurs frequently in patients with COPD, and correlates with the severity of the syndrome. Very recently, a study performed in a cohort of adult asthmatics shows a greater functional impairment and higher airway hyper-responsiveness with a reduced glucocorticoid response in those patients with lower levels of 25(OH)D [40].

Diabetes

Interest in vitamin D and diabetes dates back to 30 years when a VDR was found in the pancreatic tissue, and data were published showing that vitamin D deficiency could affect insulin secretion [41].

Evidence is accumulating on the possible role of vitamin D in the pathogenesis of type II diabetes. While a causal relationship between hypovitaminosis D and type II diabetes has yet to be fully established, there are a number of lines of evidence (epidemiological and observational, cross sectional and cohort studies) that strongly suggest a link between vitamin D deficiency and the pathogenesis of type II diabetes, as recently confirmed by a systematic review and meta-analysis [42].

Potential mechanisms by which vitamin D may affect glucose homeostasis, include pancreatic B cell function, insulin resistance and inflammation [43].

High prevalence of hypovitaminosis D and a strong correlation between 25(OH)D concentration and cardiovascular disease (CVD) has been recently claimed among type II diabetic patients in an Italian study [44]. Putative elevated cardiovascular disease risk associated with hypovitaminosis D is probably mediated by related elevations in plasma inflammatory markers. Vitamin D deficiency is associated with an increased risk of cardiovascular disease in this population. Very recently, a research group from Washington University reported that $1,25(OH)_2D$ inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type II diabetes. These results identify reduced VDR signaling as a potential mechanism leading to increased foam cell

formation and accelerated cardiovascular disease in diabetic patients [45].

Cancer

The links between vitamin D and cancer (breast, colorectal, prostate) have solid bio-epidemiologic bases.

The VDR are crucial mediators for the cellular effects of vitamin D. It has been suggested that VDR polymorphisms may influence both the risk of cancer occurrence and prognosis. A recent review concludes that data showing an association of VDR polymorphisms and cancer risk are strongest for breast cancer, prostate cancer and malignant melanoma, while data for cancer prognosis are strongest for prostate cancer, breast cancer and renal cell carcinoma [46].

The history of vitamin D and cancer prevention began in the 1970s when maps for cancer mortality rates were created. Through the study of these maps, Cedric and Frank Garland of John Hopkins University discovered a strong latitudinal gradient for colon cancer mortality rates [47].

The vitamin D hypothesis has received strong experimental support based on the ubiquitous expression of VDR and 1-α-hydroxylase in many cancer cells, which converts the plasma 25(OH)D into $1,25(OH)_2D$. Binding of VDR by $1,25(OH)_2D$ evokes multiple cellular effects such as induction of differentiation and apoptosis, inhibition of proliferation and angiogenesis.

In 2007, the NHANES III study showed that there was no association between 25(OH)D levels and total cancer mortality, but colorectal cancer mortality was significantly reduced in patients with higher 25(OH)D levels [48].

In conclusion, although the association between low UV-B radiation levels and cancer seems to be stronger for cancer mortality than for cancer incidence, there is molecular evidence that vitamin D protects against cancer, and many epidemiological data (not always consistent) seem to suggest that a sufficient vitamin D level might protect against cancer initiation and progression.

The results of a large observational study endorsed by the International Agency for Research on Cancer (IARC-WHO) in 10 western European countries indicate a strong inverse correlation between levels of pre-diagnostic 25(OH)D concentration and risk of colorectal cancer. In analyses by quintiles of the 25(OH)D concentration, patients in the highest quintile had a 40% lower risk of colorectal cancer than those in the lowest quintile [49].

Cognitive function

Evidence for a role of vitamin D in cerebral function begins with autoradiographic findings of VDR in the brain of experimental animals and the demonstration that $1,25(OH)_2D$ is present in cerebrospinal fluid. Recent studies in human brain confirm the presence of VDR as well as genes encoding catalytic enzymes in $1,25(OH)_2D$ metabolism in both neuronal and glial cells within brain structures critical for cognition (complex planning, processing and the formation of new memories) [50]. Although these findings support a functional role for vitamin D in human brain, the association between serum 25(OH)D concentration and cognitive performance is not clearly established even if there is ample biological evidence to suggest an important role for vitamin D in brain development and function [51]. At the moment, we can conclude that clinical studies indicate a limited but growing evidence of a relationship between vitamin D and cognitive function, especially in older women [52].

Mortality

Studies about mortality have greatly contributed to the spread of interest in vitamin D and to strengthen the evidence of its beneficial role on health.

Epidemiological surveys provide only an indirect evidence that vitamin D, after exposure to UV-B, acts as a protective agent. Therefore, studies concerning supplementation of vitamin D are important to establish whether or not vitamin D has a direct protective role.

The scenery is changed after a recent meta-analysis of 18 randomised trials about vitamin D intake that evaluates the effects of vitamin D on total mortality [53]. The subjects randomised for vitamin D intake have a statistically significant 7% reduction in mortality from any cause. The reduction amounts to 8% in studies in which the intervention lasted for 3 or more years. In a prospective cohort survey of aging in Tuscany (in Chianti study), 25(OH)D serum levels of more than 1,000 adults, older than 65 years, and mortality have been assessed during a follow-up period of 6.5 years. Compared to participants in the highest quartile of serum 25(OH)D (>26.5 ng/mL), those in the lowest quartile (< 10.5 ng/mL) show an increased risk of all-cause mortality (Hazard Ratio = 2.1) and cardiovascular disease mortality (Hazard Ratio = 2.6) [54]. Future studies will clarify to what extent vitamin D supplementation may affect survival in the elderly and in which groups of old subjects.

Vitamin D supplementation

Vitamin D deficiency is often clinically unrecognized, laboratory measurements are easy to perform, and treatment of vitamin D deficiency is well tolerated and inexpensive. Oral supplementation is the best tolerated and the most effective route of administration.

There is an urgent need to recommend an effective treatment for vitamin D. Elderly subjects and

postmenopausal women should have vitamin D measurement at least once yearly (i.e. at the end of October for the northern hemisphere). If indicated, a vitamin D supplementation per os using cholecalciferol (the most powerful form of vitamin D) should be started at a dosage of 1,000–2,000 IU/day (meaning about 10,000 IU weekly, to favor adherence) until April, which is the dose effective to raise the 25(OH)D plasma levels from 20 to 32 ng/mL. An alternative therapeutic option can be the oral administration of 100,000 IU every 2 months in the winter season. Higher doses of vitamin D (4,000–5,000 IU/day), however, are very well tolerated. In fact, vitamin D can be consumed safely up to 10,000 IU/day [55]. Large doses (loading) of vitamin D (cholecalciferol), rapidly and safely, normalize the 25(OH)D serum levels in the frail elderly. The purpose of vitamin D supplementation today is not only reaching high serum levels of 25(OH)D (between 30–40 ng/mL), but also maintaining these levels stable, to avoid harmful fluctuations. High vitamin D concentrations are not good if they fluctuate.

Conclusions

Vitamin D is unique in the field of nutrition because of its pleiotropic effects. In spite of a growing consciousness of the "biological–clinical" scenario about the role of vitamin D, much still remains to be done to disseminate the notion of potential preventive and protective effects of the vitamin D on the risk reduction of many extra-bone chronic diseases. Vitamin D insufficiency appears to be highly prevalent among older adults. Evidence from epidemiological studies and small clinical trials suggest an association between 25(OH)D concentration and systolic blood pressure, risk for cardiovascular disease-related deaths, osteoporosis, type 2 diabetes, cognitive deficits and mortality. Prospective, adequately powered studies with multiple non-calcemic endpoints are needed to define the clinical benefits of an optimal vitamin D status.

"Denunciation" articulated by Giovannucci [6] well identifies the major hindrances that are needed to be overtaken. In particular, four main misconceptions have hampered the improvement of vitamin D status:

the only function of vitamin D is on mineral homeostasis (bone)
intake as low as 400 IU/day is adequate
intake higher than 2,000 IU/day is toxic
sun exposure is uniformly deleterious.

The interest for vitamin D boomed in the last 5 years. As ever with booming events, however, an adequate sedimentation period is required to be able to evaluate the comprehensive impact. A prospective (5 years) very large study (the Boston study) has been launched recruiting 20,000 elderly adults (men 60 and older, women 65 and older) from across the United States to study whether high doses of vitamin D (2,000 IU/day of vitamin D3) will lower risk of some chronic diseases.

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