# Association between atherosclerosis and osteoporosis, the role of vitamin D

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**Submitted:** 15 December 2010
**Accepted:** 2 March 2011

Arch Med Sci 2011; 7, 2: 179-188
DOI: 10.5114/aoms.2011.22066


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## Abstract

The latest data support the correlation of atherosclerosis and osteoporosis, indicating the parallel progression of two tissue destruction processes with increased fatal and non-fatal coronary events, as well as higher fracture risk. Vitamin D inadequacy associated with low bone mineral density increases fall and fracture risk, leads to secondary hyperparathyroidism, calcifies coronary arteries and significantly increases cardiovascular disease. Randomized clinical trial evidence related to extraskeletal vitamin D outcomes was limited and generally uninformative. A recent recommendation on vitamin D dietary requirements for bone health is 600 IU/d for ages 1-70 years and 800 IU/d for 71 years and older, corresponding to a serum 25-hydroxyvitamin D level of at least 20 ng/ml (50 nmol/l). Further large randomized controlled trials are needed to reassess laboratory ranges for 25-hydroxyvitamin D in both diseases, in order to avoid under- and over-treatment problems, and completely clarify the relationship between atherosclerosis and osteoporosis.

**Key words:** vitamin D deficiency, low bone density, cardiovascular disease, fracture risk.

## Introduction

Both epidemiological and clinical studies have indicated that patients with low bone mineral density (BMD) are at significantly greater risk of developing cardiovascular disease (CVD) as well as unexpected cardiovascular events, more severe coronary atherosclerosis and vascular calcification [1-4].

Pathophysiological mechanisms that connect atherosclerosis and osteoporosis (OP) are complex and could be dependent and/or independent of the production of vitamin D (Vit D). A low level of Vit D decreases BMD, influences neuromuscular dysfunction (weakness of proximal muscles), increases the risk of falls and fractures, and stimulates the renin-angiotensin system, leading to the development of hypertension (HTA), left ventricular hypertrophy, and coronary artery calcification associated with congestive heart failure [5].

A recent review of randomized trials evaluating the effect of greater doses and higher achieved 25-dihydroxyvitamin D [25(OH)D] levels on health outcomes concluded that the optimal benefit of Vit D for CVD (as well as cancer) was obtained at 25(OH)D concentrations of 75-110 nmol/l (30-44 ng/ml). These levels can best be obtained with oral daily doses of Vit D in the range of 1,800 to 4,000 IU [6].

## Cardiovascular disease and osteoporosis

At present, growing evidence indicates the existence of a correlation between CVD and OP (fractures), irrespective of age [1-3]. These clinical conditions, linked by numerous common pathophysiological mechanisms and risk factors, are asymptomatic in the early clinical stages. It is a fact that 200 million people have been diagnosed with OP, whereas epidemiological studies concerning the number of atherosclerosis sufferers do not exist. The socio-economic consequences of both these diseases are very important bearing in mind the facts that OP is the second highest world health problem after CVD, and this number will increase with the growth of the elderly population over the next decades.

Cardiovascular disease and OP together account for most of the morbidity and mortality in our aging population despite significant improvements in treatment. Osteoporotic postmenopausal women are at significantly greater risk of CVD, cardiovascular mortality and bone fractures than age-matched controls [4, 5]. Patients with lower bone density and OP also have higher lipid levels, more severe coronary atherosclerosis, and a greater risk of stroke death. The common finding of simultaneous vascular calcification and OP in individual patients suggests that local tissue factors govern the regulation of biomineralization [7]. Serum 25(OH)D levels are inversely associated with important CVD risk factors. The latest results indicate a strong and independent relationship of 25(OH)D deficiency with prevalent CVD in a large representative sample of the US adult population [8].

The following facts clearly reflect the association between these two diseases. Risk factors for vascular disease, such as dyslipidaemia, systemic arterial HTA, diabetes mellitus, and hyperhomocysteinaemia, have been associated with a higher incidence of low bone mineral density. In addition, there is evidence indicating the action of antiresorptive drugs on the reduction of cardiovascular risks and the effect of statins, antihypertensives and insulin on bone mass increase [1]. The connection between low values of BMD and the risk of fractures is similar to the correlation between HTA and cardiovascular events. It has been established that myocardial infarction is the cause of approximately 50% of all fatalities.

## Fracture and pain assessment in osteoporotic patients

A myocardial infarction is often the first clinical manifestation of atherosclerosis, as well as fractures in patients with low BMD. Pain is the first clinical manifestation of OP and atherosclerosis. It can be seen that 30-40% of women aged over 50 years have low BMD and coronary disease, with the prevalence of carotid atherosclerosis of 42% in the observed population [9]. Of all postmenopausal women, 30% have OP of the hip, lumbosacral spine (LS), or in the distal segment of the radius [10]. More than 50% have had a previously diagnosed fracture of the proximal part of the femur, vertebral fracture, proximal part of the humerus, a distal segment of the forearm or of the pelvis [10]. With regard to the latest scientific knowledge, reference values of BMD for men have been shown to be on the same level of fracture risk as amongst women, which can also be linked to the risk of coronary diseases in both genders [11].

In OP, pain is a consequence of a low energy fracture or spontaneous fracture which points to late diagnosis. It is a remarkable fact that about 50% of women aged over 50 years had no idea they were suffering from vertebral fractures. Therefore, it is of particular importance for everyday clinical practice to recognise them early, because the intensity of pain is not in correlation with the presence and degree of vertebral fracture, and often is not linked with a known mechanical load. Moreover, some of these women felt no pain at all. Indeed, only 33% of vertebral fractures are considered to be diagnosed in clinical practice. On the other hand, not all patients suffer an OP diagnosed fracture during their lives, but 30-40% of patients with osteopenia had fractures as well as 10-20% of patients with a T-score within the range of reference values [10]. Fracture risk reduction correlates neither with the degree of raised BMD nor with the same BMD in relation to various geographical areas. Until recently it was considered that 70-80% of fractures were determined by BMD. Now, it is known that BMD, by around 30%, Not clear is one among a number of risk factors in the assessment of bone quality and fracture risk. Genetic factors, however, dominate all risk factors by over 60%. This position is supported by a cohort study which investigated the frequency of fractures in OP. Only 46% of women with fractures had BMD in the OP level [12]. The incidence of typical fractures in OP is low and varies in different fracture locations over a wide spectrum ranging from less than 10% to 44% [13]. Moreover, cases with a T-score within the level of OP at one measurement point do not have to have OP anywhere else. Therefore, a large number of measurement points raises the probability of better assessing fracture risk, as concluded in some published articles [11, 14].

In the latest recommendations regarding evaluation for initiating therapy, great importance is given to assessing future fracture risk (Frax algorithm) estimated over 10 years

(www.shef.ac.uk./FRAX) using previous X-ray evaluations for fractures of the vertebral column, and BMD [15].

## Association of atherosclerotic processes with bone metabolism and osteoporosis

The effect of atherosclerosis on bone metabolism and the development of OP was established owing to investigations confirming that a decreased value of BMD is a good mortality predictor during cardiovascular occurrences and coronary disease in postmenopausal women and men older than 50 years of age. In fact, the connection between CVD and OP exists not only in the process of aging. A connection has been confirmed between the decreased value of BMD, and unexpected cardiovascular mortality, as well as the incidence of CVD occurring in Caucasian women, but not in men [3, 4].

A correlation exists between OP and atherosclerosis regardless of age, body mass index (BMI) and cardiovascular risks. Cases of low BMD of the hip have a higher risk of CVD mortality in both genders [16].

The inverse correlation of cardiovascular calcification and loss of bone calcium indicates that this is the parallel progression of two processes of tissue destruction. Postmenopausal women with atherosclerotic changes of the abdominal aorta, in comparison with those having no vascular calcification, have a significantly decreased value of BMD at the lumbar spine and hip, higher hip fracture risk (× 2.9) and vertebral fracture risk (× 4.8), as well as a higher incidence of fatal and non-fatal coronary events [17].

Pathophysiological mechanisms connecting atherosclerosis and osteoporosis are complex and can be dependent or independent of the production of vitamin D. Hyperproduction of inflammatory markers such as C-reactive protein, interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-$\alpha$ (TNF-$\alpha$) can be considered risk factors and some are directly related to the severity of atherosclerosis, with pre-resorption effects and the stimulation of osteoclastogenesis [1].

## Association of lipid fraction levels with osteoblast and osteoclast function

An increase of low density lipoprotein cholesterol (LDL-C) and a reduction of high density lipoprotein cholesterol (HDL-C) levels have been associated with low BMD in postmenopausal women [18].

Lipid oxidation products such as minimally oxidized LDL-C promote arterial calcification, and its accumulation in the subendothelial space of skeletal bone arteries inhibits bone formation [19]. The hyperproduction of oxidized low density lipoprotein fraction of cholesterol stimulates atherogenesis and activates osteoblasts in the arterial pool, leading to the calcification of arterial plaque. However, the published results are controversial. It has been shown that plasma LDL-C level inversely correlated with BMD values, while low plasma triglyceride (TG) levels were associated with the presence of vertebral fractures in postmenopausal women [18-22].

Some studies found no association between serum lipid concentrations and BMD [23] and other studies found even a positive relationship between them [22-25].

The study of Sivas *et al.* [22] showed that serum lipids have an impact on vertebral fracture existence, rather than BMD alterations. The total cholesterol (TC), TG and LDL-C levels were lower in postmenopausal women who had at least one vertebral fracture. TC level was the strongest factor affecting vertebral fracture existence. And an increase of 1 mg/dl TC decreased the risk of vertebral fracture by 2.2%. In the study of Jeong *et al.* [26] after adjustment for clinical and laboratory covariates, the authors found a weak positive association between HDL-C and BMD at the lumbar spine only in postmenopausal women. This result is in accordance with the work of Yamaguchi *et al.* [18] but opposite to the results of the study by Adami *et al.* [24], in which worse lipid profiles (lower HDL-C and higher LDL-C or TG) were associated with higher bone mass, although they could not provide a documented explanation. In conclusion, the correlation between lipid profile and BMD was neither consistent at all bone sites [26], nor from study to study. Further studies are needed to clarify this relationship and the underlying mechanism.

The artery wall contains endothelial cells capable of differentiation into osteoblasts, following the same stages of differentiation as occur in bone-derived osteoblasts, and ultimately producing bone mineral. So, the same oxidized lipids that induce atherosclerosis also induce mineralization and differentiation of the osteoblastic cells in the artery wall. Consistent with this finding, hyperlipidaemia is associated with vascular calcification in mice [7]. On the other hand, hyperproduction of LDL-C and lipid accumulation in the subendothelial matrix would be expected to inhibit differentiation of osteoblasts from preosteoblasts and enhance osteoclastic differentiation and activity, which lead to decreased bone density. Oxidized lipids induce endothelial expression of monocyte chemotactic factors and the monocyte colony-stimulating factor (M-CSF), a potent inducer of osteoclastic differentiation and differentiation of osteoclast precursor cells, which consequently promote bone resorption [18, 19]. At the same time, oxidized LDL-C molecules act in the suppression of terminal

differentiation of stromal cells into osteoblasts, while HDL inhibits cytokines responsible for the osteogenic differentiation of vascular cells [27]. The mechanism of arterial calcification resembles the process of osteogenesis, involving various cells, proteins and cytokines that lead to tissue mineralization [28]. Clinical studies also support the role of lipids in both vascular calcification and OP. Lipid-lowering agents reduce coronary vascular calcification in patients, where the degree of improvement follows in direct relation to the degree of lowered lipids [29]. Lipid-lowering agents also enhance bone mineralization in rodents [30] and humans [31] and may reduce the incidence of osteoporotic fractures in patients [32-34]. These effects on bone were originally attributed to a direct effect of the specific class of lipid-lowering agents used, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). It is possible that statins may directly protect bone [20]. However, it is not yet possible to distinguish whether the improvement in bone density and reduction in fracture risk are due to lipid lowering or to a direct effect of statins on bones. It is notable that bisphosphonates, leading agents for OP, also reduce LDL cholesterol and increase HDL cholesterol levels in humans [35]. Experimental studies using animal models of vascular calcification have demonstrated that bisphosphonates completely inhibit arterial and cardiac calcification in mice [36]. The protective effect of bisphosphonates has been attributed to their direct action on the vessel wall by sensitizing macrophages to undergo apoptosis, preventing foam cell formation by inhibiting the uptake of LDL-C and affecting cell replication [37]. Also, a recent study showed that bisphosphonates induce inflammation and rupture of atherosclerotic plaques in apolipoprotein-E null mice [38]. These data support the concept that lipids contribute to both vascular calcification and OP. Osteopenia and OP correlate positively with atherosclerosis, vascular calcification, and cardiovascular events, with some evidence of age independence [3]. Thus, plasma lipids may be related to bone mass and bone fragility, and could be the common factor underlying both OP and vascular calcification, which suggests that these diseases share common pathophysiological pathways [27]. In human calcified atherosclerotic plaque, as in bone tissue, the same modulators of bone metabolism can be detected: osteopontin (OPN), osteocalcin, matrix Gla protein (MGP), osteonectin, osteoprotegerin (OPG), bone morphogenetic protein (BMP), receptor activator of nuclear factor κB ligand (RANKL), inflammatory cytokines, type 1 collagen, proteoglycan and nitric oxide (NO). The dysfunction of endothelial synthase (e-NOS) of NO is present in both processes [18, 39, 40]. Several mechanisms of vascular injury have been proposed for homocysteine, including a reduction in nitric oxide, endothelial dysfunction, increased platelet aggregation, and proliferation of vascular smooth muscle cells, among others [27].

Furthermore, bone and coronary arteries are target organs for oestrogens. Vitamin D directly affects oestrogen synthesis by regulating the activity of aromatase in osteoblasts [41] and oestrogen half-life by regulating 17 hydroxysteroid dehydrogenase in keratocytes [42]. Woman after the menopause demonstrate accelerated bone loss. Also, the beneficial effects of oestrogens on the cardiovascular system and atherosclerosis are well established [19, 43, 44].

Homocysteine is a possible risk factor for atherosclerosis [45]. Homocystinuria is a genetically inherited disease which is characterised by elevated plasma homocysteine concentrations. Its clinical manifestations, apart from skeletal disorders and OP, include a tendency towards premature atherosclerosis and thromboembolism. There is also evidence that postmenopausal woman with a heterozygous mutation in methylenetetrahydrofolate reductase (MTHFR) and, therefore, hyperhomocysteinaemia demonstrate a decrease in BMD. This supports the hypothesis that homocysteine participates in the interaction between oestrogen and bone metabolism [19, 46].

Also patients with OP and atherosclerosis exhibit insufficient vitamin K levels. Vitamin K is a cofactor required to convert the amino acid glutamate into gamma-carboxyglutamate, or Gla-proteins [47]. Gla-proteins regulate physiological processes controlled by calcium. These include blood coagulation (clotting) and bone mineralization. Accordingly, Gla-proteins are critical to the formation and replenishment of bone tissue. Unless these proteins are modified by vitamin K, they cannot properly form the matrix in which calcium and phosphorus bind together to make solid, well-mineralized bone. Vitamin K has been shown to stimulate new bone formation and reduce the incidence of vertebral fractures [48, 49]. The Gla-protein osteocalcin, normally present in bone, has been found in calcified atherosclerotic plaque lesions, and production of this protein is pathologically up-regulated in people with atherosclerosis [50]. At the same time, another vitamin K-dependent Gla-protein known as matrix Gla-protein (MGP), normally found in healthy arterial walls, is a strong inhibitor of vascular calcification [51, 52]. In other words, by increasing MGP in the arterial walls, vitamin K protects against the calcification-inducing effects of osteocalcin. Therefore, vitamin K deficiency is also a confounder in the OP/CVD relationship.

## Potential pathophysiological mechanisms which determine the role of vitamin D in atherosclerosis and osteoporosis

Except for the association of Vit D deficiency with the prevalence of traditional CVD risk factors, emerging data suggest a more direct role of Vit D in the development of atherosclerotic disease [53].

Several pathophysiological mechanisms which determine the role of Vit D in atherosclerosis/cardiovascular disease and OP have been proposed and are summarised in Table I.

Serum concentration of 25(OH)D, the main circulatory metabolite of Vit D, was accepted in 1997 by the Panel on Calcium and Related Nutrients of the Food and Nutrition Board (IOM-NAS) as a barometer for the status of Vit D. 25-hydroxyvitamin D, as a substrate of renal and extra-renal production of 1,25-dihydroxyvitamin D, reflects the total production (endogenous and exogenous sources) of Vit D. The presence of the physiological active metabolite $1,25(OH)_2D$- 1,25 dihydroxyvitamin $D_3$ shows that Vit D has a hormonal effect. Vitamin D receptors (VDR) are present in many different tissues, such as brain, breast, immune cells, muscle tissue, parathyroid glands, cardiomyocytes, vascular endothelial and vascular smooth muscle cells, endothelial cells of colon mucosae, as well as malignant colon cells [54, 55].

The expression of VDR in vascular endothelial and smooth muscle cells converts 25-OH Vit D from a biologically inactive form (in a physiological concentration) by hydroxylation in the kidneys of 1-$\alpha$ hydroxylase into $1,25(OH)_2D$ (dihydroxycholecalciferol), the active metabolic form of Vit D, regulated by parathyroid hormone (PTH) secretion. Dihydroxycholecalciferol regulates the renin-angiotensin axis by directly suppressing the renin gene. 25(OH)D binds with Vit D binding protein (DBP) and is transported to the kidneys through the circulation [54].

Kidney activity may decrease during ageing, parallel with decreased renal function, and a similar decrease in DBP, as well as a lessening of albumin in sera. Subsequently, low levels of 25(OH)D in older people with hip fractures may be a consequence of decreased DBP as the active metabolites of Vit D are mainly linked to DBP.

An inadequacy of Vit D directly promotes the development of HTA, leads to the hyperproduction of PTH and, consequently, secondary hyperparathyroidism, cardiomyocyte hypertrophy and vascular remodelling – ventricular hypertrophy. Also, this process influences inflammation by stimulating the release of cytokines from smooth muscle vascular cells [56]. Vitamin D inhibits vascular calcification by blocking the release of inflammatory

**Table I.** Potential pathophysiological mechanisms of vitamin D in atherosclerosis/cardiovascular disease and osteoporosis

| Atherosclerosis/cardiovascular disease | Osteoporosis |
|---|---|
| • VDR polymorphisms (especially Bsml)<br>• Presence of $\alpha$-hydroxylase enzyme in endothelium and VSMC<br>• Presence of VDRs in endothelium and VSMC<br>• PTH suppression<br>• Regulation of renin-angiotensin-aldosterone system<br>• Presence of VDRs in immune cells (T-lymphocytes, macrophages)<br>• Downregulation in the production of inflammatory markers (CRP) and several cytokines (IL-1, IL-2, IL-6, IL-12, interferon-$\gamma$, TNF-$\alpha$, TNF-$\beta$)<br>• Suppression of EGF in VSMC<br>• Induction of prostacyclin in VSMC<br>• Downregulation of PAI-1, thrombospondin-1 and thrombomodulin<br>• Suppression of foam cell formation<br>• Reduced gene expression of bone-forming cells in the aorta | • VDR polymorphisms<br>• Decline in renal $1,25(OH)_2D$ production<br>• Regulation of PTH secretion<br>• Decline in intestinal VDR<br>• Decline in DBP<br>• Diminished renal response to PTH and reduced intestinal calcium absorption<br>• Presence of VDRs in immune cells (T-lymphocytes, macrophages)<br>• Downregulation in the production of inflammatory markers and several cytokines<br>• Effect on oestrogen synthesis:<br>– regulating the activity of aromatase in osteoblasts,<br>– regulating 17 hydroxysteroid dehydrogenase |

*VSMC – vascular smooth muscle cells, VDR – vitamin D receptor, PTH – parathyroid hormone, CRP – C-reactive protein, IL – interleukin, TNF – tumour necrosis factor, EGF – epidermal growth factor, PAI-1 – plasminogen activator inhibitor-1, VDR – Vit D receptor, DBP – Vit D binding protein, $1,25(OH)_2D$ – dihydroxycholecalciferol*

*Adapted from: Anagnostis P, Athyros VG, Admidou F, Florentin M, Karagiannis A. Vitamin D and cardiovascular disease: a novel agent for reducing cardiovascular risk? Curr Vasc Pharmacol 2010; 8: 720-30*

cytokines and adhesion molecules and preventing abnormal changes in smooth muscle cells in vessel walls [57]. Accordingly, low vitamin D levels are associated with increased risk for development of the coronary arterial calcifications seen in atherosclerosis [58].

An inadequacy of Vit D in serum decreases the absorption of calcium (Ca) in the intestine, causes low values of serum Ca and compensatory hypersecretion of PTH and $1,25(OH)_2$. This results in mobilising Ca and phosphorous (P) from bones, in order to maintain the optimal level of Ca and P in sera for bone turnover, metabolic processes and neuromuscular functions. Nevertheless, as a result of the compensatory mechanisms a serum level of 25(OH)D may be maintained at reference values despite hypocalcaemia [59]. The disturbance of homeostatic mechanisms influences both skeletal and extraskeletal metabolic processes. An inadequacy of Vit D lowers BMD, gives rise to neuromuscular dysfunction – proximal muscular weakness – myopathy, sarcopenia, and increased risk of falls, although these are reversible processes [56].

Reduced levels of Vit D have a negative effect on the musculoskeletal system and, by increasing susceptibility to arterial calcification, cause an excess of cardiovascular risk factors. Clinical studies confirm that Vit D deficiency influences the activity of renin in plasma, which leads to HTA – via increased arterial resistance, calcification of the coronary arteries and a significant rise in CVD [60].

Vitamin D regulation of renin expression was independent of calcium metabolism and $1,25(OH)_2D_3$ markedly suppressed renin transcription by a VDR-mediated mechanism in cell cultures. Hence, $1.25(OH)_2D_3$ is a novel negative endocrine regulator of the renin-angiotensin system. Its apparent critical role in electrolytes, volume, and blood pressure homeostasis suggests that Vit D analogues could help prevent or ameliorate HTA [57].

Vitamin D deficiency is associated with congestive heart failure and blood levels of inflammatory factors, including C-reactive protein and cytokines such as interleukin-10. Cytokines have recently been identified as having an important role in atherogenesis [61]. Vitamin D analogues have been shown to inhibit the production of several proinflammatory cytokines while stimulating the effects of Th2 lymphocytes, leading to a reduction in matrix metalloproteinase and, thereby, reducing plaque production or instability [62].

Secondary hyperparathyroidism, as a consequence of Vit D insufficiency, also has negative implications for the cardiovascular system and bone metabolism. Living at higher latitudes increases the risk of HTA, CVD and prevalence of Vit D insufficiency [63].

Recent evidence suggests that Vit D intakes above current recommendations may be associated with better health outcomes. However, optimal serum concentrations of 25(OH)D for skeletal and extraskeletal functions are different in various published investigations. Nevertheless, it can be concluded that a daily dose of 400 IU of Vit D does not adequately reduce fracture risk [64].

A review by Roux *et al*. [64] applied the risk assessment method used by the Food and Nutrition Board to update the safe tolerable upper intake level (UL). For Vit D the method focuses on the risk of hypercalcaemia. The last statement concerning the upper limit (UL) indicates the level above which there is risk of adverse events. The UL is not intended as a target intake; rather, the risk for harm begins to increase once intakes surpass this level [65].

In previous reviews the general conclusion was that the UL for Vit D consumption by adults should be 10 000 IU/d [66]. This indicates that the margin of safety for Vit D consumption for adults is > 10 times any current recommended intake [67]. The 1997 UL for Vit D was 2000 IU/d for most age groups. The starting point for the current UL for vitamin D was 10,000 IU/d, because lower intakes have been linked to neither hypercalcaemia nor acute toxicity. However, this value was corrected due to uncertainty, given that toxicity is not the appropriate basis for a UL that is intended to reflect long-term chronic intake and be used for public health purposes. The correction was based on chronic disease outcomes and all-cause mortality, as well as emerging concerns about risks at serum 25(OH)D levels above 50 ng/ml (125 nmol/l). Thus, the Committee followed an approach to maximize public health protection and the UL for Vit D is now 4000 IU/d [65].

For all endpoints, the most advantageous serum concentrations of 25(OH)D begin at 75 nmol/l (30 ng/ml), with the best being between 90 nmol/l and 100 nmol/l (36-40 ng/ml). In most people, these concentrations cannot be reached with the currently recommended daily intakes of 200 IU and 600 IU Vit D for younger and older adults, respectively. Several studies suggest that many older people will not achieve optimal serum 25(OH)D concentrations during the summer months, which suggests that Vit D supplementation should be independent of season in older persons [68]. An intake for all adults of ≥ 1000 IU (25 µg) Vit $D_3$ (cholecalciferol)/daily is needed to bring Vit D concentrations up to 75 nmol/l (30 ng/ml) in at least 50% of the population [69]. An exploratory analysis of the heterogeneity demonstrated a significant positive association comparable to an increase of 1-2 nmol/l in serum 25(OH)D for every 100 additional units of Vit D although heterogeneity remained after adjusting for dose [70].

A reduction of risk of falls and fractures, without adverse effects, was proved for the dose 700-1000 IU with Ca supplementation (1000-1200 mg elementary Ca daily) [71]. This dose of Vit D has an anti-inflammatory effect and blocks plaque calcification in arterial blood flow. Toxic doses lead to medicalcinosis, which is a reversible process [57].

Furthermore, calcium supplementation by itself did not reduce risk of fractures [72]. As noted in the Institute of Medicine (IOM) review [65], in the analysis of NHANES data with more than 9,000 subjects, calcium intake was associated with hip bone density only among women with low 25(OH)D levels; in all other groups there was no relation between calcium intake and bone density. In contrast, 25(OH)D levels were consistently and positively associated with hip bone density [73]. Thus, with adequate 25(OH)D levels or sufficient Vit D intake, higher calcium intakes may not be correlated with bone health. In sum, calcium recommendations could be adjusted downward with Vit D supplementation; they could also possibly be adjusted downward for safety reasons. The IOM states that more data regarding the interaction of Vit D and calcium on bone health are needed and no recommendation was provided on their combination [74].

In other studies it was found that the level of 25(OH)D below 30 ng/ml (75 nmol/l) was strongly associated with suboptimal Ca absorption. A reduction of fracture incidence was observed when the level of 25(OH)D was above 75 nmol/l as, due to the beneficial effect on bone metabolism and muscle strength, there was a resulting lower incidence in the number of falls [75]. Also, it was noted that when the level of 25(OH)D was in the range 27.5-37.5 nmol/l, the PTH level progressively rose [7].

In patients with HTA and a value of 25(OH)D < 27.5 nmol/l (15 ng/ml), the risk of unexpected cardiovascular events was doubly increased. Only 10% of patients examined in the cohort study had 25(OH)D > 75 nmol/l or 30 ng/ml [17, 55].

Recent data (a meta-analysis of trials totalling 12 000 participants) showed that calcium supplements (without coadministered Vit D) are associated with an increased risk of myocardial infarction by about 30% [76].

It is now clear that a value of 25(OH)D of 75-100 nmol/l (30-40 ng/ml) is optimal for both bone metabolism and extraskeletal manifestation. Insufficiency was determined at 25(OH)D 25-75 nmol/l (10-30 ng/ml) and deficiency at 25(OH)D < 25 nmol/l (< 10 ng/ml). Complete deficiency leads to rickets in children and osteomalacia in adults [7, 56].

Also, studies of the health benefits of raising serum 25(OH)D levels to 100-112.5 nmol/l (40-45 ng/ml) at the population level on the basis of serum 25(OH)D level-disease outcome responses estimate about a 15% reduction in the all-cause mortality rate and a reduction in the economic burden of disease treatment of 10-20% [77, 78]. Another study estimated that if all those in the United States were to double their solar ultraviolet-B irradiance to raise their serum 25(OH)D level to 112.5 nmol/l (45 ng/ml) the net result could be as many as 400,000 reduced deaths compared with only 11,000 increased deaths from melanoma and other skin cancer [79].

The Institute of Medicine (IOM) Committee concluded [65] that the evidence of Vit D or Ca reducing the risk of non-skeletal chronic disease outcomes was inconsistent, inconclusive, and did not meet criteria for establishing cause-and-effect relationships. Randomized trial evidence was sparse, and few trials assessed these outcomes as primary prespecified endpoints. Moreover, emerging evidence suggested a curvilinear or U-shaped curve for several outcomes related to Vit D, including cardiovascular disease, vascular calcification, falls, and frailty [56], with lower risk at moderate levels and increased risk at both low and high levels of 25(OH)D [65]. However, the data used to suggest that higher serum 25(OH)D levels are associated with adverse health outcomes for several types of cancer, CVD, and all cause an increased mortality rate, are inadequate representations of findings in the literature or are, essentially, taken out of context. When other findings are combined with those findings, one finds reduced disease rates with increasing Vit D indices [80] .

In the same report by the IOM Committee, based on bone health Recommended Dietary Allowances (RDAs; covering the requirements of ≥ 97.5% of the population), were given calcium intake ranging from 700 to 1300 mg/d for life-stage groups from 1 year of age. For Vit D, RDAs of 600 IU/d for ages 1-70 years and 800 IU/d for ages 71 years and older, corresponding to a serum 25-hydroxyvitamin D level of at least 20 ng/ml (50 nmol/l), meet the requirements of at least 97.5% of the population. The 2011 Vit D Dietary Reference Intakes (DRIs) are based primarily on the integration of bone health outcomes with evidence concerning 25(OH)D levels, which suggest that levels of 16 ng/ml (40 nmol/l) meet the needs of approximately half the population, and levels of at least 20 ng/ml (50 nmol/l) meet the needs of at least 97.5% of the population (akin to the RDA). Intakes of Vitamin D required to achieve these 25(OH)D concentrations are based on a simulation of available data covering all ages under conditions of minimal sun exposure [65].

But, in the last "Comment on the IOM Vitamin D and Calcium Recommendations" by Heike Bischoff-Ferrari and Walter Willett [74] the authors present

the opinion that 25(OH)D levels far beyond 50 nmol/l (20 ng/ml) in younger and older adults are needed for optimal bone health, suggesting that the IOM threshold recommendation is too low [81]. In contrast to the IOM report, the IOF recommended in their 2010 position paper on Vit D a threshold of 75 nmol/l for optimal fall and fracture reduction and recommended 800 to 1,000 IU of Vit D per day for seniors aged 60 years and older [82, 83].

Further studies are necessary to define the relationship between atherosclerosis and OP with proved common risk factors including race and genetic and molecular determinants. The correlation between lipid profile and BMD was consistent neither at all bone sites, nor from study to study.

Existing evidence of extraskeletal Vit D outcomes from randomized clinical trials is limited and generally uninformative. Large randomized controlled trials and public health investigations are needed to reassess laboratory ranges for 25-hydroxyvitamin D in both diseases, in order to avoid under- and overtreatment problems.

Education of clinicians and patients is one of the most important tasks in the prevention of atherosclerosis and osteoporosis. Raising awareness about maintaining a good quality of life will lead to a decrease in the risk of fractures, myocardial infarction and mortality. Consequently, additional studies are needed to determine the exact mechanisms shared by atherosclerosis and osteoporosis and clarify not only this relationship but also the underlying mechanism.

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