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REVIEW

Can vitamin D deficiency cause diabetes and cardiovascular diseases? Present evidence and future perspectives

G. Muscogiuri [a,*], G.P. Sorice [a], R. Ajjan [b], T. Mezza [a], S. Pilz [c], A. Prioletta [a], R. Scragg [d], S.L. Volpe [e], M.D. Witham [f], A. Giaccari [a]

[a] *Endocrinologia e Malattie del Metabolismo, Università Cattolica, Rome, Italy*
[b] *Division of Cardiovascular and Diabetes Research, University of Leeds, UK*
[c] *Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Graz, Austria*
[d] *Epidemiology & Biostatistics, School of Population Health, University of Auckland, New Zealand*
[e] *Department of Nutrition Sciences, Drexel University, Philadelphia, PA, USA*
[f] *Ageing and Health, Centre for Cardiovascular & Lung Biology, University of Dundee, UK*

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Abstract Several studies have shown that vitamin D may play a role in many biochemical mechanisms in addition to bone and calcium metabolism. Recently, vitamin D has sparked widespread interest because of its involvement in the homeostasis of the cardiovascular system. Hypovitaminosis D has been associated with obesity, related to trapping in adipose tissue due to its lipophilic structure. In addition, vitamin D deficiency is associated with increased risk of cardiovascular disease (CVD) and this may be due to the relationship between low vitamin D levels and obesity, diabetes mellitus, dyslipidaemia, endothelial dysfunction and hypertension. However, although vitamin D has been identified as a potentially important marker of CVD, the mechanisms through which it might modulate cardiovascular risk are not fully understood. Given this background, in this work we summarise clinical retrospective and prospective observational studies linking vitamin D levels with cardio-metabolic risk factors and vascular outcome. Moreover, we review various randomised controlled trials (RCTs) investigating the effects of vitamin D supplementation on surrogate markers of cardiovascular risk. Considering the high prevalence of hypovitaminosis D among patients with high

* Corresponding author. Endocrinologia e Malattie del Metabolismo, Università Cattolica Policlinico Gemelli, Largo A. Gemelli 8, I-00168 Rome, Italy.
E-mail address: giovanna.muscogiuri@edu.rm.unicatt.it (G. Muscogiuri).

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cardiovascular risk, vitamin D replacement therapy in this population may be warranted; however, further RCTs are urgently needed to establish when to begin vitamin D therapy, as well as to determine the dose and route and duration of administration.

Vitamin D, obtained by both sunlight (ultraviolet (UV) radiation on the skin) and by food and converted on the skin, is present in different forms. Vitamin D2 (ergocalciferol) is found in non-animal products including plants, fungi, moulds and lichens. By contrast, vitamin D3 (cholecalciferol) is produced in the human skin and is widely distributed in animal tissues, fish oils and fortified foods (see http://lpi.oregonstate.edu/infocenter/vitamins/vitaminD/and http://ods.od.nih.gov/factsheets/vitamind/). Vitamin D receptors exist in a variety of cells and tissues [1], suggesting that vitamin D has a biological effect beyond the simple regulation of mineral metabolism. This observation, in association with mounting evidences indicating a high prevalence of vitamin D deficiency worldwide [2], raises the hypothesis that some clinical conditions may have a common cofactor — hypovitaminosis D and probably leading to a revision of the U.S. Dietary Reference Intakes for vitamin D (see Table 1). Several epidemiological studies have shown an association between low serum 25-hydroxyvitamin D [25(OH)D] levels and increased risk for cardiovascular disease (CVD) [3], hypertension [4], stroke [5] and hyperglycaemia [6], in which hypovitaminosis D reaches a prevalence of up to 75%. Moreover, obesity is associated with vitamin D deficiency through various mechanisms, including less exposure to sunlight because of lower exercise and mobility [7] and trapping in adipose tissue [8]. Given the relationship between obesity and CVD, low vitamin D may be considered as one of the mechanisms linking obesity with increased vascular risk. Therefore, it can be argued that vitamin D deficiency should not be considered only as a feature of osteo-mineral disorders, but also as a biomarker and a risk factor for metabolic derangements as well as CVD. This review aims to examine the role of vitamin D in nutrition status and analyse the effects of hypovitaminosis D as a metabolic disruptor and risk factor for CVD.

Table 1 United States Dietary Reference Intakes for Vitamin D.

Group	Recommended Dietary Allowance (IU/day)	Tolerable Upper Intake Level (UL) (IU/day)
Infants (0 months—6 months of age)	400	1000
Infants (6—12 months of age)	400	1500
Children (1—3 years of age)	600	2500
Children (4—8 years of age)	600	3000
Children and Adults (9—70 years of age)	600	4000
Adults (>70 years of age)	800	4000
Pregnant/Lactating Females	600	4000

Adapted from: http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx.
IU = International Unit.

Diabetes

There is a growing interest in the role of vitamin D in the aetiology of type 2 diabetes based on several reports finding vitamin D deficiency in impaired glucose tolerance and type 2 diabetes [9]. The association of vitamin D deficiency and type 2 diabetes could be easily predicted by their common link to obesity; however, several *in vitro* and epidemiological studies suggest a direct relationship between these two apparently disparate pathways. For example, a potentially direct beneficial effect of vitamin D on insulin action has been suggested by an increase in insulin receptors following 24 h of treatment with $1,25(OH)_2D_3$ in U-937 human promonocytic cells [10]. Furthermore, the role of vitamin D in ensuring adequate calcium influx through cell membranes and intracellular cytosolic calcium is of paramount importance to preserve the insulin-mediated insulin process in insulin-responsive tissues, such as skeletal muscle and adipose tissue [11]. Other researchers, however, have reported that vitamin D deficiency may blunt insulin action through elevated parathyroid hormone (PTH) levels [12]. In addition, it has been reported that an intriguing correlation between vitamin D deficiency and type 1 diabetes exists [13], may be due to the ability of vitamin D in preserving insulin release modulating the extracellular and intracellular β calcium pools [14]. A recent small, but well-conducted, study [15] suggested that cholecalciferol supplementation might increase the disposition index (the product of insulin secretion and action) in subjects at high risk of developing diabetes, warranting the need for larger studies. 'Recently, an interesting association has also been reported between hypovitaminosis D and the severity of non-alcoholic fatty liver disease (NAFLD) in terms of steatosis, necroinflammation and fibrosis. In addition, hypovitaminosis D is also thought to be a risk factor for NAFLD independently of the other components of the metabolic syndrome, although the molecular mechanism by which it would act is still unknown [16].

Dyslipidaemia

While the hypothesis of a possible link between hypovitaminosis D and CVD seems evident, data on the role of vitamin D in regulating blood lipid concentrations (one of the major risk factors for CVD) are still inconsistent [17—20]. Moreover, the few intervention trials available were not able to clearly demonstrate consistent effects of vitamin D treatment on plasma lipids [21—23].

A study specifically designed to clarify the relationship between vitamin D status and metabolic risk factors of CVD, in healthy individuals without diabetes, showed that serum 25(OH)D levels were inversely associated with multiple metabolic risk factors including serum low density lipoprotein cholesterol (LDL-C) levels [24], regardless of body mass index (BMI), but only in male subjects. Similar results were obtained by Chiu et al. [25] and by Carbone et al. [20] Supplementation with calcium and vitamin D showed no changes in lipid parameters in short-term treatment in healthy post-menopausal women [17] and in more than 5 years of treatment in the Women's Health Initiative [21]. By contrast, a similar study (confounded by a concomitant weight loss programme) found that calcium and vitamin D supplementation resulted in significantly decreased serum LDL-C levels [26], while a randomised controlled trial (RCT) [21] in overweight subjects found that over 12 months of vitamin D supplementation resulted in a significant decrease in serum triglyceride concentrations, but not in serum LDL-C levels. By contrast, Zittermann et al. [22] showed in 200 overweight subjects that vitamin D supplementation was associated with increased LDL levels but decreased triglycerides. From all the above-reported studies, it is evident that only large, specifically designed RCT will be able to clarify possible effects of vitamin D on plasma lipids.

Hypertension

Several potential biological mechanisms give plausibility to a link between vitamin D and blood pressure (BP). Vitamin D levels are inversely associated with renin–angiotensin system activity [27], can improve endothelial function, may be able to alter smooth muscle function and reduce the level of PTH, which is itself vasculotoxic and associated with the development of left ventricular hypertrophy [28].

Observational evidence strongly supports a link between vitamin D and BP. Higher serum vitamin D levels were associated with lower prevalent BP in the third National Health and Nutrition Examination Survey (NHANES) [29]. Furthermore, low vitamin D levels predict future incidence of hypertension; patients with serum 25(OH)D levels <37.5 nmol l^{-1} were three to six times more likely to develop new hypertension over a 4-year follow-up [30]. Still worse, low serum vitamin D levels appear to interact with pre-existing hypertension to dramatically raise the risk of future cardiovascular events [31].

Intervention studies are less clear, however. Few studies have examined the effect of vitamin D supplementation on BP; even fewer have focussed specifically on patients with hypertension. One meta-analysis [32] suggests no effect of serum vitamin D levels on BP in studies with normotensive individuals; however, for studies with a mean baseline systolic BP of >140 mmHg, a small (4/3 mmHg) but significant reduction in BP was seen. These results may mask greater benefit for some groups; the small number of studies performed in patients with diabetes [33] suggests a greater reduction of BP in this group. Studies in patients with hypertension are needed to better delineate who will benefit from vitamin D supplementation.

Heart failure

Chronic heart failure patients have particularly low serum 25(OH)D levels, in part due to their reduced exercise capacity and consequent lack of outdoor activity. Low serum 25(OH)D levels in heart failure are related to a number of variables known to predict outcome [34], and the biological effects of vitamin D support potential benefits in this condition. Vitamin D could potentially produce benefits in heart failure by reducing chronic inflammation, improving left ventricular remodelling via suppression of PTH, improving endothelial function and ameliorating the skeletal myopathy of heart failure.

Very few intervention studies have examined the effect of vitamin D in heart failure and have shown no effect on exercise capacity, ventricular remodelling or quality of life [35,36]. One study showed a reduction in tumour necrosis factor (TNF)-alpha levels, the other showed a reduction in B-type natriuretic peptide (BNP) levels, but these effects were not consistent across studies. Another study combined low-dose vitamin D (10 μg daily) with several other vitamins and minerals [37] and demonstrated a significant improvement in exercise capacity, but the combined intervention makes it impossible to attribute any benefit to vitamin D alone. These results do not exclude a beneficial effect on death and hospitalisation in the longer term, but much larger studies will be needed to examine these outcomes.

Endothelial dysfunction

Endothelial dysfunction is a key early event in vascular pathology, characterised by compromised barrier function of endothelial cells, increased expression of adhesion molecules and an imbalance in cellular secretory capacity. Observational and interventional studies have shown associations between low circulating levels of vitamin D and endothelial dysfunction. A small study involving 23 asymptomatic subjects has demonstrated that subjects with significant vitamin D deficiency have impaired brachial artery fibromuscular dysplasia (FMD), which improved after vitamin D replacement therapy [38]. More recently, a stepwise change in FMD according to vitamin D status was demonstrated, together with an inverse association between serum 25(OH)D levels and vascular inflammatory markers [39]. In a large study of 554 healthy individuals, with some on prophylactic therapy such as statins, serum vitamin D levels were independently associated with brachial artery FMD after adjusting for age, sex, race, BMI, serum lipid levels, plasma C-reactive protein and medications [40].

In addition to healthy individuals, vitamin D levels can influence endothelial function in disease states. Impaired brachial artery FMD was documented in 280 type 2 diabetic individuals who had low serum vitamin D concentrations [41]. However, in an RCT of vitamin D replacement involving small numbers of diabetic subjects ($n = 61$), low- and high-dose vitamin D_3 supplementation failed to modulate FMD assessed at 8 and 16 weeks following therapy, although an effect on BP was noted, indicating possible improvement in endothelial function [33]. The reasons for the negative results in this study may have been related to

the combination of the small sample size and the large heterogeneity of subjects with type 2 diabetes.

The exact mechanisms for vitamin D-induced endothelial dysfunction are not entirely clear and probably vary among individuals. Several pathways have been suggested for vitamin D control of endothelial cell function, including reduction of adhesion molecule expression, interference with endothelium-dependent contractions, modulation of renin–angiotensin–aldosterone system and inhibition of smooth muscle cell proliferation/macrophage activation [42,43]. Furthermore, endothelial dysfunction secondary to vitamin D deficiency may be mediated by raised plasma PTH levels, which directly target endothelial cells, thereby contributing to the atherosclerotic process [44].

Taken together, it seems that vitamin D plays a role in vascular health and one mechanism is related to modulation of endothelial cell function, consequently explaining the association between vitamin D deficiency and cardiovascular mortality.

Coronary heart disease

Evidence for the possible protective effect of vitamin D against coronary heart disease extends back to 1990 with the publication of a population-based case-control study of myocardial infarction from New Zealand, which found that people with 25(OH)D levels below the median had a more than doubling in their risk of myocardial infarction compared with those above the median [45]. The implication of this isolated finding remained unclear for many years because of the uncertainty over whether the reduced 25(OH)D levels in cases, collected immediately after the onset of myocardial infarction, were a cause or consequence of the disease event.

This uncertainty has been substantially allayed by the publication since 2005 of several cohort studies from the US, Finland and New Zealand [46–50], which ascertained the risk of having a coronary event during the follow-up period associated with 25(OH)D blood levels collected at baseline. The individual relative risks of coronary heart disease from these studies, for people in the lowest 25(OH)D category compared with the reference or highest category, are all above 1.00 (Fig. 1); and when they are combined in a meta-analysis, the summary relative risk is significant ($p = 0.002$), being 1.35 (95% confidence interval: 1.12, 1.62). Although this is a weak effect, it is of potentially great public health significance, given the high proportion of the general population with low 25(OH)D levels (<50 nmol l^{-1}), particularly during winter.

The strongest evidence of causation is provided by RCTs. The results from six RCTs assessing the effect of vitamin D supplementation on risk of myocardial infarction have recently been summarised [51]. The pooled relative risk was 1.02 (95% confidence intervals 0.93, 1.13) indicating no effect. However, previous RCTs have used vitamin D doses now known to be well below those required to increase 25(OH)D up to the levels associated with the lowest risk of myocardial infarction in observational studies (75–100 nmol l^{-1}). RCTs using higher vitamin D doses (=2000 IU per day) are required to determine once and for all whether vitamin D protects against coronary heart disease. Two are currently underway and are expected to provide answers within the next 5–6 years (www.vitalstudy.org, ClinicalTrials.gov identifier: NCT01169259, www.ANZCTR.org.auregistration number ACTRN12611000402943).

Stroke

Vitamin D may be relevant in the context of strokes because [52] observational studies have indicated that low serum 25(OH)D concentrations are associated with both classic risk factors for strokes (e.g., arterial hypertension) and an increased incidence of strokes [5,46,49,52,53]. In the largest prospective study on vitamin D status and strokes [46], there was a significantly twofold increased risk of incident strokes in patients with low serum 25(OH)D levels. This issue was also addressed in 7981 individuals of NHANES-III, followed up for 14 years [46]. In whites, the multivariable adjusted stroke risk was significantly twofold increased in individuals with serum 25(OH)D levels below 37.5 nmol l^{-1}. Interestingly, there was no significant association of vitamin D status with stroke risk in blacks. Most, but not all, other prospective studies have also shown that individuals with low serum 25(OH)D levels are at an increased stroke risk [5,46,49,53]. By contrast, a recent

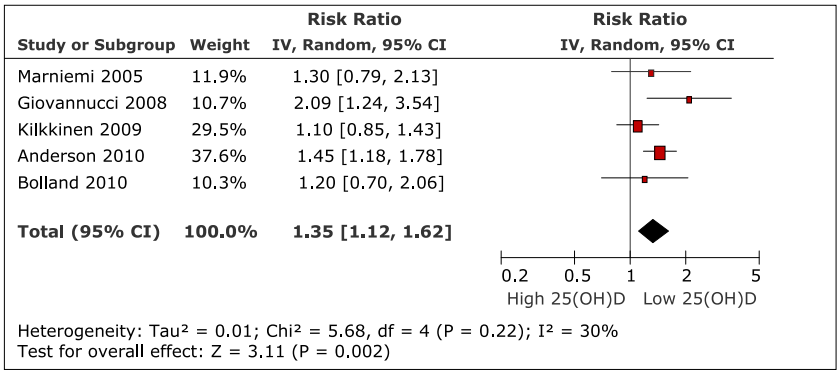

Figure 1 Forest plot of relative risks of coronary heart disease associated with the lowest 25 hydroxyvitamin D (25(OH)D) category compared with the highest (or reference) in cohort studies. Adapted from: Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2011.

meta-analysis of RCT suggests that there is no significant effect of vitamin D supplementation on the incidence of strokes [51], but studies analysed were not adequately designed to evaluate the effect of vitamin D supplementation on stroke incidence [51]. Some ongoing RCTs have been designed to answer the question whether vitamin D supplementation is effective for the prevention of cardio- and cerebrovascular events, but these studies will take several years to report. Nevertheless, the relationship between vitamin D status and stroke is evident by the extraordinarily high prevalence of vitamin D deficiency in patients suffering from acute stroke [46,52]. In this context, it is important to underline that vitamin D treatment reduces the incidence of fractures and falls, increases bone mineral density and may improve muscle strength in post-stroke patients [52,54,55]. Furthermore, vitamin D status might also play a role for the maintenance of normal neuropsychological and cognitive function involving gait control [52,56,57].

Hence, it is still unclear whether vitamin D supplementation is useful for the prevention of strokes, but we should pay close attention to the fact that poor vitamin D status in post-stroke patients is associated with an increased risk for musculoskeletal complications that can be successfully prevented with vitamin D supplementation.

Supplementation and cardiovascular diseases

Based on the hypothesis that vitamin D may exert a positive effect on CVD, several supplementation studies have been conducted, unfortunately providing conflicting results [58]. For example, Bair et al. [59] supplemented 9491 persons with low serum vitamin D concentrations; subjects with normal vitamin D levels after 1 year experienced a decrease in coronary heart disease, myocardial infarction, heart failure, stroke and renal failure. On the other hand, reports from a large Women's Health Initiative (WHI) trial failed to show any beneficial effect of moderate doses of calcium plus vitamin D_3 supplementation (400 IU daily) on coronary artery calcified plaque burden among post-menopausal women [60], nor cerebrovascular risk in healthy post-menopausal women over a 7-year follow-up period [61]. However, the WHI has some major limitations that include a vitamin D dose (400 IU daily), now considered too low plus low compliance, which probably explain the lack of effect from vitamin D on study outcomes in this trial [62].

Several intervention studies have shown that vitamin D supplementation improves endothelial function [63]. Harris et al. [63] recently suggested that supplementation with 60 000 IU per month of oral vitamin D_3 for 16 weeks is effective in improving vascular endothelial function in African-American adults. Vitamin D deficiency is also associated with increased arterial stiffness and endothelial dysfunction in the conductance and resistance of blood vessels in humans, irrespective of traditional risk burden. Normalisation of serum 25(OH)D levels was associated with increases in reactive hyperaemia index, sub-endocardial viability ratio and a decrease in mean arterial pressure after 6 months of supplementation [40].

Data reported on utility of vitamin D supplements for the treatment, prevention and reversal of many health conditions such as hypertension, diabetes, obesity and CVD have been inconsistent. In a systematic review of RCTs, Wang et al. [64] reported a non-significant trend towards reductions in CVD events in patients receiving natural vitamin D. However, Pittas et al. [65] reported that the association between vitamin D status and cardio-metabolic outcomes is uncertain.

Conclusions

The data presented in this review suggest an association between low vitamin D status and increased cardiovascular risk, based on both a direct biological effect of vitamin D on the cardiovascular system and an indirect cross-action through vitamin D signalling and multiple metabolic pathways. 'Although promising, vitamin D supplementation studies conducted thus far have been largely equivocal. In fact, the recent guidelines published by Endocrine Society recommended the supplementation with either vitamin D(2) or vitamin D(3) only for deficient patients, and concluded that there was not sufficient evidence to recommend screening individuals who are not at risk for deficiency or to prescribe vitamin D to attain the non-calcaemic benefit for cardiovascular protection' [66]. Future, adequately powered, RCTs are urgently required to establish whether vitamin D supplementation modulates cardiovascular risk and mortality in non-deficient patients, and a more detailed work is needed to outline the route, duration and optimal dose of supplementation.

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