The influence of vitamin D on cardiovascular disease

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Background: Vitamin D is essential for many biological functions in the body. Populations that are deficient in vitamin D have increased cardiovascular morbidity and mortality. Current research is controversial, and the evidence base is still developing. This review looks at the interaction between vitamin D levels and cardiovascular disease, including the major cardiovascular risk factors - diabetes, obesity, hyperlipidaemia and hypertension. **Methods**: A literature review was undertaken through MEDLINE / PubMED / Ovid / Springerlink / Web of Science databases. The terms, "vitamin D", "vitamin D deficiency", "cardiovascular risk", "cardiovascular disease", "structure", "function", "ergocalciferol", "cholecalciferol", "calcitriol", "vitamin D receptors", "1α-hydroxylase", "diabetes", "obesity", "hypercholesterolaemia", "hyperlipidaemia" and "hypertension" were used. Sixty-eight articles were selected and analysed, with preference given to studies published in English and published within recent years. **Results**: There is a correlation between adequate vitamin D levels and type two diabetes mellitus, but limited research to support this. Obesity, physical inactivity and elevated circulating lipids are more common in vitamin D deficiency. These relationships have not been shown to be causal. Some studies have shown an inverse correlation between hypertension and vitamin D levels, while others have shown no relationship. **Conclusion**: The studies analysed show there is limited evidence to suggest that cardiovascular disease may be prevented by adequate vitamin D levels. There are few well-designed studies that demonstrate the relationship between the cardiovascular risk factors - diabetes, obesity, hyperlipidaemia, hypertension, and vitamin D. Further research is needed to clarify the influence of vitamin D on cardiovascular disease.

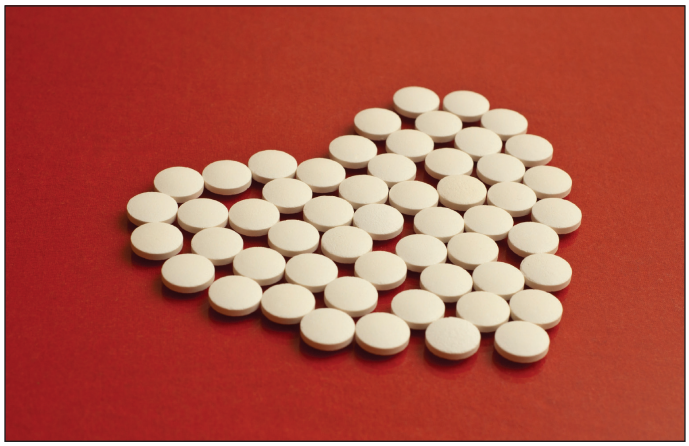
What is vitamin D, and how do you get it?

Vitamin D is a group of secosteroids, derived from steroid precursors by the opening of the steroid B-ring between carbons nine and ten. Vitamin D has a cis-triene structure which is susceptible to oxidation, ultraviolet (UV) light-induced conformational changes, heat-induced conformational changes and attack by free radicals. [1,2]

Cholecalciferol, also known as vitamin D3, is a 27-carbon molecule derived from cholesterol. [2] It is available through diet and through synthesis in the skin. [1] 7-dehydrocholesterol found in skin is converted to previtamin D3 following exposure to ultraviolet B (UVB) light. Previtamin D3 is unstable and breaks down to vitamin D3. This binds to vitamin D binding protein (VDP) and is delivered to the liver and other sites of action via the circulatory system. [3,4] Vitamin D levels are regulated in the body in a number of ways. While exposure to UVB radiation causes vitamin D3 production in the skin, excessive exposure to sunlight degrades it into inactive photoproducts. [5]

Ergocalciferol, also known as vitamin D2, is a 28-carbon molecule produced by irradiation of ergosterol found in plant and fungi, which is available through diet. [2,4] Vitamin D2 and D3 (available via diet) are absorbed with fat in the gastrointestinal system into chylomicrons, which are delivered to the liver or storage sites outside the liver, such as adipose tissue. [1]

The liver converts vitamin D3 to biologically inactive 25-hydroxyvitamin D3 (calcidiol). This is converted to biologically



active 1,25-dihydroxyvitamin D3 (calcitriol) under the influence of renal 1α-hydroxylase predominantly in the kidney. [5,6]

1α-hydroxylase is under the control of parathyroid hormone (PTH). Calcitriol is regulated by negative feedback on itself, by increasing production of 25-hydroxyvitamin D-24 hydroxylase. This enzyme catabolises calcitriol to its biologically inactive form, calcitroic acid, which is excreted in the bile and urine. Other factors such as serum phosphorus, calcium and fibroblast growth factor 23 (FGF-23) can increase or decrease production of calcitriol. Increased serum calcium levels reduce PTH, causing down-regulation of 1α-hydroxylase, reducing calcitriol, and therefore calcium levels. [5,6] A simplified diagram of the biological function of vitamin D is outlined in Figure 1.

1α-hydroxylase is the rate-limiting step in production of calcitriol. Although calcidiol is the most abundant form of vitamin D in the blood, it has minimal capacity to bind to vitamin D receptors (VDRs). 1α-hydroxylation of calcidiol to calcitriol causes vitamin D to gain affinity for VDRs. [7] In recent years, 1α-hydroxylase has been found to exist at many extra-renal sites. The role of extra-renal vitamin D activation remains controversial, but may play a role in the hypothesised actions of vitamin D. [8]

VDRs are found in almost every cell in the body. Calcitriol actions occur through intracellular receptors and interaction with DNA via the classic steroid pathway. These receptors were originally thought to regulate genes responsible for regulation of serum calcium and phosphate. [1] More recently, they have been found to regulate transcription in many tissues and cells, including immune cells, bone marrow, skin, muscle and intestine. [1,9]

How does vitamin D affect cardiovascular disease?

Vitamin D deficiency has been associated with high blood pressure, risk for cardiovascular-related deaths, symptoms of depression, cognitive deficits and mortality. [10] Calcitriol inhibits renin synthesis, increases insulin production and increases myocardial contractility. [11-13] Vitamin D deficiency reduces serum calcium levels, causing an increase in PTH, which promotes atherosclerosis and cardiovascular risk. [14,15]

The majority of evidence for the role of vitamin D in cardiovascular disease (CVD) has arisen from studies involving patients with end stage renal disease. Cardiovascular mortality is ten to twenty times higher in

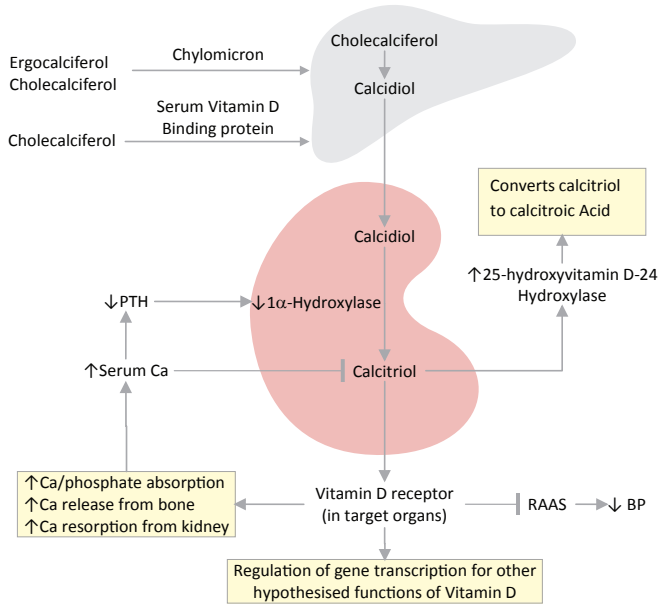


Figure 1. *The biological function of vitamin D. Extra-renal sites of 1α-hydroxylation are not shown in this diagram.*

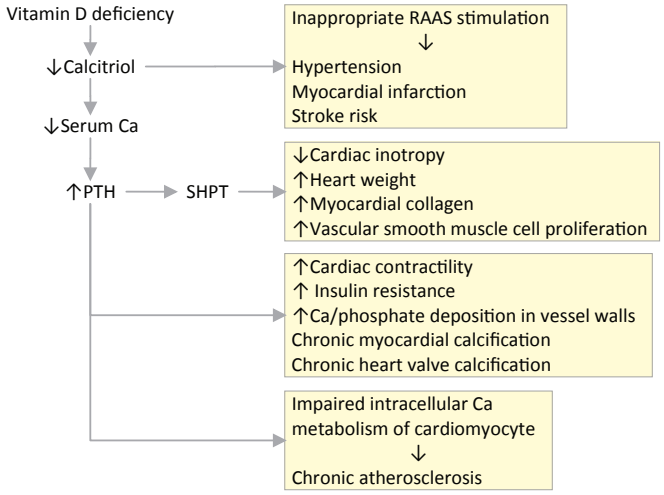


Figure 2. *The role of vitamin D deficiency in cardiovascular disease.*

patients undergoing dialysis. [16] In patients using dialysis, the risk of death from CVD can be reduced with vitamin D replacement. [17,18]

As kidney function deteriorates, calcitriol levels decline. [19] Reduced calcitriol production can lead to hypocalcemia, and in turn, compensatory elevated PTH. Overstimulation of the parathyroid gland eventually leads to secondary hyperparathyroidism (SHPT). [20] Patients with ESRD are thought to suffer from reduced cardiac inotropy, increased heart weight, increased myocardial collagen content, and increased vascular smooth muscle cell proliferation as a result of the vitamin D depletion. PTH excess may impair intracellular calcium metabolism of the cardiomyocyte and promotes chronic atherosclerosis. Elevated PTH may increase cardiac contractility, insulin resistance, calcium and phosphate deposition in vessel walls, chronic myocardial calcification, and chronic heart valve calcification. [14,15] In patients with SHPT, treatment advice usually consists of correction of calcitriol deficiency using calcitriol or vitamin D analogues. [6]

Mechanisms for cardiovascular risk reduction with vitamin D supplementation include the inhibition of smooth muscle proliferation, the suppression of vascular calcification, the down-regulation of inflammatory cytokines, the up-regulation of anti-inflammatory cytokines, and the negative regulation of the renin-angiotensin-aldosterone system (RAAS). [21-26] Inappropriate stimulation of the RAAS is associated with hypertension, myocardial infarction and stroke. [14] Calcitriol treatment has been shown to reduce blood pressure, renin activity and angiotensin II levels. [27] The effects of vitamin D deficiency on the cardiovascular system are outlined in Figure 2.

A systematic review and meta-analysis looked at the relationship between the naturally occurring level of vitamin D and cardiometabolic disorders including CVD, diabetes and metabolic syndrome. [28] Twenty-eight studies were selected, including nineteen cross-sectional studies, three case-control studies and six cohort studies, analysing 99,745 patients. [28] High vitamin D levels were associated with a 43% reduction in cardiometabolic disorders. [28] There was a significant association between high levels of vitamin D and risk of having cardiovascular disease (33% reduction), type two diabetes (55% reduction) and metabolic syndrome (51% reduction). [28] Vitamin D supplementation has been shown to have a protective effect in limited studies of CVD, but further research is needed. [29]

Diabetes

The research surrounding the interaction between vitamin D supplementation and type two diabetes mellitus is controversial. To date, there have been no adequate, large and prospective, randomised controlled trials to test the efficacy of vitamin D supplementation for the prevention and treatment of type two diabetes mellitus. The current available data allows a recommendation that further research be conducted to determine whether adequate vitamin D levels may prevent the onset of type two diabetes. Type one diabetes mellitus will not be discussed in this review.

Insulin resistance has been associated with low serum vitamin D, which improved after treatment with vitamin D. [30-36] One study demonstrated a positive relationship between calcitriol and insulin sensitivity, and a negative effect of vitamin D deficiency on beta cell function. [12] These studies are limited by small sample size, subject selection and lack of randomisation. However, there was a clinical correlation and it is worthwhile investigating further the possibility of improvement in insulin sensitivity with vitamin D supplementation. Serum blood sugar levels and prevalence of type two diabetes mellitus increases with age, and vitamin D levels tend to fall with age. [37,38] Type two diabetes is associated with systemic inflammation, which may induce beta-cell dysfunction and death. [39] Several studies show that vitamin D could directly affect beta-cell growth and differentiation via modulation of systemic inflammation and the immune response. [39-42] One of these was a double-blinded 39-week follow-up study of interleukin-1 blockade with anakinra. [40] Although being limited by small sample size and limitations in subject selection, the study showed improvement in markers of systemic inflammation 39 weeks after treatment withdrawal. [40]

Several studies indicate that calcitriol regulates beta-cell function by regulating intracellular calcium levels. This is thought to influence insulin secretion, increase beta-cell resistance to apoptosis and increase beta-cell replication. Calcitriol is thought to bind to nuclear VDRs in the beta-cell to increase preproinsulin mRNA level. Research to support this hypothesis is limited, due to being conducted in rats. [39,43-45]

Obesity and hyperlipidaemia

Studies have shown that high body mass index (BMI) is associated with low serum vitamin D levels. [46] Vitamin D is fat soluble and readily stored in adipose tissue. [1,47] Sequestration of cholecalciferol in adipose tissue reduces bioavailability in obese individuals. [1,48,49] The distribution of fat may be associated with vitamin D status, but this relationship may be dependent on metabolic factors. [49]

Vigorous physical activity is a strong and modifiable contributor to vitamin D status. This may be due to sun exposure correlated with physical activity, however, a number of studies have shown the positive effect on vitamin D status may be independent of sun exposure. [50-54] Further research is needed to clarify this.

A large, prospective study of the modifiable predictors of vitamin D

status was conducted using 2,621 healthy individuals aged 55-74 in the USA. [46] Predictors of low vitamin D status were found to be low dietary vitamin D intake, BMI > 30kg/m^2, physical inactivity and low milk and calcium supplement intake. [46] There is an inverse relationship between apolipoprotein A-I and high density lipoprotein cholesterol with vitamin D levels in a survey of 358 Belgian people. [55] This relationship was not shown to be causal, but further research is warranted to see if vitamin D provides this cardioprotective link.

Vitamin D deficiency may increase insulin resistance and thereby increase circulating lipids, but supplementation has not been shown to improve circulating lipid levels. [56,57] Statin therapy increases the circulating levels of 7-dehydrocholesterol, leading to an increase in conversion to vitamin D (in the presence of UVB radiation), and therefore vitamin D levels. [58-61]

Hypertension

To date, there are few good quality randomised controlled trials looking at the relationship between vitamin D levels and blood pressure. There is weak evidence to suggest that there may be a relationship between the two, however, further research is needed to draw any conclusions that may change the management of blood pressure.

Vitamin D may regulate blood pressure via an interaction with the RAAS, which is often activated in hypertension. Calcitriol is a known negative regulator of the RAAS. [11,21] The effects of vitamin D on the suppression of renin activity may be due to increased intracellular calcium levels. [62] It is hypothesised that vitamin D regulation of renin is independent of calcium metabolism, by regulating renin mRNA production with VDRs. [11] This study was completed using a line of cells derived from transgenic mice kidney tumours. [11]

There are some studies which show an inverse correlation between vitamin D levels and blood pressure. [63-66] A meta-analysis which included eleven randomised controlled trials (small, variable methodological quality) found weak evidence to support a small effect of vitamin D on blood pressure in studies of hypertensive patients. [67] There was a small statistically significant reduction in diastolic blood pressure, and no significant reduction in systolic blood pressure in hypertensive subjects supplemented with vitamin D or UV radiation. [67]

Several studies have shown differing results when trying to establish a relationship between vitamin D intake and hypertension. [10] There are two cross-sectional studies that have been completed using the Third National Health and Nutrition Examination Survey data. One study demonstrated a significant difference in systolic blood pressure and pulse pressure between the highest and lowest quintile groups divided by vitamin D level. [10,63] Participants with hypertension were excluded from analysis. [63] Another study revealed increased systolic blood pressure with reducing levels of vitamin D, and a twenty percent reduction in systolic blood pressure in those with vitamin D levels greater than 80 nmol/L compared with those with less than 50 nmol/L. [64] Both of these studies had a good sample size, but were limited by the methods of the study. [10] A cross-sectional study using a different data set with low prevalence of vitamin D deficiency showed no association between systolic blood pressure and vitamin D level. [10,65] A different study did not show any significant relationship between vitamin D levels and blood pressure after adjusting for confounding variables, however, this may have been due to low estimated vitamin D intake. [10,68]

Conclusion

Vitamin D is an important molecule to consider in the pathogenesis of cardiovascular disease. Current research shows that vitamin D deficiency contributes to cardiovascular morbidity and mortality. The mechanisms proposed for this include direct actions on the heart and vasculature, as well as by increasing the risk of cardiovascular risk factors such as diabetes, obesity, hyperlipidaemia and hypertension. Further research is needed to clarify the influence of vitamin D on cardiovascular disease and its risk factors, and whether vitamin D is an efficient, cost-effective and safe intervention to prevent cardiovascular morbidity and mortality.

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Conflicts of interest

None declared.

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