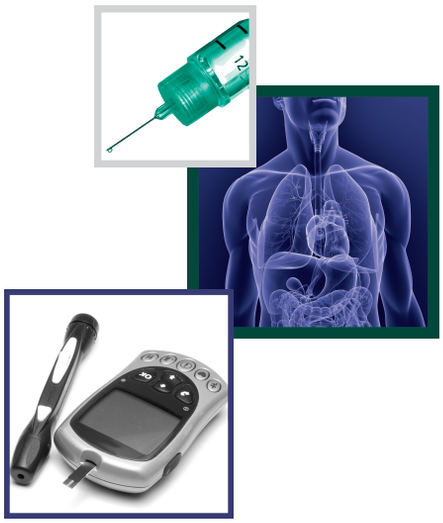
EDITORIAL

Vitamin D deficiency and cardiovascular disease: the missing link



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Historically, vitamin D has been associated primarily with bone health, and typically, a marked deficiency causes rickets in children and osteomalacia in adults. There is a well-described association between vitamin D deficiency and muscle weakness and skeletal pain [1,2]. However, the vitamin D receptor (VDR) is expressed not only in bone but also ubiquitously in other tissues and cells, including lymphocytes, cardiomyocytes, the endothelium, pancreatic β-cells and foam cells [3,4]. Thus, vitamin D may regulate suppressor T-cell populations [5], modulating immune function, inhibiting cellular growth, stimulating insulin secretion and inhibiting renin production, providing a potential mechanistic basis for a range of common conditions such as asthma [6], Type 1 diabetes [7], multiple sclerosis [8], cancer [9] and cardiovascular disease.

The focus of this article is to explore the role of vitamin D deficiency in relation to cardiovascular disease. Estimates of vitamin D deficiency in the UK suggest it may affect approximately 61–87% of adults, depending on the season [10]. Several large observational studies have linked vitamin D deficiency with cardiovascular disease [11–14].

The Framingham Offspring Study

The Framingham Offspring Study is a landmark epidemiological study, which longitudinally followed up individuals (n = 1739) for a mean length of 5.4 years [12]. There was no prior history of cardiovascular disease in this cohort, and prespecified baseline 25-hydroxy vitamin D (25[OH] vitamin D) levels were used to stratify deficiency (<10ng/ml, <15 ng/ml and ≥15 ng/ml). During the follow-up period, a composite of cardiovascular events were classified as myocardial infarction, cardiac insufficiency, angina, stroke, transient ischemic attack, peripheral claudication or heart failure. After multivariate adjustment for conventional risk factors, those with 25(OH) vitamin D levels of less than 15ng/ml had a hazard ratio of 1.62 (95% CI: 1.11–2.36; p = 0.01) for incident cardiovascular events compared with those with 25(OH) vitamin D levels of 15 ng/ml or higher. This increased risk was even more evident in those with hypertension (hazard ratio: 2.13 [95% CI: 1.30–3.48]). Furthermore, there was a graded increase in cardiovascular risk across the categories with a hazard ratio of 1.53 (95% CI: 1.00–2.36) for

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levels of 25(OH) vitamin D of 10 to less than 15 ng/ml and 1.80 (95% CI: 1.05–3.08) for levels of 25(OH) vitamin D of less than 10 ng/ml. For comparison with traditional risk factors, a recent meta-analysis demonstrated that for every 1 standard deviation increase in triglycerides and non-high-density lipoprotein cholesterol (HDL-C), the hazard ratio for coronary heart disease was 1.37 (95% CI: 1.31–1.42) and 1.56 (95% CI: 1.47–1.66), respectively [15]. While these studies provide compelling evidence for a strong association of vitamin D deficiency with cardiovascular disease, the key issue remains as to whether correction of this deficiency can slow progression or even prevent cardiovascular events. The Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial has unfortunately been terminated with the withdrawal of rosiglitazone. However, recruitment is now underway for the Vitamin D and Omega-3 Trial (VITAL), which is randomizing 20,000 healthy older men and women in the USA to receive either 2000 IU of vitamin D_3 (cholecalciferol) daily or placebo, as well as 1 g of marine omega-3 fatty acids per day or placebo, over 5 years to assess the benefits on the primary prevention of cancer and cardiovascular disease.

Diabetes

The incidence of Type 1 diabetes increases with latitude and during the winter months (owing to declining sun light and consequently vitamin D) [16]. Indeed, the Finnish birth cohort study showed a causal relationship [17]. Over 10,000 individuals were followed up for 30 years and children who were supplemented with 2000 IU daily of vitamin D in the first year of life had a relative risk of 0.22 (95% CI: 0.05–0.89) for the development of Type 1 diabetes when compared with those who were not supplemented. A meta-analysis of five observational studies has confirmed this risk reduction [18]. Activated vitamin D (1,25[OH]$_2$ vitamin D) has immunomodulatory effects, as seen in experimental models of Type 1 diabetes [19], and may represent a potential treatment to prevent the development of Type 1 diabetes. In addition, pancreatic β-cell function is modulated through the VDR. Insulin sensitivity has been shown to improve significantly in adults with impaired fasting glucose who were randomized to calcium and vitamin D supplementation [20]. Furthermore, baseline 25(OH) vitamin D levels in nondiabetic subjects have been demonstrated to predict future glycemia and insulin resistance [21]. A recent meta-analysis established that the risk of Type 2 diabetes may be reduced by 55% in individuals with high levels of vitamin D [22]. However, in two blinded, randomized, placebo-controlled trials of vitamin D and/or calcium supplementation for the secondary prevention of osteoporotic fractures, no effect on the development of Type 2 diabetes was observed [23,24], although the dose of vitamin D may have been insufficient to modulate the diabetes risk. Vitamin D deficiency itself may be related to Type 2 diabetes, thus suggesting bidirectional causality [14]. This association and possible causality of Type 2 diabetes via vitamin D deficiency merits further investigation, in particular, to assess whether an interventional trial in high-risk individuals with impaired glucose tolerance may prevent diabetes. Of course, improving glycemic control may well lower the risk of cardiovascular disease.

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Hyperlipidemia

Interestingly, 7-dehydrocholesterol provides a common metabolic pathway for vitamin D and cholesterol, as it is a precursor for both. Lower levels of 25(OH) vitamin D have been associated with lower HDL-C and hypertriglyceridemia [11,25]. In a study of patients with acute coronary syndrome, treatment with atorvastatin was not only associated with reductions in total cholesterol and triglycerides but also a very marginal (~3ng/ml) elevation of vitamin D [26]. An even more pronounced increase has been demonstrated with rosuvastatin, with a mean rise of 22.3 ng/ml in 25(OH) vitamin D after 8 weeks of treatment [27]. Furthermore, when considering the pathogenesis of atherosclerotic plaque formation, a recent study in macrophages from obese, diabetic, hypertensive patients demonstrated that culturing with 1,25(OH)$_2$ vitamin D suppressed foam cell formation by reducing acetylated or oxidized low-density lipoprotein cholesterol uptake, while deletion of the VDR in these macrophages accelerated foam cell formation induced by modified low-density lipoprotein [28]. Interestingly, statins have beneficial effects, not only on increasing bone mass [29,30] but also reducing fracture rates [31,32]. Whether these effects are entirely due to elevation of vitamin D and/or modulation of the VDR is not clear.

Hypertension

Vitamin D is known to modulate the renin–angiotensin system and in experimental studies *VDR*-knockout mice have high levels of renin, angiotensin and aldosterone, suggesting that vitamin D may be a potent inhibitor of the renin–angiotensin system axis [33–35]. Indeed, the National Health and Nutrition Examination Survey (NHANES) III study [36] showed lower blood pressure in those in the highest deciles of 25(OH) vitamin D, although there was some attenuation due to differences in race and BMI. Vitamin D_3 and calcium supplementation has also been demonstrated to reduce blood pressure compared with calcium supplementation alone [37].

Obesity & metabolic syndrome

25-hydroxy vitamin D is sequestered in adipose tissue and this may partly explain the low levels associated with obesity [38]. Hence, release of this inactive form into the circulation for transformation to active vitamin D may be reduced [38]. In one study, the content of 7-dehydrocholesterol in the skin of obese and nonobese subjects did not differ significantly between groups, nor did its conversion to 25(OH) vitamin D, after irradiation *in vitro* [39]. Therefore, this suggests that the likely mechanism of reduced bioavailability of vitamin D in the obese group is its deposition in adipose tissue [38]. Maki *et al.* found that 25(OH) vitamin D was independently associated with HDL-C and the metabolic syndrome in 257 men and women [25]. The association with the metabolic syndrome is well known and highlights that at-risk groups for vitamin D deficiency are not only those who are less ambulatory or those who have pigmented skin [40,41].

Other cardiovascular disease outcomes

Vitamin D deficiency has been related to coronary artery calcification, myocardial infarction, stroke and congestive cardiac failure [42,43]. In a recent proteomics study, increased levels of vitamin D-binding protein were found in patients admitted with ST elevation myocardial infarction (STEMI); moreover, fresh thrombotic plaques, obtained during primary angioplasty, showed increased expression of vitamin D-binding protein [44].

One large noteworthy trial was the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, which assessed a consecutive cohort of 3258 individuals scheduled for coronary angiography [13]. Sudden cardiac death and death due to heart failure were independently and inversely associated with 25(OH) vitamin D, and stroke was related to both 25(OH) vitamin D and 1,25$(OH)_2$ vitamin D levels [13]. The NHANES III study subgroup (n = 3408) analysis supported these findings as 25(OH) vitamin D was inversely associated with all-cause mortality over a mean period of 7.3 years [45]. Compared with individuals with 25(OH) vitamin D levels of 40 ng/ml or more, in those with 25(OH) vitamin D of less than 10 ng/ml, the adjusted risk was approximately 83% higher [45]. In a recent study, vitamin D deficiency was associated with an increased amputation risk in veterans with peripheral arterial disease [46].

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Assessment & replacement of vitamin D

25-hydroxy vitamin D is used to determine vitamin D status, as it accurately represents body stores [42], whereas the active form (1,25$[OH]_2$ vitamin D) has a short half-life and levels may alter over a 24-h period. Current 'healthy levels' of vitamin D (25[OH]) are recommended to have levels greater than 30 ng/dl; however, this advice is based on data derived from bone metabolic health (see **Table 1**) [47,48], rather than those levels that may be ideal in relation to cardiovascular disease. Hence, the current recommended daily amount of vitamin D intake in the UK is woefully inadequate (400 IU [10 µg] for adults) and cannot even prevent metabolic/bone complications [49] in the absence of adequate synthesis via sunlight. Furthermore, the current guidance for treatment and long-term

Table 1. Serum 25-hydroxy vitamin D concentrations and status.

25(OH) vitamin D concentration†	25(OH) vitamin D status
<10 ng/ml	Severely deficient
10 to <20 ng/ml	Deficient
20 to <30 ng/ml	Insufficient
≥30 ng/ml	Adequate
≥100 ng/ml	Possible toxicity

†To convert to nmol/l, multiply by 2.5.
25(OH) vitamin D: 25-hydroxy vitamin D.

replacement for deficiency or insufficiency is 1000–2000 IU of calciferol daily [49]. In our experience, this is inadequate as it increases vitamin D levels by approximately 10% from baseline [Alam U, Asghar O & Malik RA, Unpublished Data]. This has considerable repercussions when interpreting the outcomes of trials where an inadequate replacement of vitamin D may result in no cardiovascular benefit, which of course will be inappropriately interpreted as no benefit of vitamin D. A detailed review of vitamin D replacement is beyond the scope of this article and readers are advized to refer to the review article by Pearce *et al.* [49].

Conclusion

From observational studies, the risk of cardiovascular mortality is increased twofold in those deficient in 25(OH) vitamin D, compared with those with 'adequate' levels, although the definition of adequate may need modification in the context of nonbone/metabolic conditions. Prospective, randomized, placebo-controlled trials in cardiometabolic syndromes are urgently required to establish whether vitamin D replacement lowers cardiovascular risk.

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