The emerging role of vitamin D and its receptor in the pathogenesis of acute coronary syndromes

Background

Our understanding of the pathophysiology of acute coronary syndromes and, in particular, the interplay of a number of complex parallel processes, continues to develop.[1] These processes include inflammation, thrombosis and matrix turnover with potential gene and environmental influences. Vitamin D, known primarily as a hormone of bone metabolism, can affect the transcription of a number of genes which play a pivotal role in both the development of acute coronary syndromes and the pathogenesis of coronary artery disease (CAD). The purpose of this review is to examine the mechanisms by which vitamin D and the vitamin D receptor (VDR) might influence the development of acute coronary syndromes.

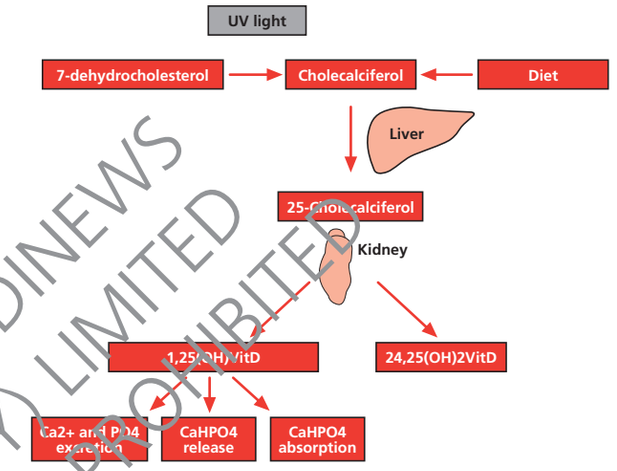
Overview of vitamin D physiology

The precursor for the active form of vitamin D is cholecalciferol (figure 1). This is synthesised in the skin from 7-dehydrocholesterol and requires UV light. The reliance of this process on UV light predisposes darker skinned people to vitamin D deficiency, particularly if they are living in the northern hemisphere. Cholecalciferol can also be derived from the diet, particularly from oily fish. The major circulatory form of vitamin D, 25 hydroxyvitamin D (25(OH)D), is hydroxylated in the liver but the active form of vitamin D, 1,25 dihydroxyvitamin D ($1,25(OH)_2D_3$), is synthesised in the kidney. The latter binds its receptor VDR, which translocates to the nucleus. VDR has been found to localise to a number of different cell types and it was this finding that initially prompted the speculation that vitamin D may have actions beyond calcium and phosphate haemostasis. It has now been found that $1,25(OH)_2D_3$ via the VDR can affect the transcription of a broad number of genes in many cell types including those involved with inflammation and immunity (see below).

The vitamin D receptor

The human VDR gene has nine exons and is known to have in excess of 40 polymorphisms, some of which have been implicated in disease.[2] Of these, the most commonly studied are FokI, BsmI, ApaI and TaqI. The FokI polymorphism is of functional significance: we have recently shown in peripheral blood mononuclear cells that the FokI and TaqI genotypes are independent predictors of VDR messenger ribonucleic acid (mRNA) levels, whilst for VDR protein levels the independent determinants were TaqI genotype and 1-25(OH_2) D levels.

Figure 1. Vitamin D synthesis and hydroxylation



The concept of vitamin D deficiency and insufficiency

25(OH)D rather than 1-25(OH_2) D is used to define levels of deficiency since the former has a half-life of 21 days rather than the few hours of the latter.[3] Vitamin D deficiency is defined as a 25(OH)D of less than 11 ng/ml (20 nmol/L) and is the level below which rickets and osteomalacia occur. This definition is based on bone metabolism and, since vitamin D has other actions, this definition may be too crude. Furthermore, calcium haemostasis is dependent on a negative feedback loop between vitamin D and parathormone – the latter being suppressed by vitamin D supplementation. Previous investigators have demonstrated that supplementation with vitamin D fails to result in further suppression of parathormone when 25(OH)D levels are greater than 20 ng/ml (50 nmol/L). Thus, insufficiency has been defined as 25(OH)D levels less than this value.[4]

Vitamin D and acute coronary syndromes

Inflammation and immunity

Inflammation plays a pivotal role in the pathogenesis of acute coronary syndromes and atherosclerosis *per se*.[5,6]

1-25(OH_2) D has been shown to have anti-inflammatory and immunosuppressive properties which are mediated by its abilities to modulate a number of cytokines and molecules.[7] 1-25(OH_2) D has been shown to suppress transcription of inducible cytokine genes in activated T cells.[8] It has also been shown to inhibit binding of[9] and to downregulate levels of[10] NF-kappa B – another nuclear factor which upregulates transcription of a number of cytokine genes.

The CD40 receptor, which is constitutively expressed on the surface of monocytes, macrophages and endothelial cells through interaction with CD154 on T lymphocytes and platelets, induces an intense inflammatory response in the vascular wall. This effect is mediated through the upregulation of adhesion molecules, matrix metalloproteinases (MMPs), cytokines and tissue factor. Intriguingly, 1,25(OH)D has been shown to downregulate CD40 expression on dendritic cells.[11] Whether similar modulation occurs in cells involved in plaque rupture and thrombosis is unknown. Vitamin D and its analogues have been shown to inhibit various processes (e.g. T cell proliferation, monocyte differentiation), all known to be involved in both the pathogenesis of ischaemic heart disease (IHD) and susceptibility to acute coronary syndromes.[5,6]

Thrombosis

The extent, stability, and type of thrombus which is formed following plaque rupture will determine the clinical spectrum of the plaque event – ranging from asymptomatic, through acute coronary syndromes, to death. Any factors which can determine this haemostatic milieu will potentially modulate the clinical manifestations of a plaque event. 25(OH)D and its analogues have recently been shown to downregulate tissue factor and upregulate thrombomodulin in monocytic cells countering the effects of tumour necrosis factor and oxidised low-density lipoprotein (LDL).[12] The potential pro-thrombotic tendencies of relative vitamin D deficiency are further highlighted by the findings that vitamin D may modulate prostaglandin E_2 production by fibroblasts,[13] prostacyclin production by endothelial cells, platelet aggregation directly,[14] and it might also modulate differentiation and proliferation of a human megakaryoblastic leukaemic cell line.[15] Any one or all of these mechanisms may be important in determining outcomes following plaque rupture.

MMP turnover

Plaque cap proteolysis (as determined by the relative expressions of MMPs and tissue inhibitors of metalloproteinases [TIMPs]) is thought to play an important role in plaque cap proteolysis and thus plaque instability.[16-19] Our group has found that vitamin D status was the sole determinant in 171 Bangladeshi volunteers of circulating levels of MMP9 (inversely) and an independent determinant of C-reactive protein (inversely). Furthermore, determinants of TIMP-1 were MMP9, systolic blood pressure (directly) and vitamin D receptor genotype (VDR Taq tt genotype). Significant reductions in MMP9 (-68%), TIMP-1 (-38%) and C-reactive protein (-23%) concentrations followed vitamin D supplementation, such that the net effect was towards a reduction in proteolytic activity.[20] Studies on fibroblasts derived from human rheumatoid arthritic joints suggest that 1,25(OH_2)D and its analogues might influence expression of MMP9, MMP3 and TIMP1 both basally and in response to interleukin 1 stimulation.[13]

Renin angiotensin system

There is mounting evidence for the role of angiotensin II in the pathogenesis of atherosclerosis.[21] Previously, clinical studies have demonstrated an inverse relationship between 1,25 dihydroxyvitamin D3 (1,25$[OH]_2D_3$) – the active component of vitamin D – and plasma renin activity in both normotensive and hypertensive men.[22-26] Indeed vitamin D supplementation has been shown to lower blood pressure,[27,28] and reduce plasma renin activity and angiotensin II levels in patients with hyperparathyroidism.[29,30] Furthermore, 1,25$(OH)_2D_3$ has been shown to suppress renin expression in cell culture.[31] VDR knockout mice have increased levels of plasma renin activity and angiotensin II.[32]

Endothelial function

Nitric oxide – which has been shown to be potentially antiatherogenic and may also be regulated by 1-25(OH_2) D – can be shown to be induced *in vitro* in a number of cell lines by 1-25 (OH_2) D.[33,34]

Interplay between VDR genotype and vitamin D insufficiency on plaque stability

We have recently studied the influence of VDR polymorphisms and 25(OH)D on prognosis in 219 white patients admitted to our coronary care unit (CCU) with non-ST elevation acute coronary syndromes.[35] The major end points of the study were death, acute myocardial infarction and readmission with unstable angina over the following year. Despite 50% of patients being vitamin D-insufficient, no association was found between vitamin D level and acute coronary syndrome outcome. In contrast, Kaplan Meier analysis revealed a significantly worse prognosis for those patients with the AA VDR Apa genotype than for those positive for the a allele (cumulative event free survival [95% survival standard error]; 0.47 [0.07] *vs.* 0.74 [0.04]; p=0.0002). Stratification by 25(OH)D deficiency showed that this excess risk in patients homozygous for AA was seen almost exclusively in those who were 25(OH)D deficient (as defined by a 25[OH]D level of less than 50 nmol/L [20 ng/ml]), such that their cumulative event-free

survival (95% survival standard error) was only 0.36 (0.10), which was significantly lower than other genotypes with or without vitamin D deficiency (p=0.0014). The hazard ratio (95% CI) associated with the AA genotype was 2.34 (1.28–4.29) by Cox proportional hazard modelling adjusted for risk factors including diabetes, troponin status, left ventricular function and vitamin D status. In addition, compared with patients without events, in those with events, there was significant excess of the bb VDR Bsm genotype (11.2% *vs.* 22.7%; p=0.022) and the tt VDR Taq genotype (9.9% *vs.* 21.2%; p=0.027) but not of the ff VDR Fok genotype (13.2% *vs.* 9.4%; p=0.61).

Vitamin D insufficiency – an important risk factor in South Asian IHD?

People of South Asian origin are at increased risk of IHD compared to the white population. Previous investigators have shown that healthy South Asian controls have higher levels of inflammation, as determined by C-reactive protein, than matched white controls.[36] Furthermore, epidemiological observation studies from Canada suggest that prevalence of IHD, as determined by carotid intimal thickness assessments, is higher in whites than in South Asians but that acute myocardial infarction is higher in South Asians than in whites.[37] Indeed, it is the excess IHD standardised mortality rates in South Asians which most convincingly demonstrate an increased risk in this population.[37] This infers that South Asians may be more prone to plaque instability rather than atherosclerosis *per se*. We and others have demonstrated that vitamin D insufficiency is a significant problem in South Asians living in the northern hemisphere.[20] It is tempting to postulate that this vitamin D insufficiency may contribute to the increased risk of acute myocardial infarction in South Asian populations by the mechanisms outlined above. Furthermore, if such a mechanism is important, then it provides, an easily treatable condition. Needless to say, much more evidence is required to test this hypothesis further.

Summary

Evidence is beginning to accumulate implicating vitamin D and its receptor in the pathogenesis of both coronary artery disease and acute coronary syndromes. Many of the processes involved in atherogenesis and plaque stability can be affected by vitamin D and its receptor. Whether such mechanisms are clinically relevant in atherosclerosis requires further investigation.

Conflict of interest

None declared.

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