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EDITORIAL

Vitamin D and Cardiovascular Disease

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Vitamin D is a lipid-soluble, steroid hormone that takes two major forms: vitamin D2 (ergocalciferol), found in plants and fortified foods, and vitamin D3 (cholecalciferol), which, in humans, is largely derived from conversion of dehydrocholesterol in the skin, although also acquired from various food sources [1]. Vitamin D3 is converted by 25-hydroxylase in the liver to its inactive metabolite, 25-hydoxyvitamin D3 [25(OH)D], which has a long half-life and is the main measurable form in blood. This, in turn, is converted in the kidneys by 1α-hydoxylase to the bioactive metabolite, 1,25 $(OH)_2$ vitamin D_3 [1,25$(OH)_2$D]. 1,25$(OH)_2$D binds to the nuclear vitamin D receptor (VDR) which regulates transcription of numerous target genes. Although vitamin D is best known for its role in calcium homeostasis and bone metabolism, the hydroxylase enzymes and VDR are expressed in many different cell types, including endothelial and smooth muscle cells, cardiomyocytes, fibroblasts and inflammatory cells. It follows that vitamin D is increasingly understood to mediate diverse actions throughout the cardiovascular system.

Vitamin D deficiency is commonly defined as a plasma 25(OH)D level of less than 20 ng/mL (50 nmol/L), and insufficiency as a level of 21–29 ng/mL. Estimates place nearly 30–50% of the global population as having low vitamin D levels, with rapidly increasing prevalence over recent decades [2]. For some time now, it has been recognised that vitamin D deficiency associates with cardiovascular risk factors (e.g. diabetes, hypertension) and disease, most strikingly myocardial infarction (MI) and heart failure, although proof of causation remains lacking [1]. An extensive body of basic and preclinical research has elucidated pleiotropic salutary effects of vitamin D on molecular pathways and cellular targets involved in cardiovascular pathophysiology. In anticipation that vitamin D supplementation may, therefore, be useful to prevent and/or treat MI and heart failure, several clinical intervention studies have been performed. Unfortunately, to date, these have generally been small, flawed and inconclusive.

Preclinical Evidence for Vitamin D's Importance in Cardiovascular Pathophysiology

The expression of VDR in different cells within the heart and blood vessels has been known about for over three decades. In mammals, VDR does not appear to be integral to normal heart development, as atrial and ventricular specification are seemingly unaffected in *VDR*-null mice. However, liganded VDR, such as by binding to 1,25$(OH)_2$D, has been shown to have anti-hypertrophic actions on cardiomyocytes in vitro, also reducing natriuretic peptide release and inhibiting proliferation [3]. Animals deficient in vitamin D are predisposed to cardiomegaly, cardiac hypertrophy and fibrosis, and, importantly, these effects are independent of calcium and phosphate. Conversely, administration of 1,25$(OH)_2$D or its less hypercalcaemic analogues to small animal models of hypertrophy (e.g. genetic, transaortic constriction pressure overload, angiotensin II or salt-induced hypertension) has resulted in inhibition of myocardial hypertrophy, usually accompanied by improvement in indices of cardiac

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contraction and/or relaxation [4,5]. One proposed mechanism for the anti-hypertrophic effect of liganded VDR is that it suppresses renin gene transcription in the heart [6]. Other data suggest that 1,25$(OH)_2$D mediates its actions on cardiomyocyte proliferation via transcriptional control of cell cycle regulator genes. Meanwhile, vitamin D binding to VDR also localises to t-tubules in cardiomyocytes, where it may interact with sarcoplasmic reticulum calcium ATP-ase to stimulate calcium uptake and increase myocyte contractility.

Cardiac fibrosis often accompanies cardiac hypertrophy and is a key contributor to myocardial dysfunction in advanced cardiomyopathy. Pro-fibrotic and pro-hypertrophic states in the heart induce an increase in VDR expression in cardiac cells, and this appears to drive a negative feedback loop which suppresses the expression of pro-fibrotic and hypertrophic mediators in cardiomyocytes and fibroblasts. Intervention studies with 1,25$(OH)_2$D in mouse and rat models of cardiac fibrosis have demonstrated its ability to reduce interstitial and perivascular fibrosis, and potentially oxidative stress, apoptosis and inflammation [7,8]. Among potential mechanisms, active vitamin D regulates myocardial extracellular matrix integrity by acting on the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [9]. It has also been found to modulate the DNA damage sensor, poly(ADP-ribose) polymerase (PARP-1) [7], and microRNAs (miRs) -29b and -30c which are known regulators of pro-fibrotic genes [8].

In this issue of the Journal, Le et al. show benefits of 1,25$(OH)_2$D in a mouse model of MI [10]. Compared to vehicle control, its daily intraperitoneal administration improved left ventricular wall thickness and contractile function 14 days after permanent coronary ligation. This was accompanied by reduction in proliferating cardiomyocytes and non-cardiomyocytes in the heart, with a trend for reduced fibrotic scar area but no difference observed in cardiomyocyte size. These authors have a special interest in cardiac stem/progenitor cells (CPCs), and they focussed on how vitamin D modulates a population of mesenchymal stem cell-like CPCs, called cardiac colony-forming unit fibroblasts (cCFU-Fs), which they have previously identified in murine [11] and human hearts [12].

Mouse cCFU-Fs originate from the proepicardium in development, before adopting a perivascular location in the subepicardium and myocardial interstitium. They express stem cell antigen-1 (Sca-1) and platelet-derived growth factor receptor-alpha (PDGFRα), but not the endothelial marker, CD31 (i.e. Sca-1$^+$ PDGFRα$^+$CD31$^-$) [10,11]. Although their roles in normal cardiac homeostasis and disease remain unknown, cCFU-Fs have multilineage differentiation capacity, adopting cardiomyocyte, endothelial, smooth muscle or fibroblast properties under inductive culture conditions. Le et al. now show that cCFU-Fs express VDR, and respond to 1,25$(OH)_2$D in vitro by slowing their clonogenic growth and proliferation, and by suppressing their transformation into fibroblasts under stimulation by transforming growth factor-beta 1 [10]. This is concordant with previous work that identified that vitamin D decreases expression of pro-fibrotic factors and increases expression of anti-fibrotic factors from other multipotent mesenchymal progenitor cells [13]. The implication proposed by Le et al. is that cCFU-Fs are another cellular target through which 1,25$(OH)_2$D may mediate its protective effects on cardiac fibrosis and remodelling after MI, and, presumably, in other cardiac diseases also. Unfortunately, the current study falls short of directly examining this mechanistic possibility in vivo. More definitive studies are, therefore, needed to understand precisely what roles cCFU-Fs play in cardiac remodelling after MI, whether they are adaptive or maladaptive, and how this interesting population of progenitor cells can be favourably modulated to support cardiac structural and functional integrity.

Beyond the myocardium, vitamin D-VDR signalling has also been investigated in atherosclerosis. Studies have shown accelerated plaque development in vitamin-D deficient and *VDR*-null mice, and anti-atherosclerotic effects from treatment of *ApoE*-null mice with oral 1,25$(OH)_2$D (reviewed by Muscogiuri et al. [1]). Different mechanisms for these results include vitamin D's immunosuppressive actions on innate and adaptive immune cells that mediate plaque inflammation, and its dampening of macrophage uptake of modified low-density lipoprotein cholesterol and, therefore, foam cell formation.

Clinical Associations Between Vitamin D Deficiency and Cardiovascular Disease

In addition to the preclinical observations summarised above, numerous lines of clinical evidence have linked sunlight exposure and vitamin D to cardiometabolic risk factors and cardiovascular disease. Epidemiological data have long associated further distance from the equator with higher prevalence of diabetes, hypertension and ischaemic heart disease, while rates of ST-elevation myocardial infarction and cardiac death are known to peak during winter months when there is less sunlight [14]. Multivariate adjusted-analysis from the Framingham Offspring Heart Study (n = 1739) found that healthy individuals with a 25(OH)D level of less than 15 ng/mL had a 60% higher risk of future major cardiovascular events [15]. Meanwhile, in the Health Professionals Follow-up Study (n = 18,225 men), normal vitamin D levels (>30 ng/mL) were associated with approximately half the risk of MI over 10 years, after adjusting for traditional cardiovascular risk factors [16]. Contemporary studies report prevalence rates of low vitamin D in MI patients that range between 74 and 96% [1,17], and risk of acute MI has consistently been shown to rise with decreasing vitamin D quartiles [18]. Furthermore, not only is hypovitaminosis D a seemingly independent risk factor for acute MI, it also appears to predict worse outcomes, including higher rates of mortality and hospitalisations for heart failure and recurrent MI [17].

Similarly, a relationship between vitamin D deficiency and heart failure has been inferred from case series of cardiomyopathy in children suffering from rickets, and from large community cohorts of adults [19,20]. Analysis of the Inter-Mountain Healthcare system showed that the risk-adjusted hazard ratios for incident heart failure were 1.3 and 2.0 for 25 (OH)D levels of 16–30 ng/mL and <15 ng/mL, respectively [19]. An Israeli study by Gotsman et al. reported that low vitamin D levels were more prevalent in patients with heart failure than controls, and that they also predicted higher mortality [20]. Finally, in a registry of 3299 patients referred for coronary angiography, severe vitamin D deficiency (<10 ng/mL) was associated with a 2.8-fold adjusted risk of death from heart failure and a 5-fold adjusted risk of sudden cardiac death [21].

Vitamin D Supplementation and Cardiovascular Outcomes

While vitamin D deficiency has generally been held up as an independent risk factor for MI, heart failure and their associated adverse outcomes, it is still far from certain that it actually contributes to disease pathogenesis. There are many possible confounding factors that have been unaccounted for in the aforementioned observational studies, and it is, therefore, possible that low vitamin D status is simply a summary marker of other cardiovascular risk factors, or a surrogate for poor health, nutrition and frailty. There also remains a paucity of randomised evidence to support benefits of vitamin D supplementation on cardiovascular outcomes in both primary and secondary prevention settings. Primary prevention randomised controlled studies have, so far, been inconclusive, showing either non-significant trends for reduced cardiovascular event rates and mortality [22], or no benefit [23–25]. Limitations of these studies have surrounded inadequate statistical power, suboptimal dosing, low adherence rates and short length of follow-up. As new information has come to hand, guidelines have also changed with respect to the desired frequency of vitamin D dosing (e.g. daily vs monthly). Recently, Scragg et al. randomised 5108 adults from the general population to monthly, high-dose oral vitamin D (200,000 IU first dose, 100,000 IU thereafter) or placebo for a median of 3.3 years [25]. No significant differences were observed for the combined endpoint of incident cardiovascular disease or death in the overall study population, or in the pre-specified subgroup with low vitamin D levels. There are even less prospective data to inform about vitamin D's use in the secondary setting of established cardiovascular disease, although it was found to improve ejection fraction and end-diastolic dimension, but not 6-minute walk distance, in the placebo-controlled VitamIN D treatIng patients with Chronic heArT failurE (VINDICATE) study of 229 patients with heart failure, reduced ejection fraction and vitamin D deficiency [26]. There is, therefore, a particular need for larger trials to investigate vitamin D supplementation after acute MI and in chronic heart failure, to confirm or dispel the vitamin D-cardiovascular disease hypothesis.

Conclusion

The study by Le et al. provides a valuable contribution to the preclinical literature, further showing potential benefits that vitamin D can confer after MI and hinting at a new cellular target by which it may do so. It now remains to be seen whether well-conducted, randomised trials can finally make the sun shine on a role for vitamin D in managing patients with cardiovascular disease in the clinic.

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References

[1] Muscogiuri G, Annweiler C, Duval G, Karras S, Tirabassi G, Salvio G, et al. Vitamin D and cardiovascular disease: from atherosclerosis to myocardial infarction and stroke. Int J Cardiol 2017;230:577–84.
[2] Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc 2013;88:720–55.
[3] O'Connell TD, Berry JE, Jarvis AK, Somerman MJ, Simpson RU. 1,25-Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation and hypertrophy. Am J Physiol 1997;272:H1751–8.
[4] Chen S, Gardner DG. Liganded vitamin D receptor displays anti-hypertrophic activity in the murine heart. J Steroid Biochem Mol Biol 2013;136:150–5.
[5] Meems LM, Cannon MV, Mahmud H, Voors AA, van Gilst WH, Sillje HH, et al. The vitamin D receptor activator paricalcitol prevents fibrosis and diastolic dysfunction in a murine model of pressure overload. J Steroid Biochem Mol Biol 2012;132:282–9.
[6] Yuan W, Pan W, Kong J, Zheng W, Szeto FL, Wong KE, et al. 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem 2007;282:29821–30.
[7] Qu H, Lin K, Wang H, Wei H, Ji B, Yang Z, et al. 1,25(OH)2 D3 improves cardiac dysfunction, hypertrophy, and fibrosis through PARP1/SIRT1/mTOR-related mechanisms in type 1 diabetes. Mol Nutr Food Res 2017;61.
[8] Panizo S, Carrillo-Lopez N, Naves-Diaz M, Solache-Berrocal G, Martinez-Arias L, Rodrigues-Diez RR, et al. Regulation of miR-29b and miR-30c by vitamin D receptor activators contributes to attenuate uraemia-induced cardiac fibrosis. Nephrol Dial Transpl 2017;32:1831–40.

[9] Rahman A, Hershey S, Ahmed S, Nibbelink K, Simpson RU. Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. J Steroid Biochem Mol Biol 2007;103:416–9.
[10] Le TYL, Ogawa M, Kizana E, Gunton JE, Chong JJH, Vitamin D. Improves cardiac function after myocardial infarction through modulation of resident cardiac progenitor cells. Heart Lung Circ 2018;27:967–75.
[11] Chong JJ, Chandrakanthan V, Xaymardan M, Asli NS, Li J, Ahmed I, et al. Adult cardiac-resident MSC-like stem cells with a proepicardial origin. Cell Stem Cell 2011;9:527–40.
[12] Chong JJ, Reinecke H, Iwata M, Torok-Storb B, Stempien-Otero A, Murry CE. Progenitor cells identified by PDGFR-alpha expression in the developing and diseased human heart. Stem Cells Dev 2013;22:1932–43.
[13] Artaza JN, Norris KC. Vitamin D reduces the expression of collagen and key profibrotic factors by inducing an antifibrotic phenotype in mesenchymal multipotent cells. J Endocrinol 2009;200:207–21.
[14] Fleck A. Latitude and ischaemic heart disease. Lancet 1989;1:613.
[15] Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503–11.
[16] Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008;168:1174–80.
[17] Ng LL, Sandhu JK, Squire IB, Davies JE, Jones DJ. Vitamin D and prognosis in acute myocardial infarction. Int J Cardiol 2013;168:2341–6.
[18] Wang L, Song Y, Manson JE, Pilz S, Marz W, Michaelsson K, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 2012;5:819–29.
[19] Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol 2010;106:963–8.
[20] Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, et al. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. Eur J Heart Fail 2012;14:357–66.
[21] Pilz S, Marz W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab 2008;93:3927–35.
[22] Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. Arch Intern Med 2008;168:103–8.
[23] Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:846–54.
[24] Ford JA, MacLennan GS, Avenell A, Bolland M, Grey A, Witham M, et al. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. Am J Clin Nutr 2014;100:746–55.
[25] Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, et al. Effect of monthly high-dose vitamin d supplementation on cardiovascular disease in the vitamin D assessment study: a randomized clinical trial. JAMA Cardiol 2017;2:608–16.
[26] Witte KK, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, et al. Effects of vitamin D on cardiac function in patients with chronic HF: the VINDICATE study. J Am Coll Cardiol 2016;67:2593–2603..