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Review

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Beneficial Role of Vitamin D on Endothelial Progenitor Cells (EPCs) in Cardiovascular Diseases

Atanu Sen,[1] **Vinnyfred Vincent**,[2] **Himani Thakkar**,[2] **Ransi Abraham**,[1] **Lakshmy Ramakrishnan**[1]

[1]Department of Cardiac Biochemistry, All India Institute of Medical Sciences, New Delhi, India
[2]Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, India

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Correspondence to
Lakshmy Ramakrishnan
Department of Cardiac Biochemistry, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, Delhi 110029, India.
Email: lakshmy_ram@yahoo.com

ORCID iDs
Atanu Sen
https://orcid.org/0000-0002-5023-6260
Vinnyfred Vincent
https://orcid.org/0000-0002-4268-0951
Himani Thakkar
https://orcid.org/0000-0002-2825-5190
Ransi Abraham
https://orcid.org/0000-0003-1954-3112
Lakshmy Ramakrishnan
https://orcid.org/0000-0002-8582-3705

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of death in the world. Endothelial progenitor cells (EPCs) are currently being explored in the context of CVD risk. EPCs are bone marrow derived progenitor cells involved in postnatal endothelial repair and neovascularization. A large body of evidence from clinical, animal, and *in vitro* studies have shown that EPC numbers in circulation and their functionality reflect endogenous vascular regenerative capacity. Traditionally vitamin D is known to be beneficial for bone health and calcium metabolism and in the last two decades, its role in influencing CVD and cancer risk has generated significant interest. Observational studies have shown that low vitamin D levels are associated with an adverse cardiovascular risk profile. Still, Mendelian randomization studies and randomized control trials (RCTs) have not shown significant effects of vitamin D on cardiovascular events. The criticism regarding the RCTs on vitamin D and CVD is that they were not designed to investigate cardiovascular outcomes in vitamin D-deficient individuals. Overall, the association between vitamin D and CVD remains inconclusive. Recent clinical and experimental studies have demonstrated the beneficial role of vitamin D in increasing the circulatory level of EPC as well as their functionality. In this review we present evidence supporting the beneficial role of vitamin D in CVD through its modulation of EPC homeostasis.

Keywords: Endothelial progenitor cell; Cardiovascular diseases; Vitamin D

INTRODUCTION

Differentiation of cells from mesodermal origin to angioblast and subsequently to endothelial cells (ECs) was thought to exclusively take place during embryonic development. But this dogma was overturned in 1997 when Asahara et al.[1] reported the existence of endothelial progenitor cells (EPCs) as putative ECs in adult human peripheral blood and their role in neovasculogenesis in postnatal life. This cell type has become of significant interest in regenerative medicine due to their potential role in repair of endothelium in cardiovascular disease (CVD).

Conflict of Interest
The authors have no conflicts of interest to declare.

Author Contributions
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Deficiency of vitamin D is a common public health problem and unfortunately most often remain unrecognized and untreated. Exposure of ultraviolet radiation of sunlight to skin tissues is considered as one of the major source of vitamin D, while deficiency of this vitamin is associated with indoor lifestyle, sun avoidance strategies, darker skin, distance from equator and winter season.[2-4] Vitamin D is well known for its role in mineral homeostasis and bone health. Since last 2 decades clinical and epidemiological studies have shed light on circulatory vitamin D deficiency and its association with the increased risk of CVDs and its risk factors including diabetes, hypertension etc.[5] Recent clinical, *in vitro* and *in vivo* studies have also shown that the vitamin D plays a pivotal role in vascular health by promoting cell proliferation, cell-cell adhesions, barrier integrity and mobilization of EPCs.[6-9] Since EPCs are known to be important in postnatal neovasculogenesis and repair of the damaged endothelium with significant role in prevention of cardiovascular disorders, individuals with reduced EPCs level or impaired functions would benefit from vitamin D based interventions.[10]

In this review we will discuss the prevailing knowledge about the role of vitamin D on EPCs in context to CVD.

EPCs IN CVD

1. EPC

Asahara et al.[1] reported for the first time in 1997 the existence of bone marrow derived EPCs in peripheral circulation. In the past, regeneration of damaged endothelium was attributed to the migration and proliferation of adjacent mature ECs but it is now recognized that local and circulating EPCs have a crucial role in repair and regeneration of the damaged endothelium and in neovascularization.[1] In response to various stimulatory factors including angiogenic growth factors, ischemia, vascular trauma, and various cytokines, EPCs can be mobilized from the bone marrow to the sites of injury to play a role in re-endothelization and neovascularization.[11]

EPCs are characterized by the surface expression of vascular endothelial growth factor receptor-2 (VEGFR-2); also known as kinase insert domain receptor (KDR), and progenitor cell surface markers (CD34, CD133, and CXCR4).[12] However, the definition and characterization of the true EPC population on the basis of cellular markers are still debated, as EPCs are a heterogenous population of cells originating from precursors within the bone marrow and are present in different stages of endothelial differentiation in the peripheral blood.[13] It was believed that the differentiation of mesodermal cells to angioblasts and subsequent endothelial differentiation occurs exclusively during embryonic development, but now we know that $CD34^+$ progenitor cell population from adults can also give rise to the endothelial phenotype. Homing of EPCs from the bone marrow to sites of cardiovascular injury occurs in response to variety of cytokines including stromal derived factor (SDF)-1α that attracts binding of progenitors expressing the CXCR4 receptor, granulocyte colony stimulating factor (GS-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), vascular endothelial growth factor (VEGF) and nitric oxide (NO). Downregulation of VEGF and other cytokines and reduced bioavailability of NO contribute to impaired migratory capacity of EPC.[14-18]

Emerging evidence suggests that EPCs show two different morphologies during *in vitro* culture, the spindle shaped early EPCs and late EPCs with cobble stone morphology. Similar

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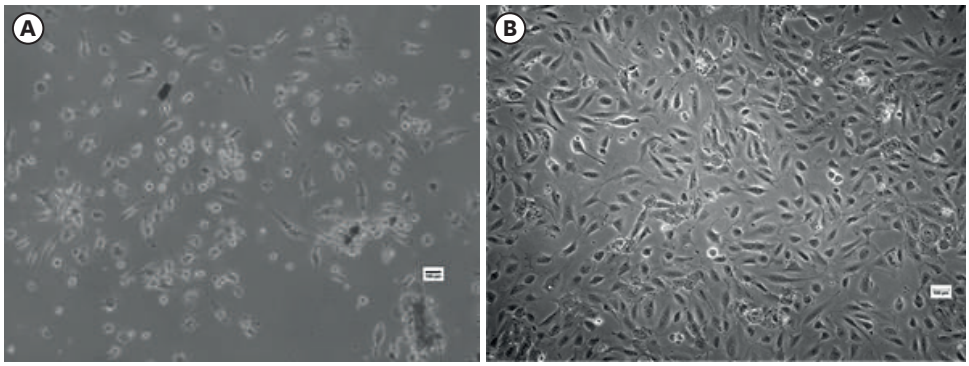

Fig. 1. Bright field microscopic images of early (A) and late (B) EPCs with spindle shape and typical cobble stone morphology. Both the images are at 10× magnification with 100 μm scale bar.

morphology of early and late EPCs in *in vitro* culture (**Fig. 1**) was observed in our studies also. The former originates from monocytes with limited proliferation potential and express CD14, a monocytic marker. The late EPCs, also known as outgrowth endothelial cells (OECs) or endothelial colony forming cells (ECFCs) exhibit a typical cobblestone morphology, originate in the bone marrow and possess a greater proliferation and survival potential. The late EPCs are negative for CD14 and pan leukocyte marker CD45. Late EPC colonies express endothelial (KDR, vWF, and CD105) as well as progenitor cell markers (CD34 and CD133). These two subtypes are differentiated based on their morphology and functional activity in terms of rate of proliferation, *in vitro* angiogenesis, and rate of survival in culture. OECs or ECFCs show higher proliferation rate than early EPCs and only OECs/ECFCs has been shown to have direct involvement in *in vitro* angiogenesis.[19-21]

2. EPCs and coronary artery disease (CAD)

The role of EPCs as a marker of endothelial dysfunction and cardiovascular injury has usefulness in assessment of CAD progression.[1] Reduced circulating progenitor cells defined as $CD34^+$ mononuclear cells and/or cells with expression of CD133 was shown to be associated with the risk of death in patients with CAD which links impaired endogenous regeneration capacity with increased mortality.[22] Schmidt-Lucke et al.[23] reported that lower levels of circulating EPC counts were associated with a higher incidence of cardiovascular events in patients with stable CAD or acute coronary syndrome (ACS). Similarly, an inverse correlation was found by Werner et al.,[24] between the level of circulating EPCs and the risk of cardiovascular events among patients with angiographically confirmed CAD. Other studies indicate that progression of CAD is associated with not only the reduced circulatory level of EPCs, but also their impaired functional activity. Impaired migratory response of EPCs was inversely correlated with disease severity in CAD patients.[25]

Reduced circulating EPC counts and their impaired functional activity, assessed with cell migration assays *in vitro*, is observed in CAD.[26] The early cellular senescence and lower EPC counts in patients with premature CAD correlates with shorter telomere length and reduced telomerase activity.[27] Likewise, Hammadah et al.[28] reported a positive association between leukocyte telomere length (LTL) and circulating progenitor cells (CPCs) characterized as $CD34^+$ and subsets as $CD34^+/CD133^+$, $CD34^+/CXCR4^+$ and $CD34^+/CXCR4^+/CD133^+$ in CAD patients. Moreover, both LTL and CPC levels were independent and additive predictors of adverse cardiovascular outcomes in CAD patients.[28] A recent prospective cohort study demonstrated that, CAD patients with renal insufficiency had lower CPC ($CD34^+$, $CD34^+/$

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CD133$^+$, CD34$^+$/CXCR4$^+$ and CD34$^+$/VEGFR2$^+$) counts among older participants (≥70 years of age) and low CPC count, a marker of impaired indigenous regenerative capacity, an independent predictor of adverse cardiovascular outcomes in patients with renal insufficiency. However, among patients with renal insufficiency, those with higher CPC count had similar cardiovascular (CV) outcomes as those without renal insufficiency, which cumulatively suggest that CV outcomes in patients with CAD and renal insufficiency is modulated by indigenous regenerative capacity contributed by CPCs.[29] In another cohort study, higher CPC (CD34$^+$, CD34$^+$/CD133$^+$, and CD34$^+$/CXCR4$^+$) count was shown to be one of the reasons behind the obesity paradox in CAD (among individuals with CAD, obesity appears to provide a favorable outcome). The lower risk of CV outcomes was limited to obese individuals with high CPC count which preserve the endogenous regenerative capacity.[30]

3. EPCs and heart failure (HF)

Endothelial dysfunction also occurs in patients with congestive heart failure (CHF).[31-33] However, limited evidence is available in support of EPCs and CD34$^+$ cell mobilization during HF. Valgimigli et al.[34] reported a higher circulating level of EPCs in patients with CHF compared to control. An inverse correlation was observed between the severity of HF and circulating EPC count with significantly higher CD34$^+$ counts in patients with mild HF compared to those with severe HF.[35] In acute CHF, stimulation of hematopoietic progenitor cells occurs, whereas in chronic stable stages of disease, depletion of the progenitor cell pool is observed, giving rise to a biphasic pattern in HF.[35] Circulating EPC numbers and colony forming units (CFU) (a functional parameter for the EPCs) are independent predictors of adverse outcomes in CHF.[36]

4. EPCs and CVD risk factors

As far as the risk factors of CVD including hypertension, diabetes, metabolic syndrome, dyslipidemia, and smoking are concerned, Oliveras et al.[37] found a reduced EPC level in peripheral blood and the level was consistent even after *in vitro* culture in patients with refractory hypertension. Further this finding suggest that the remarkable decline of EPC level is independent of other risk factors which in turn further reinforces a likely role of EPCs in the development of atherosclerosis. Fadini et al.[38] demonstrated lower circulating levels of CD34$^+$ and KDR$^+$ EPC populations in subjects with greater carotid intima-media thickness (c-IMT). Reduced circulating EPC counts and impaired functionality was observed in metabolic syndrome,[39] diabetes,[40] and those with peripheral vascular disease.[41] Hill et al.[42] demonstrated a significant association of CFU-EC level with endothelial function as assessed by flow mediated brachial artery reactivity in individuals with various degree of cardiovascular risk factors but no history of CVDs. Moreover, this study speculate circulating EPC level as better predictor of vascular health than the presence or absence of conventional risk factors.

Diet and exercise also influence the circulating levels of EPC and their functional activity. A significant positive effect of 4 weeks exercise training on EPC number as well as cellular functionality was seen in young patients with chronic HF and this effect was consistent even in older patients with chronic HF which implies the potential benefit of rehabilitation intervention for patients with chronic HF.[43] In a randomized controlled trial (RCT), the Mediterranean diet was positively associated with higher circulating levels of CD34$^+$KDR$^+$ and CD34$^+$KDR$^+$CD133$^+$ cells compared to a low-fat diet in the subjects with newly diagnosed type 2 diabetes.[44] In an another prospective randomized single-blind control trial, patients with coronary heart disease (CHD) showed improved endothelial functions as shown by higher flow mediated dilatation and increased circulatory EPCs level after consumption

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of Mediterranean diet when compared with low fat diet. In addition, reduced intracellular oxidative stress, cell apoptosis and cellular senescence of ECs as well as higher cell proliferation and angiogenesis were seen in patients who followed the Mediterranean diet.[45]

VITAMIN D AND CV HEALTH

Vitamin D is a secosteroid molecule traditionally associated with bone and calcium metabolism. Typically Vitamin D exists in 2 forms; D2 (ergocalciferol) and D3 (cholecalciferol).[46] The main sources of vitamin D3 in humans are either dietary such as fish oil or by endogenous synthesis from 7-dehydrocholesterol in the malphigian layer of the epidermis after exposure to sunlight, hence the name sunshine vitamin.[47] Hydroxylation of cholecalciferol by hepatic and microsomal enzymes occurs in the liver to form 25-hydroxy cholecalciferol (25-HCC) which gets further hydroxylated in the kidney by renal 1α hydroxylase to form the active hormonal form of vitamin D, 1,25-dihydroxy cholecalciferol (1,25-DHCC), also known as calcitriol.[48] This active form of vitamin D binds to nuclear vitamin D receptors (VDR) to regulate expression of more than 200 genes that modulate a wide range of biological functions including calcium absorption from the intestine, calcium deposition in bone, stimulation of insulin and inhibition of renin production, stimulation of macrophage cathelicidin production etc.[47,49] The vitamin D/VDR complex in conjunction with other nuclear hormone receptors, particularly the family of retinoid X receptor, bind to the vitamin D response element (VDRE), a hormone response element on DNA that can influence gene expression.[50] In the cardiovascular system, VDRs are present on vascular smooth muscle cells, endothelium and cardiomyocytes.[51]

1. Vitamin D and CVD: observational and interventional studies

Vitamin D status assumes greater importance in view of recent evidence from studies which suggest that in addition to its known effects on the musculoskeletal system, vitamin D may also influence cardiovascular health. The earliest observational study suggesting a protective role for vitamin D in ischemic heart disease came from the UK where Grimes et al.[52] observed that mortality in ischemic heart disease was inversely proportional to hours of sunlight exposure. The NHANES conducted between 1988 and 1994 on 16,603 men and women aged >18 years reported greater frequency of 25-HCC deficiency in subjects with ischemic heart disease and stroke than in the general population.[53] Other studies have observed that severe vitamin D deficiency is associated with a higher risk of developing adverse cardiovascular events,[54] including myocardial infarction (MI)[55-57] and sudden cardiac death/HF.[58] Vitamin D insufficiency (<30 ng/mL) was found to be directly associated with slow epicardial coronary flow, endothelial dysfunction as well as subclinical atherosclerosis in patients with normal or near normal coronary arteries[33] and decreased levels of vitamin D binding proteins correlates with number of affected coronary arteries in younger survivors of MI.[34] A large meta-analysis of cohort studies reported that vitamin D concentrations below 37 nmol/L was associated with sharp non-linear increase of CVD risk and mortality.[59] In contrast, another study found no association between vitamin D levels and severity of coronary lesions in patients with ST-segment elevation MI.[57] Apart from the direct effect of vitamin D on cardiomyocytes, vitamin D indirectly modifies CVD risk through its association with cardiovascular risk factors including diabetes, hypertension, systemic inflammation, and oxidative stress.[60]

Lower vitamin D levels are associated with insulin resistance in observational and case control studies,[61,62] and with increased risk of diabetes.[63,64] Vitamin D supplementation was

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associated with a slower rise in glucose levels in subjects with impaired fasting glucose.[65] The European Community Concerted Action on the Epidemiology and Prevention of Diabetes (EURODIAB) study reported a 33% lower risk of developing type 1 diabetes in children receiving vitamin D supplementation.[66]

Vitamin D levels are inversely correlated with systolic blood pressure levels, a major risk factor of CAD.[67,68] In the Health Professionals' follow-up study and the Nurses' health study, subjects with vitamin D <15 ng/mL were at 3- to 6-fold higher risk of developing incident of hypertension during a 4-year follow-up, compared to those with optimal vitamin D status.[69] Supplementation of vitamin D lowers systolic blood pressure,[70,71] possibly by suppression of renin activity and sensitization of vascular smooth muscle cells.[72] *In vivo* study reported sustained elevation of renin expression in vitamin D receptor-null mice resulting in increased production of angiotensin-II (Ang-II), a strong vasoconstrictor that promotes development of hypertension and left ventricular hypertrophy.[73] Moreover, vitamin D attenuates expression of the angiotensin-1 receptor in ECs of renal arteries from hypertensive patients, leading to improvement of endothelial function and decreased production of reactive oxygen species (ROS).[74]

Vitamin D can also exert its cardioprotective effects through an anti-inflammatory action, by inhibition of smooth muscle cell proliferation, suppression of proatherogenic T lymphocytes, preservation of endothelial function,[74-80] inhibition of foam cell formation, cholesterol uptake by macrophages, enabling high-density lipoprotein (HDL) transport[81] and by protection against advanced glycation product formation.[82] Its anti-inflammatory actions are mediated through a variety of pathways including the cyclooxygenase pathway, by upregulation of anti-inflammatory cytokines, reduction of cytokine-induced expression of cell adhesion molecules, reduction of matrix metalloproteinase (MMP)-9, inhibition of prostaglandins and downregulation of renin-angiotensin-aldosterone-system (RAAS).[83-85] Supplementation of vitamin D in patients with CHF is associated with significant increase in anti-inflammatory cytokine interleukin (IL)-10.[86] Experimental studies have provided evidence that vitamin D reduces inflammation by lowering the release of tumor necrosis factor (TNF)-α and upregulation of anti-inflammatory cytokine IL-10 as well as expression of IL-10 receptor.[87,88] Furthermore, in the Framingham offspring study, the plasma 25-hydroxyvitamin D (25[OH] D) was inversely associated with urinary isoprostane, an indicator of oxidative stress.[89]

2. Vitamin D and CVD: RCT

Though the evidence from experimental and observational studies supports beneficial effect of vitamin D on cardiovascular health, the outcomes of interventional studies investigating the role of vitamin D supplementation on CVD is equivocal and conflict the results of observational and experimental studies. Randomized placebo-controlled trial by Hin et al.[90] reported no changes in cardiovascular risk factors including arterial stiffness in healthy elderly people (≥65 years of age) consuming daily supplementation of 4,000 IU vitamin D. A prospective RCT with MI patients demonstrated that the acute effect of vitamin D supplementation (4,000 IU) for 5 days was able to attenuate the inflammatory cytokines, such as C-reactive protein (CRP) and IL-6, but cell adhesion molecules intercellular adhesion molecule-1 (ICAM-1), E-selectin and other factors including vascular endothelial growth factor, TNF-α remains unchanged. However, the limitations of this study were small sample size and short duration of intervention.[91] In an another double blind RCT, weekly ergocalciferol (50,000 IU) administration for 12 weeks to CAD patients did not result in significant improvement of vascular and endothelial functions.[92] Likewise, supplementation of vitamin D bolus (100,000 IU) to 5,110 community resident adults aged 50–84 years with

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baseline 25(OH)D <50 nmol/L for a mean duration of 3.34 years showed no significant effect on the incidence of CVD.[93] In the same line, a US based nationwide randomized placebo-controlled trial conducted on 25,871 individuals found no association between vitamin D supplementation and risk of cardiovascular events and cancer after a median duration of 5.3 years.[94] In contrast, a randomized placebo-controlled double blind study of stable CAD patients receiving 0.5 μg vitamin D3/day for 6 months, reported a significant decrement of SYNTAX scores for CAD severity as well as significant decrease in high-sensitivity CRP level and renin-angiotensin system activity.[95]

ROLE OF VITAMIN D ON EPCs AND ECs

1. *In vitro* studies

Vitamin D exposure at supra-physiological (10^{-9} mol/L) concentrations to cultured early EPCs improved cell proliferation and colony formation in type-2 diabetic patients. However, there was no effect of calcitriol on EPCs angiogenic marker expression and transcription factor Kruppel-like factor 10 (KLF10) which is known to participate in various aspects of cellular growth, development, and differentiation.[7] A dose-dependent increase in production of NO via activation of endothelial nitric oxide synthase (eNOS) was observed in human umbilical vein endothelial cells (HUVECs) when treated with vitamin D. Increased NO production resulted in significant increase in phosphorylation of eNOS and intracellular kinases including p38, AKT and ERK which are known to be involved in intracellular signaling pathway associated with NO synthesis. Concomitant administration of ZK191784 (VDR agonist) and vitamin D to HUVECs resulted in greater production of number as compared to vitamin D or VDR agonist treatment alone, implying involvement of the VDR in production of NO.[96] In a recent study, *in vitro* vitamin D treatment in a dose dependent manner on early EPCs from systemic lupus erythematosus (SLE) patients shows improvement in EPC number and functionality in terms of migratory and proliferative potential as well as upregulation of EPC's NO biosynthesis. In addition to that, intracellular EPC's $NO^{\cdot}$ level was positively correlated with EPC number and functions which further may predicts the role of vitamin D in the improvement of EPC number and functions via $NO^{\cdot}$ signaling pathway.[97]

In another study, vitamin D treatment on ECFCs derived from cord blood sample of healthy pregnant women during delivery exhibited a significantly increased functional activity reflected by higher formation of entire length of tubular structure on matrigel matrix and an increased cell proliferation compared to vehicle treated controls. In addition, an increased VEGF mRNA expression and elevated activity of pro-MMP-2 was demonstrated in ECFCs when treated with vitamin D. However, these positive effects of vitamin D were reversed when VDR and VEGF cascade pathways were specifically blocked, suggesting that the effects on ECFCs are secondary to up regulation of VEGF expression. Since angiogenesis is crucially associated with pathophysiology of preeclampsia, this study speculated the beneficial effect of vitamin D supplementation in early pregnancy particularly during placental development in reducing the risk of developing preeclampsia.[98]

Several studies have shown markedly reduced migratory capacity and angiogenesis of cord blood-derived ECFCs when exposed to serum from preeclamptic compared to normal women.[99,100] Vitamin D restored the functional properties and abolished the negative effect of preeclampsia on ECFCs. This positive effect of vitamin D appeared to be mediated through VEGF signaling pathway as Flk-1/KDR (VEGF) receptor tyrosine kinase inhibitor SU5416

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was able to suppress the ECFC's tubule formation, an effect similar to VDR blockade by pyridoxal phosphate. Unlike the findings of the previous study by Grundmann et al.,[98] the positive effect of vitamin D on ECFC's angiogenesis in this study was independent of the FBS concentration in treated media.[100] In addition, attenuation of ECFCs migration was seen in response to conditioned media obtained from placenta under aberrant oxygen conditions; 2% O_2 (hypoxia) or 21% hyperoxia compared to normoxic (8% O_2). Vitamin D at a concentration of 10 nM restored the ECFC's functionality. The reduced tube formation and migration from VDR blockade was partially reversed by vitamin D, but VEGF pathway inhibition could not be restored by vitamin D. These findings suggest that vitamin D can overcome some of negative effects of preeclamptic condition on ECFC, an effect that is mediated via the VDR.[99]

Adverse prenatal exposure is one of the leading causes of developmental origin of chronic diseases such as cardiovascular diseases in adulthood.[101,102,103] Based on this paradigm prenatal exposure of preeclampsia (PE) is well known as an independent risk factor for long-term cardiovascular morbidity of the offspring and studies suggest that vitamin D deficiency is one of the factors to be responsible for the increased incidence of PE.[104] A study suggested the role of human fetal EPCs in maternal endothelial function during pregnancy as evidenced by fetal EPC's transmigration to the maternal blood stream and homing to locations of maternal uterine vasculogenesis.[105] In an *in vitro* model, Brodowski et al.[106] explained that fetal blood derived ECFCs when exposed to fetal serum from PE pregnancy, become impaired in integration and invasion into the monolayer of mature HUVECs, which may explain the role of fetal circulating factors in disruption of endothelial functions and the mechanism by which angiogenesis and endothelial homeostasis are disrupted in PE. Exogenous vitamin D administration at physiological concentrations led to a substantial reversal of fetal serum mediated inhibitory effect on ECFCs.[106]

In another *in vitro* study, Zhong et al.[107] reported stimulation of VDR expression by vitamin D in a time and dose dependent manner on ECs. Vitamin D also up regulated the expression of VEGF and its receptor as well as antioxidant CuZn-superoxide dismutase expression in ECs. Hypoxia mediated oxidative stress by $CoCl_2$, a hypoxia mimetic agent can lead to downregulation of VDR and CuZn superoxide dismutase expression and this was prevented by administration of vitamin D in *in vitro* culture.[107]

Uberti et al.[110] reported that vitamin D alone or in combination with VDR ligand ZK191784 prevent human EC death from oxidative stress via modulation of the interplay between apoptosis and autophagy. Vitamin D negated the effects by attenuating apoptosis related gene expression involved in both intrinsic and extrinsic pathways and augmenting activation of pro-autophagic beclin 1 as well as phosphorylation of ERK1/2 and Akt.[108]

An increase in expression of vascular cell adhesion molecule-1 (VCAM-1) and MT1-MMP is seen in human ECs when stimulated with lipopolysaccharide (LPS) and incubated with platelets. This effect was significantly attenuated by pre-treatment of cells with vitamin D. Moreover, a reduced CD62P expression in platelets in direct contact with pretreated ECs has been found compared to platelets incubated with untreated ECs. Vitamin D was able to suppress the platelet activation and expression of VCAM-1, MT1-MMP in human ECs.[109]

Schröder-Heurich et al.[6] reported that the vasoprotective effect of vitamin D could be through its impact on ECFC homeostasis. The effect included maintenance of stability of ECFC monolayers by enhancement of endothelial interconnection through vascular endothelial

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cadherin (VE-cadherin) junctions. In addition, this study also showed the positive effect of vitamin D on directional ECFC mobilization mediated through enhanced expression of adhesion proteins and change in F-actin formation.[6]

The formation of advanced glycation end products (AGE) and their tissue accumulation is common phenomena in diabetes, chronic renal failure and aging,[110] and is associated with development of multiple complications, particularly vascular atherosclerosis.[111,112] In an *in vitro* study by Talmor et al.,[113] a beneficial effect of vitamin D on human ECs affected by AGE was seen. Cells induced with AGE-human serum albumin (HSA) showed reduced eNOS gene expression and enzyme activity, but administration of calcitriol to AGE-HSA treated cells ameliorated the effect of AGE by blunting the AGEs receptor mRNA expression and proteins. In addition, calcitriol administration in ECs effectively reduced AGEs-induced elevated levels of IL-6 mRNA and nuclear factor (NF)-κB-p65 DNA binding activity, a phenomenon associated with elevated expression of IκBα.[113]

MicroRNA (MiRNA), the non-coding RNA, play a role in regulating expression of a number of genes by binding at the 3' untranslated region region of target mRNA of protein coding genes and induce the translational repression and/or mRNA cleavage.[114,115] MiRNAs miR-659 and miR-510 are up regulated in human ECs pretreated with AGE-HSA whereas miR-181c, miR-411, miR-126, miR-15a and miR-20b are down regulated. Administration of calcitriol reverted this pattern of miR expression.[116] Paricalcitol, a vitamin D analog and calcitriol downregulated markers involved in the inflammatory response of ECs exposed to AGE-HSA.[117]

Gestational diabetes mellitus (GDM) is a common cause of manifestation of CVD in later life of the mother and the offspring.[118] The fetal ECFCs from gestational diabetes mellitus pregnancies exhibited a significant impairment in functional activity as well as the number of colonies *in vitro* when compared with fetal ECFCs from uncomplicated pregnancies. In the same study, fetal ECFCs obtained from uncomplicated pregnancies showed a significant functional deficit in terms of cell migration and tubule formation upon exposure to mildly hyperglycemic conditions. But a significant reduction in the inhibitory effect of GDM and mild hyperglycemic on fetal ECFCs functionality was seen after *in vitro* treatment of vitamin D.[119]

Endothelial dysfunction has been seen in type-2 diabetes mellitus patients with vitamin D insufficiency or deficiency and supplementation of vitamin D can improve the EC function.[120] Bioinformatics analysis explains the vitamin D induced molecular mechanism of differentially expressed miRNA, mRNA, circular RNA (circRNA) and long noncoding RNA (lncRNA) in bone marrow derived EPCs pretreated with high level of glucose. Following vitamin D administration, competent endogenous RNA (ceRNA) which comprises circRNA, lncRNA has been found to attenuate the effects of miRNAs on the expression of mRNAs in EPCs and may suggest the role of vitamin D in alleviation of EPCs dysfunctions through the associated ceRNA regulatory network in diabetes.[121] The mechanism of action of vitamin D on endothelial and or endothelial progenitor cells has been summarized in **Fig. 2**.

Inflammation to endothelium is the hallmark of endothelial activation and development of atherosclerosis.[122] This cellular inflammatory effect results in stimulation of excessive cytokines and adhesion molecule expression which further exacerbate endothelial dysfunction.[123,124] Angiotensin-II is known to upregulate NF-κB and which further induce expression of TNF-α, IL-6, cell adhesion molecules ICAM-1, VCAM-1 and E-selectin, resulting vascular injury.[124] However, vitamin D has a role in inhibition of inflammatory reaction

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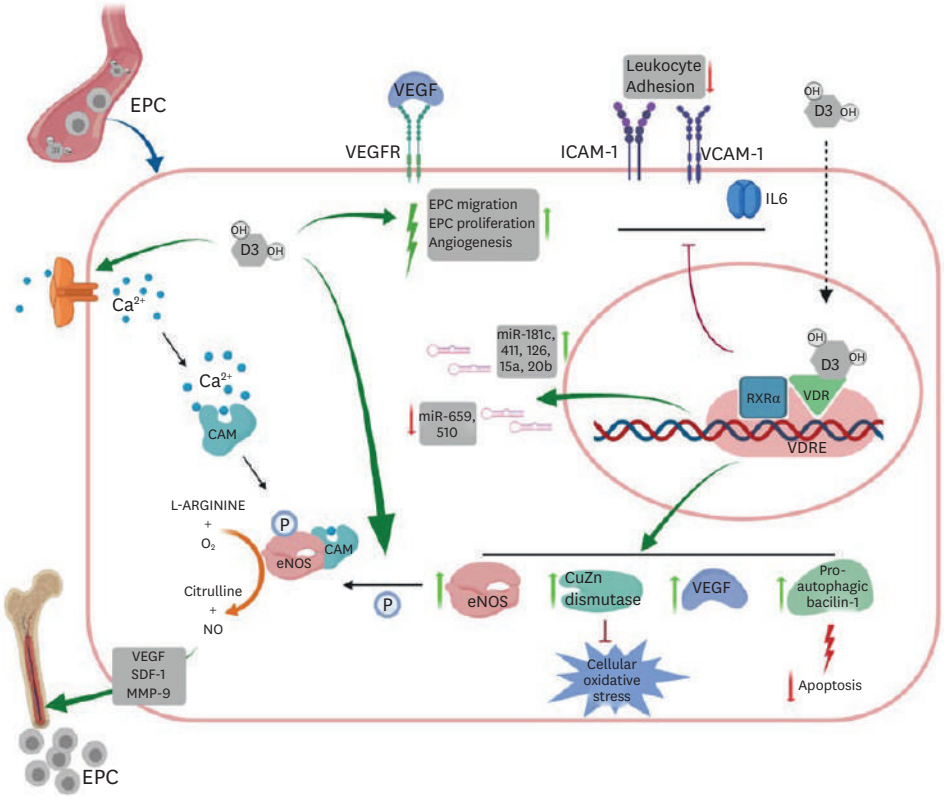

Fig. 2. Schematic representation of effect of vitamin D3 on EPCs and/or endothelial cells. Binding of vitamin D to nuclear VDR in combination with RXR on VDRE triggers the expression of number of genes, such as eNOS, VEGF, CuZn dismutase, and pro-autophagic bacilin-1. Vitamin D3 mediates activation of eNOS by phosphorylation resulting in the augmentation of NO synthesis. Intracellular Ca^{2+} influx is caused by vitamin D and subsequent calcium calmodulin complex stabilizes the catalytic state of eNOS which catalyzes the synthesis of NO from L-Arginine and molecular oxygen. In association with VEGF, SDF-1 and MMP-9, NO leads to the migration of EPC from the permissive vascular zone of bone marrow into the circulation. The upregulation of CuZn dismutase by vitamin D3 via VDR activation attenuates the cellular oxidative stress, while upregulation of pro-autophagic bacilin-1 by VDR mediated vitamin D3 reduces the cellular apoptosis. Increased VEGF mRNA expression and protein synthesis mediates EPC migration, proliferation, and *in vitro* angiogenesis. Upregulation of microRNA (miR-659, miR-510) and downregulation of microRNA (miR-181c, miR-411, miR-126, miR-15a, miR-20b) seen in hyperglycemic conditions like diabetes are reverted by vitamin D3 via VDR signaling pathway. The adhesion of leukocyte and platelets to the endothelium is suppressed by vitamin D3 through downregulation of VCAM-1 and ICAM-1 expression as well as proinflammatory cytokine IL-6. This illustration was created using BioRender.com.
EPC, endothelial progenitor cell; VDR, vitamin D receptor; RXR, retinoid X receptor; VDRE, vitamin D response element; eNOS, endothelial nitric oxide synthase; VEGF, vascular endothelial growth factor; NO, nitric oxide; SDF, stromal derived factor; MMP, matrix metalloproteinase; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; IL, interleukin.

and thus protect vascular damage.[95] Recent study demonstrate that, impaired cell viability, migration ability and angiogenesis as well as cell apoptosis has been noticed in EPCs when treated with Ang-II and vitamin D administration ameliorate the effect of Ang-II via inhibition of cellular oxidative stress, NF-κB activation and inflammatory cytokines.[125]

2. *In vivo* studies

A recent *in vivo* study demonstrated amelioration of hyperlipidemia as well as progression of atherosclerosis by intravenous transplantation of genetically modified late outgrowth EPCs with VDR over-expression in ApoE-knockout mice. Additionally, VDR over-expressed EPCs (ovVDR-EPCs) transplanted group had higher HDL-cholesterol level, lower levels of total cholesterol, low-density lipoprotein, apoB and Lp(a), elevated serum NO levels, increased expression of serum and vessel wall eNOS, reduced expression and activity of

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MMPs and decreased expression and activity of their tissue inhibitor (tissue inhibitors of metalloproteinase, TIMPs) compared to controls. These findings demonstrate the beneficial role of EPCs over-expressing VDR in protecting against atherosclerotic risk and suggest that transfusion of ovVDR-EPCs might be used in angiogenic therapy.[126]

SLE, an autoimmune disease is associated with increased risk of CVD and endothelial dysfunction.[127,128] Premature CVD in patients with SLE is precipitated by failure of endothelial repair.[128] Vitamin D deficiency introduced by dietary restriction in lupus prone MRL/lpr mice caused endothelial dysfunction. Improved differentiation of EPCs was observed after vitamin D3 supplementation. Vitamin D deficiency was associated with upregulation of interferon-stimulated gene expression in both MRL/lpr mice and patients with SLE.[129]

The initiation and progression of atherosclerotic plaque formation results from EC activation followed by leukocyte recruitment and adhesion to the activated endothelium. The knockdown of VDR expression in *in vitro* human ECs induces a significant reduction of peripheral blood mononuclear cells (PBMC) rolling velocity over the endothelial monolayer and enhanced rolling flux and adhesion of PBMCs to the endothelium. The enhanced rolling velocity and adhesion of PBMCs was seen to be mediated by upregulation of VCAM-1 and ICAM-1 in VDR knockdown ECs along with significant elevation of IL-6 secretion. Down-regulation of VDR in ECs exhibited reduced level of IκBα as well as aggregation of p65 transcription factor (a member of NF-κB family) in the nucleus. VDR deletion in apoE$^{-/-}$ mice exhibited elevated aortic expression of VCAM-1, ICAM-1 and IL-6. *In vivo* deletion of VDR is associated with larger aortic arch and aortic root lesions along with higher macrophage content in apoE$^{-/-}$ mice. The lack of VDR signaling in ECs may lead to increased leukocyte-EC interactions causing atherosclerotic plaque development in apoE$^{-/-}$VDR$^{-/-}$ mice.[9]

3. Clinical studies

The receptor for vitamin D is widely distributed in almost all tissues and hence the use of vitamin D as a therapeutic agent has been shown to be beneficial in many conditions including CVDs and cancers.[130] At least 60 genes are regulated by vitamin D, which acts as a steroid hormone upon binding to the hormone response element of the genes.[131,132] A positive correlation between serum levels of vitamin D and circulating EPCs as well as cultured angiogenic cells suggests a possible role of vitamin D as a developmental hormone for stem cells that differentiate into the endothelial phenotype.[133,134] Study done by Mikirova et al.,[135] indicated a positive correlation between serum level of vitamin D (25[OH]D) and circulating EPC as well as cultured angiogenic cells suggesting a possible role of vitamin D3 as a developmental hormone for stem cells which differentiates into endothelial phenotype.

Reduced VDR expression on circulating EPCs has been reported in CAD patients, particularly among those with elevated HbA1c.[8] VDR mRNA expression was significantly decreased when EPCs were treated with high glucose (22 mmol/L) for 24 and 48 hours. Similarly, VDR expression on EPCs among hemodialysis patients was lower than that in control subjects, while upregulation of VDR expression on EPCs had been observed among those treated with oral/IV vitamin D.[136] Depletion of circulatory proangiogenic progenitor mononuclear cells as CD14^{+}CD309^{+}Tie-2^{+} cells were closely associated with the vitamin D status especially vitamin D3 in patients with metabolic syndrome (MetS) without known CVD. This study suggests a link between vitamin D deficiency and impaired endogenous endothelial repair system which in turn might lead to vascular complications in patients with MetS.[137] Reduced circulating progenitor cells (CD34^{+}) in patients with rheumatoid arthritis (RA) was positively

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Table 1. Association between serum vitamin D and circulatory EPC levels

References	No. of subjects	Subject characteristics	Serum vitamin D concentration	Levels of EPCs in circulation		Associations observed
Mikirova et al.[135]	n=41	Healthy adults	<40 ng/mL	Mean %	0.045	Positive correlation between serum VitD concentration and circulatory EPC level.
			>40 ng/mL		0.068	
			<30 ng/mL		0.046	
			>30 ng/mL		0.060	
Yiu et al.[134]	n=96, VitD deficient	Diabetic	<20 ng/mL	$CD34^+/KDR^+$ (%): 0.746±0.465 $CD133^+/KDR^+$ (%): 0.219±0.189		Circulatory level of $CD133^+/KDR^+$ EPC found to be positively correlated with VitD deficiency and insufficiency group.
	n=115, VitD insufficient		<30 ng/mL	$CD34^+/KDR^+$ (%): 0.628±0.354 $CD133^+/KDR^+$ (%): 0.283±0.197		
	n=69, VitD sufficient		≥30 ng/mL	$CD34^+/KDR^+$ (%): 0.747±0.412 $CD133^+/KDR^+$ (%): 0.364±0.172		
Chan et al.[139]	n=297	CVD (coronary artery disease, ischemic stroke)	<20 ng/mL	log, unit ($\times10^{-3}$/mL)	0.97±0.31	Positive association between serum 25(OH)D and $CD34^+KDR^+$, $CD133^+KDR^+$ EPC.
			20–29 ng/mL		1.05±0.42	
			30–39 ng/mL		1.08±0.41	
			≥40 ng/mL		1.15±0.39	
Gurses et al.[140]	n=27, control group	Premenopausal women with VitD deficient	34.40±10.30 ng/mL (for control group)	$CD34^+/KDR^+$ EPC (/uL): 64.50±17.10 $CD133^+/KDR^+$ EPC (/uL): 49.40±23.10		Positive correlation between baseline VitD level and circulatory level of $CD34^+/KDR^+$, $CD133^+/KDR^+$ cells.
	n=31, VitD deficient group		10.60±4.70 ng/mL (for VitD deficient group)	$CD34^+/KDR^+$ EPC (/uL): 26.20±20.50 $CD133^+/KDR^+$ EPC (/uL): 27.40±18.50		
Berezin et al.[137]	n= 10, 25(OH)D3	MetS without known CVD	>100 nmol/L	$CD14^+CD309^+Tie2^+$ cells/uL	0.039 (0.032–0.047)	Positive association VitD deficiency significant predictor for reduced circulatory proangiogenic progenitor cells as $CD14^+CD309^+Tie2^+$.
	n=12, 25(OH)D3		50–100 nmol/L		0.035 (0.028–0.044)	
	n= 14, 25(OH)D3 level		30–50 nmol/L		0.030 (0.022–0.041)	
	n=11, 25(OH)D3		<30 nmol/L		0.028 (0.016–0.033)	

VitD, vitamin D; EPC, endothelial progenitor cell; CD, cluster differentiation; KDR, kinase insert domain receptor; Tie2, tyrosine kinase receptor 2; 25(OH)D, 25-hydroxyvitamin D; MetS, metabolic syndrome.

correlated with lower vitamin D levels as well as with endothelial functions including pulse wave velocity and carotid intima-media thickness which may predict the contribution of vitamin D in endothelial homeostasis in patients with RA.[138] Chan et al.[139] have reported that statin therapy significantly raises serum vitamin D levels and vitamin D level was found to associate independently with higher circulating levels of $CD34^+KDR^+$, $CD133^+KDR^+$ EPC and a reduction in burden of carotid atherosclerosis in patients with cardiovascular disease.

Premenopausal women with vitamin D deficiency (<20 ng/mL) had impaired endothelial function as evaluated by flow mediated dilatation (FMD), and lower $CD34^+/KDR^+$ (26.20±20.50 /μL) and $CD133^+/KDR^+$ (27.40±18.50 /μL) EPC counts, together with lower levels of IL-10 and elevated level of IL-17. Six months (50,000 IU/week) vitamin D supplementation significantly increased vitamin D levels and ameliorated endothelial function as evidenced by higher FMD, $CD34^+/KDR^+$ and $CD133^+/KDR^+$ EPC counts as well as a shift of cytokine profile towards more anti-inflammatory cytokines.[140] In contrast, a 12-week randomized control trial of oral vitamin D supplementation of 5,000 IU/day in patients with suboptimal serum 25(OH)D levels (<30 ng/mL) did not show any significant improvement in FMD, pulse wave velocity and circulating levels of EPC in type 2 diabetic patients.[141] With reference to RCTs, the beneficial effect of vitamin D supplementation on CVDs is a topic which has not been explored adequately and hence concrete evidence does not yet exist. **Table 1** summarizes the clinical studies on vitamin D status and its effect on circulatory EPCs.

CONCLUSION AND PERSPECTIVES

An optimum serum level of vitamin D is important not only to maintain the body's normal calcium homeostasis but also to reduce the risk of cardiovascular events, diabetes and

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hypertension. Vitamin D exerts its beneficial role in several ways including antithrombotic, antihypertensive, anti-inflammatory, anti-fibrotic and antidiabetic effects. However, despite of showing the beneficial effect of vitamin D in the prevention of CVD, there are conflicting results from experimental and clinical studies on the role of vitamin D in the pathogenesis of CVD. This notion is contradicted by the data from the RCTs, RCTS have not shown beneficial effects of vitamin D on CVD, these trials were not designed to investigate cardiovascular outcomes in vitamin D-deficient individuals.[142] There could be a subset of individuals with CAD who could benefit from vitamin D supplementation.

Recent research suggest that vitamin D also plays an important role in vascular remodeling and healing of damaged endothelium by increasing the circulatory level and functionality of EPCs. Since 1997, when Asahara et al.[1] reported the existence of EPCs and their role in postnatal neovascularization, a large number of studies have shown the importance of EPCs in the process of repair of damaged endothelium during vascular trauma and ischemia, and recent *in vitro* and *in vivo* studies have revealed some important signaling pathways through which vitamin D exerts its beneficial effects on EPCs. In the field of regenerative medicine, EPCs have been recognized as one of the novel therapeutic agents in vascular disease and several pilot studies on animals have already shown encouraging results. Further studies focused on investigating the mechanism of action of vitamin D on EPC number and cell viability will likely yield metabolic and molecular pathways that more precisely elucidate the role of vitamin D in EPCs. Determining the mechanistic pathways of beneficial functions of vitamin D on EPCs will be critical for the translation of vitamin D as therapeutic agent in a subset of individuals with defective EPC functions or vitamin D deficiency.

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