

# Association of vitamin D and cardiovascular health

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## Abstract

Vitamin D insufficiency or deficiency is highly prevalent due to limited sun exposure especially in urban and elderly population. Vitamin D is now increasingly recognized as a hormone responsible for numerous physiologic functions in different cells and tissues of the human body including heart. Vitamin D has been shown to be linked with hypertension, acute coronary syndrome, heart failure, and atrial fibrillation. This review briefly overviews the relationship between vitamin D deficiency, its supplementation and outcome in cardiovascular health.

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## Introduction

Vitamin D is available in its two major forms: vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol).<sup>1</sup> Few foods naturally contain or are fortified with vitamin D whereas ultraviolet B irradiation to the skin converts 7-dehydrocholesterol to pre-vitamin D<sub>3</sub>, and is one of the important sources of vitamin D<sub>3</sub> in human body. Vitamin D from skin and food is metabolized in the liver to form 25-hydroxyvitamin D [25(OH)D; D represents D<sub>2</sub> or D<sub>3</sub>], which is used to determine patient's vitamin D status.<sup>2</sup> However, 25(OH)D is inactive and its further hydroxylation in the kidney is required to produce active form 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D, calcitriol].<sup>1,3</sup> Many experts define vitamin D deficiency, insufficiency, and sufficiency as levels of < 20ng/ml (50 nmol/L), 20 to 30ng/ml (50 to 75 nmol/L), and > 30 ng/mL (75 nmol/L), respectively.<sup>1,4-6</sup>

## Prevalence of vitamin D deficiency

It has been estimated that about a billion of world's population are either vitamin D deficient or insufficient.<sup>1</sup> Irrespective of age group, ethnic community and latitude of study populations, 13.0% of the 55,844 European people had serum 25(OH)D levels <30nmol/L on average in a year and when the level was <50nmol/L (20ng/ml), the prevalence was 40.4%.<sup>7</sup> A national sample of 11,247 Australian adults showed that 31% (22% men, 39% women) had 25(OH)D < 50nmol/L (20ng/ml) whereas 73% had levels < 30ng/ml.<sup>8</sup> The National Health and Nutrition Examination Survey 2005 to 2006 data of 4495 adult participants showed that overall prevalence of 25(OH)D ≤ 20ng/ml (50nmol/L) was 41.6%, with the highest rate seen in blacks (82.1%), followed by Hispanics (69.2%).<sup>9</sup> The prevalence of vitamin D deficiency was about 70% or higher in South Asia whereas varied from 6 to 70% in Southeast Asia, when 25(OH)D level <20ng/ml was used as cut-off.<sup>10</sup>

## Risk factors for vitamin D deficiency

Risk factors for vitamin D deficiency or insufficiency are old age,<sup>11</sup> dark skin pigmentation,<sup>12</sup> smoking,<sup>13</sup> obesity,<sup>14</sup> kidney

disease,<sup>15</sup> chronic liver disease,<sup>16</sup> and intestinal malabsorption syndromes (including, celiac disease, cystic fibrosis, short bowel syndrome, inflammatory bowel disease).<sup>17</sup> In addition to this, vitamin D deficiency is also associated with environmental variables such as air pollution,<sup>18</sup> winter season,<sup>19</sup> decreased exposure to sun light (for example indoor worker and shift worker)<sup>20</sup> and in people with decreased outdoor physical activity, frailty and institutionalized elderly.<sup>21</sup>

## Pathophysiology of vitamin D deficiency and cardiovascular disease

Vitamin D receptor proteins have been identified in different human tissues<sup>22</sup> including heart.<sup>23</sup> 1,25(OH)<sub>2</sub>D directly regulates the proliferation of cardiac myocyte and induces the myocyte hypertrophy.<sup>24</sup> Different studies suggest that vitamin D decreases renin-angiotensin-aldosterone activity.<sup>25</sup> The cardiac hypertrophy seen in vitamin D receptor knockout mice is due to the activation of both the systemic and cardiac renin-angiotensin system (RAS) suggesting that 1,25(OH)<sub>2</sub>D regulates the cardiac function, at least in part, through the RAS.<sup>26</sup> The secondary hyperparathyroidism and altered level of vitamin D found in chronic renal failure patient contribute to cardiovascular pathology and also to the excess mortality from cardiovascular causes found in these uremic group of patients.<sup>27</sup> A strong association was seen between vitamin D deficiency and slow coronary flow phenomenon, endothelial dysfunction and subclinical atherosclerosis, during coronary angiography in patients with normal or near-normal coronary arteries.<sup>28</sup> Administration of activated forms of vitamin D (1,25[OH]<sub>2</sub>D or analogs) to patients with end stage renal disease and secondary hyperparathyroidism results in regression in myocardial hypertrophy.<sup>29</sup>

## Vitamin D and hypertension

Meta-analysis done from randomized controlled trials of oral vitamin D supplementation found that supplementation of vitamin D significantly reduced systolic blood pressure (BP) by

2.44 mmHg, but did not decrease the diastolic BP.<sup>30</sup> A Mendelian randomization study to meta-analyse 146,581 participants found that each 10% increase in genetically instrumented 25(OH)D was associated with decrease in diastolic BP (-0.29 mmHg,  $p=0.01$ ), systolic BP (-0.37 mmHg,  $p=0.052$ ), and an 8.1% decreased odds of hypertension ( $p=0.002$ ).<sup>31</sup> Randomized controlled trials in participants with mean baseline BP >140/90 mmHg showed a non-significant reduction in systolic BP and a small significant reduction in diastolic BP (3.1 mmHg), whereas no significant reduction in BP was seen in patients who were normotensive at baseline.<sup>32</sup> Role of vitamin D or ultraviolet B radiation in BP regulation done in 10 trials found no significant effect of vitamin D on BP.<sup>33</sup> However, when limiting the analysis to studies that used higher doses of vitamin D supplementation (at least 1,000 IU/day), a small but statistically significant effect was seen. No significant BP-lowering effect of vitamin D supplements was seen in a meta-analysis which evaluated cardiovascular outcomes. The study stated that there was significant heterogeneity associated with this analysis.<sup>34</sup> Genetically determined variants were associated with low 25(OH)D and such population had higher blood pressure.<sup>35</sup> Meta-analysis of 16 randomized clinical trials revealed that there is no significant reduction of systolic and diastolic BP with vitamin D supplementation.<sup>36</sup> Subgroup analysis showed a significant reduction in diastolic BP in participants who had cardiometabolic disease.

#### Vitamin D and acute coronary syndrome

In the Health Professionals Followup Study of 18,225 men, lower levels of vitamin D were linked with increased risk of acute myocardial infarction (MI), even after controlling the risk factors known to be associated with coronary artery disease. People with normal vitamin D levels (> 30 ng/mL) were found to have half the risk of acute MI at 10-year follow-up compared to those with deficient vitamin D level.<sup>37</sup> A multicenter cohort study was done in United States with acute coronary syndrome and found that 96% of these patients at hospital presentation had vitamin D levels < 30 ng/mL.<sup>38</sup> Vitamin D deficiency was independently associated with more severe acute coronary syndrome and was a predictor of more extensive coronary lesions in patients with type 2 diabetes mellitus.<sup>39</sup> In patients with ST elevated MI and non-ST elevated MI, serum 25(OH)D levels were significantly low and that low serum 25(OH)D were significantly associated with severity and extent of coronary artery disease as assessed by SYNTAX score.<sup>40</sup> A metaanalysis showed that an adjusted overall relative risk of 1.52 for total cardiovascular events, 1.42 for cardiovascular mortality and 1.38 for coronary heart disease when compared with lowest to highest categories of baseline circulating vitamin D concentration ranging from 20 to 60 nmol/L.<sup>41</sup> When parathyroid hormone levels were high, increased level of 25(OH)D was associated with a lower risk of coronary heart disease, whereas no association was seen for participants with low level of parathyroid hormone.<sup>42</sup> Low vitamin D in acute coronary syndrome is linked with longterm major adverse cardiovascular events, which includes rehospitalization for acute decompensated heart failure or for successive acute coronary syndrome. Patients with acute myocardial infarction and 25(OH)D 3 level more than 7.3ng/ml were found to have approximately 40% lower risk for major adverse cardiac events.<sup>43</sup>

#### Vitamin D and heart failure

Vitamin D deficiency is highly prevalent in the elderly population, and there has been strong association between vitamin D deficiency and increased risk of heart failure in the elderly.<sup>44</sup> Supplementation of vitamin D decreased the serum levels of parathyroid hormone and inflammatory mediators like tumor necrosis factor- $\alpha$  and C-reactive protein in heart failure

patients whereas no beneficial effects were seen in terms of left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide (BNP), and six minute walk distance.<sup>45</sup> Vitamin D supplementation decreased the severity of heart failure as seen by reduction in serum pro-BNP levels and increase in six minutes' walk distance,<sup>46</sup> whereas no significant difference in six minute walk distance was seen in heart failure patients with vitamin D supplementation.<sup>47</sup> Low level of vitamin D was associated with various major cardiovascular risk factors and cardiac structural changes including impaired systolic and diastolic function.<sup>48</sup> Low vitamin D level has been associated with risk of heart failure, ventricular remodelling, and clinical outcomes in heart failure, including mortality. However, till date there are inadequate data to recommend routine assessment or supplementation of vitamin D for the prevention or treatment of chronic heart failure.<sup>49</sup>

#### Vitamin D and atrial fibrillation

Vitamin D deficiency was associated with new-onset atrial fibrillation (AF) in hypertensive patients.<sup>50</sup> Vitamin D level was not linked with AF in any of the three multivariate models tested (models adjusted for socio-demographic factors and life-style factors).<sup>51</sup> Vitamin D deficiency was related to non valvular AF but not with valvular AF.<sup>52</sup> Studies suggest that there may be an association between vitamin D deficiency and AF, incomparable study designs and methodological limitations hinder interpretation for definite evidence.<sup>53</sup> Incidence of post operative atrial fibrillation after coronary artery bypass surgery was significantly higher in patients with vitamin D deficiency or insufficiency than the patients with normal vitamin D level.<sup>54</sup>

#### Vitamin D level and cardiovascular disease outcome

In a 1739 Framingham offspring study participants, people with 25(OH)D <15ng/ml had a multivariate-adjusted hazard ratio of 1.62 (95% confidence interval 1.11 to 2.36) for incident cardiovascular events in comparison to those with 25(OH)D  $\geq$ 15ng/ml.<sup>55</sup> The effect was evident in participants with hypertension but not in those without hypertension. In a meta-analysis of 26916 participants with median follow-up time of 10.5 years, compared to 25(OH)D 75-99.99 nmol/L, adjusted hazard ratio of death from cardiovascular causes (95% confidence interval) for 25(OH)D 50-74.99, 40-49.99, 30-39.99, and <30 nmol/L were 1.37 (1.12-1.67), 1.65 (1.39-1.97), 1.61 (1.46-1.77), and 2.21 (1.50-3.26) respectively.<sup>56</sup>

#### Vitamin D supplementation and cardiovascular disease outcome

Even though vitamin D has been shown to be associated with cardiac disease but supplementation of vitamin D does not show convincing results. Vitamin D supplementation did not show clear evidence of benefits for preventing heart failure or influencing its clinical course.<sup>57</sup> Recent review from randomized controlled trials demonstrated that supplementation of vitamin D is ineffective in improving cardiovascular health among diverse patient populations, including those with or without vitamin D deficiency.<sup>58</sup> In the absence of specifically designed long-term study of vitamin D supplementation on cardiovascular effects, it is difficult to reject that supplementation of vitamin D has no cardiovascular benefit.<sup>59</sup> Some favourable reports were also seen in vitamin D supplementation. Supplementation of vitamin D might protect against heart failure in elderly but does not seem to protect against myocardial infarction or stroke.<sup>60</sup> There are weak signals of benefit of vitamin D supplementation in cardiac failure while vitamin D is found to be ineffective in lowering blood pressure. Although low vitamin D levels are associated with coronary artery disease, atrial fibrillation, peripheral vascular disease, and stroke, there is no significant benefit after vitamin D supplementation.<sup>61</sup>

## Summary

Patients with cardiovascular disease, especially those with heart failure that is severe enough, usually spend less time outdoor thereby do have minimal exposure to sun light. Cardiovascular disease affected patients are generally elderly. Both advanced age and decreased sun exposure are the risk factors for vitamin D insufficiency or deficiency. It has been found that there are associations of vitamin D deficiency with cardiovascular disease but to date, the review of vitamin D supplementation on cardiovascular patients has not shown convincing significant outcomes. Hence, vitamin D deficiency in these patients would only be because of their frailty and limited sun exposure. Due to the occurrence of vitamin D receptors in human heart tissue and the effect of vitamin D on structural changes of the heart, it cannot be neglected that vitamin D does not possess any role in cardiovascular health. It is therefore necessary to conduct large placebo (such as time spend indoor and outdoor with or without sun exposure) controlled randomised trials so as to give any definite conclusions.

## Conclusions

The studies done till date show mix results about the link of vitamin D deficiency with cardiovascular health. More large randomised placebo-controlled trials may be needed before any recommendations.

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