Vitamin D and cardiovascular disease – Have we found the answers?

S. Harikrishnan a,*, G. Sanjay b

a Additional Professor, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India
b Assistant Professor, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India

Vitamin D is a fat soluble vitamin which also functions as a hormone. Now there is ample evidence that low levels of Vitamin D has been found to be associated with diabetes, systemic hypertension, metabolic syndrome, coronary heart disease (CHD), heart failure and vascular inflammation.1

In this issue of IHJ, Ambuj Roy et al2 report a study on the independent association of vitamin D deficiency with coronary heart disease.

1. Vitamin D – the basics

There are 2 major forms of vitamin D, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is contained in plants and Vitamin D3 can be obtained through conversion of 7-dehydrocholesterol in the human skin upon exposure to ultraviolet B (UVB) radiation.

The Vitamin D is converted to 25(OH)D by liver, which is converted to 1,25(OH)2D (calcitriol) mainly by the kidney. Although 1,25(OH)2D is considered to be the active form of vitamin D, its levels in the serum do not correlate with the true vitamin D status, whereas 25(OH)D (calcidiol) level is found to be a more clinically relevant estimate.

The optimal levels of 25(OH)D vary based on different recommendations, but it has been suggested that the most advantageous serum concentrations of 25(OH)D begin at 30 ng/mL (75 nmol/L).2 Severe deficiency have been defined as <10 ng/mL.

2. The association between Vitamin D levels and cardiovascular disease

The association of low levels of vitamin D and CVD have been proven in epidemiological cohort studies in Europe and the United States. In a systematic review of longitudinal cohort studies from Europe and the United States, lower serum 25(OH)D concentration was associated with increased all-cause and cardiovascular mortality in subjects without pre-existing cardiovascular diseases with a risk ratio of 1.41 (CI 1.18–1.68).3 It was found that a curvilinear relationship exists between the serum concentrations of 25(OH)D and cardiovascular disease mortality. However, some authors have reported a possible ‘J’ or ‘U’ shaped association with higher cancer and cardiovascular disease risk both at low and high serum concentrations of vitamin D.5

The mechanism of Vitamin D deficiency leading to atherosclerotic vascular disease is complex. It involves raised parathormone levels leading to heightened RAAS (renin-angiotensin-aldosterone) activity, insulin resistance and inflammation. (Fig. 1). At the cellular level, vitamin D acts through the vitamin D receptor (VDR), which is found in virtually all tissues of the body including cardiovascular tissues like cardiomyocytes, endothelial, and vascular smooth muscle cells. Cardiovascular effects of vitamin D share the common initial steps of nuclear and plasma membrane VDR activation in the above cells. (Fig. 2).

There are few reports of association of CHD and vitamin D levels from India. An observational study of hospitalized patients with AMI from Bengaluru reported 83.5% prevalence of Vitamin D deficiency.6 The association between low vitamin D levels and cardiovascular risk factors have also been noted in previous studies from India.7

This study by Ambuj Roy et al2 is the first reported case control study regarding the association of CHD with low Vitamin D levels from India.

In this case–control study the authors compared 120 consecutive cases of first incident acute myocardial infarction (MI) and 120 age and gender matched healthy controls.

* Corresponding author.
E-mail address: drharikrishnan@outlook.com (S. Harikrishnan).
http://dx.doi.org/10.1016/j.ihj.2015.02.016
0019-4832/© 2015, Cardiological Society of India. All rights reserved.
Vitamin D deficiency, as defined by the most widely used criteria \([25(OH)D < 30 \text{ ng/ml}]\) was highly prevalent in cases and controls (98.3% and 95.8% respectively) with median levels significantly lower in cases (6 ng/ml and 11.1 ng/ml respectively). Severe vitamin D deficiency \([25(OH)D < 10 \text{ ng/ml}]\) conferred a significant risk of MI compared to controls. (odds ratio 4.5, CI 2.2–9.2).

A few points need to be discussed at this juncture.

1. High prevalence of Vitamin D deficiency in the general population in India.
2. Vitamin D deficiency – is it a cause or an association?
3. Will supplementation of Vitamin D improve the outcomes or can it harm?

Studies across India undertaken in diverse populations and geographical locations emphasize the universal prevalence of Vitamin D deficiency in the country to the tune of 70–100%. These studies have defined Vitamin D deficiency as serum 25(OH)D levels below 20 ng/ml or 30 ng/ml.

Even in this study by Roy et al., the prevalence of severe Vitamin D deficiency as defined as levels <10 ng/ml was high even in controls and only 4.2% of the controls had ‘sufficient’ Vitamin D levels. It is surprising that India which has abundant sunshine and those majority in the rural areas involved in the agricultural sector who are exposed to the sun have low vitamin D levels. One factor proposed as a predisposing factor in Indians is the low dietary calcium intake. Darker skin acts as a ‘natural sunscreen’ too.

The alternative way to look at relation of Vitamin D and CHD is to look into the evidence from supplementation studies. In the west, fortification of milk and other food products with either D3 or D2 is practiced and in some countries, it is mandatory. However, in India, this is not prevalent. Due to higher melanin content of the skin, minimum daily 45 min of direct sunlight exposure is recommended to obtain adequate Vitamin D in Indians. Supplementation is usually practised for metabolic bone disease. A daily dose of not exceeding 4000 IU (D3) is a common mode of supplementation. The weekly 60,000 IU (D3) regime with calcium for 8 weeks does not result in sustained improvement of Vitamin D levels in the long term.

Even though the evidence for association of low 25(OH)D levels with CHD is robust in both clinical and community level settings, supplementation of Vitamin D with or without calcium in diet does not seem to readily translate into improvement of cardiovascular disease morbidity or mortality independently as we discuss below.

A recent systematic review of 40 randomized control trials concluded that Vitamin D supplementation [in ergocalciferol (D2) or cholecalciferol (D3) form] to raise the serum 25(OH)D concentrations beyond 50 ng/ml did not reduce the relative risk of CHD in community dwellers by more than 15%. In another systematic review by Choudhury et al involving 22 studies (comprising of community level studies and clinical registers, average ages ranging from 56 to 85 years) and 30716 subjects, supplementing Vitamin D3 (and not D2) was found to result in a modest 11% relative risk reduction for all-cause mortality (risk ratio 0.89, CI 0.8–0.99). No impact on Vitamin D supplementation has been found in the control of hypertension in the recently published DAYLIGHT trial. There is paucity of data regarding the role of Vitamin D supplementation in secondary prevention of CHD. There are even studies reporting harm at higher serum levels of Vitamin D.

The actual reason for the difference in observations between association studies versus supplementation trials is not fully understood. This could be due to the possibility of low Vitamin D levels being an indicator of frailty and general ill-
health as evidenced by its association with elderly, obese, tobacco use, insulin resistance, chronic diseases, inflammatory conditions, malignancies etc. Rather than being the cause of these conditions, it might indicate an effect on its own.

Secondly it could be the result of the cut-off levels used for definition. The value of 30 ng/mL was derived based on the relationship between serum PTH and 25(OH)D levels which demonstrate a plateau in suppression of PTH when the 25(OH)D level reaches approximately 30 ng/mL. This might not be an optimal cut-off for the non-skeletal effects of the hormone, as evidenced by severe ‘deficiency’ in both cases and controls. We do not have normal levels specifically derived from the Indian population.

Another parameter which could influence the functional status of the hormone is the degree of protein binding and the concentration of the active hormone. There could be multiple confounding variables between a measured serum level and hormonal effect. Finally, the impact of an intermediate term supplementation of D2 or D3 with no consensus on the dose on a chronic disease process like CHD might not be significant.

The VITAL study is an ongoing research study in 25,875 men and women across the U.S. investigating whether taking daily dietary supplements of vitamin D3 (2000 IU) or omega-3 fatty acids (1 g) reduces the risk for developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses. This study is expected to provide a definite answer regarding the role of Vitamin D supplementation.

3. Perspectives from the current study

The study poses more questions for the researchers regarding the pathogenesis of atherosclerotic vascular disease. The association needs to be established by longitudinal studies with an objective to assess the impact if any on young age escalation of CHD in India. Such information could help in adoption of various life-style and dietary practices to improve vitamin D activity from an early age as an attempt to tackle the tsunami of CVD facing the country currently.

REFERENCES