

The Saga of Vitamin D: Does It Have a Role Beyond Musculoskeletal System and Calcium Homeostasis?

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Lower serum levels of vitamin D are strongly linked with an increased risk of all-cause and cardiovascular (CV) mortality [1, 2]. Several biological mechanisms have been proposed to elucidate etiological links underlying these associations. In some studies, supplementation with vitamin D has been found to be useful in reducing the risk of colon, rectum, and breast cancers [3, 4].

A number of epidemiological studies that examined associations between vitamin D deficiency and all-cause and CV mortality have limited external validity due to studied population subgroups [2, 5]. There is a possibility that the selected subgroups did not reflect true status of vitamin D and its impact on the prevention of all-cause or CV mortality in otherwise asymptomatic population. In addition, large number of the observational studies has used quartile based analytic approach to estimate associations between vitamin D status and mortality which could obscure findings at extremes of vitamin D from respective cohorts [6]. Moreover, the cutoff boundaries for selected quartiles were not uniform; for example, the mean serum vitamin D levels in the lowest quartiles ranged from 5.6 to 17.8 ng/mL [1, 2, 5, 7].

The relationship between vitamin D deficiency and systemic inflammation (as measured by circulating inflammatory biomarkers such as C-reactive protein, homocysteine and interleukins) in healthy individuals is also not yet settled. It appears that the anti-inflammatory properties of vitamin D may not be noticeable unless offered to individuals with severely low serum vitamin D levels. Moreover, vitamin D may play a detrimental role by increasing inflammation once it rises beyond a certain level [8]. Tarcin et al reported marked improvement in endothelial dysfunction, markers of oxidative stress and insulin sensitivity index among individuals [mean vitamin D levels of < 10.01 ng/mL (base line)] whose vitamin D levels improved to 30.04 ng/mL (after vitamin D supplementation for three months) [9].

Literature also suggests that the relationship between serum 25 (OH) D and mortality is non-linear such that there is an increased risk of death both at higher as well as lower circulating levels of vitamin D [1, 10, 11]. While data from the observational studies is overwhelming, randomized controlled trials are needed to establish causality between vitamin D status and mortality especially among individuals with no pre-existing CV disease or high CV risks. Based on the lack of established benefits of vitamin D supplementation, the Endocrine Society's Clinical Practice Guidelines did not recommend screening individuals who are not at risk of vitamin D deficiency or prescribing vitamin D for non-calcemic benefits [12].

With ongoing skepticism on its role in primary and secondary prevention, it seems that the long-drawn-out practice of vitamin D supplementation will soon lose its significance. However, healthcare providers are strongly encouraged to identify target patient population that could benefit from vitamin D supplementation for its non-calcemic and non-musculoskeletal effects on body. Until, randomized controlled trials do not completely rule out (or rule in) a substantial role of vitamin D supplementation in limiting CV disease progression, lowering certain cancer incidence, and decreasing all-cause mortality, the saga of a potential role of vitamin D beyond musculoskeletal and calcium homeostasis will continue.

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