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Editorial

Anti-Inflammatory Effect of Vitamin D via Suppression of YKL-40 Production: One of the Possible Mechanisms for Cardiovascular Protection

Hack-Lyoung Kim, MD, PhD

Division of Cardiology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

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Correspondence to
Hack-Lyoung Kim, MD, PhD
Division of Cardiology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea.
Email: khl2876@gmail.com

ORCID iDs
Hack-Lyoung Kim
https://orcid.org/0000-0002-6703-1472

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It is well known that vitamin D is transformed into an activated form by sunlight and hepatic/renal metabolism, which increases calcium absorption and plays a crucial role in maintaining bone health. In addition to its classical role in influencing bone metabolism, the vitamin D receptor is expressed in almost every tissue in the body and thus has numerous biological effects. In recent years, the function of vitamin D in other organs has become increasingly recognized.

Many studies have demonstrated the pathophysiology of vitamin D's cardiovascular protective effects. Vitamin D lowers renin production and weakens the renin-angiotensin system's activity, leading to delays in the onset of hypertension, atherosclerosis, and heart failure. In addition, vitamin D suppresses inflammatory reactions, thrombosis, and calcification. Vitamin D also inhibits myocardial fibrosis and improves myocardial contractility. Based on these mechanisms, several epidemiological and observational studies have shown the association between low blood levels of vitamin D and high rates of cardiovascular disease (CVD).[1]

The inflammatory response is deeply related to CVD, such as causing the endothelial dysfunction, vascular calcification and progression of atherosclerotic plaques and rupture.[2][3] Vitamin D is known to suppress the inflammatory response through a variety of mechanisms. Vitamin D acts on immune cells to increase the production of antibacterial substances, and regulates T cells to reduce the production of cytokines, such as interleukin (IL)-1, IL-6, IL-12, IL-17, and tumor necrosis factor-α, that cause inflammatory responses.[4]

YKL-40 is a proinflammatory glycoprotein secreted from endothelial cells, vascular smooth muscle cells, and various inflammatory cells.[5] YKL-40 protein expression is particularly high in atherosclerotic lesions, and is involved in endothelial cell dysfunction and atherosclerosis. Several studies have reported that elevated serum YKL-40 levels were associated with more severe coronary artery disease, and a higher YKL-40 level was an independent predictor all-cause and cardiovascular mortality.[6]

In this issue of the *Korean Circulation Journal*, Kocabas[7] performed an animal experiment and provided evidence that vitamin D supplementation effectively suppressed serum YKL-40 levels in a hypercholesterolemia rat model. First, the researchers found that blood levels

Data Sharing Statement

The data generated in this study is available from the corresponding author upon reasonable request.

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of YKL-40 were increased in rats fed a high-cholesterol-rich diet compared to rats fed a normal diet. Second, the effect of increasing blood YKL-40 by the high-cholesterol diet was more pronounced when the vitamin D-removed feed was given. Third, when vitamin D was supplied, the increase in blood YKL-40 caused by the high-cholesterol diet was attenuated. Consistent with these findings, several human studies have also reported an association between vitamin D and YLK-40. Can et al.[8] reported that plasma YKL-40 levels were significantly lower in subjects with vitamin D deficiency compared to age and sex-matched healthy subjects. In another study, Omidian et al.[9] showed that vitamin D supplementation significantly reduced serum YKL-40 levels in type 2 diabetic patients. All these results suggest that vitamin D may be related to the decrease of YKL-40, leading to the suppression of chronic inflammation.

As mentioned above, both vitamin D and YKL-40 are substances deeply involved in the occurrence of CVDs and have recently attracted attention. Although the effect of vitamin D supplementation on cardiovascular system is less clear,[10] the association between low vitamin D levels and worse cardiovascular outcomes is evident.[1] Therefore, vitamin D deficiency has been suggested as one of the cardiovascular risk factors. However, the mechanisms of the association between vitamin D levels and CVD are still largely unknown. Vitamin D deficiency is frequently identified in various chronic inflammatory diseases, and many studies have shown that vitamin D has anti-inflammatory activity. The anti-inflammatory action of vitamin D is expected to contribute at least to some extent to its cardiovascular protective effect. In this regard, recent animal study has suggested that YKL-40, an inflammatory glycoprotein, is an important target of vitamin D.[7] Further studies are needed to determine whether vitamin D supplementation also lowers YKL-40 concentrations in human blood and whether the cardiovascular prognosis is affected by the YKL-40 concentrations. Recently, disappointing results have been published that vitamin D supplementation does not improve cardiovascular outcomes in humans.[10] It is also very meaningful and interesting to re-analyze the effect of vitamin D on long-term cardiovascular prognosis based on the individuals' inflammatory status including YKL-40 concentration. Accumulating results from studies in humans suggest that drugs having inhibitory action for YKL-40 production are good treatment options for cardiovascular protection.

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