

## Invited Editorial / Davetli Editöryal Yorum

### Association between Vitamin D and arterial stiffness

#### Vitamin D ve arteriyel sertlik arasındaki ilişki

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Vitamin D is a type of fat-soluble pleiotropic hormone. In addition to known effects regarding calcium metabolism, numerous reports of effects on the cardiovascular system have recently been published.<sup>[1-3]</sup> Low vitamin D concentration (defined as serum 25-hydroxy vitamin D concentration either below 50 nmol/L or 20 ng/ml) can impair vascular function. Vitamin D deficiency may cause vascular inflammation, endothelial dysfunction, smooth muscle proliferation, vascular calcification, and left ventricular hypertrophy by altering the renin angiotensin system, as well as insulin sensitivity.<sup>[4,5]</sup> Expression of inflammatory mediators, such as IL-6, or nuclear factor  $\kappa\beta$ , is increased in cases of vitamin D deficiency. Vitamin D is also of importance in terms of smooth muscle function. For example, vitamin D analogues may promote vascular relaxation through the endothelin genes. Vitamin D function in the maintenance of vascular compliance has been demonstrated in preclinical studies.<sup>[6,7]</sup> Many clinical trails with results concerning the association of vitamin D and cardiovascular disease have been published. Dobnig et al. reported that patients with vitamin D deficiency had higher all-cause mortality and cardiovascular mortality than patients with normal vitamin D values, in a study in which 3258 patients were recruited, with follow-up of 7.7 years.<sup>[8]</sup> In addition, arterial stiffness, an independent predictor of cardiovascular events and all-cause mortality, was associated with vitamin D.<sup>[9,10]</sup>

After it had been shown in preclinical trials that vitamin D analogues improved vascular parameters, the potential of improved vascular parameters by means of vitamin D replacement was investigated in patients with vitamin D deficiency. However, results conflicted. In a study conducted by Chitalia et al., im-

provement in endothelial function was reported with vitamin D replacement in patients with vitamin D deficiency.<sup>[11]</sup> Similarly, Tarcin et al. showed that endothelial dysfunction was associated with vitamin D deficiency, and was regressed with replacement therapy.<sup>[12]</sup> However, McGreevy et al. showed that vitamin D replacement had no effect on arterial stiffness.<sup>[13]</sup> Ryu et al. reported an association between arterial stiffness and vitamin D, but that replacement of vitamin D did not improve arterial stiffness.<sup>[14]</sup> In a meta-analysis conducted by Rodriguez et al., which included 18 trials, it was demonstrated that vitamin D replacement had no positive effect on arterial stiffness.<sup>[15]</sup>

Sunbul et al. reported, in a study published in this issue of the Archives of the Turkish Society of Cardiology, that vitamin D replacement improved arterial stiffness, and that an association was observed in patients with vitamin D deficiency and normal cardiac function.<sup>[16]</sup> Arterial stiffness was evaluated prior to and following vitamin D replacement therapy (50000 IU/week for 8 weeks, 2000 IU/d, thereafter). Results demonstrated that arterial stiffness indices (pulse wave velocity and augmentation index) were significantly diminished following replacement therapy. A statistically significant association between arterial stiffness and vitamin D values was also reported.

Heterogeneity of studies evaluating the association between vascular parameters and vitamin D may partially explain divergent results. Baseline vitamin D values, treatment doses, and duration of follow-up have been the primary discrepancies. Treatment dose of vitamin D has ranged from 1000 IU/day to 5700 IU/day. Replacement doses have also been administered at divergent intervals, including once daily

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or once weekly. Vitamin D values were within normal range following replacement in certain studies, whereas values were still markedly decreased in others. McGreevy and et al. reported that replacement of vitamin D did not affect arterial stiffness, but values were in a lower range (<20 ng/ml).<sup>[13]</sup> It may be speculated that vitamin D deficiency values obtained immediately following replacement may skew the data. In addition, duration of replacement therapy was discrepant (1–12 months). These factors may explain the differences in results. In the study conducted by Sunbul et al., base vitamin D values were very low (6 nmol/L). After 12-week replacement therapy, they were still under the normal limit (29 nmol/L). However, arterial stiffness parameters improved, following treatment. These favorable results were elicited with very low baseline vitamin D values. In addition, high doses of vitamin D replacement therapy (50000 IU/w) were administered in the first 8 weeks, which may have contributed to the favorable findings.

One can say that there is a relationship between vitamin D deficiency and vascular parameters. However, whether it is a cause or a result is debatable. Similar to relating higher homocysteine and lower high-density lipoprotein levels to atherosclerosis, as well as demonstrating the uselessness of the normalization of these levels, vitamin D deficiency may be associated with vascular disorders. However, this is not the cause but the result of vascular impairment.

Therefore, for the time being, adequate data demonstrates that vitamin D replacement can prevent cardiovascular events. Besides, the definition of vitamin D deficiency has been determined based on endocrinological efficiency. It is possible that the need for re-definition arises from the cardiovascular perspective. In addition, the cut-off value for vitamin D deficiency should be determined for the cardiovascular system. Data to determine the dose and duration of vitamin D replacement are needed. Together with standardization of these definitions, we believe that the importance of vitamin D replacement and the correlation between vitamin D levels and the cardiovascular system will be clarified, in terms of cardiovascular parameters.

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