Vitamin D: a novel player in endothelial function and dysfunction

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Vitamin D is produced endogenously in the skin after exposure to the ultraviolet B spectrum of sunlight. Importantly, only few foods are natural sources of a consistent amount of vitamin D. Consequently, vitamin D insufficiency and deficiency are widespread among humans due to limited sun exposure and insufficient consumption of foods or beverages containing vitamin D.

Vitamin D, as an inactive precursor, needs to undergo several steps to be converted into the active form. First, in the liver, vitamin D is converted into 25-hydroxyvitamin D [25(OH)D]. This inactive precursor is of clinical significance since it represents the standardized measure of the vitamin D status. It is commonly recognized that plasma levels < 20 ng/ml are insufficient [1]. 25(OH)D is then converted in the renal proximal tubule to the active form calcitriol [1,25$(OH)_2$D] whose levels are regulated by the parathyroid hormone (PTH).

The primary physiological role of vitamin D in regulating calcium homeostasis is well established: hypovitaminosis D is known to contribute to osteoporosis through a decline in calcium absorption, subsequent secondary hyperparathyroidism, and increased bone resorption. For this reason, decreased vitamin D levels are usually associated with increased PTH levels, and vitamin D supplementation significantly reduces PTH plasma levels [2].

Importantly, vitamin D receptors are expressed by virtually all tissues, including vascular smooth muscle cells and cardiomyocytes [3]. Therefore, the attention of researchers has recently shifted towards finding a link between hypovitaminosis D and cardiovascular diseases.

Several physiological mechanisms link vitamin D to hypertension because calcitriol acts as an endogenous inhibitor of the Renin Angiotensin System (RAS), finally determining intracellular calcium levels in vascular smooth muscle cells. Mice lacking vitamin D receptor show excessive plasma renin activity with associated hypertension [4]. Interestingly, such observations have also been confirmed in human disease, with cross-sectional studies demonstrating higher levels of calcitriol associated with lower plasma renin activity [5]. However, only observational studies support a link between vitamin D levels and blood pressure, whereas there are no interventional studies confirming a potential effect of vitamin D supplementation on blood pressure.

Endothelial dysfunction represents an early event in cardiovascular diseases which is relatively easy to assess nowadays. It is worthy to note

that both observational and interventional studies have established an association between vitamin D levels and endothelial dysfunction. In a small cohort of young asymptomatic patients, flow mediated dilatation (FMD) measurements were significantly lower in 25(OH)D-deficient subjects than controls, and improved after acute treatment with calcitriol [6]. Moreover, vitamin D negatively correlated with brachial artery FMD also in pathological conditions, as shown in a large cohort of patients affected by type 2 diabetes.

The study published in *Archives of Medical Science* [7] was designed to address whether 25(OH)D plasma levels in normotensive women were associated with vasodilator function of the endothelium, as assessed by reactive hyperaemia index (RHI).

The authors studied a homogeneous, although quite small, group of healthy, normotensive, non-smoking, normolipidaemic and normoglycaemic women, who were classified according their plasma levels of 25(OH)D. This represents to original subset of patients, with no interference of confounding elements such as smoking, medications or pre-existing cardiovascular abnormalities. In addition, endothelial function was evaluated through reactive hyperaemia index (RHI), assessed by digital (fingertip) peripheral arterial tonometry (PAT), a validated operator-independent technique [8]. It is important to note that the vasodilator response following transient regional ischaemia is a well established measure of vascular function both in brachial artery and in digital microcirculation, although the two vascular beds may reflect distinct aspects of vascular function.

In accordance with pre-existing literature, RHI was significantly lower in subjects deficient for vitamin D than in controls, and serum 25(OH)D levels emerged as the best positive predictor for RHI. Surprisingly, diastolic blood pressure turned out to be significantly lower in the low vitamin D group, differently from what would have been expected.

However, caution is advised in interpreting these results, considering the relatively small study group. Also, as the authors themselves stated, blood pressure measurements were not based on 24-h registration. The question arises whether the menopausal or post-menopausal status could have revealed different outcomes in endothelial function during the follow up of the same patients. It appears that all the patients studied were pre-menopausal, even if the authors did not explicitly clarify this important aspect. Given the relatively narrow range of age, which was close to the menopausal transition, it would be extremely interesting to evaluate potential differences in deterioration of endothelial function related to the vitamin D status [9].

In conclusion, a large body of evidence suggests a link between vitamin D and cardiovascular diseases, but available data are still insufficient to conclude that low levels of vitamin D lead to an increased cardiovascular risk, especially in view of the fact that most of the data are based on observational studies. Vitamin D supplementation studies conducted so far are mainly equivocal. For this reason, recent guidelines published by the Endocrine Society do not recommend screening for vitamin D insufficiency for cardiovascular protection [10]. Large randomized clinical trials with vitamin D, which have recently started, have as their primary endpoint the evaluation of cardiovascular outcome. Hopefully, several years will be enough to establish a real causal link between the vitamin D status and cardiovascular risk, and to finally shed more light on the pathophysiology of endothelial dysfunction in relation to the vitamin D status.

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