Is At Least One Vitamin Helping Our Vasculature?
Evidence for an Important Role of the Endothelial Vitamin D Receptor in Regulating Endothelial Function and Blood Pressure

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Cardiovascular risk factors such as diabetes mellitus, arterial hypertension, chronic smoking, and hypercholesterolemia are cardiovascular risk factors known to be associated with endothelial dysfunction, a condition that may predict long-term progression of atherosclerosis as well as cardiovascular event rates (for review, see Münzel et al). Although the mechanisms underlying this phenomenon are complex and multifactorial, there is growing body of evidence that oxidative stress attributable to increased production of reactive oxygen–derived free radicals may play a pivotal role in this process. Increased superoxide production by enzyme systems such as the nicotinamide adenine dinucleotide phosphate oxidase may then cause oxidative modification of the protective endothelial NO synthase. This phenomenon termed eNOS uncoupling switches the enzyme from a antiatherosclerotic NO producing to a pro-oxidative, superoxide-producing enzyme.

Although the concept of increased oxidative stress burden in cardiovascular disease is in general accepted, the results of trials with antioxidants such as vitamin B1, C, and E and with folic acid in combination with B vitamins are in general disappointing, and in some aspects, vitamins are accused even to precipitate cardiovascular events. For example, in a meta-analysis, vitamin E treatment has been shown to increase mortality, and the Heart Outcomes Prevention Evaluation (HOPE) and HOPE The Ongoing Outcome (TOO) trials revealed that vitamin E more often leads to the development of heart failure and left heart decompensations. Vitamin C supplementation caused more cardiovascular events in postmenopausal women with diabetes mellitus, and treatment of patients with folic acid and B vitamins (Norwegian Vitamin Trial [NORVIT]) increased mortality in patients with acute myocardial infarction. In addition, the combination of folic acid and B vitamins effectively lowered plasma homocysteine levels, but failed to improve prognosis in patients with vascular disease.

What do we know about vitamin D? The vitamin is traditionally known for its role in bone metabolism, and importantly, it is in general accepted that vitamin D deficiency is frequently encountered as an independent risk factor for cardiovascular disease. To date, it remains to be elucidated whether these associations are of causal nature. It is known that vitamin D supplementation improves endothelial dysfunction in patients with low vitamin D levels, and a recent Cochrane analysis revealed that vitamin D treatment causes a moderate but significant reduction in cardiovascular mortality in elderly people. However, further evidence in form of randomized, placebo controlled trials is needed.

What are the potential underlying mechanisms by which vitamin D treatment can improve prognosis in patients with cardiovascular disease? The article by Ni et al provides some insight by demonstrating that the endothelial vitamin D receptor (VDR) plays an important role in endothelial function and in the regulation of blood pressure. The authors found that knock-out of the endothelial VDR causes a significant impairment of the acetylcholine-induced vasodilation as well as a reduction in eNOS expression, a finding that is in accordance with a recently published study in mice carrying a mutant, functionally inactive VDR. Because of decreased levels of bioavailable NO, a reduction in the activity of the cGMP-dependent kinase as assessed by phosphorylation of the vasodilator-stimulated phosphoprotein (VASP) was observed (Figure). Because vascular NO bioactivity is strongly regulated by the interaction with superoxide, the authors also addressed this issue by performing dyhydroethidine staining of vessels from animals with and without endothelial VDR deletion. The authors hereby found a significant increase in endothelial superoxide, which may contribute to endothelial dysfunction. Further studies revealed that infusion of angiotensin II, a well-accepted animal model of arterial hypertension attributable to increased oxidative stress, caused a higher blood pressure and a higher expression of fetal genes such as type-A natriuretic peptide and type-B natriuretic peptide and a higher expression of hypertrophy markers such as collagen 3a1 in the myocardium of animals with VDR knockout. Mechanistically, this observation is likely attributable to enhanced angiotensin II signaling mediated by angiotensin II receptor subtype 1 upregulation and increased cathespin D levels, a lysosomal protease that displays renin-like enzymatic activities. Collectively, these results clearly demonstrate the protective role of the endothelial VDR in vascular tissue and the myocardium.

Although these results are in part novel and exciting, there are many questions to be solved in the future. What is the precise mechanism of eNOS activation in response to VDR activation? Why is the expression of eNOS diminished? The demonstration of increased superoxide production within the endothelial layer in VDR knockout animals, is it simply the...
consequence of decreased NO production or is there an activation of the nicotinamide adenine dinucleotide phosphate oxidase or even eNOS uncoupling?

In addition to the need for more basic science studies to gain mechanistic insights, additional clinical trials are required to understand the vascular effects of vitamin D in patients and its consequences for blood pressure/myocardial function.

Although it is accepted that vitamin D deficiency is an independent cardiovascular risk factor, the results of clinical trials investigating whether vitamin D supplementation can reduce cardiovascular risk are still conflicting. Therefore, we are urgently awaiting the results of large randomized controlled trials testing the effects of vitamin D supplementation on outcome in patients with heart failure and on cardiovascular and cancer mortality in older subjects. In that respect, it seems important to treat only patients with cardiovascular disease and vitamin D deficiency but not all patients with CVD regardless of vitamin D plasma levels, otherwise disappointing results like with the vitamin E trials may be encountered.

The results published by Ni et al. will open a new era of research, and there is some hope that vitamin D may represent a vitamin, which ultimately will help to improve vascular function and thus to prevent and to treat cardiovascular disease.

None.

References

Figure. The vitamin D metabolite 1,25 dihydroxyvitamin D (1,25(OH)2D) binds to the endothelial vitamin D receptor (VDR) and increases the activity and expression of the endothelial NO synthase. Accordingly, NO production is increased as is the intracellular signaling including an activation of the cGMP-dependent kinase I, detected by higher phosphorylation of the vasodilator-stimulated phosphoprotein (VASP). Activation of the VDR stimulation also inhibits the expression of the angiotensin II receptor type 1 (AT1) receptor, thus leading to less activation of the endothelial and smooth muscle nicotinamide adenine dinucleotide phosphate oxidase, one of the most significant superoxide source in our vasculature. It has also been shown that NO is a potent inhibitor of the NADPH oxidase, all of which may explain why VDR activation reduces vascular oxidative stress. cGK-I indicates cyclic GMP dependent kinase I; and sGC, soluble guanylyl cyclase.
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