Vitamin D, Hypertension, and Ischemic Stroke
An Unresolved Relationship

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Hypertension, one of the most common chronic diseases worldwide, is a major risk factor for coronary heart disease, cerebrovascular disease, congestive heart failure, end-stage kidney disease, and peripheral vascular disease and consequently results in major disability and mortality. One of the most dreaded complications of hypertension is ischemic stroke. Efforts for over 4 decades have been directed to identify genes that are causally involved in the pathophysiology of hypertension and those that constitute genetically determined risk factors for the development of hypertension and its complications. Can the factors, genetic or otherwise, predisposing to hypertension-related ischemic stroke be identified and can a preventive strategy be derived, based on such information?

It has long been suggested that a low plasma vitamin D level is one of the factors that may be associated with hypertension and ischemic stroke. This notion comes from biological studies in animals and observational studies in humans that relate low active vitamin D levels to the renin–angiotensin system and to arterial wall thickness or stiffness.[1–6] Since then, multiple observational studies have tried to demonstrate an inverse correlation between plasma vitamin D levels and hypertension. However, a recent systematic review and meta-analysis of randomized controlled trials on the effect of vitamin D supplementation on blood pressure failed to show that vitamin D supplementation effectively lowers blood pressure,[7] casting doubt on the clinical relevance of such correlation. The question nonetheless remains whether there is a real causal relationship between low vitamin D levels and ischemic stroke that is associated with hypertension.

In the current issue of *Hypertension*, Afzal and Nordestgaard[8] approached the problem by asking whether lifelong exposure to low vitamin D level in a native Danish population is indeed a risk factor for high blood pressure on the one hand and for ischemic stroke on the other. The investigators adopted a dual design, consisting of an observational study and a Mendelian randomization methodology. The difference between the 2 approaches is that the former is susceptible to confounding effects of multiple other established risk factors for ischemic stroke (Figure), whereas the latter is less susceptible to confounders and is seemingly free from reverse causation. In the Mendelian randomization arm of the study, the authors included a mega-cohort derived from 2 studies performed in Copenhagen, which they combined. In a total of 116 655 individuals, they sought genetic variants in the *DHCR7* and *CYP2R1* genes that have been associated with lower levels of vitamin D. Even though actual measurements of vitamin D levels were performed in only 35 258 (30%) of these subjects, the working assumption of the investigators was that this would suffice to infer low levels of vitamin D levels in the remaining subjects. In the observational arm of the study, the investigators used a cohort consisting of 35 517 individuals derived from the same 2 studies but not overlapping. The investigators assessed in both cohorts the potential consequences of low vitamin D levels on blood pressure and ischemic stroke.

The data that were derived from the observational arm demonstrated that in individuals with 25-hydroxyvitamin D levels <25 nmol/L, systolic and diastolic blood pressure was 2.56 and 1.88 mm Hg, respectively, higher than in individuals with levels >50 nmol/L. They also showed that there is an inverse relationship between blood pressure and the risk of developing hypertension and ischemic stroke for vitamin D levels <50 nmol/L. The data from the Mendelian randomization arm of the study indicated that a combined allele score of 6 to 8 genetic variants in *DHCR7* and *CYP2R1* was associated with 8.4 nmol/L lower vitamin D levels than a score of 0 to 1 variant alleles. In the same cohort, 1-U increase in weighted *DHCR7* and *CYP2R1* allele scores translated to an increase in systolic and diastolic blood pressure of 0.07 and 0.04 mm Hg, respectively. The inverse correlation between vitamin D levels and systolic and diastolic blood pressures was also demonstrated by the instrumental variable estimate. The results thus confirmed an inverse association between the number of allele variants of the 2 genes and 25-hydroxyvitamin D plasma levels on the one hand, and a direct relationship with blood pressure on the other. Unfortunately, the analysis failed to demonstrate a parallel increase in the odds ratios for ischemic stroke in the presence of increased blood pressure. The investigators summarized their finding by stating that even though the observational studies supported a relationship between plasma levels of 25-hydroxyvitamin D, a higher blood pressure and ischemic stroke, the genetic studies failed to confirm a causal relationship with the outcome of ischemic

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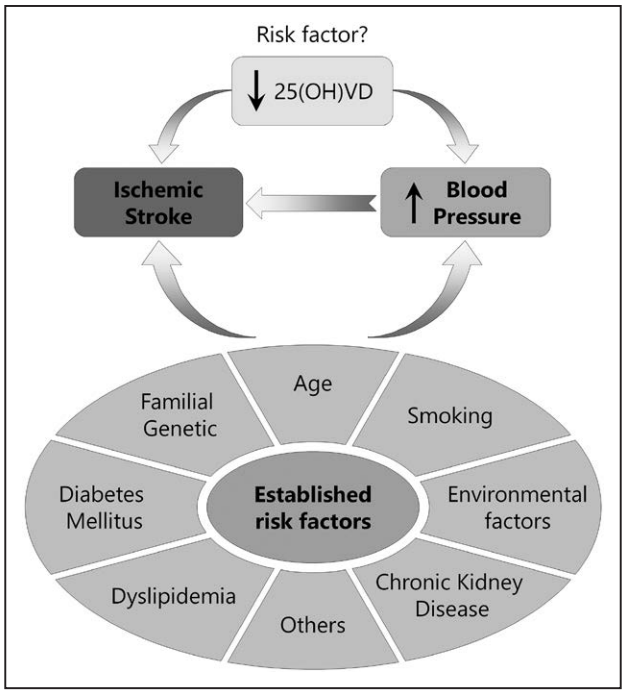

Figure. Multiplicity of risk factors for hypertension and ischemic stroke. 25(OH)VD indicates 25-hydroxyvitamin D.

stroke. The authors concluded that their study could neither support nor exclude such causal relationship.

The discrepancy between the observational and Mendelian randomization studies suggests that additional confounding factors are likely to come into play in the development of ischemic stroke in the presence of low vitamin D levels. And yet, the Mendelian randomization study did confirm an inverse relationship between vitamin D levels and blood pressure. The question, therefore, arises why was the increase in blood pressure in the presence of low vitamin D levels not sufficient to account for ischemic stroke? One possible answer is that the low vitamin D levels were associated with only a very minor effect on blood pressure, not of sufficient magnitude to be directly associated per se with ischemic stroke. Indeed, in the current study, 10 nmol/L lower genetically determined vitamin D levels were translated into a 1.4 mm Hg difference in blood pressure per (the corresponding value in the observational cohort was 1.2 mm Hg). If the association between vitamin D levels and blood pressure is based on the assumption that vitamin D effectively negatively regulates the renin–angiotensin system, why were low vitamin D levels associated with only such a minor effect on blood pressure? There are several possible answers to this question. First, the evidence for a strong association between vitamin D plasma levels and blood pressure came primarily from animal studies performed by Li et al[2] in a VDR (vitamin D receptor)-null mouse model and subsequently by Weng et al[1] in a diet-induced vitamin D deficiency model on the background of low-density lipoprotein receptor– and ApoE (apolipoprotein E)-null mouse. In these models, the phenotype of the animals was hypertension, and the magnitude of the blood pressure effects was major. In contrast, observational studies in humans that investigated the effect of vitamin D supplementation on blood pressure showed only a minor or no effect on blood pressure, thus weakening the evidence for an inverse association between vitamin D and hypertension.[3–6] The lack of consistency between the animal and the human studies may not be unexpected, as positive findings in a vitamin D receptor knockout model or in a vitamin D–deficient mouse cannot necessarily be extrapolated to humans with low vitamin D plasma levels who are provided vitamin D supplementation. Second, the mechanism whereby the vitamin D receptor has been viewed to affect blood pressure by downregulating the renin–angiotensin system may be an oversimplification of a complex system. Because the vitamin D receptor has wide tissue distribution, it may affect many systems beyond the renin–angiotensin system, including the inflammatory response, that has been implicated in the pathophysiology of hypertension.[9] The nature of this interaction is, however, unclear. In this sense, assuming that vitamin D deficiency is a reflection of vitamin D receptor knockout may be too naive, and so it may not be surprising, therefore, that vitamin D supplementation fails to correct elevated blood pressure. It can also be claimed that only very severe vitamin D deficiency would significantly affect blood pressure. Indeed, the current study shows an almost linear increase in blood pressure and risk of hypertension and ischemic stroke with decreasing 25(OH) concentrations <50 nmol/L (determined by observational estimates). Third, hypertension, except for few forms with clear monogenic inheritance, is a complex polygenic disease. It is likely that many more genes are involved beyond those affecting vitamin D levels, and that each exerts its own small contribution to the overall phenotype, rather than a master regulatory gene(s). Furthermore, a change in 1 arm of the system could be overcome by another change in yet unknown arm with no significant change in blood pressure.

In conclusion, in the current study, low levels of vitamin D were positively associated with higher blood pressure, but it is likely that the magnitude of the rise in blood pressure per se was insufficient to account for the development of ischemic stroke. And yet, despite the negative findings as to the relationship of vitamin plasma levels, hypertension, and ischemic stroke, this study is an important and significant step forward in the attempt to answer the question whether we should regard vitamin D as an important modifiable risk factor for hypertension. Our prediction, based on currently available data, is that because vitamin D is likely to be only one of the many factors that affect blood pressure and the risk of ischemic stroke (Figure), supplementation of vitamin D may exert beneficial effects only if it is incorporated into a polypill with additional components that significantly affect blood pressure and stroke as well. Efforts, therefore, to prevent cardiovascular and cerebrovascular disease, morbidity, and mortality by mere vitamin D supplementation are likely to prove futile. This prediction is consistent with very recent studies that have failed to show improved cardiovascular survival after vitamin D supplementation.[10]

Disclosures

None.

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