What Do We Know and Do Not Know About Vitamin D?: A Causal Association Between Vitamin D Receptor Genetic Polymorphism and Hypertension

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In this issue of the *Journal*, Jia and colleagues[1] conducted a genetic association study in which they evaluated the relationship between vitamin D receptor (VDR) polymorphism and hypertension in a Chinese Han population. In a case-control model, the study included 2409 patients with known hypertension and initial office blood pressure (BP) elevation as well as 3063 control patients with normal BP and no history of hypertension. Patients and controls were recruited through a community-based epidemiological survey, and both groups included participants of Han Chinese ethnicity only. Basic demographic and clinical features of the study population were gathered through interview with standard questionnaire. Fasting blood samples for studying serum glucose level and lipid profile were obtained.

A rigorous methodology was used to select candidate single nucleotide polymorphisms (SNPs) in the VDR gene region. The authors selected three SNPs by setting minor allele frequency at ≥0.05 from Hapmap of Han Chinese and applied the linkage disequilibrium method to determine tagging SNPs with $r^2 \geq 0.80$ as candidate SNPs. Finally, three SNPs (rs11574129, rs2228570, and rs739837) were selected. Genomic DNA was extracted from circulating leucocytes in all patients and controls by means of a commercial system.

There was no sex difference seen, although patients were significantly older compared with controls. Serum fasting triglyceride and glucose concentrations as well as systolic and diastolic BPs were significantly higher in patients compared with controls. There was no difference in terms of rate of smoking status and high-density lipoprotein concentration between the groups.

The patient and control groups were no different in terms of genotype and allele frequencies of all three SNPs studied, even after adjusting for covariates. The authors also performed a stratified analysis based on sex, age, and smoking. Only SNP of rs2228570 showed a statistically significant association with decreased risk of hypertension in the male group and smokers separately. However, other SNPs did not show such a significant association in stratified analyses.

Finally, the authors divided patient group into naive hypertensives and patients who were already taking antihypertensive treatment to control for the effect of antihypertensive medications, and compared genotypes in terms of impact on systolic and diastolic BP levels. Quantitative trait analysis using a general linear model revealed that the TC/CC group of rs2228570 had lower systolic BP compared with the TT genotype in the treated hypertensive subgroup even after adjustment for confounding factors. Moreover, naive hypertensive patients with TT genotype of the latter SNP showed higher SBP compared with the TC/CC genotype. Other SNPs did not show such a relationship in the patient cohort.

In brief, the authors concluded that rs2228570 SNP in the VDR gene region was associated with decreased risk of hypertension and systolic BP in a Chinese Han population.

SNP rs2228570, also known as FokI, has been associated with increased risk of a number of disease states including systemic lupus erythematosus,[2] renal cell carcinoma,[3] and ovarian cancer.[4] This plethora of studies reporting polymorphism associations with various levels of vitamin D metabolism point to the important role that vitamin D plays in inflammation, vascular health, apoptosis, fibrosis, and cell proliferation and differentiation.[5] In recent years, interest has focused on the association between vitamin D levels and BP, perhaps owing to the pandemic proportions of both hypertension and vitamin D deficiency.

Experimental studies showed clear and strong associations between vitamin D deficiency and increased BP.[6] A number of pathophysiologic mechanisms have been put forward to explain this association of hypovitaminosis D with increased BP. These postulated mechanisms included upregulation of the renin angiotensin system, impaired function of vascular smooth muscle cells and endothelium, and modulation of inflammation.[6] However, epidemiologic studies investigating 25(OH) vitamin D level and BP association did not produce consistent results.[7] Intervention studies in which the effect of vitamin D supplementation on BP was evaluated showed also inconsistent results. Recently, Kunutsor and colleagues[8] performed a meta-analysis looking at the effects of vitamin D supplementation on systolic and diastolic BPs. The authors also

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performed a Mendelian randomization analysis to determine any causal relationship between 25(OH) vitamin D level and BP levels. Pooled random effects meta-analysis of 16 trials of vitamin D supplementation showed a nonsignificant reduction in systolic BP and diastolic BP (1.10 mm Hg and 0.14 mm Hg, respectively). On the other hand, there was a significant reduction in diastolic BP in patients with cardiometabolic disease. The authors looked for genome-wide association studies to find SNPs exclusively associated with 25(OH) vitamin D levels and compiled studies if they included one of these SNPs. Only the associations of rs6013897 in CYP24A1 with systolic BP and diastolic BP were nominally significant while 4 other genes playing important roles in the vitamin D metabolic pathway were not related with BP levels.

Some pitfalls may explain these negative results in the Mendelian randomization analyses. First, common genetic variants of vitamin D metabolism are only responsible for a small variation in circulating vitamin D levels. Thus, Mendelian randomization studies demand a large number of participants in order to be able to detect subtle associations of genetic variants with BP levels. Second, there are many points in the vitamin D metabolism that are regulated by gene activity. Thus, there might be rarer genetic variants with stronger effects on 25(OH) vitamin D levels and BP. SNPs, not surprisingly, change along with ethnicity. Heterogeneity and different ethnicities in these randomized controlled studies may complicate interpretation of the results and underestimate the power of a given genetic variant.

FokI polymorphism has been previously associated with essential hypertension in a small study from an Indian population.[9] Wang and colleagues[10] conducted a prospective study including 1211 US men who were not hypertensive at baseline with a follow-up period of 15.3 years. During the follow-up period, 695 men developed hypertension. The results of the study showed that there is an inverse association between plasma 25(OH) vitamin D level and risk of hypertension as well as significant associations between VDR BsmI and FokI polymorphisms with hypertension risk. Only the recessive model (ff vs fF and FF) for FokI was associated with an increased risk of hypertension. Interestingly, the relationship between plasma 25(OH) vitamin D and risk of hypertension did not differ by VDR BsmI and FokI polymorphisms.

In the current study, serum 25(OH) vitamin D levels were not measured. Serum vitamin D levels are determined not only by genetic factors but also by environmental and dietary factors. This issue should be addressed in future studies. Moreover, some evidence exists that the relationship between 25(OH) vitamin D and BP could be mediated by serum parathyroid hormone levels.[11,12] Thus, better characterization of these serum markers and associations with genetic polymorphisms will help better delineate the role of vitamin D in the genesis of elevated BP.

Since genetic background varies from one ethnicity to the other, demonstration of an association between BP and a given polymorphism cannot be generalized to other people with different ethnic backgrounds. Thus, as the authors state, this study is the first report of the association between FokI recessive allele with decreased frequency of hypertension. Lack of Mendelian randomization in addition to the case-control method hampers drawing causal consequences of the observed associations.

Conflict of interest: The authors declare that they have no conflict of interest.

Disclosure: None.

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