Editorial Commentary

Does a Vitamin D Boost Help in Resistant Hypertension Control?

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Resistant hypertension (RH) is an heterogeneous condition pragmatically defined on the basis of the number of drugs being taken by individual patients. Secondary forms of hypertension, including obesity, chronic kidney disease, renal artery stenosis, hyperaldosteronism, obstructive sleep apnea, and rare forms of hypertension such as pheochromocytoma and coarctation of the aorta, are more frequently resistant to treatment than essential hypertension (EH). However, due to the large prevalence of EH in the general population, at community level, EH is the most prevalent cause of RH. Resistance to treatment portends a high risk for cardiovascular events and left ventricular (LV) hypertrophy, which is per se a strong risk factor for heart failure, coronary heart disease events, and arrhythmia, is a hallmark of this condition. RH should be regarded as a relevant public health issue because observations in the frame of the National Health and Nutrition Examination Survey documented a doubling in the prevalence of RH for 20 years, the prevalence of RH being 5.5% in National Health and Nutrition Examination Survey 1988 to 1994 and 11.8% in National Health and Nutrition Examination Survey 2005 to 2008.1

Excess Adiposity, Hyperaldosteronism, Vitamin D, and Hypertension

Obesity and excessive adipose mass is a dominant causal factor for hypertension and RH via insulin resistance. Several clinical studies documented a direct, strong link between plasma aldosterone levels and metrics of adiposity, including body mass index and waist circumference.2 Emerging data point to aldosterone, a steroid which is almost universally high in overweight and obese people, as a player in insulin resistance. The high prevalence (17%–22%) of primary aldosteronism in patients with RH3 suggests that aldosterone excess may be a causal factor in RH. High aldosterone impairs β-cell function in the pancreas and insulin sensitivity in skeletal muscles and promotes the synthesis of proinflammatory cytokines in the adipose tissue, resulting in inflammation and glucose intolerance. Mineralocorticoid receptor blockade improves β-cell function, insulin-dependent glucose utilization, and endothelium-dependent vasorelaxation. Thus, hyperaldosteronism has negative metabolic effects that contribute to insulin resistance, which may in turn trigger RH as well as cardiovascular disease and chronic kidney disease. However, biological pathways exist whereby vitamin D deficiency may be implicated in obesity-related RH. Relatively lower plasma levels of 25-hydroxyvitamin D (25 OHVD) associate with adiposity and metabolic disturbances, including insulin resistance and other components of the metabolic syndrome.4 Observational studies in humans and cogent findings in experimental models point to an inverse link between blood pressure and vitamin D levels.5 Furthermore, a randomized, double-masked clinical trial aimed at testing the effect of an active form of vitamin D on albuminuria in type 2 diabetes mellitus documented a significant, clinically relevant hypotensive effect of vitamin D in these patients.6 Vitamin D deficiency per se may be a relevant player in hyperaldosteronism because 25 OH vitamin D levels were definitely in the deficiency range in a large series of patients with aldosterone-producing adenoma or with bilateral adrenal hyperplasia.7 The mutual relationships among aldosterone, vitamin D, insulin sensitivity, inflammation, and the biological interplay among these factors are schematized in the Figure.

Because of the heterogeneous nature of RH and the dominant focus on antihypertensive drugs in the therapeutic approach to RH, little attention has been dedicated to potentially modifiable intermediate mechanisms leading to hyperaldosteronism and hyperinsulinemia in this condition. The issue is of relevance because notwithstanding a formidable armamentarium of antihypertensive agents, control of RH remains largely unsatisfactory.1 Because of side effects of intensive application of these agents, the quality of life of patients with RH is often poor. In the pathophysiological scenario of RH (Figure), vitamin D supplementation seems to be as a rational, interesting possibility for mitigating RH. About 3% of the whole human genome is regulated by the vitamin D endocrine system and the vitamin D receptor is highly expressed in myocardocytes and in vascular smooth muscle cells and endothelial cells.8 Vitamin D deficiency and insufficiency constitute a true public health problem with a 30% prevalence or higher in the adult population.9 Although a meta-analysis of cohort studies suggests a cardiovascular-protective effect of vitamin D,10 to date there is no strong evidence demonstrating clear benefits of vitamin D on the cardiovascular system. The Paricalcitol capsules benefits in Renal failure Induced cardiac Morbidity (PRIMO), a randomized trial that tested whether paricalcitol (19-nor-1,25 OH2 vitamin D2) administered for 52 weeks may reduce LV hypertrophy in patients with chronic kidney disease, that is, a population where RH is much frequent, failed to show a benefit.
Can Vitamin D Attenuate RH?

Whether vitamin D supplementation may attenuate treatment RH has never been investigated. Thus, the authors of the study published in this issue should be commended for having performed an independent randomized controlled trial testing the effect of vitamin D3 (cholecalciferol, a safe and cheap form of vitamin D) on 24-hour ambulatory blood pressure and LV mass in patients with RH. Participants to this trial were adult patients with office blood pressure of >140/90 mmHg who were on ≥3 antihypertensive drugs and with biochemical evidence of vitamin D deficiency, that is, with serum 25 OH vitamin D levels <75 nmol/L (<30 ng/mL). These patients were randomized to receive 300 000 U of vitamin D3 (in a liquid, oral formulation) or a matched placebo every 2 months. The primary end point of the trial was between-group difference in mean 24-hour ambulatory systolic blood pressure at 6 months between cholecalciferol and placebo-treated patients with RH. Furthermore, patients with LV mass index of >110 g/m² (men) or >95 g/m² (women) entered a substudy where LV mass was measured by state-of-the-art MRI. The results of this study clearly documented that the vitamin D regimen tested was efficacious in correcting vitamin D deficiency but largely ineffective on BP control. Indeed, the main study end point (24-hour systolic BP) remained unchanged during the trial in patients in the active arm of the study. Similarly, treatment had no meaningful effect on LV mass index.

Positive clinical studies make headlines and get immediate interest among patients and within the medical community. Negative data often remain in the desk drawer of the investigator and may not get published for years or be not published at all. However, these studies are important in that they may serve to set the stage for planning new trials with similar drugs and for better defining relevant clinical end points to be targeted in future trials. In the study by Witham et al., 24-hour ambulatory blood pressure monitoring and office BP remained remarkably constant in the vitamin D arm but systolic BP clearly tended to fall in the placebo arm (24-hour ambulatory blood pressure monitoring, −7 mmHg; and office BP, −9 mmHg) documenting the difficulties of testing new interventions in trials in RH, a high-risk condition where cointerventions and changes in antihypertensive therapies are frequent.

Although the present study makes a strong case against the hypothesis that vitamin D3 at the doses administered in this trial may produce tangible benefits in RH in whites, the issue clearly deserves further study. Patients enrolled into this trial of this compound on the primary end point and on blood pressure (BP) as well. Yet a post hoc, exploratory analysis of this trial showed a highly significant reduction in left atrial volume and an attenuated rise of brain natriuretic peptide overtime in paricalcitol-treated patients. Thus, testing the effect of vitamin D in chronic kidney disease is of relevance for advancing knowledge on the potential of these compounds for cardiovascular prevention in patients with RH.

![Diagram](http://hyper.ahajournals.org/)

**Figure.** Obesity and overweight associate with renin–angiotensin–aldosterone system activation. Aldosterone activates NADPH and promotes oxidative stress via a genomic mechanism augmenting protein kinase B activity, which triggers the inflammation cascade. Oxidative stress promotes phosphorylation of the insulin receptor and by this mechanism induces insulin resistance. Insulin resistance then activates a positive feedback loop mediated by protein kinase B further amplifying resistance to insulin. Vitamin D deficiency, a common alteration in overweight and obese people, amplifies angiotensin II–dependent mechanism(s) of insulin resistance and vascular dysfunction in these conditions. Furthermore, vitamin D deficiency potentiates protein kinase B activation and inflammation in the same conditions.
were all whites. Vitamin D produced a small dose-dependent BP-lowering effect in blacks in a trial published in the Journal this year. A beneficial effect of vitamin D on endothelial function in diabetics emerged in another trial by the same authors of this study. The number of patients with diabetes mellitus in the present study was small and although inactivated forms of vitamin D were apparently more effective than activated forms in a meta-analysis performed in 2009, the paricalcitol trial in diabetics published after this meta-analysis showed that this drug lowers BP in type 2 diabetes mellitus. However, because this study was not designed to examine the effect of paricalcitol on BP, new clinical studies are needed to confirm that active forms of vitamin D may ameliorate BP control in patients with diabetes mellitus, including those with RH. Finally, 6 months may be a too short period for detecting meaningful effects of vitamin D on LV mass and function. Also, in light of post hoc analyses in PRIMO and experimental data in rats showing that only activated forms of vitamin D reduce myocardial fibrosis, longer trials and detailed studies of diastolic function, a parameter critically dependent LV compliance, are needed to better investigate the cardiac effects of vitamin D in various forms of hypertension and in RH.

Disclosures
None.

References
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