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Phosphate, the forgotten mineral in hypertension

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Abstract

Purpose of review: To review the current literature related to the role of inorganic phosphate (Pi) in the pathogenesis of hypertension

Recent findings: An increasing number of publications has revealed a detrimental role of inorganic Pi, which is commonly used as a flavor enhancer or preservative in the processed food, in promoting hypertension in otherwise healthy individuals. Animal experimental data indicate that dietary Pi excess engages multiple mechanisms that promote hypertension, including overactivation of the sympathetic nervous system, increased vascular stiffness, impaired endothelium-dependent vasodilation, as well as increased renal sodium absorption or renal injury. These effects may be explained by direct effects of high extracellular Pi levels or increase in phosphaturic hormones such as fibroblast growth factor 23 (FGF23), or downregulation of klotho, a transmembrane protein expressed in multiple organs which possess anti-aging property.

Summary: Dietary Pi, particularly inorganic Pi, is an emerging risk factor for hypertension which is ubiquitous in the western diet. Large randomized clinical trials are needed to determine if lowering dietary Pi content constitutes an effective nonpharmacologic intervention for prevention and treatment of hypertension.

Keywords

Dietary Phosphate; western diet; sympathetic nervous system; hypertension

Introduction

The 2017 AHA/ACC Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults have provided a ground breaking new definition for

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Conflicts of interest

None

hypertension by lowering universal target blood pressure (BP) goal to < 130/80 mmHg [1*]. It is a major departure from the recommendation from target goal of < 140/90 mmHg which was first proposed by the fifth Joint National Committee (JNC) guideline committee more than 2 decades ago. The rationale for the new guidelines is based on strong and consistent evidence that lower BP is associated with lower cardiovascular risk. A major implication of the new guideline is that the prevalence of hypertension has now risen to approximately 50% of the US population, representing an additional 31.1 million adults nationally [2]. Given the tremendous burden of hypertension, effective strategy in the prevention and treatment of hypertensive and hypertensive-related target organ complications is urgently needed.

Numerous studies have established that the key role of dietary sodium (Na) intake in the pathogenesis of hypertension and lowering dietary Na intake is now adopted as an important non-pharmacologic intervention to prevent and treat hypertension [3]. An Increasing number of studies, however, has implicated the detrimental role of dietary phosphate (Pi) loading on BP [4*, 5*, 6**]. This is highly relevant to that the western diet forms are particularly rich in processed food items containing a large amount of inorganic Pi-based food additives, which are highly absorbable from the gastrointestinal tract [7]. It is estimated that the average US adult consumes approximately 1,200 mg/day of Pi, which is almost twice the recommended daily allowance of 700 mg/day [7, 8]. Pi-containing additives are present in more than 40% of popular grocery items, including prepared frozen foods (e.g. microwavable meals), processed meat, bread, soup, cola soft drinks and bakery items [9, 10]. Despite this high level of Pi consumption, a recent nutritional survey indicated a further upward trend in the pattern of dietary Pi intake among US adults in the recent years [7]. The rise in Pi consumption is evident when data are expressed as absolute levels of Pi intake and in relation to total caloric intake.

Role of dietary Pi excess in BP regulation

This pattern of dietary Pi consumption is worrisome as the existing data indicate Pi excess to be an independent risk factor for accelerated aging, left ventricular (LV) hypertrophy, and adverse cardiovascular outcome in individuals with and without chronic kidney diseases (CKD) [11-13]. While numerous studies have been conducted to elucidate the direct effect of Pi on LV structure and function, little attention has been paid the potential role of dietary Pi excess in the pathogenesis of hypertension and hypertensive-related target organ damage.

Cross-sectional studies in patients with end-stage renal disease showed that the presence of hyperphosphatemia was significantly associated with high BP [14], LV hypertrophy [15], LV diastolic dysfunction [15], heart failure with preserved ejection fraction [16], as well as stroke [17]. A meta-analysis of 7 cohort studies also has demonstrated an association between elevated serum Pi and increased risk of all-cause mortality in the CKD population [18*]. It was estimated that mortality risk is increased by 20% per 1-mg/dL increase in serum Pi level in non-dialysis-dependent patients with CKD [18*]. A similar association has been demonstrated in the general population without CKD [19**]. Elevated levels of serum Pi was associated with a blunted decline in nocturnal BP in hypertensive patients without CKD in one study [20]. A large prospective observational study in more than 9,000 hypertensive patients in the Glasgow Blood Pressure Clinic cohort showed that elevated

baseline serum Pi is associated with poor BP control over 5 years of follow-up [19**]. Prospective studies in the general population in the US and Netherlands also showed that elevated serum Pi is associated with cardiovascular mortality and all-cause mortality [8, 21]. However, serum Pi is a poor marker of overall dietary Pi intake as it is also influenced by renal function and a number of hormones involved in maintaining phosphorus homeostasis, including fibroblast growth factor 23 (FGF23), vitamin D, and parathyroid hormone [22, 23]. A recent study conducted in African American participants enrolled in the Jackson Heart Study provided no evidence for an association between dietary Pi intake and 24-hour ambulatory BP (ABP) [24]. However, the interpretation of these results may be limited for several reasons. First, dietary Pi intake was estimated by food recall rather than 24-hour urinary Pi excretion. It is well known that oral bioavailability of plant phosphorus is limited due to its binding to phytates which requires phytase enzyme in order for Pi to be released [10]. Since this enzyme is not present in humans, plant-derived phosphorus is poorly absorbed relative to its total phosphate content. In contrast, inorganic Pi, commonly used as food additives or preservatives in the form of phosphoric acid and many others, possesses high oral bioavailability. Second, labeling of phosphorus content in the food items is not currently required by the USDA and the estimated Pi intake based on the food recall on any given food items may not capture the precise amount of inorganic Pi added during food processing which is highly variable depending on the manufacturer [9]. Third, the cross-sectional nature of the study design may limit ability to detect a causal link.

A recent prospective randomized study has established a more definitive BP-raising effect of inorganic Pi in healthy young adults without hypertension or any antihypertensive drug treatment [25**]. Mohammad et al. demonstrated that administration of neutral NaPi (each 1 mM Na contains 0.55mM of Pi) at the dose approximately 30 mmol of Pi/day for 11 weeks induced a significant increase in 24-hour ABP by 4/3 mmHg when compared to the control group treated with equivalent amounts of sodium as NaCl in combination with Pi binder lanthanum carbonate to reduce Pi absorption [25**]. Interestingly, the increase in 24-hour ABP was accompanied by a small but significantly increase in 24-hour heart rate (HR) as well as 24-hour urinary excretion of metanephrine and normetanephrine, suggesting sympathetic activation. The increase in BP was observed both during the daytime and nighttime. In the same study, Vitamin D supplementation had no significant effect on 24-hour ABP when administered to subjects in either low or high Pi group. Although the impact of dietary Pi loading on BP appears to be small, meta-analysis of studies showed 24-hour ABP as a stronger predictor of cardiovascular mortality and all-cause mortality than clinic BP [26*, 27]. It is estimated that each 10-mmHg increase in 24-h ambulatory systolic or diastolic BP was associated with relative increase in cardiovascular mortality by 50-60% [26*]. Thus, the finding of Pi loading leading to BP elevation may have a major implication in terms of preventing hypertension and its subsequent cardiovascular complications.

Mechanisms underlying dietary Pi loading-induced hypertension: Role of sympathetic nervous and renin-angiotensin-aldosterone system

Although human studies demonstrated a significant increase in urinary normetanephrine excretion during high Pi intake, these elevations may not necessarily reflect increased central sympathetic neural drive or increased secretion of the neurotransmitter. It is well known that

circulating levels of norepinephrine, a precursor of normetanephrine, represent only less than 10% of the amount secreted from sympathetic nerve terminals as the majority is removed by neuronal and extraneuronal pathways [28].

To determine the direct role of sympathetic nervous system, we measured renal sympathetic nerve activity (SNA) in the normotensive Sprague Dawley (SD) rats using direct electrode recording after feeding them with a high Pi diet for 12 weeks. The high Pi diet contained twice the amount of total Pi than the control diet which is considered to be optimal for rodents (1.2% vs. 0.6% total Pi, respectively). We found that consumption of a high Pi diet induces hypertension and tachycardia in the resting condition and augments cardiovascular and sympathetic responses during muscle contraction [6**]. Previous studies showed that hypertensive rats and humans not only display elevated levels of SNA at rest, but also during exercise [29]. This exaggerated rise in sympathetic and BP responses to exercise are mediated, in part, by an overactive reflex originating from the skeletal muscle, known as the exercise pressor reflex. The augmentation in exercise pressor reflex function is evoked both by muscle afferents associated with metaboreceptors, which are activated by metabolic byproducts accumulated in the skeletal muscle during exercise, and mechanoreceptors, which respond immediately to muscle deformation. In our study, high dietary Pi intake potentiated BP, HR and renal SNA responses to both passive muscle stretch to evoke mechanoreflex activation and intra-arterial capsaicin administration in the hindlimb to induce metaboreflex activation. Thus, short-term dietary Pi loading is able to transform autonomic regulation of BP in normotensive rats to the phenotype observed in hypertensive rats. These findings may have a major implication in otherwise healthy populations since BP and renal SNA are increased, while both renal function and LV structure as well as function are unaltered by high Pi diet in otherwise normal SD rats.

The mechanisms underlying sympathetic activation induced by dietary Pi loading are unknown. A type II NaPi co-transporter, such as NaPi-2c, has been identified in many brain regions, including the amygdala and third ventricle. Expression of these transporters is altered by dietary Pi intake and concentration of Pi in the cerebrospinal fluid (CSF). Another Pi transporter, PiT-2, has also been identified in the choroid plexus of sharks and implicated in removal of Pi from the CSF [30]. Whether consumption of high Pi diet induces stimulation of these central transporters causing direct stimulation of brainstem centers involved in the generation of muscle reflex-induced central sympathetic outflow remains to be determined.

Other than activation of sympathetic nervous system, high Pi diet was shown to increase renin expression, resulting in increased circulating angiotensin levels and LV hypertrophy in healthy rats [4*]. In another study, high Pi and zinc-free diet induced BP elevation in both spontaneously hypertensive (SHR) rats and Wistar Kyoto rats. High Pi induced LV systolic dysfunction and myocardial fibrosis in SHRs, which was prevented by antioxidant N-acetyl-L-cysteine (NAC) [5*]. However, NAC had no effect on BP in SHRs treated with a high Pi / zinc-free diet.

Role of phosphotoxicity on endothelial cells and vascular smooth muscles

Many *in vitro* studies have shown acute impairment in endothelium-dependent vasodilation when aortic rings are exposed to culture media with high Pi milieu [31, 32]. Similarly, studies in aortas isolated from rats fed a high Pi diet (1.2%) for 16 days showed impaired endothelium-dependent vasodilation when compared to aortas isolated from rats fed with a normal (0.6%) or low Pi diet (0.02%). These unfavorable effects of high Pi diet on vascular endothelial function thought to be related to reduction in nitric oxide (NO) bioavailability mediated by decreased endothelial NO synthase (eNOS) activation or increased oxidative stress which inactivates NO [32, 33]. Increases in endothelin-1 production via upregulation of aortic endothelin-converting enzyme-1 protein expression has been demonstrated in one study in aortic endothelial cell culture upon exposure to high extracellular Pi condition [34].

However, studies in human have yielded conflicting evidence. Studies in young healthy men showed that brachial artery flow-mediated dilation (FMD), an indirect index of endothelial function, was reduced acutely after consumption meals containing inorganic Pi additives between 800-1200 mg [35-37], while FMD was unaffected by meals with 400 mg of inorganic Pi additives [36]. A longer term study showed reduction in brachial artery FMD after 2 weeks of high Pi (1,500 mg/day) administration in healthy middle-aged adults [32]. In contrast, exposure to a high Pi diet of approximately 30 mM/day (or 900 mg/day) for 6-11 weeks did not alter vascular endothelial function in healthy young adults as evidenced by arterial pulsatile volume changes in the fingers, another noninvasive index of endothelial function [25**]. The discrepancy in the study findings may be related to differences in the technique of endothelial function assessment and/or the dose of Pi loading. Whether a chronic high phosphate diet impairs brachial artery FMD remains to be further investigated.

In addition to the direct effects of phosphate on the vascular endothelial function, two studies have investigated the possibility that impaired vascular endothelial function may, in part, be mediated by phosphaturic hormones, such as FGF23. FGF23 is a major hormone released from osteocytes to augment renal phosphate excretion to minimize phosphate overload. However, the study results are inconsistent to date [31, 38], suggesting that high Pi milieu, rather than FGF-23 excess, may play a greater role on vascular endothelial dysfunction. The action of FGF23 on the kidneys and many organs requires klotho, an anti-aging protein which functions as a co-receptor for signal transduction. A high Pi diet has also been shown to downregulate klotho expression in the kidneys and reduce soluble klotho levels in the serum of mice [39]. Klotho-deficient mice displayed evidence of endothelial dysfunction, which could be restored by parabiosis with wild-type mice [40]. Future studies are needed to clarify the role FGF23 excess and klotho downregulation on vascular cells and BP regulation during dietary Pi loading.

Increased arterial stiffness mediated by vascular smooth muscle calcification is another potential mechanism underlying hypertension related to high Pi intake. It is well recognized that increased aortic stiffness contributes to the pathogenesis of isolated systolic hypertension which is predominant form of hypertension after the fifth decade of life [41]. *In vitro* studies have shown that Pi directly promotes vascular stiffening by transforming vascular smooth muscle cells to osteochondrogenic phenotype. When extracellular Pi levels were increased from 1.4 mM (physiological level) to 3 mM (the levels observed in

individuals with renal impairment), upregulation of genes involved in bone formation including Runx2/Cbfa1, osterix, osteopontin, and alkaline phosphatase, was observed in the vascular smooth muscle cells which may contribute to increased vascular stiffness [42*]. Type III Na-dependent Pi co-transporters, PiT-1 and PiT-2, are expressed in the vascular smooth muscle cells. PiT-1 promotes vascular calcification while PiT-2 has a protective effect [43**]. However, the relevance of these findings in humans is unknown as randomized clinical trials have not shown a benefit of dietary Pi restriction or Pi binders in reducing aortic pulse wave velocity (PWV), an index of arterial stiffness, despite improvement in serum FGF23 [44]. Similarly, recent small studies in healthy volunteers with normal renal function did not show reductions in aortic PWV after Pi binder Lanthanum carbonate administration when compared to inorganic Pi (900-1,500 mg/day) administration for 2-11 weeks [25**, 32]. One of the limitations of these studies is related to large coefficient of variation associated with the noninvasive indices of arterial stiffness as well as endothelial function discussed in the earlier section. Thus, randomized placebo-controlled clinical trials with adequate sample size are needed to determine hemodynamic and vascular effects of a high Pi diet to Pi binder administration in humans.

Renal Mechanisms

Prospective observational studies have shown association between high dietary Pi intake and incident CKD in the population without kidney disease [45] as well as an accelerated decline in renal function among those with CKD [46]. Since CKD is one of the major risk factor for development of hypertension, deterioration in renal function constitutes another potential mechanism by which dietary Pi excess promotes hypertension. Dietary Pi loading also increases release of FGF23, which directly regulates membrane abundance of the Na⁺:Cl co-transporter (NCC) in the distal tubule. Previous study has shown that mice treated with exogenous administration of FGF23 and transgenic mice overexpressing FGF23 display increased renal Na⁺ reabsorption, expansion of plasma volume, and elevated BP [47**]. Increases in circulation renin and angiotensin II levels induced by dietary Pi loading may further contributes to Na⁺ retention independent of renal impairment [4*]. Nevertheless, Mohammad et al. have not found any influence of increased dietary Pi on plasma renin or angiotensin II concentrations nor on 24-hour urinary aldosterone excretion rates despite a significant increase in 24-hour ABP [25**]. Thus, the contribution of renin-angiotensin-aldosterone system activation in Pi-induced hypertension remains unproven.

Conclusion

An enlarging body of literature lends credence to the notion that inorganic Pi engages multiple mechanisms to promote hypertension, including activation of sympathetic nervous system, increased vascular stiffness, impaired endothelium-dependent vasodilation, as well as increased renal Na⁺ absorption or renal injury (Figure 1). A recent study in mice also showed a detrimental effect of dietary Pi loading on exercise capacity by impairing fatty acid availability and mitochondrial fatty acid oxidation in the skeletal muscle, which may further increase sedentary activity and cardiovascular risk [48**]. A small randomized study in healthy young adults has provided support for the BP raising effect of inorganic Pi when it is added to a regular diet with relatively low Pi content [25**]. A larger randomized clinical

trial is underway to determine if Pi restricted diet will have impact on 24-hour ABP and SNA using a direct intraneural recording in otherwise healthy subjects with normal renal function. If the Preventing Hypertension and Sympathetic Overactivation by Targeting Phosphate (PHOSTOP,) trial confirms the findings in animal experiments, the results may lead to revision of food labeling to include inorganic Pi content. The study results may also lead to a new paradigm in preventing hypertension in the population at high risk for progression to hypertension.

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Key points

- Inorganic phosphate (Pi) is highly abundant in the western diet and has emerged as an important dietary risk factor for hypertension.
- The potential mechanisms underlying dietary Pi excess-induced hypertension include activation of sympathetic nervous system, impaired endothelial function, and increased vascular stiffness and renal sodium retention.
- Large randomized controlled trials are necessary to determine if reducing dietary Pi content is an effective strategy for the prevention and/or treatment of hypertension.

Figure 1.

Schematic diagram showing potential mechanisms underlying hypertension induced by dietary phosphate excess. The associated mechanisms include increased sympathetic vasoconstrictor activity, expansion of plasma volume, vascular stiffness, and impaired endothelium-dependent vasodilation. eNOS: endothelial nitric oxide synthase, EPR: exercise pressor reflex, FGF23: fibroblast growth factor 23, HTN: hypertension, Na^+ : sodium ion, NaPi-2c : type II sodium-phosphate co-transporter, NCC : sodium-chloride co-transporter, NE : norepinephrine, Pi : Phosphate, PIT-1 and PIT-2 : type III sodium-dependent phosphate co-transporters, SNA : sympathetic nerve activity, PTH : Parathyroid hormone