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Diet, Nutrients, and the Prevention of Hypertension

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Abstract A large part of blood pressure variation among individuals cannot be explained by known nutritional and dietary factors, and thus, many studies are in progress. We reviewed recent observational and interventional studies investigating the relationship of dietary and nutritional factors to blood pressure in human populations. During the past few years, a cross-sectional study of large-scale international populations, the INTERMAP (International Study of Macro/Micronutrients and Blood Pressure), reported the favorable effects of several nutrients, including minerals (phosphorus, calcium, magnesium, and non-heme iron), glutamic acid, n-6 and n-3 polyunsaturated fatty acids, and starch, and reduced intake of cholesterol, glucose, and fructose. Observational and interventional studies also showed new evidence suggesting unfavorable effects resulting from higher intakes of red meat, fructose, and sugar-sweetened beverages, and favorable effects resulting from higher intake of lactotripeptides and polyphenol-rich dark chocolate. For the Dietary Approaches to Stop Hypertension (DASH) dietary pattern, further evidence on blood pressure–lowering effects and other favorable outcomes has accumulated. These new findings should be established by further studies for the future update of dietary guidelines to prevent and manage hypertension.

Keywords Blood pressure · Hypertension · Diet · DASH diet · INTERMAP · Nutrients · Foods · Health education · Prevention · Cardiovascular disease · Nutrients · Minerals

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Introduction

Over the past several decades, many epidemiologic observations (cross-sectional and longitudinal) have revealed that human blood pressure (BP) level is affected by various nutritional factors, including dietary factors, physical activity, obesity, and alcohol consumption. Substantial shifts in BP distribution in entire populations have been observed in many countries, most of which can be explained by nutritional factors and not by genetic factors. Many interventional studies have also observed BP reduction associated with reducing or adding nutritional or dietary factors to prove causal relationships. The Dietary Approaches to Stop Hypertension (DASH) trial made great progress in the prevention and treatment of hypertension; this is a "combination" dietary pattern, with increased intake of fruits, vegetables, poultry, fish, and low-fat dairy products, and reduced intake of red meat, fats, cholesterol, and sweets that substantially lowered BP [1]. Sodium reduction further contributed to BP lowering in another DASH-Sodium trial [2]. However, a large part of BP variation among individuals could not be explained by known nutritional and dietary factors, and thus, many studies are in progress.

In this article, we review recent observational and interventional studies investigating the relationship of dietary and nutritional factors to BP in human populations. Associations with BP have been reported for dietary intakes of lipids, carbohydrates, amino acids, peptides, and minerals, and for dietary patterns and certain food groups.

Lipids

The International Study of Macro/Micronutrients and Blood Pressure (INTERMAP), a population-based, cross-sectional, epidemiologic study in four countries from East and West, recently reported several findings on the relationship between dietary lipid intake and BP. The study surveyed 4,680 men and women ages 40 to 59 years from 17 population samples in Japan, the People's Republic of China, the United Kingdom, and the United States. Nutrient intake data were based on four in-depth, multipass, 24-hour dietary recalls per person and two timed 24-hour urine collections per person, and BP was measured eight times at four visits. The study reported an independent inverse relationship of dietary linoleic acid to BP—estimated effect sizes of −1.4 mm Hg systolic BP (SBP) and −0.9 mm Hg diastolic BP (DBP) with 9.0-g/d higher linoleic acid intake [3]. Linoleic acid is rich in vegetable oils, and 80 t0 90 % of polyunsaturated fatty acids (PFAs) come from linoleic acid in many countries. Another report from the INTERMAP showed an independent inverse relationship of total n-3 PFAs to BP—estimated effect size was small (~−1.0 mm Hg with 1.9-g/d higher n-3 PFA intake) [4]. This report showed a similar inverse relationship of linolenic acid, one of the n-3 PFAs, to SBP/DBP, and a similar weaker inverse relationship of long-chain n-3 PFAs (eicosapentaenoic acid and docosahexaenoic acid [DHA]) to DBP. The INTERMAP also reported a low-order independent, positive relationship of dietary cholesterol to SBP—an estimated effect size of about 1.0 mm Hg SBP with 131 mg/1,000 kcal higher cholesterol intake [5•]. These low-order effects on BP could be revealed from a large observational study of diverse populations with high-quality data, although it has been difficult to investigate in small, short-term intervention trials.

For the BP-lowering effect of n-3 long-chain PFAs, an 8-week randomized trial in 324 people in Europe showed that salmon consumption (150 g) three times weekly can decrease DBP similar to fish oil (1.3 g/d) and significantly more than lean fish (150 g of cod) [6]. This study also showed that lower baseline DHA in erythrocytes was associated with greater DBP reduction, which suggests a greater effect of n-3 PFAs on BP in people with lower fish intake. On the other hand, the effect of dietary monounsaturated fatty acids (MFAs), which are rich in the Mediterranean diet, on BP has been controversial. A recent meta-analysis of 10 intervention trials on the effect of high-carbohydrate or high-*cis*-MFA diets on BP reported that diets rich in carbohydrates may be associated with slightly higher BP (1.3 mm Hg SBP) than diets rich in *cis*-MFA [7]. Another small trial from Greece showed that combined consumption of wine and olive oil, which are rich in MFAs, provided beneficial postprandial effects on hemodynamics (reduction in augmentation index) [8]. Further studies are needed on the effect of MFAs on BP.

Carbohydrates

The Western obesity epidemic has focused attention on the relationship to cardiovascular risk factors of diets rich in added sugars, particularly glucose, sucrose, and fructose P (eg, high-fructose corn syrup abundant in sugar-sweetened beverages [SSBs]). Limited short-term human trial data indicate pressor effects of glucose, fructose, and sucrose on BP. The most compelling evidence to date comes from the PREMIER study, a behavioral intervention trial of 810 prehypertensive and hypertensive individuals in which reduced intake of SSBs or sugar over 18 months was associated with reduced BP [9••]. Reduction in SSB consumption by 355 mL/d was associated with lowering of SBP/DBP by 1.8/1.1 mm Hg and 0.7/0.4 mm Hg, with adjustment for change in body weight. The Coronary Artery Risk Development in Young Adults (CARDIA) study also showed, from 20-year follow-up data on 2,774 adults, that higher SSB consumption (across quartiles) was associated with greater risk of hypertension (adjusted relative risk, 1.06; P for trend=0.023) [10••]. The former mentioned that INTERMAP, a cross-sectional study in four countries, found a direct association of SSB consumption with BP, and direct associations of fructose and glucose intake with BP were stronger among individuals with higher urinary sodium excretion [11••]. For individuals with above-median 24-hour urinary sodium excretion, fructose intake higher by 5.6 % kcal was associated with SBP/DBP differences of +3.4/+2.2 mm Hg (both $P<0.001$). The kidneys would be particularly sensitive to the effects of fructose because high loads of this sugar reach renal tissue [12]. In addition, fructose increases reabsorption of salt and water in the small intestine and kidney; thus, the combination of salt and fructose has a synergistic effect in the development of hypertension. Fructose and SSBs have become a new serious threat to the prevention of hypertension.

Effects of dietary starch—glycemic polysaccharide carbohydrate composed of glucose molecules (major sources of cereals, root vegetables, and legumes)—on BP have been studied less extensively. The INTERMAP reported that the relationship of starch intake to BP was modestly inverse [13]. Starch intake higher by 14.1 % kJ was associated with SBP/DBP differences of −1.0/−0.9 mm Hg ($P=0.09$ and $P<0.05$). The relation reduced to −0.5/−0.7 mm Hg ($P=0.47$ and $P=0.13$) with separate adjustment for vegetable protein.

Amino Acids and Peptides

The INTERMAP found a significant inverse relationship of vegetable protein intake to BP [14]. Among those who consumed predominantly vegetable protein compared with animal protein, intake of glutamic acid—the most common dietary amino acid—made up a higher percentage of total protein, as did (to a lesser degree) cystine, proline, phenylalanine, and serine. A detailed analysis in the INTERMAP further reported that dietary glutamic acid (percentage of total protein intake) was inversely related to BP [15••]. Across multivariate regression models, estimated average BP differences associated with a glutamic acid intake that was higher by 4.72 % of total dietary protein (2 SD) were −1.5 to −3.0 mm Hg SBP and −1.0 to −1.6 mm Hg DBP (z-scores, −2.15 to −5.11). Results were similar for the glutamic acid–BP relationship with each of the other amino acids also in the model (eg, with control for 15 variables + proline, SBP/DBP differences were −2.7/−2.0 mm Hg [z-scores −2.51, −2.82]). This report concluded that glutamic acid, the most common dietary amino acid, especially in vegetable protein, may be a key component accounting for the previously reported inverse relationship of vegetable protein intake to BP. Another report from the INTERMAP on amino acids intake showed that higher intake of dietary branched-chain amino acids, including leucine, isoleucine, and valine, was associated with lower prevalence of overweight/obesity [16].

Beyond the well-known effects on BP of the DASH and Mediterranean diets, a recent meta-analysis suggested that some peptides derived from food proteins may lead to a significant reduction in BP [17]. In particular, these peptides, which are encrypted within the primary structure of milk proteins and can be released by enzymatic hydrolysis during gastrointestinal digestion or food processing, have been reported to exert some angiotensin-converting enzyme inhibitory activity. The best characterized peptides are those found in fermented milk and bearing the amino acid sequence (lactotripeptides) isoleucine–proline–proline (IPP) and valine–proline–proline (VPP). Cicero et al. [18] performed a meta-analysis of 18 placebo-controlled clinical trials examining the effect of lactotripeptides on BP control in individuals with a wide range of baseline BP levels. Pooled effect of peptides was a reduction of −3.73 mm Hg for SBP and −1.97 mm Hg for DBP. The effect was more evident in Asian patients (SBP, −6.93 mm Hg; DBP −3.98 mm Hg) than in Caucasians (SBP, −1.17 mm Hg; DBP, −0.52 mm Hg), and apparently not related to age, baseline BP values, dose of lactotripeptides assumed, or length of treatment. VPP and IPP lactotripeptides assumed as functional foods may significantly reduce SBP, particularly in Asians. The authors indicated that a small action of lactotripeptides on plasma renin activity could lead to a larger antihypertensive activity in Asians, and that another possibility is different pharmacokinetics of lactotripeptides in Asians, also in the context of a different dietary and nutrigenomic pattern. Two new reports also appeared from Denmark [19] and Finland [20].

Minerals

Several epidemiologic studies and a meta-analysis have examined the role of various measures of iron in coronary heart disease and diabetes, with conflicting conclusions. Some studies have shown an increased risk of coronary heart disease with greater heme iron intake (originating mainly from animal sources), but not with total iron intake. The effect of non-heme iron (all other sources of iron) has not been explored; neither has consumption of iron from dietary supplements or fortified foods. Furthermore, the relationship between iron and BP has been largely unclear. Iron is a redox active transition metal that may contribute to the production of reactive oxygen species, oxidative stress, and inflammation—all possibly adversely related to BP levels. A report from the INTERMAP investigated associations of dietary iron intake (total, heme, and non-heme) and found that dietary non-heme iron intake that is higher by 4.13 mg/1,000 kcal (2 SD) was associated with lower SBP by −1.45 mm Hg ($P<0.001$) [21]. In most multivariate-adjusted models, heme iron intake from food was positively and nonsignificantly associated with BP. This report also showed red meat intake was directly associated with BP; 102.6 g per 24 h (2 SD) higher intake was associated with 1.25-mm Hg higher SBP, and the associations persisted after adjustment for multiple confounders.

Mineral intake is important, especially sodium and potassium, and possibly also calcium and magnesium, but little attention has been paid to the possible effects of phosphorus intake on BP, despite its role in cellular structure and function, calcium turnover, and regulation. The INTERMAP also reported the independent relationship of dietary phosphorus to BP and on estimated combined influences of higher versus lower intakes of phosphorus, calcium, and magnesium [22]. Estimated BP differences per 232 mg per 1,000 kcal (2 SD) of higher dietary phosphorus were −1.1 to −2.3 mm Hg SBP and −0.6 to −1.5 mm Hg DBP. Dietary calcium and magnesium, correlated with phosphorus (partial $r=0.71$ and $r=0.68$), were inversely associated with BP. BP was lower by 1.9 to 4.2 mm Hg SBP and 1.2 to 2.4 mm Hg DBP for people with intakes above versus below country-specific medians for all three minerals. These results indicated the potential for increased phosphorus/mineral intake to lower BP as part of the recommendations for healthier eating patterns for the prevention and control of prehypertension and hypertension.

Data indicate an inverse association between dietary calcium and magnesium intakes and BP; however, much less is known about associations between urinary calcium and magnesium excretion and BP in general populations. The relationship of BP to 24-hour excretion of calcium and magnesium was assessed in two cross-sectional studies, the INTERMAP and the INTERSALT [23]. After adjustment for multiple confounders (including weight, height, alcohol intake, calcium intake, urinary sodium level, and urinary potassium intake), SBP was 1.9 mm Hg higher for each 4.1 mmol per 24 h (2 SD) of higher urinary calcium excretion in INTERMAP. Thus, altered calcium homoeostasis, as exhibited by increased calcium excretion, may be associated with higher BP levels.

One small randomized trial (n=48) from Greece investigated the effect of oral magnesium supplementation on ambulatory BP and intracellular ion status in patients with mild hypertension. In the magnesium supplementation group, small but significant reductions in mean 24-hour BP levels were observed, which was in contrast to the control group (SBP, −5.6 vs −1.3 mm Hg; $P<0.001$) [24]. These effects were consistent in both daytime and nighttime periods.

DASH Dietary Pattern

Several findings were reported on the effect of DASH dietary pattern on BP during the past few years. Because the BP-lowering effect of the DASH diet was confirmed in short-term studies, one study from France investigated the long-term effect of the DASH diet in a clinical trial of antioxidants with more than 5 years of follow-up [25]. After adjustment for potential confounders, higher fruit and vegetable consumption was associated with a lower 5-year increase in SBP (−2.1 mm Hg in the fourth compared with the first quartile; P for trend=0.004) and DBP (−0.7 mm Hg in the fourth compared with the first quartile; P for trend= 0.03). The DASH scores created by a hypothesis-oriented pattern variable were also significantly associated with a lower BP increase. The authors concluded that high fruit and vegetable intake may be associated with a lower BP increase with aging.

Because the DASH diet was developed and promoted in the United States, its applicability and acceptability were assessed in a free-living United Kingdom population [26]. Fourteen healthy individuals followed the adapted DASH diet for 30 days, during which they self-selected all food and beverages. The DASH diet was easily adapted to fit with United Kingdom food preferences and was well-tolerated and accepted by these individuals. While on the DASH-style diet, individuals reported consuming significantly ($P<0.01$) more carbohydrates and proteins and less total fat, and SBP/DBP decreased significantly ($P<0.05$), by 4.6/3.9 mm Hg. Another study in community-based primary care clinics in the United States performed a nested, two-by-two, randomized controlled trial of physician intervention versus control and/or patient intervention versus control [27]. Physician intervention included Internet-based training, self-monitoring, and quarterly feedback reports. Patient intervention included 20 weekly group sessions, followed by 12 monthly phone counseling contacts and focused on weight loss, DASH dietary pattern, exercise, and reduced sodium intake. The largest impact on SBP at 6 months was observed with the combination of physician and patient intervention (−9.7±12.7 mm Hg). A key finding of the trial was that the effect of the patient intervention was significantly enhanced by simultaneous exposure of the primary care provider to the quality improvement intervention.

On the other hand, the mechanism underlying BP reduction in the high fruit and vegetable consumption part of the DASH diet is unknown but may include potassium, magnesium, and fiber. A randomized trial was conducted to separate the effects of minerals and fiber from those of other components of the DASH diet on BP [28]. Fifteen obese hypertensives and 15 lean normotensives were randomly assigned to DASH or usual diet supplemented with potassium, magnesium, and fiber to match DASH, then crossed over to the complementary diet. In obese hypertensives, BP was lower after 3 weeks on DASH than on usual diet (−7.6±1.4/−5.3±1.4 mm Hg; $P<0.001$ and $P<0.02$) and usual diet supplemented (−6.2±1.4/−3.7±1.4 mm Hg; $P<0.005$ and $P<0.06$). The report concluded that the DASH diet was more effective than potassium, magnesium, and fiber supplements for lowering BP in obese hypertensives, which suggests that the high fruit and vegetable consumption in the DASH diet lowers BP and improves endothelial function in this group via nutritional factors in addition to potassium, magnesium, and fiber. Another small trial investigated whether the low-sodium DASH diet reduces oxidative stress more than the DASH diet in salt-sensitive individuals (which is high in antioxidants) [29]. The study results suggested that low-sodium DASH decreases oxidative stress, improves vascular function, and lowers BP in salt-sensitive, but not salt-resistant volunteers. Moreover, the investigators in the DASH study recently reported further results on the effects of the DASH diet on plasma renin activity [30]. The study suggested that a blunted counterregulatory response of the renin-angiotensin system was associated with the BP-lowering effect of a fruits/vegetables-rich diet and the DASH diet.

Health effects of the DASH diet, other than a BP-lowering effect, have been investigated in many studies. A randomized trial examined the effects of the DASH diet, exercise, and caloric restriction on neurocognition in overweight adults with high BP [31]. A total of 124 overweight/obese participants with elevated BP were randomly assigned to the DASH diet alone, DASH combined with a behavioral weight management program, or a usual diet control group, and intervened for 4 months. Participants on the DASH diet combined with a behavioral weight management program exhibited greater improvements in executive function/memory/learning (P=0.008) and psychomotor speed (P=0.023), and DASH diet alone participants exhibited better psychomotor speed (P=0.036) compared with those in the usual diet control group. The report showed that combining aerobic exercise with the DASH diet and caloric restriction improves neurocognitive function among sedentary and overweight/obese individuals with prehypertension and hypertension.

Other Nutrients and Foods

Although a variety of factors may contribute to the beneficial effects of plant foods on BP, a great deal of attention has been given to the plant polyphenols. Apart from fruits and vegetables, cocoa products contribute to a major proportion of total phenol intake. Consumption of flavanol-rich cocoa was found to lower BP; however, the effects were observed with doses of cocoa above the habitual intake and only in the setting of short-term interventions, with a maximum follow-up of 2 weeks. A recent randomized trial in Germany examined the effects of low doses of polyphenol-rich dark chocolate on BP [32]. Participants were randomly assigned to receive 6.3 g/d of dark chocolate or matching polyphenol-free white chocolate for 18 weeks. Dark chocolate intake reduced mean SBP by −2.9 mm Hg ($P<0.001$) and DBP by −1.9 mm Hg ($P<0.001$). A meta-analysis of randomized controlled trials assessing the antihypertensive effects of flavanol-rich cocoa products was also conducted [33•]. Ten randomized controlled trials comprising 297 individuals were included in the analysis. The populations studied were healthy normotensive adults or patients with prehypertension/stage 1 hypertension, and treatment duration ranged from 2 to 18 weeks. The mean BP change in the active treatment arms across all trials was −4.5 mm Hg ($P<0.001$) for SBP and −2.5 mm Hg ($P<0.001$) for DBP. However, heterogeneity across studies was found, and the most appropriate dose and the long-term side effect profile were still not clear.

Accumulating evidence suggests that *Ginkgo biloba* is cardioprotective in part through its vasodilatory and antihypertensive properties. However, definitive data on its BP-lowering effects in humans are lacking. The effects of *Ginkgo biloba* extract (240 mg/d) on BP and incident hypertension were determined by a randomized trial with a 6-year follow-up of 3,069 older adult participants [34]. However, *Ginkgo biloba* did not reduce BP or the incidence of hypertension in older adult men and women.

Conclusions

Recent research, including the DASH study, has indicated that multiple improvements in dietary patterns lower BP. However, findings from randomized controlled trials on the effect of single nutrients or food groups on BP are sometimes inconsistent because of small sample size and short trial duration, with consequent limitations in the ability to detect small BP differences. To detect the small impact of single nutrients on the BP of individuals, it is useful to collect standardized, high-quality data in observational investigations of large samples of diverse populations, as performed in the INTERMAP. During the past few years, the INTERMAP reported the favorable effects of several nutrients, including minerals (phosphorus, calcium, magnesium, and non-heme iron), glutamic acid, and n-6 and n-3 PFAs, and reduced intake of cholesterol, glucose, and fructose over and above the known favorable BP effects of reduced salt, increased potassium, prevention and/or correction of overweight/obesity, and reduced alcohol intake. With multiple nutrients having "small," independent influences, the combined effect becomes sizable for lowering the BP level of individuals. For the DASH dietary pattern, further evidence on BP-lowering effects and other favorable outcomes has accumulated. These new findings should be established by further studies for the future update of dietary guidelines to prevent and manage hypertension.

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- •• Of major importance

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