CASE REPORT

A Review Nutraceuticals with Antihypertensive Properties

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Abstract

Supplementation with key nutrients that favorably influence vascular health is a promising integrative intervention in the management of hypertension. Thus far, the clinical use of such adjuncts has been limited due to a history of minimal regulatory standards for supplements. In recent years, clinical trials researching the impact of supplements on hypertension has begun to catch up to the marketplace, which may promote increased use of supplements to more effectively control hypertension. The following review aims to facilitate informed use of supplements as pharmaceutical agents, termed nutraceuticals, by summarizing the current knowledge on commonly used supplements with antihypertensive effects. The nutraceuticals Coenzyme Q10, Vitamin C, L-arginine, magnesium and potassium are reviewed. What is known about dosage, pharmacokinetics, pharmacodynamics, adverse effects, and nutraceutical-drug interactions are discussed in order to summarize the clinically relevant information.

Keywords

Hypertension, Preventative medicine, Cardiovascular disease, Nutraceuticals

Introduction

Hypertension a prominent risk factor for mortality, and is ranked in the top three most common causes for disability-adjusted life years [1]. Hypertension affects nearly all individuals, with the lifetime risk for development in all persons being 90% [2]. In the coming years, this problem will be even further amplified as new data has prompted the American Heart Association (AHA) to modify guidelines, defining hypertension at even lower blood pressures. Due to these newly accepted values for what qualifies as hypertension, an additional 31 million patients will need treatment, and 29 million patients currently being treated will need to improve their current treatment plan [3]. For this reason, adjunctive therapies that are accessible and attainable for patients are needed.

The pathophysiology of hypertension is complex and multifactorial, and includes atherosclerotic changes to blood vessels, arterial stiffening, and over-activation of both the sympathetic nervous system and the rennin-angiotensin-aldosterone pathway [4]. Atherosclerotic changes that occur during the genesis of hypertension are accelerated in the setting of high sugar and high fat diets [5]. Furthermore, high salt intake leads to endothelial dysfunction, which accelerates atherosclerotic changes and the development of hypertension [6]. For these reasons, dietary interventions for hypertension are commonly recommended, and can be very effective. For example, the DASH (Dietary Approaches to Stop Hypertension) diet advises high intake of fruits, vegetables and whole grains while limiting the intake of sweets, surgery beverages, and red meat [7]. In large clinical trials, the DASH diet has been shown to decrease blood pressure by 5-6 mmHg systolic, and by 3 mmHg diastolic. Other studies have reported even larger drops in blood pressure due to the DASH diet, with one recent trial demonstrating a drop in 12-11 mmHg systolic and 6-7 mmHg diastolic relative to the control diet [8].

Unfortunately, even though dietary approaches are effective, long-term changes in dietary habits are very hard for patients to adopt. In a recent study following...
4386 patients attempting to follow the DASH diet, only 22 percent of patients were able to adhere [7]. Similarly, studies encouraging lower salt intake as a means to reduce BP have found that only 20-40% of patients are able to reduce their intake below the maximum recommended limit of 2,300 mg/day, even with proper education and access to healthier options [9-11].

Rather than fully altering their diet, many patients may find it more attainable to add nutrients to their diet that promote vascular health. Supplementation with a nutraceutical is a comparatively easy intervention to adopt. This concept is supported by a cross-sectional study involving 343 patients with cardiovascular disease, which found that 82.5% of patients regularly used supplements for various health conditions [12]. Several nutraceuticals, dietary components with pharmacologically active properties, have been repeatedly shown to reduce blood pressure to a degree that is comparable to the entirety of the DASH diet [13].

Despite the potential role for nutraceuticals as adjunctive hypertensive therapies, implementation into clinical practice is uncommon. This may stem from a lack of clinical practice guidelines for usage, and limited education of practitioners on what is safe. Ultimately, this is likely a result of poor regulatory standards for supplements. Since the Dietary Supplement Health and Education Act was signed into law in 1994, it is the supplement manufacturers, rather than the FDA (Food and Drug Administration) that has responsibility for ensuring the composition of their products [14]. This has allowed some supplements to be placed on the market without prior clinical trial testing. Public concern for this matter has caused the advent of third party companies, such as the Natural Products Association (NPA, formerly NNFA) and NSF (National Sanitation Foundation International), which certifies companies as having “good manufacturing practices”. These third party companies run toxicology testing, assessing for potential contaminants, and testing to verify that products correspond to their label [14]. Therefore, recommending supplements from reputable companies to use in treatment regimens is safer now than in the past.

The following review aims to facilitate the use of antihypertensive nutraceuticals in clinical practice by summarizing clinically relevant information, including dosage, pharmacokinetics, pharmacodynamics, adverse effects, and nutraceutical-drug interactions. Due to information from meta-analyses and common usage, as well as an understanding of their antihypertensive properties, the nutraceuticals Co-Enzyme Q-10, L-arginine, Vitamin C, Magnesium, and Potassium are reviewed.

**Methods**

Searches on PubMed, Micromedex, Lexicomp, and the Natural Medicines Comprehensive Database were used to gather relevant articles. In order to ensure generalizability, the effectiveness and dosages reported all come from randomized controlled trials and meta-analyses of randomized controlled trial’s. Case reports were also included for adverse effects, and nutraceutical-drug interactions. All information comes from human trials, unless otherwise noted.

### The Use of L-Arginine

#### Dosage

A recent review of 7-meta analyses revealed that 8-11 g/d of L-arginine supplementation is associated with a 2.2 to 5.4 mmHg decrease in SBP and 2.7 to 3.1 decrease in DBP [15]. A separate meta-analysis containing 11 randomized, double-blind, placebo-controlled trials involving 387 participants with oral L-arginine intervention ranging from 4 to 24 g/d, showed an average drop in systolic BP by 5.39 mmHg and diastolic BP by 2.66 mmHg [16]. A third review concluded that oral arginine at 6 g/d was comparable to the DASH diet, however while study found that supplemental arginine was effective in lowering blood pressure in salt sensitive hypertensives, it was less effective in essential hypertension [17]. A summary of the meta-analyses included can be seen in Table 1.

#### Pharmacology

L-arginine and related endogenous methyl-arginine’s are the primary precursors for the production of the endothelium-derived relaxant factor, nitric oxide, NO [18]. Formation of NO depends on exogenous L-arginine intake, despite normally sufficient plasma and extracellular arginine concentrations [19]. This phenomenon is known as the arginine paradox. Furthermore, exogenous arginine can increase renal vascular and tubular NO bioavailability, thereby influencing renal perfusion and function, in addition to arterial pressure [20].

#### Pharmacokinetics

L-Arginine is moderately absorbed from the GI tract, with 20% becoming bioavailable about an hour after ingestion [21]. It is metabolized mainly in the liver by arginase to form urea and ornithine, which will be excreted and used as a substrate for gluconeogenesis respectively [22]. Clearance of L-arginine appears to be biphasic, with rapid renal excretion followed by slower metabolism, giving L-arginine a half-life of approximately 80 minutes [21,23].

#### Adverse effects

In general, oral L-arginine appears to be well tolerated with minimal side effects [24-26]. However, abdominal cramps, bloating and weight loss have been reported [27,28]. Additionally, L-arginine supplementation has been associated with headache development in some cases [28-30]. Notably, in one study of breast cancer patient [31]. L-arginine supplementation stimulated tumor protein synthesis, suggesting that it may stimulate
tumor growth. As a precaution, therefore, L-arginine should be avoided in the patient sub-population.

**Nutraceutical-drug interactions**

L-arginine may induce an extracellular shift of potassium from cells and should therefore be avoided in combination with potassium sparing diuretics, such as amiloride, spironolactone, and triamterene [32]. Concomitant use with diabetic drugs should also be closely monitored, as research has shown L-arginine’s use may decrease blood glucose levels in type II diabetics [33]. Finally, L-arginine induces production of nitric oxide, leading to vasodilation that is theoretically additive to other blood pressure lowering medications, and should therefore be closely monitored when used in combination of anti-hypertensives, nitric oxide donors, and phosphodiesterase inhibitors to avoid hypotension [34,35].

**Rigor of the Included meta-analyses**

The review by McRae, et al., [15] combined the evidence of 7 meta-analyses. All of the meta-analyses were assessed for their disclosure of quality, statistical heterogeneity (Cochran Q test and I² statistic), and publication bias (inspection of funnel plots and the Egger or Begg regression test). The meta-analysis by Dong, et al., [16] included 11 randomized double blind controlled trials, which were assessed for quality using the 5 point Jadad scale, which includes criteria surrounding randomization, blinding and withdrawals. Therefore, the research determining the impact of L-arginine on hypertension has a high level of rigor.

**The Use of Vitamin C**

**Dosage**

A meta-analysis of 29 randomized controlled trials found that a dose of 500 mg/d for an average of 8 weeks corresponded to a decrease in SBP by 4.85 mmHg and DBP - 1.67 mmHg (P < 0.01) in hypertensive individuals [36]. Similarly, a separate meta-analysis of thirteen clinical trials found that 500 mg/day for 6 weeks corresponds to a systolic blood pressure decrease of 3.9 mmHg, and a decrease of 2.1 mmHg for diastolic pressure [37]. This combined data suggests for a dosage of 500 mg/d for anti-hypertensive usage. A summary of this information, as well as other details, can be seen in Table 1.

**Pharmacology**

Multiple mechanisms have been proposed for vitamin C’s effect on BP [2]. Importantly, Vitamin C is used as a cofactor in NO and PGI₂ (prostacyclin) production, therefore its’ bioavailability leads to smooth muscle dilation and reduced total peripheral resistance [38]. Furthermore, vitamin C appears to decrease the binding affinity of Angiotensin II Type I (AT1) receptor for Angiotensin II by disrupting receptor disulfide bridges [39]. Vitamin C has also been shown to decrease adrenergic-steroid production, which leads to more favorable sympatho-vagal balance [40].

**Pharmacokinetics**

Vitamin C is absorbed from the intestine with a saturable transporter, making its' absorption lower at higher doses [41]. At a 500 mg dose, 63% is absorbed. Vitamin C is primarily excreted by the kidneys, with a half-life of about 7.4 hours [42].

**Adverse effects**

Vitamin C is well tolerated with adverse effects, such as nausea, vomiting, abdominal cramps, headache and fatigue, occurring at intake above 2000 mg/day [43]. Chewable forms of Vitamin C may lead to dental erosion, therefore tablets may be preferred [44]. In certain patients, urine acidification due to Vitamin C intake may cause cysteine, urate or oxalate stones to precipitate [45], and should therefore be avoided for any patient with a history of stone formation.

**Nutraceutical-drug interactions**

Vitamin C has anti-oxidant properties, therefore it could theoretically reduce the effectiveness of free-radical generating chemotherapeutics, such as cyclophosphamide, doxorubicin, chlorambucil and busulfan [46]. However this view is controversial, and more evidence is needed to fully elucidate these effects [47]. Vitamin C’s antioxidant properties may also allow it to regenerate oxidized estrogen, which could increase plasma estrogen concentrations when taken in combination with oral contraceptives or hormone replacement therapy, however this affect appears to be only in previously Vitamin C deficient patients [48,49]. Vitamin C may attenuate the HDL lowering effects of combined niacin and simvastatin therapy [50]. Finally, use of calcium channel blockers such as nicardipine, felodipine, isradipine, and nisoldipine may inhibit the uptake of Vitamin C [51].

**Rigor of the Included meta-analyses**

The review by McRae, et al. [37] included thirteen trials and a total of 284 participants. Their analysis weighted the results found in each trial based on the population size to calculate their recommended dose. Six of the 13 trials used randomized double blind placebo controlled trials, 2 single-blind placebo controlled parallel designs, one single blind placebo crossover design, and one randomized double-blind cross over design with magnesium as the other arm of the trial. The review by Juraschek, et al. [36] included 29 randomized controlled trials, which were assessed for quality of randomization, blinding of participants and investigators, methods for assessing participant compliance, and a description of adverse events.

**The Use of Co-enzyme Q**

**Dosage**
A meta-analysis of randomized, placebo-controlled clinical trials suggested that oral treatment of 100 mg of CoQ10 resulted in mean decreases of 11 mmHg SBP and 7 mmHg BDP after four weeks of

| Nutraceutical | Meta-analysis & Number of randomized clinical trials included | BP lowering affects (mmHg) | Length of time & Dosage | Common adverse effects | Potential herb-Drug interactions |
|---------------|-------------------------------------------------------------|---------------------------|------------------------|------------------------|--------------------------------|
| Magnesium     | Dibaba, et al. [76]; Meta-analysis of 11 RCT's             | SBP = -4.2(-0.4, -0.03); p < 0.05 DBP = -0.3; (-0.5, -0.03); p < 0.5 | 380 mg/d 3 months     | -Nausea, -Vomiting,     | Anticoagulants -Anti-platelets |
|               | Zhang, et al. [74]; Meta-analysis of 34 RCT's              | SBP = -2.0(-0.4, -3.6); p < 0.05 DBP = -1.8 (-0.7, -2.8); p < 0.05 | 365-450 mg/d 1-6 months | -Diarrhea               | Bisphosphonates -Digoxin -Gabapentin -Sulfonylurea’s |
|               | Kass, et al. [75]; Meta-analysis of 22 RCT’s               | SBP = Reported range of -3 to -4 DBP = Reported range of -2 to -3 | Mean of 410 mg/d 3-24 weeks | -Impacts cardiac conduction at Toxic doses | -Impacts cardiac conduction at Toxic doses |
|               | Jee, et al. [77]; Meta-analysis of 20 RCT’s                | SBP = -4.3(-6.3, -2.2); p < 0.001 DBP = -2.3(-4.9 ,0.0); p = 0.09 | 10-40 mmol/day 3-24 weeks | -Nausea, -Vomiting, -Heartburn | -Bisphosphonates -Digoxin -Gabapentin -Sulfonylurea’s |
| Coenzyme Q10  | Ho, Bellusci Wright; Meta-analysis of 3 RCT’s              | SBP = -11(-8, -14); p < 0.00001 DBP = -7(-5, -8); p < 0.00001 | 100-120 mg/d 3 weeks | -Nausea, -Vomiting, -Heartburn | -Warfarin Chemotherapeutic agents |
|               | Rosenfeldt, et al. [53]; Meta-analysis of 12 RCT’s        | SBP = -16.6 (-12.6, -20.6); p < 0.001 DBP = -8.2(-6.2, -10.2); p < 0.001 | 76-360 mg/d 8-12 weeks | -Nausea, -Vomiting, -Heartburn | -Bisphosphonates -Digoxin -Gabapentin -Sulfonylurea’s |
| Potassium     | Filippini [108]; Meta-analysis of 18 RCT’s                | SBP = -4.5(- 3.1, -5.9) DBP = -2.9 (- 1.1, 4.8) | > 90 mmol/day > 4 weeks | Gastrointestinal upset | -Angiotensin converting enzyme inhibitors -Angiotensin receptor blockers -Potassium sparing diuretics -Anti-cholinergic medications |
|               | Whelton [109]; Meta-analysis of 33 RCT’s                  | SBP = -3.1(-1.9, -4.3); p < 0.001 DBP = -1.9 (-0.5, -3.4); p < 0.001 | 60-200 mmol/ day 5 weeks (median) | -Paresthesias, Generalized Weakness, Hypotension, and Cardiac arrhythmias at Toxic levels | -Paresthesias, Generalized Weakness, Hypotension, and Cardiac arrhythmias at Toxic levels |
|               | Binia, et al., [110]; Meta-analysis of 15 RCT’s           | SBP = - 4.7(-2.4, -7.0); p < 0.05 DBP = -6.8(-4.3, -9.3); p < 0.001 | 60-100 mmol/d (median) 4 weeks | -Rare esophageal stricture when using sustained-release tablets | -Rare esophageal stricture when using sustained-release tablets |
| Vitamin C     | Juraschek, et al. [36]; Meta-analysis of 15 RCT’s        | SBP = -4.8p = 0.01 DBP = -1.7 p = 0.17 | 500 mg/d 8 weeks (median) | -Nausea, Vomiting, and Abdominal cramps when taken in surplus (> 2000 mg/day) -May increase risk of kidney stones in susceptible individuals | -Chemotherapeutic agents -Estrogen and oral contraceptives -Simvastatin -Calcium channel blockers |
|               | McCrae [37]; Meta-analysis of 13 RCT’s                   | SBP = -3.9 (-3.6, -0.3); p = 0.04 DBP = -2.1 (-3.1, 1.1); not significant | 500 mg/d 6 weeks (mean) | -Nausea, Vomiting, and Abdominal cramps when taken in surplus (> 2000 mg/day) -May increase risk of kidney stones in susceptible individuals | -Chemotherapeutic agents -Estrogen and oral contraceptives -Simvastatin -Calcium channel blockers |
treatment in hypertensive patients [52]. A separate meta-analysis with twelve clinical trials concluded that CoQ10 has the potential to lower systolic blood pressure by up to 17 mmHg and diastolic blood pressure by up to 10 mmHg without significant side effects, with the greatest effects occurring for patients with higher blood pressures at a dose ranging from 76-360 mg/d [53]. A summary of the meta-analyses included can be seen in Table 1.

Pharmacology

Co-Enzyme Q10, also known as Ubiquinone, is an antioxidant, free radical scavenger that reduces oxidation of LDL and also acts as a coenzyme in oxidative phosphorylation [2]. It is theorized that its’ main anti-hypertensive effects stem from a CoQ10 deficiency seen in the majority of hypertensive patients [54]. While the exact mechanism remains unclear, CoQ10 serum and tissue levels are seen to decrease with age, and there is evidence of deficiency at the population level in hypertension, heart failure, and statin-treated hypercholesterolemic patients [53].

Pharmacokinetics

CoQ10 is a large molecule that is poorly absorbed, leading to its’ high recommended dosages [55,56]. Some research suggests that emulsified CoQ10 may improve absorption [2]. Peak levels of CoQ10 occur about 5-10 hours after ingestion [57]. It appears to be distributed to the inner mitochondrial membrane, with a demonstrated effect in cardiac tissue, platelets, lipoproteins, and sperm cells [58-61]. CoQ10 is mainly metabolized in the liver and distributed in VLDL packaging [62].

Adverse effects

CoQ10 is generally well tolerated; in numerous clinical trials, there were no reports of significant adverse events [58], [63-66]. However less than 1% of patients may experience gastrointestinal side effects such as nausea, vomiting, diarrhea, appetite suppression, heartburn, and epigastric discomfort [58,67,68].

Nutraceutical-drug interactions

Coenzyme Q10 is chemically similar to K-vitamins, therefore it theoretically can interfere with warfarin; an affect that has been reported in several individuals [69,70]. However preliminary research suggests that CoQ10 might not significantly decrease the effects of warfarin in patients with a stable INR [71]. Additionally, the anti-oxidant properties of CoQ10 may lower the effectiveness of chemotherapeutic agents that work through oxidative stress, such as cyclophosphamide and cytoxin [72,73].

Rigor of the included meta-analyses

The meta-analysis by Rosenfeldt, et al., [53] included 12 clinical trials and a total of 362 patients. The trials included three randomized controlled trials, one crossover study, and eight open label studies. The analysis by Ho, et al. [52] used only double-blind, randomized, placebo-controlled trials with parallel or crossover designs. Their criteria led to a total inclusion of three clinical trials with 96 participants in total.

The Use of Magnesium

Dosage and meta-analyses

The most recent meta-analysis included 34 randomized double-blind clinical trials. This study found that magnesium (Mg) supplementation of 380 mg/day over three months reduced SBP by 2.0 mmHg (95% confidence interval, 0.4-3.6) and DBP by 1.8 mmHg (95% confidence interval, 0.3-2.8) [74]. Similar results were observed in a separate analysis of 22 trials with a mean supplementation of 410 mg/day for 3-24 weeks, which resulted in blood pressure decreases of 3-4 mmHg systolic/2-3 mmHg diastolic [75]. An analysis specifically examining magnesium’s effect on blood pressure in patients with insulin resistance found 365-450 mg/d of magnesium for 1-6 months reduced blood pressure by 4.18/2.27 mmHg; SBP (SMD: -0.20; 95% CI: -0.37, -0.03) and DBP (SMD: -0.27; 95% CI: -0.52, -0.03) [76]. Some evidence suggests that BP lowering effects of magnesium may be dose-dependent. A review including 20 randomized clinical trials (n = 1220) found a reduction in SBP of 4.3 mmHg (p < 0.001) and in DBP 2.3 mmHg (p = 0.09) for every 10 mmol increase in daily magnesium intake ranging from 10-40 mmol/day for 3-24 weeks [77]. The daily intakes reported in the above reviews (365-450 mg/d) are comparable to the usual dose recommended for magnesium deficiency prophylaxis, which is 400 mg/day [78]. A summary of this information can be seen in Table 1.

Pharmacology

Magnesium concentrations affect calcium, sodium and potassium concentrations through the renal Mg-
ATP driven sodium-potassium pump, and Mg-calcium pump [79]. The effect on calcium concentrations appears to significantly impact BP by altering vascular smooth muscle intracellular calcium concentrations [80]. Here, magnesium driven reduction of calcium concentration results in the release of prostacyclin, an endothelium-derived vasodilator [81,82]. Magnesium is also thought to be an antagonist of Angiotensin II’s pressor and steriodogenic effects by blunting its’s signaling via the Ca++ messenger system [81]. Further, vascular remodeling in hypertension is slightly blunted by magnesium due to a reduction in free radical generation through modulation of glutathione and thioredoxin synthesis. Vascular remodeling is additionally affected via a regulatory effect on cell growth by magnesium activation of tyrosine kinases, phosphoinositide 3-kinase, Rho/Rho kinase and mitogen-activated protein kinases [80]. For these reasons, small changes in Mg++ concentrations have been demonstrated to have major effects on vascular tone.

Pharmacokinetics

Magnesium is absorbed through the jejenum and ileum by active and passive transport, and requires both parathyroid hormone and vitamin D for absorption [83,84]. Its’ bioavailability after absorption is about 33% [81]. Magnesium is largely free floating, with only 33% protein bound. In contrast, half of absorbed calcium (50%) is distributed to bone, and half into tissues, where 45% is located in intracellular fluid and 5% remains in extracellular fluid [84]. Magnesium is excreted entirely by the kidneys at a rate that is directly proportional to the plasma concentration and glomerular filtration rate. It is thought to undergo a filtration-reabsorption process; there is reabsorption in the proximal tubule, and loop of Henle, resulting in 3-5% of the filtered load being excreted [85,86].

Adverse effects

Magnesium is generally well tolerated at appropriate doses, with clinical research indicating no substantial differences in adverse effects when compared to controls [87-89]. However, gastrointestinal discomfort, nausea, vomiting and diarrhea have been reported [87,90]. At toxic doses, above 9.7 mg/dL, magnesium impacts cardiac conduction time by lengthening P-R and QRS intervals, and slowing the SA nodal impulse [84,91,92]. Patients with hyper-magnesemia will present with muscle weakness, electrocardiogram changes, sedation, hypotension, and confusion, which may progress to absent deep-tendon reflexes, respiratory paralysis, and heart block [84]. Patients with renal failure, or metabolic derangements may develop magnesium toxicity at lower concentrations [93,94].

Nutraceutical-drug interactions

Magnesium appears to have an additive effect on calcium channel blockers due to inhibition of calcium movement into smooth muscle cells [95-97]. While this may produce a desirable effect in some patients, caution should be used to avoid hypotension. In addition, the hypotensive effects may be more severe with concomitant use of nifedipine, potentially leading to neuromuscular weakness, although the evidence for this is unclear [98]. There is some evidence to suggest that magnesium sulfate inhibits platelet functioning and increases bleeding time [99,100]. The degree to which this happens is not fully defined, however caution should be used with concomitant use of anti-coagulants or anti-platelets. Magnesium, and other cations, can decrease bisphosphonate absorption, and should therefore be taken at least two hours apart [101]. Magnesium similarly reduces absorption of digoxin [102,103] as well as gabapentin [104], and tetracycline antibiotics [105]. In contrast, magnesium increases the absorption of sulfonylureas, potentially leading to a risk of hypoglycemia [106]. Theoretically, potassium sparing diuretics may increase levels of magnesium, and should therefore be used with caution in combination with magnesium [107].

Rigor of the included meta-analyses

The FDA categorizes magnesium as an anti-hypertensive with a Class Iib recommendation, which means it is recommended in some cases, but not most cases. It also states that the evidence for magnesium as an anti-hypertensive is Category A, meaning evidence is based on data derived from meta-analyses of randomized controlled trials with homogeneity of results and involving large numbers of patients [78]. This is supported by the meta-analyses above that report doses in a comparable range (365-450 mg/d), producing similar responses. The exclusion criteria of the review by Zhang Xi, et al., in 2016 [74] was the most rigorous and had the following exclusion criteria: (1) Studies including pregnant or lactating women; (2) Studies including patients with malignancy, severe infectious disease, active liver or renal disease, or other severe illnesses; (3) Supplements combined with other minerals that affect BP and duration of Mg supplementation ≤ 1 week; and (4) Non-random, open-label, or self-controlled trials. The review by Kass, et al., [75] in 2012 included placebo-controlled, randomized trials with either parallel or cross-over designs. Of these, 21/23 were double-blind, one included trial was single-blinded, and one was not blinded at all. Similarly, 16/20 trials included in the review by Jee, et al. [77], in 2002 were double-blind; all trials included were randomized, controlled, and had sufficient statistical power.

The Use of Potassium

Dosage and meta-analyses

The most recent meta-analysis of 18 randomized controlled trials included a total of 1,163 participants,
and found 30-120 mmol/day for 4 to 15 weeks’ decreases blood pressure by 4.5 mmHg systolic, and 2.9 mmHg diastolic [108]. A review of 33 randomized clinical trials with a dosage of 60-200 mmol/day for a median of 5 weeks reduced BP by 3.11 mmHg/1.97 mmHg [109]. Potassium supplementation was seen to have a larger effect in trials that included only hypertensive patients. Binia, et al. found that potassium supplementation at 60-65 mg/day for 4 to 24 weeks reduced BP by a mean of 6.8/4.6 mmHg [110]. A summary of the included studies can be seen in Table 1.

**Pharmacology**

Potassium likely exerts its’ anti-hypertensive effects through several mechanisms [82]. Potassium has been shown to act as a diuretic by reducing proximal tubule sodium reabsorption, and increasing glomerular filtration rate through reduced renal vascular resistance [111]. Potassium reduces renal vascular resistance, and systemic resistance, by causing endothelial cell hyperpolarization through stimulation of the sodium-potassium pump and activation of plasma membrane potassium channels, resulting in endothelium-dependent dilation [112]. Potassium may also impact blood pressure through sympatholytic actions by influencing noradrenaline turnover [113]. Finally, potassium may also have some anti-oxidant effects [114].

**Pharmacokinetics**

Oral potassium is well absorbed, and equivalent in both slow release and liquid preparations [115]. Total body concentration is regulated tightly by renal excretion, and is also buffered by skeletal muscle and liver. Once distributed, potassium largely remains intracellular [116]. Potassium is filtered and excreted by the kidneys, with 80% of filtered potassium being recovered from the urine [111].

**Adverse effects**

Oral potassium can cause gastrointestinal upset in some cases [109,117,118]. However, newer formulations with liquid/rapid-release tablets or wax-matrix tablets are less likely to cause gastrointestinal upset [119,120]. At high concentrations, above 5 mEq/L, hyperkalemia can cause paresthesia’s, generalized weakness, flaccid paralysis, confusion, hypotension, cardiac arrhythmias, and heart block [109,121]. ECG changes are the most important indicator of potassium toxicity, which could appear as peaked T-wave, ST depressions, disappearance of the P wave, prolongation of the Q-T interval, or widening of the QRS complex [122]. Extremely high plasma potassium concentrations (8 to 11 mEq/L) may cause death from cardiac depression, arrhythmias or arrest [123]. There have also been several reports of esophageal ulceration and stricture associated with continuous use of sustained-release potassium chloride tablets [123-125].

**Nutraceutical-drug interactions**

Angiotensin-Converting Enzyme (ACE) inhibitors lower aldosterone levels, leading to potassium retention. Therefore, concomitant use of potassium supplements with ACE inhibitors may result in hyperkalemia, with subsequent arrhythmias [126,127]. This may be especially important for patients that have renal dysfunction in addition to ACE inhibitor therapy [128]. Hyperkalemia may also occur with angiotensin-receptor blockers, and potassium sparing diuretics [129,130]. Finally, concurrent administration of potassium with anticholinergic drugs, such as atropine, may amplify anti-cholinergic effects, leading to slow gastric motility and potentially leading to GI lesions [109].

**Rigor of the Included meta-analyses**

Filippini, et al., included 18 randomized placebo-controlled trials, however only 9/18 were double-blinded, and 4/18 were single-blinded [108]. This review assessed quality of study and bias risk with the Cochrane assessment tool. The review by Whelton, et al., [109] contained randomized, controlled trials; 23/33 were double-blind, 3/33 were single-blind, and 7/33 were open-label studies. Binia, et al., [110] had the most rigorous analysis, reviewing only randomized, double-blind, controlled trials greater than four weeks in duration, and assessed for bias using the Cochrane classification scheme. Importantly, this review found BP reductions similar to other, less-rigorous reviews.

**Conclusion**

The inability of nearly half of hypertensive patients to keep their blood pressure under control indicates the need for adjunctive antihypertensive therapies. Adding dietary supplements that are beneficial to vascular health may be an attainable intervention for patients. The nutraceuticals presented above have been shown to improve BP to a clinically relevant degree in controlled trials. Based on the above data, CoQ10 appears to be the nutraceutical with the largest impact on blood pressure, with a reported ability to lower BP by 11/7 mmHg with supplementation of 100 mg/d [52], and some accounts recording BP drops of up to 17/10 mmHg. However, CoQ10 has the least rigorous trials, and the least data as compared to the other nutraceuticals reviewed. Randomized controlled trials involving L-arginine and potassium show BP lowering effects at 8-24 mg/day and over 90 mmol/day, respectively, and follow as the second most efficacious nutraceuticals. Both L-arginine and potassium have been more highly evaluated with meta-analyses of double-blind randomized controlled trials. Magnesium produces BP lowering effects above 350 mg/day and is categorized as an anti-hypertensive agent by the FDA with a Class Iib recommendation, which means it is recommended in some but not all cases.
Importantly, both magnesium and potassium can cause cardiac arrhythmias at toxic dosages. Finally, some analyses have found that Vitamin C produces blood pressure lowering effects above 500 mg/day, however this association has not been found to be significant in all analyses.

Ultimately, this guide is intended to help individuals tailor their supplement use based on reported adverse events, preference, and nutraceutical-drug interactions. Future work should continue to research the implications of nutraceutical use, as the above report reviews only the current data available. Longitudinal trials evaluating long-term safety is particularly needed, as well as a pharmaco-economic analysis for each supplement. Further, as nutraceuticals are still under the less stringent guidelines of the DSHEA, rather than the FDA, more work should be done to assess the integrity of each nutraceutical company involved in supplement production.

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