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Soda and Stroke Risk: A Pop Connection?

ABSTRACT & COMMENTARY

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Dr. Marcolina reports no financial relationships relevant to this field of study.

Synopsis: Two large, well-known, U.S. prospective cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study, evaluated both sugar-sweetened and diet (low-calorie, also called artificially sweetened) soda consumption over 20 years and found one or more daily servings to be associated with a significantly higher risk of stroke. Conversely, alternative beverage choices of either skim milk, caffeinated coffee, or decaffeinated coffee were associated with diminished stroke risk. This association appeared to be stronger for women than men and independent of established dietary and nondietary cardiovascular disease risk factors, including body mass index and energy intake. Beverage choice may be a modifiable risk factor for cerebrovascular events.

Source: Bernstein AM, et al. Soda consumption and the risk of stroke in men and women. *Am J Clin Nutr* 2012;95:1190-1199.

THIS EPIDEMIOLOGIC STUDY EVALUATED BEVERAGE TYPES AND AMOUNTS consumed by two large representative male and female populations of health professionals over more than two decades in detail via biennial validated food frequency questionnaires (FFQs) in addition to their health status questionnaires. The types of sodas included on the FFQs included low-calorie, caffeinated, and decaffeinated colas; other low-calorie, non-cola carbonated beverages; sugar-sweetened colas with and without caffeine; and other carbonated, caffeinated, and decaffeinated beverages with sugar. Soda was categorized as sugar-sweetened or low-calorie, and then participants were divided into categories of cumulative average serving intake of each type (sugar-sweetened and low-calorie soda consumption), which included none, up to once per week, once per week up to

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Summary Points

- The consumption of one or more daily servings of sugar-sweetened and diet sodas may contribute to stroke risk, particularly in women, due to the fructose content (from sucrose and high fructose corn syrup) which can adversely increase blood pressure, weight, visceral fat, and blood levels of uric acid, small density LDL cholesterol, and triglycerides, all of which increase cardiovascular and cerebrovascular risk.
- Mindful alternative beverage choices — such as water, which provides necessary hydration without additional calories or cost — may be an important risk reduction strategy that can also improve general health.

once per day, and once per day or more.

The investigators evaluated the associations between sugar-sweetened and low-calorie soda intake and total stroke (hemorrhagic and ischemic) incidence in both populations. In multivariable analyses adjusted for dietary risk factors (intakes of alcohol, fruit and vegetable servings, cereal fiber, fish, red meat, trans fats) and non-dietary cardiovascular disease risk factors (exercise, smoking, family history, menopausal status [women], aspirin, and multivitamin use), increased consumption of both sugar-sweetened and low-calorie colas and non-cola

carbonated beverages was associated with a greater risk of overall stroke. For men, one or more daily servings of sugar-sweetened soda was associated with an insignificant relative risk (RR) of total stroke of 1.08 (95% confidence interval [CI], 0.82-1.41; $P = 0.43$); whereas in women, the statistically significant RR was 1.19 (95% CI, 1.00-1.42; $P = 0.02$). For men who consumed one or more daily servings of low-calorie soda, the RR for total stroke was 1.10 (95% CI, 0.92-1.32; $P = 0.13$) and in women was 1.18 (95% CI, 1.05-1.33; $P = 0.003$). The pooled multivariable risk of stroke among both sexes was 1.12 (95% CI, 1.02-1.24; $P = 0.02$) for one or more daily servings of sugar-sweetened soda and 1.09 (95% CI, 1.04-1.15; $P = 0.0001$) for one or more daily low-calorie soda servings.

Interestingly, compared with men and women who did not consume sugar-sweetened soda, those who consumed one or more daily servings had higher rates of hypertension, hypercholesterolemia, and lower physical activity. Greater consumption of low-calorie soda was associated with higher body mass indices (BMIs) and rates of chronic disease.

The authors evaluated the pooled risk ratios for consumption of alternative beverages in regard to stroke risk and found that compared with one daily serving of sugar-sweetened soda, daily servings of decaffeinated and caffeinated coffees were associated with modest reductions of 10% and 9% in stroke risk, respectively. When compared with one daily serving of low-calorie soda, consumption of one daily serving of skim milk, caffeinated coffee, or decaffeinated coffee was associated with decreases in stroke risk of 11%, 11%, and 13%, respectively. Although the 95% CIs suggested a modest benefit with the water for soda substitution, the authors suggest that the chlorogenic acids, lignans, and magnesium content of coffee and the potassium magnesium and calcium content of milk act both as antioxidants and mediators of glucose metabolism and blood pressure, which may be associated with the reduced stroke risk result seen with these beverages.¹

■ COMMENTARY

Stroke is the third major cause of death and the leading cause of functional impairment, with 15-30% of survivors left with permanent disability and lost independence. It is a major public health concern in the United States. Effective primary prevention remains the optimal way to reduce the burden of disease and disability, since more than 70% of strokes occur as first-time events.²

The benefit of information obtained from large, long-term cohort studies such as this one is that it prompts us to consider ways in which individuals, in conjunction with their health care providers in the medical home context, can mitigate risk by virtue of dietary and lifestyle interventions that are low-cost, effective, and achievable.

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Over the past 25 years, sugar-sweetened and diet soda consumption has increased 135% in the United States in parallel with the prevalence of obesity.³ The temporal association has a scientific basis in view of the fact that sodas are nutrient-poor beverages consumed in lieu of potentially nutrient-rich beverages such as enriched non-dairy milks, milk, calcium-fortified juices, or just plain water, which provides necessary hydration without additional cost or calories. Additionally, the caramel coloring in sugar-sweetened and low-calorie colas has advanced glycation endproducts, which have been linked to inflammatory processes that enhance initiation, growth, and destabilization of atherosclerotic plaques.⁴

Another factor in the soda-stroke linkage may be the fructose content of soda either as sucrose (the “sugar” disaccharide composed of 50% fructose and 50% glucose) or high-fructose corn syrup (55% fructose and 45% glucose). Due to this high volume and content of rapidly absorbable carbohydrates, sodas may increase the risk of metabolic syndrome and type 2 diabetes by increasing dietary glycemic load, leading to insulin resistance, weight gain, beta cell dysfunction, and inflammation. Ingested fructose is metabolized almost entirely in the liver; this hepatic metabolism favors lipogenesis, which increases triglyceride levels and reduces low-density cholesterol lipoprotein particle size. Such alterations in the lipoprotein profile increase atherogenicity. Hepatic metabolism of fructose also increases serum uric acid, which reduces endothelial nitric oxide and can result in blood pressure elevation, a known risk factor for stroke.⁵

Additionally, fructose has different metabolic effects than glucose. It does not increase postprandial insulin and leptin (satiety hormone) or suppress ghrelin (appetite-stimulating hormone) levels, thus suggesting another means by which it promotes weight gain.⁶

Several other epidemiologic studies have shown an association between consumption of sugar-sweetened beverages and the development of metabolic syndrome and type 2 diabetes, both of which contribute to risk of stroke.⁷

Although deKoning et al found no association between low-calorie soda intake and diabetes risk,⁸ low-calorie soda consumption of two or more daily servings has been associated with albuminuria and progression of kidney disease.⁹

Another consideration is that many carbonated beverages contain a large amount (> 10 mg in a 12 fluid-ounce serving) of inorganic phosphorus (P) in the form of additives such as phosphoric acid or monosodium phosphate. These P salts readily dissociate and are absorbed to a much greater extent compared to the more tightly protein-bound organic P present in natural sources such as beef, chicken, and egg yolks (> 90% absorption vs 40-60% intestinal absorption, respectively). Such additional bioavailable

P increases serum P levels and urinary P excretion and decreases serum and urine calcium concentrations. These changes induce a secondary hyperparathyroidism, with its negative consequences for bone health.¹⁰

The pitfalls with this study, as with any observational study, is that the soda-stroke association cannot confer causality due to confounding from as yet unidentified and unmeasured factor(s). The association may also be an indirect one, linked by other disease processes that may be mitigated by dietary beverage choice including inflammation, endothelial dysfunction, and dyslipidemia. Further information regarding whether, what type, and how much soda consumption can affect stroke risk will depend upon randomized, controlled trial results.

In the meantime, we can all drink to our health by following the advice offered by Dr. William Osler in his 1893 *Principles and Practices of Medicine* text that “the sugar should be kept to a minimum.”¹¹ ■

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Acupressure: The Evidence Presses On

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ACUPRESSURE IS A THERAPEUTIC INTERVENTION THAT HAS its roots in Traditional Chinese Medicine (TCM) and is based on the same meridian theory used in acupuncture. However, rather than using needles, acupoints are typically stimulated using pressure from fingers, hands, elbows or, in some cases, by devices. The basis of meridian theory is that illness and symptoms result from alterations in the normal flow of qi in the body, defined as a life-supporting bioenergy that moves along a predictable network of pathways. Symptoms and illness can be improved by accessing these pathways through acupoints on the surface of the body and stimulating them in a prescriptive fashion, normalizing the flow of qi. Mechanism of action hypotheses based on Western concepts of human physiology include release of endorphins, functional peripheral and central nervous system changes, and changes in circulating and local bioactive substances such as cytokines and neurotransmitters.¹

Acupressure has innumerable therapeutic applications in TCM. In conventional Western medicine, it is an attractive complementary and alternative medicine (CAM) intervention because of its low risk and cost, and the fact that it can often be self-administered. Over the last decade, research methodology on acupressure has improved, prompting several systematic reviews. Recent evidence of efficacy for the use of acupressure in a variety of clinical conditions is the focus of this review.

Clinical Trials

Nausea and Vomiting. Postoperative nausea and vomiting (PONV) has been a focus of acupuncture and acupressure studies as anesthesiologists continue to search for interventions that improve patient outcomes without the costs and risks of side effects associated with antiemetic drugs. The majority of studies have evaluated the effectiveness of stimulation of a single acupoint: the Pericardium (P6) acupoint at the wrist, 4 cm proximal to the wrist crease between the palmaris longus and flexor carpi radialis tendons. A 2011 Cochrane review identified 40 trials of P6 acupoint stimulation for PONV, 17 of which used acupressure.² Of these 17 trials of acupressure, eight

Summary Points

- Acupressure is based on the same meridian theory used in acupuncture.
- Various hypotheses exist regarding mechanisms of action from a Western medical perspective.
- Clinical trials suggest that acupressure may be effective for nausea and vomiting associated with the post-op period, pregnancy and possibly cancer treatment, as well as for the treatment of select pain syndromes, and specific instances of insomnia and fatigue.
- Acupressure is considered safe and noninvasive.

were determined by the reviewers to contain high risk of bias because of selective reporting. Most of these acupressure trials used a wrist band device (Sea-Bands®). There was no difference in the effect of acupressure compared to more invasive techniques, such as acupuncture or electrical stimulation, in this review. Stimulation of the P6 acupoint compared to sham treatment significantly reduced the risk of PONV and the need for antiemetic rescue (relative risk [RR] 0.71, 95% confidence interval [CI] 0.61-0.83; RR 0.70, 95% CI 0.59-0.83; RR 0.69, 95% CI 0.57-0.83, respectively). Risks of PONV were similar with acupoint stimulation and antiemetic drugs. Reviewers concluded that patients with a high risk of PONV would likely benefit from P6 acupoint stimulation.

A systematic review of acupressure for symptom management by Lee et al included six trials for nausea and vomiting related to pregnancy, four trials for nausea and vomiting related to chemotherapy or radiation, 11 trials for PONV, one trial for motion sickness, and one trial for nausea and vomiting due to myocardial infarction. Again, nearly all of the reviewed trials employed wrist bands for the acupressure intervention. These authors concluded that evidence of efficacy for acupressure compared to sham or control for nausea and vomiting prevention and treatment in general was equivocal, primarily due to small samples or methodological flaws.³

However, in a systematic review of 71 studies of acupressure intervention for a variety of clinical problems, Robinson et al concluded that the intervention was actually supported by strong evidence for reducing PONV risk, thanks to the analyses in the Cochrane review mentioned above, and moderate evidence for pregnancy-related nausea and vomiting. These authors conclude that there is some quality evidence from systematic reviews for chemotherapy-induced nausea and vomiting support-

ing acupressure, but only a small number of the reviewed interventions was true acupressure.⁴

Pain. Robinson et al reported in their review that pain was the most common issue addressed by acupressure. They included a systematic review, six randomized controlled trials (RCTs), and several studies with various methodological flaws including non-randomization of treatment or control groups, or lack of a control group. The review concluded that there was consistent evidence showing that acupressure is more effective than control for reducing dysmenorrhea, lower back pain, and labor pain. Less conclusive evidence is available for minor trauma and injection pain; evidence for headache is insufficient.⁴ A small ($n = 33$) RCT compared local and distal acupressure with a control group that did not receive any stimuli for the treatment of chronic neck pain. In this study, acupressure at both locations improved pain outcomes compared to the no-treatment control group ($P < 0.05$). Interestingly, autonomic function changed only in the group receiving local acupressure ($P < 0.05$).⁵ A systematic review of acupuncture and similar techniques for dysmenorrhea concluded from two RCTs that auricular acupressure (application of pressure over acupoints on the auricle) was beneficial for improving menstrual pain.⁶

Insomnia. Five RCTs of acupressure for insomnia and fatigue were included in the systematic review by Lee et al, who noted that all investigators concluded that acupressure was useful for reducing insomnia and fatigue; however, studies were of low quality.³ Robinson et al, in their review of the same and five additional studies, reported that acupressure for insomnia, fatigue, and depression due to renal disease has moderate evidence of efficacy similar to placebo, while evidence for improving sleep quality in institutionalized elderly is strong, though again failing to consistently support specific effects of acupressure compared to sham.⁴ A review of insomnia and the use of CAM by Sarris et al included two RCTs on acupressure; the authors concluded that there was evidence to support the treatment of chronic insomnia with acupressure ($d = 1.42-2.12$).⁷

Other Conditions. Lee et al reviewed four trials of acupressure for dyspnea related to chronic lung disease, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and asthma. These studies included subjective and objective parameters (pulmonary function tests, oxygen saturation, and exercise capacity) as outcomes. In all four studies, acupressure improved outcomes compared to either placebo or standard care controls.³ Again, all of the studies were of low quality. Chang et al reported that acupressure improved symptoms of urodynamic stress incontinence and pelvic floor strength ($P < 0.05$) compared to both sham treatment and usual care (pelvic floor training).⁸ Pelvic floor muscle strength was the primary outcome measure in this study, evalu-

ated by perineometry, measuring vaginal squeeze pressure. Unfortunately, the study was only single-blinded, as the investigator was the intervention provider. However, this is one of very few clinical trials that have included an objective outcome measure.⁸ Another well-designed, single-blind crossover study noted decreased heart rate in stroke patients treated with acupressure compared to sham acupressure.⁹ A recent small pilot study compared acupressure to standard treatment for atopic dermatitis and noted improvement in lichenification ($P < 0.03$) and decreased pruritis ($P < 0.05$) in the acupressure group compared to usual care control.¹⁰ A systematic review of acupressure for treating neurological disorders included a total of six controlled trials. The authors concluded from one RCT and three controlled clinical trials that there is some evidence that acupressure improves function and symptoms in patients with stroke but that all trials were limited by methodological flaws and high risk of bias.¹¹ A randomized, single-blind, crossover trial by Harris et al concluded that self-administered acupressure can modify alertness in students in a classroom setting.¹² Based on the results of this study, Zick et al studied the effects of self-administered stimulatory or relaxation acupressure in patients with cancer-related fatigue, hypothesizing that both low- and high-dose stimulatory acupressure would reduce fatigue symptoms and relaxation acupressure would help control for the placebo effect. Surprisingly, their results showed that relaxation acupressure significantly reduced fatigue compared to stimulatory acupressure.¹³ Jin et al reported that acupressure as an adjunct to usual care inhibited the development of diabetic complications in patients with type 2 diabetes.¹⁴ Their trial included a control group receiving only usual care, but no sham treatment group. Of interest is that the acupressure treatments were 90 minutes each and delivered by a practitioner 4-6 times per week for 3 years, a rather intensive intervention. Multiple objective outcome measures showed improvement in the acupressure treatment group compared to controls: total cholesterol, triglycerides, LDL, HDL, and nerve conduction velocities. Kidney function also was stable in the treatment group compared to controls.¹⁴ Still, without a sham intervention of similar practitioner-patient intensity, it is hard to ascertain the specific effects of acupressure.

Adverse Effects

Acupressure is considered safe and non-invasive. Local skin reactions, blistering, and swelling with wrist band acupressure devices have been reported in some studies. It is considered normal to feel a temporary heaviness, aching, or tingling at the point of the acupressure administration. These symptoms were mentioned in a few of the articles reviewed. In TCM, these sensations are an indication that qi has entered the area, a desired treatment effect.

Conclusion

Clinical trials of acupressure appear to be steadily improving with respect to methodology over the last several years. Current research evidence supports that acupressure is effective for reducing the risk of nausea and vomiting in high-risk, postoperative patients, in pregnant patients, and possibly in cancer patients. There is consistent evidence of efficacy for reducing dysmenorrhea, low back pain, and labor pain. Acupressure appears to improve sleep quality in elderly institutionalized patients, and reduces fatigue in patients with chronic renal failure. Limited data supports acupuncture for stress incontinence and prevention of diabetic complications. Still, nearly all of the evidence is compromised by methodological flaws and bias. For example, sample sizes are characteristically small; acupressure doses for various conditions vary widely from a few minutes to a few days; and acupressure regimens also vary widely in technique and number and choice of acupressure sites, even when applied for the same condition. In many studies, there is a lack of information about practitioner-patient interaction for control and treatment groups, creating a potentially serious confounding variable. The Cochrane review on nausea and vomiting reports several common serious sources of bias in the acupressure studies: selective reporting, lack of allocation concealment, and no blinding of outcome assessor. Wide confidence intervals in most studies suggest that we still know very little about the effect sizes of acupressure interventions. More high-quality acupressure studies are needed, addressing the methodological flaws and bias that exist in the current body of work. Future studies including objective outcomes may add insight into the mechanisms of action of acupressure and meridian therapies in general.

Recommendations

Acupressure is a low-risk intervention that has an additional advantage in that it can be self-administered for some conditions, increasing its potential cost-effectiveness. Acupressure can be recommended as first-line therapy and adjunctive therapy for prevention of nausea and vomiting postoperatively, during pregnancy, and during cancer treatment. Acupressure may help low back pain patients, women in labor, and patients suffering from dysmenorrhea, and it can be offered to patients as an alternative or adjunct to medication. Elderly in nursing homes may benefit from acupressure to improve sleep quality, avoiding the pitfalls of sleep medication and providing an intervention that could be administered, after training, by local staff.

Acupressure therapists are not consistently regulated in the United States; acupressure therapy often falls outside the regulatory legislation and certification mandates

that apply to massage therapy and other forms of bodywork. However, many massage and acupuncture schools in the United States offer acupressure courses and a certifying examination in Asian Bodywork Therapy is available through the National Certification Commission for Acupuncture and Oriental Medicine. Online tutorials and courses are also available for acupressure training. Patients can and do access these tutorials to learn about acupressure self-administration and it is also likely that the training and experience of acupressure providers in communities varies widely. Thus, physicians and other professionals recommending acupressure as an intervention for their patients and clients are wise to investigate the services available in their area thoroughly, seeking and recommending practitioners who are formally trained and certified. ■

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Garlic and Cardiovascular Disease

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CARDIOVASCULAR DISEASE (CVD) IS A COMPLEX GROUP OF heart-related conditions that are the leading cause of death among Americans and Europeans.¹ The prevalence of CVD is growing rapidly in developing countries also.² Finding safe and effective strategies to prevent and treat CVD is a major priority around the world.

Many factors contribute to the development of CVD, which encompasses high blood pressure, coronary artery disease, heart failure, stroke, and congenital cardiovascular defects. Epidemiological studies exploring cardiovascular risk factors have pointed to the role of elevated serum lipids (including cholesterol and triglycerides), elevated blood pressure, increased platelet aggregation, increased plasma fibrinogen and coagulation factors, al-

terations in glucose metabolism, and smoking.³ Reduced risk of CVD is associated with increased serum levels of high-density lipoprotein (HDL-C), normalization of abnormal lipid levels, inhibition of platelet aggregation, and, in some studies, increased antioxidant status.

Dietary factors are known to play a role in CVD, with Mediterranean diets, fish, fruit, and whole grains known to reduce CVD risk.¹ One study in which patients admitted with acute vascular disease were interviewed found that 78% were taking natural health products; such usage had been documented by pharmacists in 41% of patients, by physicians in 22%, and by nurses in 19%.⁴ These numbers include some overlapping in documentation. Garlic (*Allium sativa*, Family Liliaceae) continues to be in the top five best-selling herbs, and is the most popular herb used by patients with CVD.⁵

History

Garlic has been an important component of peoples' diets in many cultures for centuries.² Ancient Ayurvedic texts refer to health benefits of garlic in terms of improving blood flow and strengthening the heart.⁶ The Egyptian Codex Ebers (1500 BC) recommended garlic for heart disease, and also for tumors, worms, bites, and many other conditions. The Greek physician, Hippocrates (400 BC), and the Roman authority, Pliny the Elder (77 AD), recommended garlic for the cardiovascular system.⁷

Clinical work as early as 1926 found garlic to have beneficial effects on cardiovascular disease. These effects were again mentioned in the 1960s and 1970s when a number of studies noted reductions in serum cholesterol and triglyceride levels.⁶ However, these early studies were conducted with raw garlic administered at very high doses (between seven and 28 cloves per day).

Pharmacology

Garlic's odor problem has led to much work being done to find more palatable and less odorous formulations. The odor, as well as garlic's cardiovascular effects, is caused by sulfur-containing compounds.⁸ Garlic cloves contain almost all their sulfur in a storage compound called alliin (a name coming from garlic's botanical name, *Allium sativum*). Raw garlic also contains an enzyme called alliinase. When raw garlic is cut or crushed, the alliinase interacts with alliin to produce allicin.⁹ The distinctive aroma and taste of garlic is due to allicin, which is very volatile and unstable, breaking down either in a few hours at room temperature or after a few minutes of cooking. An in vitro study found that garlic's ability to inhibit platelet aggregation was not changed after 3 minutes or less of immersion in boiling water. After 6 minutes, garlic cloves had no activity, while crushed garlic retained some activity. After 10 minutes, all activity was gone. Microwaving for about

Summary Points

- Garlic's beneficial cardiovascular effects appear to be due to its content of various sulfur-containing compounds.
- Use of garlic is associated with modest reductions in total cholesterol and triglyceride levels, and blood pressure.
- Garlic should not take the place of conventional pharmaceuticals for the treatment of cardiovascular disease, but may be considered a potentially useful adjunct when used appropriately.

2 minutes removed all activity from all samples.¹⁰

As allicin breaks down or is metabolized, dozens of other more stable sulfur compounds are formed. Many of these are biologically active. If garlic is macerated with oil, allicin is converted into ajoene and polysulfides that can be stable for more than a year.¹¹ However, the precise activity of each specific compound remains uncertain.¹⁰ Most regard the sulfur-containing compounds as crucial to the health benefits of garlic, although those compounds are also responsible for garlic's odor-problems. The various ways garlic is processed lead to preparations with different compounds, which may account for some of the inconsistency observed in clinical trials. Table 1 lists the characteristics of some of the most commonly available formulations.

Mechanism of Action

In spite of considerable numbers of in vitro studies, the ingredient(s) in garlic responsible for cardiovascular effects remain unclear.¹² Garlic impacts the cardiovascular system via several mechanisms, but many of its constituents are biologically active and uncertainty remains about how they all interact. Ajoene and other compounds inhibit platelet aggregation, which can help prevent CVD.² Allicin has antiplatelet aggregating activity, although its instability makes it difficult to study its clinical effects. Several garlic constituents inhibit liver enzymes involved in making cholesterol, including HMG-CoA reductase (the enzyme inhibited by statins), and others lower plas-

ma cholesterol and triglyceride levels via unclear mechanisms of action.¹³ Garlic also contains antioxidants that can counteract the development of atherosclerosis. Other constituents cause smooth muscle relaxation, which could contribute to reduced hypertension.

Various sulfur compounds derived from garlic cause the release of hydrogen sulfide (H₂S) from human red blood cells.¹⁴ H₂S is a naturally occurring cell signaling molecule with several cardioprotective effects, including vascular smooth muscle relaxation, decreased blood pressure, and protection against oxidative damage. This new research sheds light on garlic's potential mechanisms of action, and may lead to a means of standardizing garlic preparations.¹⁵

Clinical Studies

Many laboratory and animal tests have demonstrated that garlic and its constituents have biological activities related to CVD; however, controversy continues over the clinical significance of these findings.¹⁶ Results of trials have been contradictory, with early studies often finding beneficial effects which were not replicated in more recent trials that were usually larger, longer, and of higher methodological quality.¹²

The impact of garlic ingestion or supplementation on serum cholesterol and lipid levels has received the most research attention.¹¹ Two meta-analyses published in 1993 and 1996 generated much interest in garlic because they reported 9% and 12% reductions in total cholesterol

Table 1. Various Garlic Preparations

Product Type	Main Compounds	Other Characteristics
Garlic essential oil	Oil-soluble sulfur compounds (diallyl sulfides) No water-soluble sulfides	No safety data 8-15 mg/day used in trials
Garlic oil macerate	Oil-soluble sulfur compounds and alliin Not well standardized	No safety data Unclear dosing
Garlic powder	Alliin and a small amount of oil-soluble sulfur compounds Some products are well standardized, but others are not	Most frequently studied No safety data 900 mg/day commonly recommended
Aged garlic extract (AGE)	Mainly water-soluble compounds Well standardized Small amount of oil-soluble sulfides	Some high-quality studies Well-established safety profile 1-7 g/day used in trials
Fresh garlic	Not standardized Few studies	1 or 2 cloves daily

Adapted from: Cavagnaro PF, et al. Effect of cooking on garlic (Allium sativum L.) antiplatelet activity and thiosulfinates content. J Agric Food Chem 2007;55:1280-1288.

levels, respectively.¹⁷ More recent meta-analyses have come to different conclusions; one published in 2009 concluded that there was no evidence from randomized controlled trial (RCTs) of garlic having any beneficial effects on serum cholesterol.¹⁸ However, the search strategy in that meta-analysis has been criticized for not being comprehensive.¹² The most recent evaluation reviewed literature published up to October 2011¹² and included 26 RCTs reporting the effects of garlic on various serum lipids. Overall, garlic significantly reduced serum total cholesterol by 0.28 mmol/L ($P = 0.001$) and triglycerides by 0.13 mmol/L ($P < 0.001$). At the same time, no significant differences were found for low-density lipoprotein cholesterol (LDL-C), HDL-C, apolipoprotein B, and total cholesterol/HDL-C ratio. The reviewers considered these results “unimpressive” and “modest,” especially in comparison with dietary interventions and statin therapy. They calculated that the significant differences were equivalent to a 5.4% reduction in total cholesterol levels for someone with a baseline level of 5 mmol/L and a 6.5% reduction in triglyceride levels for someone starting with a 2 mmol/L level. The daily doses most commonly used in the studies reviewed were 10-15 mg garlic oil, 900 mg garlic powder, and 1-7 g aged garlic extract.¹² Study duration ranged from 2 weeks to 12 months, with most trials lasting 3 or 6 months.

Many studies have examined the role of garlic preparations in lowering blood pressure. A 1994 meta-analysis of 10 randomized, controlled trials reported an overall significant reduction in systolic and diastolic blood pressure of 8 and 5 mmHg, respectively.¹¹ Another meta-analysis published in 2008 included 11 RCTs and reported an overall reduction of 4.56 mmHg in systolic blood pressure for those taking garlic ($P < 0.001$).¹⁹ Diastolic blood pressure did not change significantly compared to placebo. A planned sub-group analysis was conducted comparing those who were normotensive or hypertensive at baseline. The hypertensive subgroup had significant reductions of 8.4 and 7.3 mmHg for systolic and diastolic blood pressures, respectively. The normotensive subgroup did not show significant reductions. The reviewers noted that reductions of 4-5 mmHg systolic and 2-3 mmHg diastolic are held to be clinically significant. At the same time, some RCTs have found no significant differences between groups taking garlic and placebo.

Although many of garlic's components have demonstrated antioxidant properties, relatively few studies have been conducted on the clinical significance of these effects. Most of the research to date has involved in vitro or animal studies, especially with one particular standardized garlic powder extract called Kwai. Another product called aged garlic extract (AGE; brand name Kyolic) is made by soaking garlic slivers in alcohol for 20 months, removing most allicin, and leaving an extract high in anti-

oxidant capacity.⁷ An RCT with 65 patients examined the impact of AGE (250 mg/d) and multivitamins on subclinical atherosclerosis.²⁰ After 1 year, those in the AGE group had significantly better outcomes than the control group for oxidative markers, vascular function, and progression of atherosclerosis. Another RCT found that those taking 960 mg AGE had significantly more reduction in systolic blood pressure (by 10.2 mmHg; $P = 0.03$).²¹ However, the total number of clinical studies evaluating AGE remains small.

Garlic and its components have been found to impact platelet aggregation and other aspects of blood clotting.¹⁵ Fibrinolysis leads to the breakdown of blood clots, and this process is promoted by various types of garlic preparations.⁷ Platelet aggregation has been beneficially affected by garlic in a small number of clinical trials.³ However, an Agency for Healthcare Research and Quality review concluded that these results must be taken as preliminary.²² While all the studies identified for this review had beneficial results, the studies were all very small, of limited duration, and some had serious methodological flaws.

Adverse Effects

Garlic is well-known for its problematic breath and body odor after oral ingestion. These are the most commonly reported complaints from trial participants.²³ Eating raw garlic and high doses of some supplements also can cause mouth and gastrointestinal irritation, heartburn, nausea, vomiting, and diarrhea.²⁴ Some people also are susceptible to allergic reactions to garlic, with one observational study estimating that 1.1% of people are susceptible to allergic reactions at therapeutic doses.²³

The effects of garlic on platelet aggregation and fibrinolysis may increase the risk of bleeding, but this is mostly theoretical.²³ While few studies or case reports have found such adverse effects, people taking anticoagulants, those scheduled for an invasive procedure, or those with bleeding problems should be aware of this potential adverse effect.¹⁵ Some case reports of postoperative bleeding have been reported.²³ However, a randomized, controlled trial found no change in bleeding events among people taking warfarin when given either garlic (AGE formulation) or placebo.²⁵ In vitro analyses have identified enzymes whose activities are impacted by aged garlic extracts.²⁶ These results raise concerns that garlic may interfere with the metabolism of various drugs. Few actual interactions have been reported, although patients taking HIV protease inhibitors did have reduced drug serum levels after taking garlic.

Formulation

The two most commonly used powdered formulations are dried garlic powder and aged garlic extract (AGE).

During the aging process, the volatile components are lost, thus leading to AGE being called odorless garlic. Garlic oil also is available, made using three different methods, with each leading to different mixtures of lipid-soluble sulfur compounds. The most commonly used form in clinical trials is a standardized garlic powder extract called Kwai (200-300 mg tid).¹² A small number of high-quality studies have been conducted with AGE (Kyolic).

Conclusion

Overall, garlic preparations have some value as a complementary agent in reducing some risk factors associated with cardiovascular disease. The evidence from studies conducted in the 1990s suggested a broad range of modest benefits. However, many of these studies had small numbers of participants, were of short duration, or had other methodological weaknesses.² Most recent, higher-quality studies have found more limited benefits. Modest reductions in total cholesterol, triglycerides, and blood pressure have been identified in meta-analyses. Several other CVD-related beneficial effects have been found with in vitro research. Given its good safety profile, garlic may provide some protection against CVD.

Recommendation

In light of the many associations between garlic and cardiovascular health, and the results of some research studies, garlic can be recommended as part of an overall heart-healthy diet. One clove a day (maybe two) should provide sufficient sulfur compounds, though this is debated and very much open to personal taste. However, given the modest benefits, garlic should not be used instead of conventional medical treatments for CVD. While garlic supplements are generally safe, people taking garlic along with other medications should be closely monitored for drug interactions, especially those taking HIV protease therapy. The diversity of garlic formulations available makes it difficult to recommend specific brands with confidence. Unless carefully standardized, products claiming to eliminate the odor may remove all the therapeutic effectiveness as well. Eating a clove or two daily can certainly be recommended. ■

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C My BP? Vitamin C for Hypertension

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: A systematic review of 29 studies using vitamin C to help lower blood pressure showed a slightly positive effect, though of debatable clinical value. The study highlights the variable nature of existing data in this realm with regards to quality and methodology.

Source: Juraschek SP, et al. Effects of vitamin C supplementation on blood pressure: A meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2012;95:1079-1088.

THE RESEARCHERS CONDUCTED A SYSTEMATIC REVIEW AND meta-analysis of randomized, controlled trials to determine the effects of vitamin C supplementation on blood pressure (BP) in adults. Trials were identified by searching Medline, EMBASE, and the Cochrane Central Register of Controlled Trials databases for papers published from January 1966 through December 2010, without language restrictions. In addition, bibliographies of original research were reviewed. Pre-specified inclusion criteria were: 1) use of a randomized controlled trial design; 2) trial reported effects on systolic (SBP), diastolic (DBP), or both; 3) trial used oral vitamin C supplementation and concurrent control groups; and 4) trial had a minimum duration of 2 weeks. Two investigators independently abstracted the articles (which included crossover trials, factorial studies, and parallel trials) and achieved consensus where initial disagreement occurred. The authors determined between-group differences in BP change for vitamin C and placebo groups, and then pooled the results. Mean BP was used for trials reporting multiple BP measurements. Subgroup

Summary Points

- The best way to get vitamin C into one's system is through the regular eating of vegetables and fruit.
- Existing data focusing on vitamin C supplementation and hypertension come from studies that differ widely in methodology and quality, making firm conclusions difficult if not impossible.
- The clinical importance of vitamin C for blood pressure control appears less than compelling.

analyses were performed that focused on specific participant and trial characteristics including vitamin C dosage, sample size, and study duration. Heterogeneity and individual study quality (degree of blinding, adverse events reporting) also was assessed.

A number of studies were excluded for reasons such as coadministration of additional vitamin-C containing supplements or beverages, incomplete reporting of BP data, and lack of concurrent control group. A total of 29 studies were included in the primary analysis (sample sizes ranged from $n = 10$ -120, with mean participant age ranging from 22-74 years; duration ranged from 2-26 weeks). Vitamin C dosage ranged from 60-4000 mg/d. Fifteen trials permitted concurrent use of antihypertensive agents.

Vitamin C supplementation reduced SBP by an average of -3.84 mm Hg (95% confidence interval [CI]: -5.29, -2.38 mm Hg; $P < 0.001$) and DBP by -1.48 mm Hg (95% CI: -2.86, -0.10 mm Hg; $P = 0.036$) in pooled analysis. BP effects did not differ by hypertensive status for either SBP ($P = 0.28$) or DBP ($P = 0.85$); however, more significant SBP reductions were observed in trials with younger participants, and greater impact on both SBP and DBP was noted in studies with fewer total measurements.

Based on the results of their analyses, the researchers conclude that supplemental vitamin C may have a useful role in lowering BP, but make clear that the existing data are largely flawed.

■ COMMENTARY

Systematic reviews and meta-analyses often provide valuable information, but it almost always comes at a steep price, usually in the form of caution in interpreting the results. The best researchers, such as the authors of this study, demonstrate the difficulties inherent in performing the task of meta-analysis by pointing out the variable nature of the studies at hand that use different dosages over disparate timeframes in far-ranging patient populations where a variety of measurements were obtained. And then a clinically relevant conclusion is expected.

An accompanying editorial in the journal comments that the problems associated with interpreting systematic reviews are compounded by the difficulties in performing nutrition research.¹ It is an excellent read.

Most practitioners would agree that the best way to encourage patients to get vitamin C into their systems is by eating a healthy diet that emphasizes fresh or frozen vegetables and fruits. Most practitioners also understand that the majority of people do not follow widely recognized nutrition guidelines of eating 5-9 servings of vegetables and fruit per day, and that dietary supplement use is commonplace. Vitamin C supplementation is widely considered safe (save for an increased risk of urolithiasis), but questions about pro-oxidant actions and other potential adverse effects have lingered, and recommendations about dosage, while not consistent, are trending lower.

Hypertension as a public health issue remains inadequately addressed for multiple reasons that include issues of access, funding, and compliance with medical recommendations. A simple and inexpensive supplement that might help lower blood pressure generally would certainly be attractive. As relates specifically to vitamin C, however, the jury is still out.

The authors of this review did a terrific job of parsing the available data and worked hard to create the cogent conclusion that vitamin C may indeed be a useful adjunct in the care of people with high blood pressure. They also painstakingly describe the lack of uniformity among the trials, making firm conclusions nearly impossible. Heterogeneity and methodological shortcomings aside, the clinical import of the reported effects from vitamin C supplementation on BP is not compelling, and the ultimate impact of vitamin C on heart disease and stroke, while promising, is still being investigated.

Vitamin C has many proponents, especially among those promoting a healthy diet as a centerpiece of a healthy lifestyle. Supplemental vitamin C also has its proponents, and while fewer in number they are often passionate in their support for the agent. That's all well and good provided the dosage employed is relatively low and that patients understand, at least in the setting of hypertension, that a clear scientific rationale for using the agent has yet to be firmly established. ■

Reference

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CME Objectives

After completing the program, physicians will be able to:

- a. present evidence-based clinical analyses of commonly used alternative therapies;
- b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

1. **Which of the following statements is true regarding metabolic effects of fructose?**
 - a. It enhances lipogenesis.
 - b. It is largely metabolized by the liver.
 - c. It increases serum uric acid levels.
 - d. All of the above
2. **Fructose undergoes extensive hepatic clearance.**
 - a. True
 - b. False
3. **Acupressure stimulation of the P6 acupoint shows the strongest evidence for preventing which of the following conditions?**
 - a. Low back pain
 - b. Postoperative nausea and vomiting
 - c. Dysmenorrhea
 - d. Motion sickness
4. **Acupressure is a highly regulated therapy in the United States, requiring practitioner certification with the National Certification Commission for Acupuncture and Oriental Medicine before therapists can be licensed to practice.**
 - a. True
 - b. False
5. **A variety of garlic products have been found to have problems with:**
 - a. consistent amounts of active ingredients.
 - b. breath and body odor.
 - c. concerns about potential drug interactions.
 - d. All of the above
6. **The area of potential cardiovascular benefit that has received the most research attention with garlic has been for:**
 - a. reducing serum cholesterol and lipid levels.
 - b. preventing platelet aggregation.
 - c. lowering blood pressure.
 - d. reducing serum antioxidant capacity.

In Future Issues:

Fish Consumption and Colorectal Cancer
Effects of Exercise on Aging
Exercise During Cancer Treatment