What is the evidence that vitamin C supplements lower blood pressure?1–3

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Systematic reviews represent a rigorous method for objectively synthesizing a body of scientific evidence. Their findings are used as the basis for clinical practice and public health guidelines and consensus statements and to identify research gaps or methodologic concerns to guide future research recommendations. Systematic reviews of the evidence regarding nutrition questions are both more recent and more challenging than their counterparts in clinical medicine, raising greater substantive concerns (1). Likewise, interpretation and application of the findings have been subject to far greater controversy than their clinical counterparts due, at least in part, to the challenges of designing good original research studies. These challenges are the same ones that have stymied the application of evidence review findings both to clinical practice and to public health guidelines. In this issue of the Journal, Juraschek et al (2) systematically review the evidence that supplemental vitamin C lowers blood pressure (BP), a question of potentially immense importance given the prevalence of hypertension (3), the health care funds spent on antihypertensive medications, and the countless efforts aimed at promoting lifestyle changes to reduce BP. Yet, compliance with antihypertensive medication is often poor; a proportion of individuals fail to respond even when compliant, and lifestyle changes often fall short, resulting in yet greater outlays for cardiovascular disease treatment. The idea that a relatively benign and inexpensive vitamin supplement might play a role in controlling hypertension therefore has particular appeal. The physiologic rationale for an effect of vitamin C on BP dates back to the 1940s and is supported by epidemiologic evidence.

Unfortunately, the current meta-analysis identifies only a minor BP-lowering effect, which is undoubtedly too small clinically to support a recommendation that individuals with hypertension replace or even supplement their antihypertensive medications with vitamin C. Nevertheless, this meta-analysis teaches valuable lessons about the design of original studies and systematic reviews. The remainder of this editorial outlines the more salient of these lessons according to the schema systematic reviewers use to consider the important characteristics of clinical trials for pooling: participants, interventions, comparators, outcomes, and time course.

PARTICIPANTS

Few of the included studies excluded individuals taking antihypertensive medications, considered compliance with these medications, controlled for the class of drug, or considered the potential for varying interactions with vitamin C (some evidence suggests that vitamin C may potentiate the effects of diuretics, one class of antihypertensive medications). Moreover, most studies appear to have ignored age (studies with an average age that was significantly lower than the average age of diagnosis may be applicable to prevention but not to treatment), intake of vitamin C and other antioxidants from foods, use of vitamin C supplements before study commencement (most studies excluded current supplement users or proscribed further use), or baseline vitamin C status.

INTERVENTIONS

The variation in vitamin C administration in the included studies raises numerous methodologic issues. Many of the included studies administered vitamin C along with other vitamins, minerals, or both (without controlling for the coadministered nutrients); thus, observed effects could not be attributed to vitamin C. Furthermore, no included trials conducted dose-response assessments, although a recent review on vitamin C pharmacokinetics suggests that plasma vitamin C reaches threshold concentrations well below maximally tolerated and consumed doses (4). Although a sensitivity analysis did not identify an effect of baseline vitamin C status, few included studies actually assessed baseline status or attempted to ensure a stable intake of vitamin C from food sources. Unfortunately, functional measures of vitamin C status are not currently available; plasma concentrations, the easiest to measure, are unlikely to reflect true tissue concentrations of bioactive ascorbate (5). Furthermore, a recent study that used a mouse model of vitamin C deficiency found that the effect of vitamin C intake on functional concentrations of vitamin C depends on the source (dietary supplements compared with food) and amount; saturating concentrations were required to achieve normal tissue concentrations (6). For its part, the review did not ascertain whether studies provided participants with vitamin C supplements or whether the vitamin C

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content of these supplements was verified at the time of dispensing and did not ascertain compliance levels or concentrations of vitamin C attained.

COMPARATORS

Recent data suggest that >40% of American adults take vitamin C supplements (7) and that the average daily vitamin C intake is ~208 mg (54% from supplements) (8). Few studies appear to have averted high intakes of vitamin C (from dietary supplements or foods) by control participants. Of equal concern, as described above, only some studies controlled for the use of other antioxidants and antihypertensive medications.

OUTCOMES

The review identified differences in outcomes between studies that used ambulatory BP monitoring and those with ≤4 BP measures. Such methodologic differences could reflect broader differences in study quality. Long-term trials of vitamin C supplementation have not shown effects on clinical outcomes, but these studies may have suffered the same limitations as those included in this review. They recommended better long-term trials of the effects of vitamin C on clinical endpoints; yet, such trials are even more challenging than shorter-term trials with intermediate endpoints. Another concern is publication bias: a number of excluded studies failed to report BP outcomes (tests of publication bias for the included studies were negative). The review also finds that few studies reported adverse events, and itself omits those events. The potential adverse effects of large doses of vitamin C in the older adult population, although likely rare, cannot be ignored. Finally, the review fails to consider what constitutes a minimum clinically important difference, ie, how small a decrease in BP is noteworthy?

TIME COURSE

The review excluded long-term studies because of the risks of confounding. Longer-term studies might enable assessment of the stability of observed effects as well as whether they led to meaningful changes in clinical outcomes.

To conclude, Juraschek et al’s review is of reasonably high quality on the basis of established assessments of methodologic (9) and reporting (10) quality. Although the findings clearly fail to support advocating vitamin C supplements to lower BP, the review nevertheless serves an important purpose in that it highlights the pitfalls in nutrition research design.

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REFERENCES