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ORIGINAL ARTICLE

Vitamin C and blood pressure–an overview

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***Background*: Laboratory and some epidemiological studies suggest that antioxidants, such as vitamin C, are protective for cardiovascular disease. This protective effect may be mediated through blood pressure (BP). This is the first systematic review of epidemiological studies of vitamin C and BP.**

***Method*: Published cross-sectional studies, prospective studies and trials in humans were identified that examined the association between vitamin C intake or plasma vitamin C levels and BP. Relevant references were located by MEDLINE search 1966–1996, EMBASE search 1980–1996, by searching personal bibliographies, books and reviews and from citations in located articles.**

***Results*: Cross-sectional data were available from 18 populations. Ten of 14 reported an inverse association between plasma vitamin C and BP and three of four reported an inverse association with vitamin C intake. The two non-randomised and four randomised controlled trials were all small. Of the randomised trials one reported a significant decrease in BP, one a non-significant decrease and two were uninterpretable.**

***Conclusions*: We found a consistent cross-sectional association between higher vitamin C intake or status and lower BP, though no study controlled adequately for confounding by other dietary factors. Further cross-sectional studies are required to establish whether an independent association exists. If this is shown to be the case larger and longer term trials will be needed to confirm the association is causal. Potentially the impact on cardiovascular disease of a modest change in mean population vitamin C intake is large.**

Keywords: vitamin C; blood pressure; systematic reviews

Introduction

Laboratory studies and animal experiments suggest that oxidative modification of low density lipoprotein (LDL)-cholesterol plays an important role in the early development of atherosclerotic lesions.[1,2] This suggestion has prompted examination of the relationship between intake of dietary antioxidants, such as vitamin C, and cardiovascular disease. Although several observational studies in humans have reported a protective association for stroke and heart attack with increased intake of vitamin C,[3–5] a recent systematic review concluded that overall the evidence is not persuasive.[6]

A putative protective effect of vitamin C on cardiovascular disease could be mediated through an effect on blood pressure (BP),[7] or an effect on lipids,[8] platelets[9,10] or haemostatic factors.[11] A number of studies and review articles[8,12,13] have examined the hypothesis that vitamin C lowers BP but to our knowledge no systematic overview has been done. This report aims to fill this gap in the literature.

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Materials and methods

We sought to include all relevant reports (including abstracts) of cross-sectional studies, prospective studies and trials in humans that examined the association between vitamin C and BP.

We concluded observational studies that measured either intake of vitamin C or plasma vitamin C levels. We excluded therefore studies that reported their results in terms of foods and BP even if these foods were rich sources of vitamin C. We included only trials of vitamin C alone and excluded trials of a combination of micro nutrients[14,15] and trials of dietary change, even if the result (among others) was to increase the vitamin C intake by dietary means.[16] These studies were excluded as it would be impossible to estimate the effect of vitamin C alone.

Where several reports were made by the same group on the same study, (for example see references 17 and 18), the results from what was judged to be the definitive report, in this case reference 18, were selected. For the US NHANES I sample, two sets of analyses performed by different groups were included as they were considered to be substantially different, though the study was still only considered to have contributed one study population.[19,20] However, a further report on NHANES I[21] was excluded from the analyses as the population had been dichotomised into normotensive and hypertensive subgroups in contrast to all the other studies considered

Table 1 Cross-sectional studies that reported on the observed association between vitamin C intake and BP[a]

Population	*Author*	*No.*	*Age Sex*	*Inclusions*	*Exclusions*	*Vitamin C*	*Confounders*	*Δ SBP*	*Δ DBP*	*Notes*
Sample of US population	Stanton JL *et al*, 1982[19]	10 419	⩾18, both	Dietary information	Treated BP Unusual diet	24 h recall	—	—	—	Correlation vit C and SBP –0.03, DBP –0.04 ($P<0.001$ both).
Sample of US population	Harlan WR *et al*, 1984[20]	2055	25–74, both	Subset had extra information	Hypertensives	24 h recall	Biochemical, socio-economic variables	—	—	Vit C not in models finally selected.
Sweden, Gothenburg	Lapidus L *et al*, 1986[28]	1462	38–60, women	Census based sample	CHD, refusal, interview unsatisfactory	24 h recall	—	—	—	No significant correlation with SBP.
Hawaiian Japanese	Joffres MR *et al*, 1987[29]	615	61–82, men	Hawaii resident Japanese ancestry	CHD, special diet, hypertensive.	24 h recall	Age, BMI	–3.6 mm Hg Q4 *vs* Q1 ($P=0.02$)	–1.1 mm Hg Q4 *vs* Q1 (NS)	Vit C intake (mg/day): Q1 0–96 Q4 602–9574
US Elderly	Jacques PF, 1992[31]	696	60–100, both	Free living volunteers	Hypertensive, on treatment that effects BP	3 day dietary diary	Age, sex, BMI, smoking, alcohol, Na/K, Ca, Mg, PUFA	–10.6 mm Hg (low *vs* high) ($P=0.01$)	–3.2 mm Hg (low *vs* high) ($P<0.01$)	Vit C intake (mg/day) <60 *vs* ⩾240 (low) (high) Suggestion of threshold effect

[a]The following abbreviations are used in the tables: BMI = body mass index; Ca = calcium; Ca/P = calcium phosphate ratio; CCF = congestive cardiac failure; CHD = coronary heart disease; CVA = Stroke; DBP = diastolic blood pressure;DM = diabetes mellitus; GI = gastrointestinal; Mg = magnesium; MI = myocardial infarction; Na/K = sodium potassium ratio; NS = non significant; PAA = plasma ascorbic acid; PUFA = polyunsaturated fatty acids; Q4 *vs* Q1 = The difference between the highest vitamin C quartile and the lowest; RDA = recommended daily allowance; SAA = serum ascorbic acid; SBP = systolic blood pressure; Vit C = vitamin C.

Table 2 Cross-sectional studies that reported on the observed association between plasma vitamin C and BP[a]

Population	*Author*	*No.*	*Age Sex*	*Inclusions*	*Exclusions*	*Vitamin C*	*Confounders*	*Δ SBP*	*Δ DBP*	*Notes*
Mississippi black	Koh ET, Stewart T, 1978[25]	304	5–80, both	—	—	Fasting PAA	—	—	—	Correlation vit C and SBP –0.12, DBP –0.11 ($P<0.05$ both).
Mississippi black and white	Koh ET, Chi MS, 1980[26]	439	>34, both	—	—	Fasting PAA	—	—	—	Significant -ve correlation vit C and BP, but vit C dependent variable in regression models.
Japanese farm workers	Yoshioka M *et at*, 1984[27]	194	30–39, men	Healthy	Hypertensive	Fasting SAA	—	–17.8 mm Hg per 50 μmol/L ($P<0.001$)	–9.4 mm Hg per 50 μmol/L ($P<0.001$)	—
Finnish men	Salonen JT, 1987[18]	722	54, men	Around Kuopio born 1930–1931	CHD, hypertensive	Fasting PAA	18 confounders	–6.5 mm Hg (low *vs* high) ($P<0.001$)	–3.9 mm Hg (low *vs* high) ($P=0.001$)	Complex models. Groups of PAA (μmol/L) <22.7 *vs* > 61.6. (low) (high)
North Karelia SW Finland Scotland South Italy	Riemersma RA *et al*, 1990[22]	99 85 131 80	44–49, men	Middle-aged Caucasian	—	PAA	Smoking, cholesterol	—	—	PAA did not correlate with BP.
US Chinese	Choi ES *et al*, 1991[30]	247	60–96, both	Boston area volunteers Chinese ancestry	Housebound In Institution chronic disease	Fasting PAA	Age, sex, BMI, smoking, alcohol, Na/K, Ca/P, physical activity	–11 mm Hg for 50 μmol/L ($P<0.01$)	–4.5 mm Hg for 50 μmol/L ($P=0.02$)	24 h recall data not reported
US elderly	Jacques PF, 1992[32]	696	60–100, both	Free living volunteers	Hypertensive, on treatment that effects BP	Fasting PAA 3 day dietary diary	Age, sex, BMI, smoking	—	—	BP log transformed in regression. Vit C and SBP -ve association both sexes, DBP in women only.

(*Continued*)

Table 2 *Continued*

Population	*Author*	*No.*	*Age Sex*	*Inclusions*	*Exclusions*	*Vitamin C*	*Confounders*	*Δ SBP*	*Δ DBP*	*Notes*
Poland, Warsaw	*Moor de Burgos A et al*, 1992[35]	102	16–63, women	Obese, sample not described	Supplement takers	Fasting PAA	—	–11.2 mm Hg (low *vs* high) ($P<0.05$)	–9 mm Hg (low *vs* high) ($P<0.01$)	Groups of PAA (μmol/L) <35 *vs* >52. (low) (high)
US Augusta	Moran JP *et al*, 1993[34]	168	19–70, both	Healthy volunteers	Hypertensive major disease special diet supplements above RDA	Fasting PAA	Smokers excluded	–4.2 mm Hg for 50 μmol/L ($P<0.02$)	–3.9 mm Hg for 50 μmol/L ($P<0.008$)	Small number also with 3-day diet and white cell AA.
Seventh Day Adventists, Dallas	Toohey L *et al*, 1996[35]	102	mean age 48, both	African–Americans, Seventh Day Adventists	Hypertensive on treatment	PAA	Age, waist, malondi-aldehyde equivalents	—	—	-ve correlation vit C with SBP –0.39 ($P<0.0001$), DBP –0.25 ($P<0.025$).
UK, Norfolk	Ness AR *et al*, 1996[36]	1860	45–74, both	GP practices	—	PAA	Age, sex, BMI	–3.6 mm Hg for 50 μmol/L ($P<0.001$)	–2.6 mm Hg for 50 μmol/L ($P<0.001$)	—

[a]For list of abbrevations used see footnote to Table 1.

where BP was treated as a continuous variable. Reports that included data from more than one distinct population sample were allowed to contribute more than one study population.[22]

We searched MEDLINE (1966–1996) and EMBASE (1980–1996) using the search terms 'blood pressure' and 'ascorbic acid'. This was complemented by a search of personal bibliographic files, books and relevant reviews,[7,8,12,13] and follow-up of citations in references already located. We continued the process of cross-referencing until no new references were identified. These searches were not restricted to English language journals but all the articles located were written in English. The relevant information was extracted on to a standard form (adapted from one used for a previous systematic review),[23] by two of the authors (ARN and DC). The information was cross-checked and any discrepancies or differences of opinion reconciled.

The observed difference in BP in cross-sectional studies was calculated for a difference in vitamin C intake of 100 mg per day or in plasma concentration of 50 μmol/L. Over a limited range of intakes, the relationship between intake and plasma levels is linear so that a difference in intake of 100 mg of vitamin C a day results in a difference in plasma level of roughly 50 μmol/L.[24]

In some studies the difference in BP was presented for tertiles or quartiles of vitamin C intake or status. For these studies the difference in BP between the highest and lowest groupings was divided by the mean vitamin C value for the highest, less the mean for the lowest and then multiplied by either 50 for plasma or 100 for intake. Where the mean vitamin C values for the quartiles were not provided, or other arbitrary groupings were used, the difference observed between the groupings in the study is presented along with a description of these groupings.

The confounders recorded in the results are those used to adjust the observed association between vitamin C and BP.

Results

Sixteen observational studies[18–20,22,25–36] and six trials,[37–42] published between 1978 and 1996, were located and fulfilled the inclusion criteria. These sixteen observational studies reported cross-sectional analyses in 18 populations.

Five studies[19,20,28,29,31] reported on the association between vitamin C intake and BP in four populations. Three of these five studies showed a significant inverse association between vitamin C and BP. The results of these observational studies are summarised in Table 1.

Eleven studies[18,22,25–27,30,32–36] reported on the association between blood levels of vitamin C and BP in 14 populations. In 10 of these 14 populations a significant inverse association was reported, but in only four[27,30–34,36] was it possible to estimate directly the difference in BP for a 50 μmol/L difference in plasma ascorbic acid. The observed difference for diastolic BP (DBP) ranged from –2.6 mm Hg to –9.4 mm Hg, and for systolic BP (SBP) ranged from –3.6 mm Hg to –17.8 mm Hg. The results of these observational studies are summarised in Table 2.

One prospective study has reported on the association between vitamin C intake and BP. SBP was 2.0 mm Hg lower in those eating 125 mg of vitamin C per day compared with those eating 75 mg per day after 10 years.[43]

Two uncontrolled trials showed an inverse relationship.[37,38] The results of these uncontrolled trials are summarised in Table 3.

Four controlled trials[39–42] have been reported. The first of these[39] was in 67 people but only the effect on the treatment arm has been reported. The second[40] was in 20 people, including both borderline hypertensive and normotensive subjects; it showed a reduction of systolic but not DBP. The third[41] was among 27 hypertensive patients; it was difficult to interpret because of interaction between the crossover periods. The most recent trial[42] was among 48 elderly hypertensive patients. It showed a non-significant reduction in both systolic and DBP. The results of these randomised controlled trials are summarised in Table 4.

Discussion

We found a consistent cross-sectional association between lower BP and either higher intake of vitamin C or higher levels of plasma ascorbic acid, although the trials of vitamin C supplementation so far reported have generally been too small and too varied to provide confirmatory evidence for a causal relationship.

As well as trials of vitamin C alone two trials of multivitamin supplementation have been reported.[14,15]

Table 3 Uncontrolled trials of vitamin C supplementation and BP[a]

Population	*Author*	*No.*	*Age Sex*	*Inclusions Exclusions*	*Design*	*Intervention*	*Compliance*	*SBP*	*DBP*	*Notes*
Mississippi	Koh ET, 1984[37]	23	35+ women	SBP 140–160 DBP 90–100 no medication no drugs	Uncontrolled unblinded 3 months	1 g daily	—	–7.6 mm Hg (P=0.08)	–4.0 mm Hg (P=0.065)	—
Augusta	Feldman EB *et al*, 1992[38]	21	mean = 43 both	healthy no smokers	Uncontrolled 4 week	500 mg twice daily	PAA urine AA	–4.2 mm Hg (P=0.05)	–3.0 mm Hg (P=0.05)	PAA (μmol/L) at baseline 52.4, at 4 week 101.6

[a]For list of abbreviations used see footnote to Table 1.

Table 4 Randomised controlled trials of vitamin C supplementation and BP[a]

Population	*Author*	*No.*	*Age and Sex*	*Inclusions and Exclusions*	*Design*	*Intervention*	*Compliance*	*SBP*	*DBP*	*Notes*
Mississippi	Mostafa SE *et al*, 1989[39]	67	Not stated	Volunteers University of Mississippi	double-blind placebo, 6 mths	500 mg daily	Not stated	–3.2 mm Hg ($P<0.05$)	no difference	Comparison only of before and after in the vit C arm
Mississippi	Osilesi O *et al*, 1991[40]	20	35–74 both	Disease free, no supplements, not hyperlipidaemic, normotensive, no drug affecting vit C.	Double-blind placebo crossover 18 wks - 4 wk run in 6 wk drug 2 wk break 6 wk drug	1 g daily	PAA	–6.3 mm Hg ($P<0.05$)	0.6 mm Hg (NS)	12 borderline hypertensives, 60% in previous trials.
UK elderly	Lovat LB *et al*, 1993[41]	27	60–83 both	SBP >160, DBP >90 despite drugs but placebo run in, no CCF, creatinine <240, no CVA, no GI disease	double-blind placebo crossover 10 wks, 2 wk run in 2 × 4 wk drug	200 mg twice daily	3 withdrawals tablet count SAA	–0.2 mm Hg to –5.3 mm Hg (NS)	–0.2 mm Hg to –1.9 mm Hg (NS)	Interaction between treatment periods SAA confirmed *'patients were receiving the correct treatments in the period'*
Wales	Ghosh SK *et al*, 1994[42]	48	mean age 74 both	Untreated systolic and essential hypertension, no uncontrolled BP, no MI, no CVA, no DM, no medical illness last 3/12, no changes in diet last 8 wks	double-blind placebo 2 wk run in 6 wk drug	250 mg twice daily	PAA	–2.5 mm Hg NS	–1.2 mm Hg NS	PAA (μmol/L) placebo: baseline *vs* 6 wk 57.7 *vs* 50.8 treated: baseline *vs* 6 wk 44.6 *vs* 80.7

[a]For list of abbreviations used see footnote to Table 1.

In one, 80 anti-oxidant deficient men were given an anti-oxidant cocktail, including 600 mg of vitamin C. The study found no effect.[14] A larger multivitamin trial carried out among over 3000 Chinese men and women with oesophageal dysplasia reported a small but statistically significant fall in SBP after 6 years of follow-up. Though any one (or more) of the biologically active substances contained in the multivitamin supplement, which included 180 mg of vitamin C, could explain the effect, it is certainly consistent with the hypothesis that vitamin C reduces BP.[15]

We were unable to arrive at a summary measure of the reported protective association between vitamin C and BP because of the failure of some studies to describe null findings and because of the lack of detail on the reported association contained in others. While the associations observed in studies are likely to underestimate the true underlying association because of the regression-dilution problem,[44] (most studies have relied on single measures of vitamin C intake or blood vitamin C level and BP), possible publication bias[45] and confounding could work in the opposite direction. By cross-referencing we have minimised the chance that relevant published studies have been missed, though as null findings may be buried in published reports (as footnotes to tables for example),[22] we cannot exclude this possibility. It is also quite conceivable that some null findings have not been published, although if one or two null reports were missed or unpublished this would not substantially alter our findings.

None of the cross-sectional studies we reviewed was able to control adequately for confounding by other dietary factors. Though a number of studies used standard protocols to collect data on diet,[18–20,28–32] most relied on a single 24-h recall to estimate usual intake.[19,20,28–30] Neither of the studies with food records had more than single 4-day dietary record.[18,31,32] Consequently habitual intake of important confounders such as sodium, potassium and other antioxidants was estimated with considerable error.

It is also possible that the observed association with plasma vitamin C reflects reverse causality with high BP causing increased metabolism or increased renal excretion of vitamin C.

A high intake of fresh fruit and vegetables is inversely related to BP.[46] Fruit and vegetables are rich in a number of other nutritional factors, as well as vitamin C, that may influence BP including potassium, magnesium, calcium and fibre; nevertheless, these data are consistent with the hypothesis that vitamin C lowers BP.

There are several plausible mechanisms by which vitamin C might influence BP. These include: an effect on cytosolic calcium and thus smooth muscle contractility,[27] an effect on circulating sodium levels and protein fractions,[37] prevention of prostacyclin synthetase inhibition by free radicals,[17] through an effect on leukotriene metabolism,[12] through an effect on nitric oxide[47] and through direct promotion of endothelial prostacyclin production.[48,49]

This association, if causal, has considerable implications. McMahon and Peto[50] have estimated that a sustained reduction of mean population DBP of 2 mm Hg is associated with 14% less stroke and 8% less coronary heart disease. An effect on BP of this magnitude for a difference in vitamin C intake of 100 mg per day, the content of a medium sized orange (which contains just over 50 per 100 g),[51] is consistent with that observed in cross-sectional studies.

In summary there is an apparent inverse association of vitamin C with BP which is reasonably consistent across different studies and populations, with a variety of study designs. Further cross-sectional studies are required that are able to control adequately for other dietary confounders. If an independent cross-sectional association exists, larger and longer term trials of vitamin C supplementation will be required to establish whether or not the observed association with BP is causal.

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