Vitamin C and the risk of acute myocardial infarction

Rudolph A Riemersma, Kathryn F Carruthers, Robert A Elton, and Keith AA Fox

ABSTRACT

Background: Low-fat soluble-antioxidant status is associated with an increased risk of heart disease.

Objective: The aim of this study was to examine whether low plasma concentrations of vitamin C confer an independent risk of acute myocardial infarction (AMI).

Design: Male patients (n = 180) aged < 65 y with a first AMI and without an existing diagnosis of angina (> 6 mo) who were admitted within 12 h after onset of symptoms were compared with apparently healthy volunteers (n = 177). Plasma concentrations and dietary intakes of vitamin C were determined during hospitalization and 3 mo later.

Results: Compared with the control subjects, the patients had higher total cholesterol and lower HDL-cholesterol concentrations and more of them smoked. The relative risk of AMI for the lowest compared with the highest quintile of plasma vitamin C during hospitalization (14.5 and > 60.5 μmol/L, respectively) was 8.37 (95% CI: 2.88–21.4) after adjustment for classic risk factors. At 3 mo, mean (±SEM) plasma vitamin C concentrations in patients had increased significantly, from 19.6 ± 1.2 to 35.1 ± 1.9 μmol/L (P < 0.001) and no longer conferred a risk of AMI [relative risk: 1.02 (95% CI: 0.51, 2.03)]. Habitual dietary vitamin C intake of patients (before AMI) did not differ significantly from that of control subjects. The increase in plasma vitamin C after recovery from the infarction could not be explained by a similarly large increase in dietary vitamin C.

Conclusions: A low plasma concentration of vitamin C was not associated with an increased risk of AMI, irrespective of smoking status. The apparent risk of AMI due to a low plasma vitamin C concentration was distorted by the acute phase response. Am J Clin Nutr 2000;71:1181–6.

KEY WORDS Vitamin C, ascorbic acid, acute myocardial infarction, smoking, acute phase response, risk, diet, men, Scotland

INTRODUCTION

Consumption of fruit and vegetables, which are rich in antioxidant vitamins, has been associated with a reduced rate of mortality from coronary heart disease (CHD) (1). Antioxidant vitamins may protect LDL from oxidative modification and thereby prevent CHD (2). A low plasma vitamin C concentration is associated with an increased risk of angina, but not after adjustment for smoking status (3). Previous prospective studies of vitamin C intake and risk of cardiovascular disease were inconclusive (1, 4–8) and some associations may have been spurious (9). A relative risk of CHD of 1.25 over a 20-y follow-up period was nonsignificant (10). Vitamin C deficiency was associated with a predisposition to acute myocardial infarction (AMI) in a Finnish study (11). In the present study we examined whether a low plasma vitamin C concentration was associated with an increased risk of AMI, irrespective of smoking status (12, 13), socioeconomic factors (13), and acute phase response (14).

SUBJECTS AND METHODS

Subjects

Male patients (n = 180) aged < 65 y who were admitted to the Royal Infirmary of Edinburgh with AMI within 12 h after onset of symptoms were studied between March 1992 and August 1994; the last follow-up clinic was held in early November 1994. Patients were excluded if they had had angina pectoris (>6 mo duration) or a previous AMI and therefore might have changed their diet. Patients with major psychiatric disorders, established diabetes, or major life-threatening illnesses; patients who abused drugs or alcohol or were institutionalized; and nonwhite patients were also excluded. The diagnosis of AMI was based on electrocardiographic and enzyme changes. Peak creatine phosphokinase (CPK) activity was 962 ± 58 U/L, whereas the reference range for men is 30–200 U/L. The response rate was 96% of eligible patients.

Vitamin C status declines during AMI (14). We therefore reexamined patients 83 ± 14 d after AMI. Follow-up took place > 100 d after AMI in 10 patients. There were 3 deaths and 13 refusals to attend follow-up. Patients with AMI could be referred to a dietitian 4–6 wk after discharge. After March 1993, patients attended group sessions to reduce their CHD risk but were not advised to use vitamin C supplements.

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TABLE 1
Demographic and classic risk factors of apparently healthy control subjects and patients with a first acute myocardial infarction (AMI)

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>AMI patients</th>
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<tbody>
<tr>
<td></td>
<td>(n = 177)</td>
<td>(n = 180)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>53.4 ± 0.56</td>
<td>53.1 ± 0.6</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>23</td>
<td>622</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.2 ± 0.1</td>
<td>6.5 ± 0.1</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.31 ± 0.03</td>
<td>1.16 ± 0.02</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>1.8 ± 0.1</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 ± 0.3</td>
<td>25.9 ± 0.8</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125 ± 17</td>
<td>113 ± 17</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79 ± 1</td>
<td>72 ± 1</td>
</tr>
<tr>
<td>Family history of CHD (%)</td>
<td>32</td>
<td>496</td>
</tr>
<tr>
<td>Deprived category (%)</td>
<td>3.4</td>
<td>10.06</td>
</tr>
</tbody>
</table>

1 Significant difference from control subjects (chi-square test with Yates’ correction): 2 P < 0.001, 3 P < 0.01, 4 P < 0.03.
5 Significant difference from control subjects (t test): 6 P < 0.01, 7 P < 0.001.
8 Measured in patients 3 mo after AMI while the patients were receiving drugs. Not tested statistically.
9 Categories 6 and 7.

The names and addresses of the control subjects were obtained from the Lothian Health Board Central Register, which listed a systematic sample of men aged 30–64 y. These men were age-matched (within a 5-y band) with the patients. The original cohort consisted of 486 men. The general practitioners of these potential control subjects were asked to exclude men by using the same exclusion criteria described above or for any other conditional factors. Sixty men could not be traced. Sixteen general practitioners refused to participate. Eight men had died and 93 were excluded because of CHD, diabetes, hypertension, hyperlipidemia, or major illness. The general practitioners excluded another 37 men for various other reasons. Letters of invitation were sent to 272 men. One reminder was mailed within 2–3 wk if necessary. The response rate was 65%.

The confounding influence of the effect of socioeconomic difference between patients and healthy volunteers was minimized by matching deprivation categories (15), which take into account male unemployment rates and car and house ownership in postal-code sectors of Edinburgh, as determined by the 1991 census. The deprivation score on a scale of 1–7 is strongly related to mortality rates in the United Kingdom (15). Plasma vitamin C concentrations of men in Edinburgh vary throughout the year (3); seasonal influence was avoided by studying control subjects and patients during the same period. All subjects gave written, informed consent to their participation in the study, which was approved by the Ethics Committee of the Lothian Health Board.

Methods

A self-administered questionnaire was used to record subjects’ demographic information, medical histories, and family histories of premature CHD (before age 55 y) (16). Patients who had not smoked for >28 d before admission were classified as exsmokers. The patients’ heights and weights were measured by one observer. Patients completed the Caerphilly semiquantitative food-frequency questionnaire (17) during their hospital stay (to define their habitual diets before AMI) and after recovery (to determine their current dietary habits). Supine blood pressure was also measured in patients by one observer with a random-zero sphygmomanometer (on reexamination).

Blood samples (6 mL, in heparin-containing tubes) for the determination of plasma vitamin C concentrations require immediate centrifugation (16). Therefore, nonfasting blood samples were collected from patients only between 0800 and 1700, whereas fasting blood samples were collected from healthy volunteers and patients on reexamination. All subjects refrained from rich sources of vitamin C (eg, orange juice and vitamin C tablets) before their morning appointments.

Vitamin C was analyzed enzymatically (18). Plasma vitamin C concentrations were corrected for the decline of 1%/mo that occurs during storage at −40°C; the CV was 2.1%. Plasma lipids (cholesterol, HDL cholesterol, and triacylglycerol) were determined in nonfasting admission blood samples (6.3 ± 3.7 h after onset of symptoms). Blood was collected on reexamination from patients and control subjects, all of whom fasted from 2100. Plasma lipids were determined enzymatically (16). Samples from patients and control subjects were analyzed simultaneously by staff who did not know the origin of the samples.

Statistical analyses

Results were summarized as means (±SEM). Statistical comparisons between groups were done by using t tests for continuous data and chi-square tests with Yates’ correction for nominal (binary) data. Vitamin C and triacylglycerol were analyzed after square root and logarithmic transformations, respectively. Multiple logistic regression was used to examine factors related to changing plasma vitamin C concentrations and to test for the effect of vitamin C on AMI after adjustment for the effect of other factors. The adjusted odds ratios for AMI were calculated in relation to the distribution of plasma vitamin C in control subjects (16). The statistical analysis was carried out by using SPSS for WINDOWS (version 6; SPSS Inc, Chicago).

RESULTS

Classic risk factors

Patients had higher total cholesterol and lower HDL-cholesterol concentrations on admission and 3 mo later (data not shown) than did control subjects. After 3 mo, patients also had higher fasting triacylglycerol concentrations (2.6 ± 0.1 compared with 1.8 ± 0.1 mmol/L; P < 0.05). Compared with control subjects, more patients smoked and had a family history of CHD. Body mass index did not differ significantly between patients and control subjects (Table 1), even after adjustment for smoking status (data not shown). At follow-up, most patients were receiving treatment for hypertension. None of the control subjects received drugs to reduce blood pressure (hypertension was one of the exclusion criteria), making a comparison of blood pressure meaningless. Twenty percent of patients and 12% of control subjects reported high blood pressure in the questionnaire; the difference between the 2 groups was not significant.

Plasma vitamin C

Plasma vitamin C concentrations measured in the patients during the hospital stay were significantly lower than those of the control subjects (Table 2), irrespective of smoking status (Figure 1). These concentrations tended to be slightly lower in
materially deprived patients ($r = -0.14$, $P = 0.07$) but were not related to classic risk factors, collection delay, or CPK$_{\text{max}}$. Patients with ventricular tachycardia or fibrillation tended to have lower vitamin C concentrations than did patients without these conditions (13.3 ± 2.2 compared with 19.7 ± 2.1 μmol/L; $P = 0.095$).

Patients' plasma vitamin C concentrations increased during recovery (Table 2) but remained strongly related to those measured in the acute phase ($r = 0.75$, $P < 0.001$, Figure 2). After adjustment for in-hospital vitamin C concentrations, the only factor that significantly predicted change in plasma vitamin C was smoking status at recovery ($P < 0.01$). The increase from 18 to 32 μmol/L in patients who reported stopping smoking was slightly larger than that in persistent smokers (from 12 to 20 μmol/L).

The odds ratio of a first AMI was high in the lowest relative to the highest quintile of plasma vitamin C concentration and a significant trend was observed over the 5 quintiles. However, when the plasma vitamin C concentration after recovery was used, the risk of AMI was no longer significant (Table 3).

**Dietary vitamin C**

The patients' habitual intake of vitamin C before AMI did not differ significantly from that of control subjects (58.4 ± 1.8 compared with 54.8 ± 1.8 mg/d, respectively). Vitamin C intake did not change after hospital discharge in most patients but in a minority it increased (Figure 3); the average intake after recovery was 60.8 ± 1.9 mg/d, which was significantly different from habitual intake ($P < 0.05$, paired $t$ test). The change in plasma vitamin C concentrations during the 3-mo recovery period in patients was not related to a change in dietary vitamin C intake. Plasma vitamin C concentration was related to the intake in the control subjects ($r = 0.45$) and in the patients after recovery ($r = 0.50$, both $P < 0.001$). Plasma vitamin C in the acute phase did not correlate as strongly with habitual intake ($r = 0.28$, $P < 0.001$). These results remained true after adjustment for classic risk factors or deprivation score.

**DISCUSSION**

The patients' in-hospital plasma vitamin C concentrations were very low compared with those of control subjects. This applied equally to smokers, exsmokers, and nonsmokers. The apparent relative risk of AMI was high and independent of smoking status. Serum vitamin C is inversely related to plasma cortisol and infarct size (14). There was no relation between plasma vitamin C and peak CPK activity in our study. Serial measurements might have shown such a relation. It is not clear why plasma vitamin C should behave in this acute phase response–like manner. Stimulation of the adrenal function by tetracosactin (an analogue of corticotropin) in healthy volunteers was shown previously to cause a 30% reduction in vitamin C concentrations (14). The aim of the present study was not to identify factors responsible for the reduced in-hospital vitamin C concentrations.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Vitamin C (μmol/L)</th>
</tr>
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<tbody>
<tr>
<td>Control subjects ($n = 172$)</td>
<td>37.0 ± 1.8</td>
</tr>
<tr>
<td>AMI patients</td>
<td></td>
</tr>
<tr>
<td>Hospital stay ($n = 179$)</td>
<td>19.5 ± 1.2$^2$</td>
</tr>
<tr>
<td>Recovery ($n = 163$)</td>
<td>35.1 ± 1.9</td>
</tr>
</tbody>
</table>

$^1$SEM. To convert values to mg/dL, divide by 56.78.

$^2$Significantly different from control subjects, $P < 0.001$ (ANOVA).

**FIGURE 1.** Plasma vitamin C concentrations in patients with acute myocardial infarction ($n = 179$) and apparently healthy control subjects ($n = 172$), by smoking status. Plasma vitamin C was measured in patients with acute myocardial infarction during the acute phase and ≈3 mo after recovery from the infarction.
but to reexamine whether the high risk of AMI in patients with low vitamin C concentrations during the acute phase would disappear 3 mo after an AMI. This was clearly the case.

Several limitations of this study need to be considered. Plasma vitamin C concentrations could not be measured in 16 patients (9%) at follow-up because 3 patients died and 13 patients refused to attend follow-up. The in-hospital vitamin C concentrations of these patients were not significantly different from those of other patients. In 10 patients, recovery blood samples were collected > 100 d after hospitalization for various reasons, mainly because of illness or reinfarction. Exclusion of the results of either group did not affect the conclusions: Plasma vitamin C increased significantly in patients after discharge and no longer differed from that of control subjects.

The question remains as to whether plasma vitamin C concentrations returned to normal. Several factors could influence vitamin C concentrations post-AMI: stopping smoking, continuing acute phase response, acquiring an infection, and changing diet. The increase in plasma vitamin C concentrations from acute phase to recovery was observed in nonsmokers, exsmokers, and current smokers. Interestingly, the increase was slightly larger in patients who reported stopping smoking than in persistent smokers, but without knowing cotinine concentrations we may have underestimated the effect of smoking cessation. Most patients had a vitamin C intake 3 mo after AMI that was identical to their habitual intake. Only a minority of patients increased their vitamin C intake considerably. This type of data is subject to reporting bias and we do not know whether such bias was reduced at follow-up. However, the small increase in vitamin C consumption could not explain the large change in plasma concentrations.

The increase in plasma vitamin C after recovery from AMI remained constant in 47 patients who could be followed for a

![FIGURE 2. Relation between plasma vitamin C concentrations in patients with acute myocardial infarction during the acute phase and 3 mo after recovery (n = 163). Note the line of identity.](https://academic.oup.com/ajcn/article/71/5/1181/4729261)

### TABLE 3
Unadjusted and adjusted odds ratios and 95% CIs of acute myocardial infarction by plasma vitamin C concentration determined during the acute phase and 3 mo after recovery

<table>
<thead>
<tr>
<th>Quintiles of plasma vitamin C (μmol/L)</th>
<th>1 (&lt; 14.5)</th>
<th>2 (14.51, 25.96)</th>
<th>3 (25.97, 42.0)</th>
<th>4 (42.01, 60.5)</th>
<th>5 (&gt; 60.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of controls (n = 35 controls)</td>
<td>(n = 34 controls)</td>
<td>(n = 34 controls)</td>
<td>(n = 34 controls)</td>
<td>(n = 34 controls)</td>
<td>(n = 35 controls)</td>
</tr>
<tr>
<td>Acute phase(^1),(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>89</td>
<td>44</td>
<td>25</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Unadjusted odds ratio</td>
<td>12.7 (4.83, 34.9)</td>
<td>6.5 (2.38, 18.3)</td>
<td>3.68 (1.29, 10.8)</td>
<td>2.06 (0.67, 6.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Adjusted odds ratio(^4)</td>
<td>8.37 (3.28, 21.4)</td>
<td>5.50 (2.10, 14.4)</td>
<td>3.73 (1.37, 10.2)</td>
<td>2.99 (1.02, 2.17)</td>
<td>1.0</td>
</tr>
<tr>
<td>Recovery(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>42</td>
<td>25</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Unadjusted odds ratio</td>
<td>1.20 (0.58, 2.49)</td>
<td>1.44 (0.70, 2.96)</td>
<td>0.86 (0.40, 1.86)</td>
<td>1.03 (0.49, 2.18)</td>
<td>1.0</td>
</tr>
<tr>
<td>Adjusted odds ratio(^4)</td>
<td>1.02 (0.51, 2.03)</td>
<td>1.18 (0.60, 2.34)</td>
<td>0.79 (0.38, 1.64)</td>
<td>1.02 (0.50, 2.06)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\(^1\)Values in parentheses accompanying the quintiles represent the limits defining plasma vitamin C quintiles in control subjects.

\(^2\)Nonfasting plasma vitamin C in patients.

\(^3\)Significant trend, P < 0.001.

\(^4\)Adjusted for classic risk factors (smoking, cholesterol, HDL cholesterol, triacylglycerol, and family history) and deprivation category.
much longer period; the 3- and >12-mo values were 42.4 ± 3.8 and 44.8 ± 7.7 μmol/L, respectively.

Our combined dietary and plasma vitamin C data strengthen the view that the vitamin C concentration at recovery is a good reflection of the usual concentration (ie, before hospital admission). Thus, subjects with a low plasma vitamin C concentration do not have an increased risk of AMI, irrespective of smoking status. This is at variance with other data. Vitamin C protects LDL particles against oxidative damage (19–21) and inhibits smoking-induced formation of lipid peroxidation products (22, 23) and smoking-induced leukocyte adhesion in vivo (24). Vitamin C can also improve endothelial dysfunction (25). Low vitamin C concentrations also were associated with hypertension, and vitamin C supplements reduced blood pressure by 7.5 mm Hg (26). However, large supplements of vitamin C (750–3000 mg) were given over relatively short periods and therefore the relevance of these observations to atherogenesis or CHD over a lifetime remains to be seen.

Another limitation originates from the differential response rate, which was higher in patients than in control subjects. These data mask the varying response rate by deprivation score, which was almost 80% in the least-deprived groups (deprivation score 1, 2, and 3) and as little as 30% in the most-deprived groups. More potential control subjects from the latter groups were excluded by their general practitioner on grounds of ill health. Thus, some of the control subjects in this study were healthier than the group they represented. Given that we did not have dietary information or plasma samples of the nonrespondents, we do not wish to speculate. However, it is now clear that plasma vitamin C concentrations are lower in subjects with chronic infections (acute phase–like response); exclusion of such subjects would have increased the average plasma vitamin C concentration of the control group. Support for this view comes from our observation that there was only a weak association between deprivation score and plasma vitamin C concentration, which would have been expected if there had been an overrepresentation of healthy, vitamin C-deprived subjects. However, if such bias had been present in our control group the effect would have been to increase the difference in plasma vitamin C between patients and control subjects. Thus, such bias cannot explain the lack of association between this antioxidant and risk of myocardial infarction.

We studied survivors of AMI and thus cannot exclude the possibility that plasma or dietary vitamin C status is lower in patients who die out of hospital during their first AMI. However, low dietary vitamin C intake in Scotland was not associated with increased risk of fatal CHD in another study (27). The tendency of an increased incidence of serious ventricular arrhythmia in the patients in our study who had the lowest plasma vitamin C concentrations may reflect the well-known relation between infarct size and clinical complications. Blood samples for analysis of vitamin C were collected at any time during the hospital stay and the concentration at the onset of arrhythmia is unknown. It is therefore premature to suggest any causal link between low plasma vitamin C and arrhythmia.

Our results agree with the results of clinical and epidemiologic studies that suggest that plasma or dietary vitamin C do not influence the risk of CHD markedly. Confounding by lifestyle factors may explain the fact that subjects who took large vitamin C supplements regularly were less likely to develop cardiovascular disease over a 10-y period (8, 9). The results of a Finnish case-control study of patients with fatal or nonfatal AMI suggest that vitamin C deficiency is a risk factor for CHD, but it is uncertain whether this was the primary endpoint of that study (11). The concentration that defined our lowest quintile of plasma vitamin C was almost identical to that used to identify subjects at risk of vitamin C deficiency in the Finnish study (14.5 and 11 μmol/L, respectively). There was no greater risk of AMI in near–vitamin C deficient Edinburgh men, unadjusted or adjusted, than in those with high concentrations of vitamin C (>60.5 μmol/L). Plasma vitamin C concentrations were lower in patients with an acute coronary syndrome (unstable angina or AMI within 2 wk) than in patients with stable CHD who were living in Boston (28). The 20% difference in vitamin C concentration was attributed to increased activity within the coronary lesion. Low plasma vitamin C was not associated with a greater extent of CHD (28).
the Scottish Heart Health Study, low dietary vitamin C was linked with an increased risk of total, but not of fatal, CHD in men (27). This suggests that the difference between the results of our study and those of the Finnish study was not likely to have been due to a strong association between vitamin C deficiency and fatal CHD in Finland. Whatever the explanation for the apparent difference in results, the ultimate conclusions are the same and do not argue in favor of the use of large vitamin C supplements to prevent CHD.

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REFERENCES