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Vitamin C deficiency in cancer patients

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Purpose: To assess the prevalence of vitamin C deficiency within a group of hospice patients. To assess the relationship between plasma vitamin C, dietary intake and subsequent survival. **Methods:** Patients with advanced cancer were recruited from a large hospice. Data were collected on demographic details, physical functioning and smoking history. An estimate was obtained of the number of weekly dietary portions consumed equivalent to 40 mg of vitamin C, the recommended daily intake. Plasma vitamin C was measured by a single blood sample. The study had local ethical approval. **Results:** Fifty patients were recruited (mean age 65.2 years, 28 female). Plasma vitamin C deficiency was found in 15 (30%). Dietary intake of vitamin C was correlated to plasma vitamin C ($r = 0.518$, $P < 0.0001$). Low dietary intake, low albumin, high platelet count, high CRP level and shorter survival were all significantly associated with low plasma vitamin C concentrations (< 11 μmol/L). There was no correlation between plasma vitamin C, smoking history or physical functioning. **Conclusion:** Vitamin C deficiency is common in patients with advanced cancer and the most important factors determining plasma levels are dietary intake and markers of the inflammatory response. Patients with low plasma concentrations of vitamin C have a shorter survival. *Palliative Medicine* 2005; **19:** 17–20

Key words: ascorbic acid; cancer; inflammatory response; vitamin C

Introduction

Fatigue, dyspnoea, anorexia and depression are all common symptoms of malignant disease. These symptoms also represent the early nonspecific signs of vitamin C deficiency.[1,2] When body stores of vitamin C become depleted, the classic signs of scurvy become prominent – gingivitis, perifollicular haemorrhages, poor wound healing, petechiae and ecchymoses.[3,4] The contribution of micronutrient deficiencies to symptoms, for example fatigue, is poorly researched in this population[5] despite such deficiencies being potentially amenable to therapeutic intervention. Treatment of scurvy is relatively simple and consists of up to 250 mg of vitamin C daily for a week.[6]

Ascorbic acid is a water-soluble antioxidant and reducing agent which is present in all tissues. Its main role is in the hydroxylation of proline to hydroxyproline, which is necessary for the formation of collagen. However it is also involved in the metabolism of iron and copper and maintenance of the oxidoreductive state.

Humans are unable to synthesize ascorbic acid from glucose so they need an exogenous source of vitamin C. Ascorbic acid is absorbed from the small intestine and then distributed to the cells of the body. The normal body pool size is approximately 1500 mg.

Clinical scurvy can appear after four weeks on an ascorbic acid-deficient diet when the body pool size is less than 300 mg.

By contrast, at the dose range of approximately 1 g/day or more there is potential for toxicity. This can manifest as abdominal discomfort and diarrhoea.

Deficiency tends to occur in certain high-risk groups, for example, the elderly, living alone or those with an unusual diet.[2,4,7,8] However, factors such as impaired taste, dysphagia, nausea and vomiting that can result from cancer could also contribute to an unbalanced dietary intake.[7]

The aim of this study was to assess the prevalence of plasma vitamin C deficiency in a group of patients with advanced cancer. We wanted to examine whether vitamin C deficiency, as opposed to reduced protein and calorie intake, was a sufficiently common problem to offer scope for further investigation. Additionally, we aimed to assess the relationship between plasma vitamin C levels, dietary intake and subsequent survival.

Methods

Fifty patients were recruited from a large hospice. All were patients with advanced cancer who were able to give

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written consent and only those judged to be too unwell to consent were excluded. The assessment consisted of a questionnaire and a single blood sample to measure plasma vitamin C and further haematological and biochemical parameters. The study had local ethical approval from the Leeds Research and Development Committee.

Questionnaire

Demographic data. Data were recorded on age, sex, diagnosis and home circumstances (lived alone or not). The modified Barthel index was used to measure performance status.[9] This index comprises ten different activities of daily living with the maximum score being 100. A smoking and alcohol history was recorded. The patient's date of death was also noted.

Dietary history. The Reference Nutrient Intake (RNI) was used as the dietary reference value for vitamin C.[3] This is defined as 'the amount sufficient or more than sufficient for the nutritional needs of practically all healthy persons in a population'. RNI represents the best estimate of requirement, and for the majority of the population would be substantially more than individual needs, but would also incorporate those with particularly high needs. The current recommendation is 40 mg/day.[3]

Food products were selected with high vitamin C content. These were fresh orange juice, oranges, grapefruit, boiled potatoes, boiled broccoli and brussel sprouts.[10] A portion was calculated as the amount of the individual food or drink that would supply 40 mg vitamin C (the recommended RNI). Seven portions are required each week to provide sufficient vitamin C for an individual. Patients were asked how often they had consumed each of these foodstuffs over the past week and from this a total number of dietary vitamin C portions for the week was calculated. All patients were asked about vitamin supplementation. Our questionnaire received input from the hospice dietician.

Laboratory determinations. A single blood sample was used to measure haemoglobin, platelets, International Normalized Ratio (INR), albumin, urea, C-reactive protein (CRP) and vitamin C.

Blood samples and questionnaire data were collected within three days of each other.

Plasma vitamin C was measured by high performance liquid chromatography. This method has been validated as a rapid and specific measurement of vitamin C.[11] The plasma vitamin C level was used in the analysis as opposed to the leukocyte vitamin C level, as the latter measurement can be influenced by any changes in absolute or differential white cell count. Plasma levels have also been shown to correlate with dietary vitamin C intake.[3,12] A value of less than 11 μmol/L was considered to represent plasma vitamin C deficiency. Levels between 11 and 23 μmol/L represent a group at risk of developing plasma vitamin C deficiency.[12] The researcher was blind to the biochemical measurements at the time of interview.

Data analysis. Statistical analysis was conducted using the Windows version of Statistical Package for Social Sciences (SPSS – Windows Version 11). Statistical significance was set at the level of $P < 0.05$.

Results

Biochemical data from all 50 patients were used in the analysis although one patient became too unwell to complete the dietary questionnaire. The demographic details are shown in Table 1.

From the 49 dietary histories, the mean number of total portions was 5.8 (range 0–24, SD 5.2). The largest proportion was represented by the consumption of orange juice (mean number portions 2.6). Only one patient was taking vitamin C supplements.

There was a significant correlation between the estimated portions of vitamin C consumed in the previous week and the plasma vitamin C levels ($r = 0.518$, $P < 0.0001$).

Table 1 Demographic details

Gender	
Male	22
Female	28
Mean age (SD)	65.2 years (11.6)
Primary tumour site (frequency)	
Brain	2
Breast	5
Bronchial	6
Urogenital	10
Gastrointestinal	16
Prostrate	6
Haematological	1
Head and neck	1
Other	3
Lives alone	
Yes	23
No	27
Smoker	
Yes	13
No	37
Alcohol consumption	
None	28
<10 units	20
10 units or more	2
Barthel index (median)	82
Range	8–100

Within the sample, 15 patients (30%) had plasma vitamin C levels less than 11 μmol/L. A further 21 patients had a plasma level between 11.1 and 23 μmol/L (42%).

There was a significant inverse correlation between plasma vitamin C and CRP level ($r = -0.529$, $P < 0.0001$). There was also a significant correlation between plasma vitamin C and survival ($r = 0.370$, $P = 0.013$), and plasma vitamin C and serum albumin ($r = 0.63$, $P = 0.0001$).The sample was divided into patients with low plasma levels of vitamin C (less than 11 μmol/L) and those having normal plasma levels. A comparison of the results for the two groups is shown in Table 2.

Univariate analysis demonstrated that low dietary intake, low albumin, high platelet count, high CRP level and shorter survival were all significantly associated with low plasma vitamin C concentrations. The group with low levels of plasma vitamin C had half the mean dietary intake compared to those with a normal plasma level (3.2 versus 6.8 portions, $P = 0.005$). Their mean survival was much shorter (29 versus 121 days, $P = 0.001$) and they had twice the mean CRP level (105.6 versus 52.0, $P = 0.003$).

We then went on to analyse further using logistic regression analysis. This is a statistical method of measuring how different variables independently predict the outcome of another variable. In this case we wanted to evaluate to what extent dietary intake, CRP, albumin and platelet count independently predict low plasma vitamin C levels and so ascertaining which variable is the most significant.

Using this method of statistical analysis, albumin was the only significant independent variable in the final model (Table 3).

There was no statistically significant correlation between plasma vitamin C level and age, sex, Barthel score, alcohol or smoking history.

Table 2 Dietary portions, demographic and biochemical data between low and normal plasma vitamin C groups

	Mean scores (SD)		Significance
	Low plasma vitamin C*	Normal plasma vitamin C	
Survival	29 days (19)	121 days (132)	$P = 0.001$
Age	64.4 years (7.8)	65.5 years (13.0)	Not significant
Barthel	74 (14)	79 (22)	Not significant
Dietary portions	3.2 (2.8)	6.8 (5.7)	$P = 0.005$
Haemoglobin	11.0 (1.8)	11.6 (1.4)	Not significant
INR	1.4 (0.6)	1.1 (0.3)	Not significant
Albumin	27.3 (3.1)	33.6 (6.4)	$P = 0.001$
Platelets	459 (155)	350 (172)	$P = 0.042$
Urea	6.7 (3.9)	7.8 (5.9)	Not significant
CRP	105.6 (51.7)	52.0 (56.1)	$P = 0.003$

*Low plasma vitamin C < 11 μmol/L.

Discussion

Our findings indicate that 30% of patients with advanced cancer had plasma vitamin C deficiency, which is much higher than has been previously reported.[7] This study shows that dietary intake, albumin, platelet and CRP levels were significantly associated with plasma vitamin C levels. Patients with low plasma levels of vitamin C have a significantly worse prognosis than patients with normal plasma levels.

Although we have shown that dietary intake is an independent determinant of plasma vitamin C levels, cancer-induced oxidative stress (as indicated by raised CRP and low albumin) is probably a more important influence. The release of free radicals from advancing cancer is likely to result in an increased demand for, and consumption of, vitamin C because of its action as an antioxidant.[13] One interpretation is that plasma vitamin C in this context reflects poorer health, determined by the activity of the cancer, and that dietary intake is a symptom of this poorer health. This would probably result in supplementation having little impact on either symptoms or survival.

In a study of critically ill patients,[14] median plasma vitamin C concentrations were less than 25% of healthy control values and reflected the severity of illness. Vitamin C concentrations showed an inverse relationship with CRP and the use of parenteral nutrition did not prevent the fall in vitamin levels. This supports the concept that illness (i.e., the acute-phase response) is a more important influence on plasma vitamin C levels than dietary intake or supplementation. However, in one study of 219 cancer patients, six cases of scurvy were observed although the actual plasma vitamin C level within all these patients was not analysed.[7] Those who were treated with vitamin C showed improvement, suggesting that this population of patients does indeed have the potential to benefit from supplementation.

We found that patients with low concentrations of vitamin C had a much shorter survival and that this relationship was stronger than that between survival and either CRP or dietary intake.

Previous studies have focused on issues regarding survival benefit in the context of advanced cancer and high dose vitamin C supplementation.[15,16] No survival benefit was observed but these studies did not identify patients with vitamin C deficiency at outset. It remains unknown whether vitamin C supplementation in advanced cancer patients with biochemical deficiency would influence plasma levels of vitamin C, particularly in the context of oxidative stress. The effects of correcting such deficiency on survival or symptom burden are also unknown.

The method of assessment was a retrospective estimate and hence dependent on the patient's recall of their

Table 3 Logistic regression model of variables significantly associated with low plasma vitamin C levels (variables entered in backward conditional method with 'low plasma vitamin C level' as binary outcome)

Outcome predicted	Variables entered	Final model significance	Variables in final model	Standardized coefficient	Variable P value
Low plasma vitamin C level	Dietary intake CRP Albumin Platelets	P = 0.002 (chi square = 12.013, df 2)	Dietary intake	0.229	0.081
			Albumin	0.230	0.006

dietary intake for the previous week. The study is also limited by the fact that the patients recruited were a convenience sample and hence selection bias cannot be excluded. Although this is a small sample of patients, there is no other reported survey estimating prevalence of vitamin C deficiency within this population. On the basis of these findings, plasma vitamin C deficiency is more common than previously reported within cancer patients and is significantly related to poorer prognosis. Both dietary intake and oxidative stress are independently related to plasma vitamin C levels, but it seems likely that survival is determined by advancing cancer, which depletes vitamin C, rather than vitamin C deficiency resulting in shorter prognosis. This study has not addressed the relationship between vitamin deficiency and symptoms in this population though this remains an important area for research. However, demonstrating a biochemical response to supplementation in this context would be essential to inform further symptom-based research.

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