Original Communication

Poor Vitamin C Status is Associated with Increased Depression Symptoms Following Acute Illness in Older People

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Abstract: *Background:* Vitamin C has important physical and mental health benefits and plasma concentrations reflect recent intakes. Inflammation associated with any acute illness can lead to poor appetite and low food intake in older people. The aims of this report were to assess the prevalence and clinical significance of vitamin C deficiency among hospitalized acutely-ill older patients. *Methods:* Three hundred and twenty two patients (152 [47 %] female), aged 65 yrs. and over who took part in a randomized, double blind, placebo-controlled trial had their nutritional status assessed from anthropometric, hematological and biochemical data at baseline, and after 6 weeks and 6 months. Vitamin C was measured using a fluorimetric technique and logistic regression analysis was performed to determine the influence of a number of clinical indicators, including tissue inflammation measured using C-reactive protein on vitamin C concentrations. Clinical outcome measures including symptoms of depression were also compared between patients with vitamin C deficiency and those with normal levels. *Results:* At baseline, 116 (36 %) patients had a vitamin C concentration below 11 μmol/L indicating biochemical depletion. The figures at 6 weeks and 6 months were 28 (22 %) and 44 (28 %) patients, respectively. Older age, male gender, smoking, increased dependency and tissue inflammation were associated with lower vitamin C concentrations. Patients with vitamin C biochemical depletion had significantly increased symptoms of depression compared with those with higher concentrations at baseline ($p=0.035$) and at 6 weeks ($p=0.028$). *Conclusions:* A high proportion of older patients had sub-optimal vitamin C status and this was associated with increased symptoms of depression.

Key words: Vitamin C, acute illness, older people

Introduction

Vitamin C has an antioxidant activity and also important in reducing the tocopheroxyl radical formed by the oxidation of vitamin E in membranes and plasma lipoproteins [1]. Vitamin C deficiency results in mood and psychomotor performance changes, skin lesions and impaired wound healing[1]. There is also some evidence that vitamin C may help to protect against infections by enhancing the immune system through its radical-trapping antioxidant activity and also increasing the motility of the neutrophils [2, 3]. The major dietary sources of vitamin C are fruit and vegetables[1]. Elderly people from the UK may have difficulty preparing and eating fruit and vegetables and food from 'meals on wheels' has been shown to lose up to 90 % of the vitamin C content by the time of delivery [4]. In addition, acute illness in older patients leads to tissue inflammation and the release of inflammatory markers such as C-reactive proteins and cytokines. This process is known to be associated with decreased appetite and food intake and may lead to vitamin deficiency [5, 6]. The latter may also be due to decreased absorption, increased demands or a combination of all factors. Furthermore, older people are particularly at risk because of the decreased nutritional reserves as a result of repeated illness [6]. Therefore, we hypothesize that inflammation associated with any acute illness may lead to poor appetite, low food intake in older people and consequently vitamin C deficiency. The aims of this report were to assess the prevalence of vitamin C deficiency among hospitalized acutely-ill older patients and to assess the relationship between vitamin C status and clinical risk indicators in these patients.

Methods

Subjects

Three-hundred and twenty-two patients out of the 445 patients who took part in a randomized, double blind, placebo-controlled trial had their vitamin C status assessed at baseline. The number of patients with repeat measurements at 6 weeks and 6 months was 128 and 157, respectively. Exclusions were due to early deaths or the refusal to have a repeat blood sample taken at follow-up visits. Details of the trial (ISRCTN01133608) have been published elsewhere [7]. All patients in the index trial had nutritional supplements or a placebo in addition to the standard hospital diet for a period of 6 weeks, either entirely in hospital or continued in the community for patients discharged earlier than 6 weeks. The composition of the supplement was to provide, in total, 995 kcal of energy (45 % carbohydrate, 35 % fat, 20 % protein) and 100 % of the Reference Nutrient Intakes for a healthy older person for vitamins and minerals, including vitamin C. The placebo was identical to the supplement but contained no protein or micronutrients and had minimum calorie content (60 kcal). Briefly, hospitalized acutely ill patients included in the study were those aged 65 years and over, medically stable and able to swallow and sign an informed written consent form. The most common diagnoses of the study population included ischemic heart disease, chest infection, chronic obstructive lung disease, heart failure, falls, stroke, syncope, urinary tract infection, anemia, septicemia, diabetes, osteoarthritis, rheumatoid arthritis and fractured limbs. Patients with severe medical or psychiatric illness, dementia, malignancy, living in an institution and patients already on supplements were excluded from the study. The study was approved by the local research ethics committee and informed written consent was obtained from all of the recruited patients.

Clinical assessment

Following informed written consent and recruitment to the study, patients had baseline, 6 week and 6 month assessments. The assessments included demographic and medical data including current diagnosis, history of chronic illnesses, smoking, alcohol and drug intake, nutritional status, infections, length of stay, disability, mood and quality of life. Disability at baseline was assessed using the Barthel score on a 20-point scale. The Barthel scores 10 functions on a scale 0 (fully dependent) to 20 (independent) [8]. Smoking history was collected from all subjects. Subjects who answered yes to the question "Do you smoke" and those who stopped smoking for less than one month prior to admission were categorized as smokers; subjects who used to smoke and had stopped smoking for more than one month were categorized as ex-smokers; all others were categorized as never smoked. Depressive symptoms were assessed using the 15 item Geriatric Depression score (GDS). The 15 item GDS is suitable as a screening test for depressive symptoms in the elderly; it is ideal for evaluating the clinical severity of depression, and therefore for monitoring treatment. It is easy to administer, needs no prior psychiatric knowledge and has been well validated in many environments [8]. Acute phase response (severity of illness) was measured using C-reactive protein (CRP) concentration [6].

Measurement of vitamin C

Total ascorbic acid was measured using a fluorimetric technique [9]. The principle of the assay is that ascorbic acid is oxidized to dehydroascorbic acid during incubation with ascorbic acid oxidase. The dehydroascorbic acid produce then reacts with 1,2-diphenylenediamine to produce a fluorescent compound, which is detected by fluorescence detection automated for the Cobas bioautoanalyser (Roche Diagnostics). This is compared with results from the standard curve, which are stored in the memory. The assay measures total vitamin C; the coefficient of variation for vitamin C measurements was 8.4 %.

Statistical Methods

Statistical analyses were performed with SPSS software, version 21 (SPSS Inc., Chicago). Mann-Whitney-U and Kruskal-Wallis H tests were used to test between group differences with a p-value of <0.05 regarded as statistically significant. Logistic regression analysis was performed to determine the influence of age, gender, disability, smoking and co-morbidity, including chronic illness, medications and tissue inflammation on vitamin C concentration (<11µmol/L versus ≥ 11µmol/L) as the dependent variable. Partial correlation was used to assess the association between vitamin C levels and Geriatric depression scores after adjusting for age and tissue inflammation (CRP).

Results

Figure 1 shows vitamin C concentrations of the study patients at baseline, and after 6 weeks and 6 months. At baseline, 116 patients out of 322 (36 %) had a vitamin C concentration below 11 µmol/L, indicating biochemical depletion [10]. The figures at 6 weeks and 6 months were 28 (22 %) and 44 (28 %) patients, respectively. Table I reveals that older age, male gender smoking,

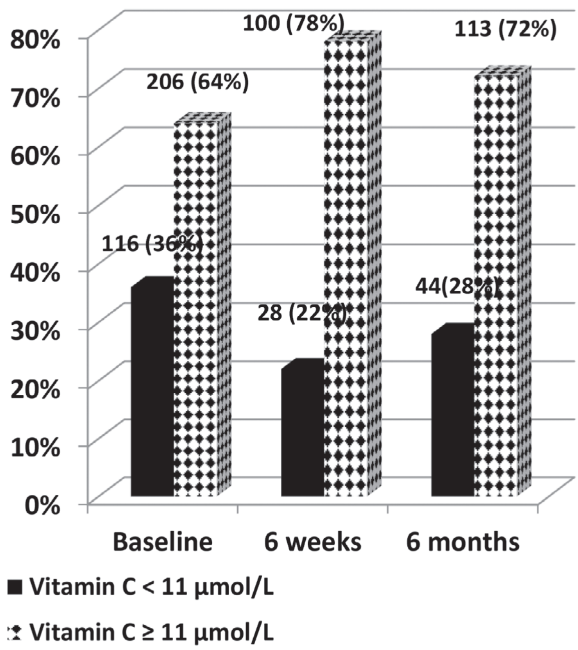

Figure 1: Number (percentage) of patients with vitamin C deficiency (<11µmol/L) compared with patients with normal levels (≥ 11µmol/L) during the study period.

Table I: Vitamin C concentrations (µmol/L) of the study population stratified by age, gender, disability, smoking status and presence or absence of inflammation during the study period, mean (SD).

		Baseline (µmol/L)	6 weeks (µmol/L)	6 months (µmol/L)
Age	<75 yrs.	26 (21)	38 (25)	33 (23)
	=>75 yrs.	22 (21)*	27 (19)*	31 (26)
Gender	Male	21 (19)	31 (24)	26 (23)
	Female	26 (24)*	35 (23)	39 (34)*
Disability+	Independent	25 (22)	34 (23)	30 (28)
	Dependent	18 (20)*	26 (21)	39 (36)
Smoking	Never	27 (27)	38 (22)	41 (38)
	Ex	23 (19)	32 (24)	29 (21)
	current	20 (17)	24 (20)*	18 (19)
Inflammation ±	Absent	29 (24)	36 (23)	30 (23)
	present	20 (19)*	29 (24)	30 (28)

+Independent= Barthel 12–20, Dependent= Barthel 0–11; ± Inflammation: absent = normal CRP (≤10 mg/L), present = high CRP (>10 mg/L). *$p<0.05$

Table II: Logistic regression analysis of the relationship between age, gender, disability, co-morbidity, smoking and tissue inflammation and vitamin C levels (< 11 μmol/L versus ≥11μmol/L) at baseline, 6 weeks and at 6 months.

	Baseline (n = 302)		6 weeks (n = 112)		6 months (n = 82)	
	Odds ratio for unit change (95 % C.I)	P value	Odds ratio for unit change (95 % C.I)	P value	Odds ratio for unit change (95 % C.I)	P value
Age (< 75; ≥75 yrs.)	2.6 (1.49 to 4.36)	0.001	3.1 (1.13 to 8.30)	0.028	1.18 (0.55 to 2.43)	0.674
Gender (male/female)	0.62 (0.37 to 1.0)	0.061	1.16 (0.45 to 2.30)	0.755	0.64 (0.29 to 1.38)	0.255
Barthel score (< 11; ≥11)	0.56 (0.30 to 1.07)	0.079	0.67 (0.17 to 2.70)	0.576	1.28 (0.31 to 5.2)	0.736
Chronic illnesses number/patient	0.84 (0.67 to 1.05)	0.119	0.79 (0.50 to 1.25)	0.311	1.11 (0.76 to 1.63)	0.599
All medications number/patient	0.95 (0.83 to 1.10)	0.506	1.12 (0.91 to 1.54)	0.211	0.90 (0.72 to 1.12)	0.324
Smoking (Never, Ex, Current.)	1.4 (1.01 to 2.04)	0.045	1.8 (0.83 to 3.88)	0.137	1.53 (0.88 to 2.66)	0.128
CRP (< 10; > 10 mg/L)	1.3 (0.77 to 2.25)	0.308	1.59 (0.6 to 4.24)	0.357	1.37 (0.64 to 2.94)	0.416

increased dependency and tissue inflammation were associated with lower vitamin C levels compared with younger, female, non-smokers and independent patients and those without measurable inflammatory response. Table II shows the results of a logistic regression analysis for the association between vitamin C and important prognostic clinical indicators. Among those included in the logistic regression models, age and smoking revealed a statistically significant association with vitamin C concentrations at baseline. At 6 weeks, only age was a significant predictor of vitamin C concentrations. However, the results at 6 months did not reach statistical significance. Patients with vitamin C concentrations indicating biochemical depletion (below 11 μmol/L) had significantly increased symptoms of depression compared with those with higher concentrations (Table III). Total vitamin C concentrations showed significant negative correlations with depression symptoms at 6 weeks and at 6 months ($r = -0.197$, $p = 0.043$ and $r = -0.167$, $p = 0.061$, respectively) after adjusting for age and tissue inflammation measured by CRP. Baseline vitamin C levels were not associated with any other clinical outcome measures, including infections, length-of-stay, discharge destination, non-elective readmission, quality of life measures or mortality.

Table III: Depression symptoms (mean ± SD) in patients with vitamin C levels < 11μmol/compared with those with vitamin C levels ≥11μmol/L during the study period.

	Baseline GDS scores	GDS at 6 weeks	GDS at 6 months
Vitamin C < 11 μmol/L)	5.64 (3.6)	6.40 (3.4)	4.40 (2.9)
Vitamin C ≥11 μmol/L)	4.76 (3.3)	4.63 (3.6)	4.43 (3.6)
P value	0.035	0.028	0.963

*The Geriatric Depression Score (GDS) maximum score is 15. In clinical practice a score of 0–4 = no depression; 5–10 = mild depression; ≥ 11 = severe depression

Discussion

A significant number of acutely ill patients had vitamin C concentrations below 11μmol/L indicating biochemical depletion. The mean vitamin C figures for the study population are comparable to those reported in the institution group included in the British National Nutrition Survey of people aged 65 years and over [10]. However, figures were lower than those reported for the free-living group of the British National survey. We also found that older age, male gender smoking, increased dependency and tissue inflammation were associated with lower vitamin C concentrations. No significant associations were found between vitamin C levels and clinical outcome measures apart from depression symptoms. Acute illness leads to poor appetite and consequently poor food intake. Because plasma concentrations of vitamin C reflect recent intakes, this may be one of the reasons for the low vitamin C status during and following acute illness. However, metabolic changes which accompany acute illness seem to have the largest influence on biochemical vitamin C status. In a previous report related to this study, we demonstrated a graded association between inflammatory responses and vitamin C concentrations [6]. Inflammation also influences fluid distribution, as well as protein, carbohydrate and lipid metabolism [11, 12]. Louw et al. have also demonstrated a transient but significant decrease in blood vitamin concentrations including vitamin C during acute phase response and suggested that biochemical vitamin concentrations determined during acute phase response should be interpreted with care [5]. Six months after the acute illness when tissue inflammation was expected to have subsided, vitamin C figures in our patients were still lower than those reported for free-living older patients. In addition to inflammation, deterioration in vitamin C status may equally be due to reduced gastrointestinal absorption, enhanced turnover and/or demands. This is because vitamin C is needed to supply the immune system and protect the body from the potent actions of the inflammatory response or as an antioxidant [2, 3]; this is clearly an area for future research. Lower vitamin C concentrations have also been attributed to the confounding effects of non-dietary factors in older people. For example, the National Nutrition Survey reported age, sex and smoking as some of the non-dietary influences on plasma vitamin C concentrations [10]. Indeed, in this present report and in previously related ones, we have demonstrated that a number of non-dietary factors including older age, male gender smoking, and increased dependency negatively influence vitamin C biochemical status [10, 13, 14]. The mechanism through which age, gender, disability and smoking influence vitamin C biochemical is not clear but it is likely to be a combination of factors including reduced intake, increased demands and/or turnover. Incidentally, low grade inflammation is known to accompany older age, disability and possibly smoking even in the absence of acute illness. Previous studies have also reported that smokers consumed significantly fewer fruits and vegetables than nonsmokers leading to lower intakes of folate and vitamin C [15, 16]. Furthermore, smoking is known to be associated with an increased demand as a result of oxidative stress reactions present in smokers [16].

We found an association between low vitamin C concentrations and increased symptoms of depression; however, this is less so at 6 months, possibly because of stopping the supplement between 6 weeks and 6 months. A number of previous studies have reported a high prevalence of vitamin C deficiency in hospitalized acutely ill patients including older ones and low vitamin C concentrations have been found to be associated with psychological disorders [17–19]. Furthermore, vitamin C supplementation improved mood in vitamin C-deficient acutely hospitalized patients [20]. The mechanism responsible for the influence of vitamin C on mood disorders is thought to be related to the role of oxidative stress in the pathogenesis of psychological disorders and vitamin C as an antioxidant [19]. However, some of these studies were small in size and it is not yet clear whether vitamin C deficiency was due to insufficient vitamin C intake, turnover or redistribution.

Other potential health benefits of optimal vitamin C status have been highlighted in a recent review by Grosso et al. The review was an attempt to summarize recent advances in vitamin C research and its clinical implications. The authors stated that vitamin C has the potential to counteract inflammation and subsequent oxidative damage, which play a major role in the initiation and progression of several chronic and acute diseases [21]. Another recent study demonstrated an inverse association between antioxidants including vitamin C and immune activation markers in patients with coronary artery disease, suggesting a useful role for vitamin C in chronic immune activation [22].

An important strength is that our study population comes from the UK population, and is therefore similar to those included in the National Nutrition Survey of British people aged 65 years and over; we also used the same method for biochemical vitamin C measurements [9]. Our results for baseline vitamin C concentrations in hospital were comparable to those reported in the institution group included in the British National survey [10]. However, the results have to be interpreted with caution because it is a subgroup analysis. Another methodological issue which may have affected our results was the number of exclusions due to the refusal to have a repeat blood sample taken at follow-up visits.

In conclusion, we found a high proportion of older patients with low vitamin C concentrations indicating biochemical deficiency, but the clinical significance of this finding is not clear. There is a need, however, to identify the reasons behind the low vitamin C status in acutely ill hospitalized patients and the clinical significance, if any. Only powerful larger trials can provide answers to these questions and also evaluate the therapeutic benefit of vitamin C during acute illness, particularly in older patients.

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Author's contribution

SG is the principal investigator and wrote the manuscript, including data analysis and the discussion. SG read and approved the final manuscript.

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