Effects of vitamin C and vitamin D administration on mood and distress in acutely hospitalized patients[1–4]

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ABSTRACT

Background: Hypovitaminosis C and D are highly prevalent in acute-care hospitals. Malnutrition with regard to these vitamins has been linked to mood disturbance and cognitive dysfunction.

Objective: The objective was to determine whether vitamin C or D supplementation improves mood state or reduces psychological distress in acutely hospitalized patients with a high prevalence of hypovitaminosis C and D.

Design: A randomized, double-blind, active-control clinical trial compared the effects of vitamin C (500 mg twice daily) with those of high-dose vitamin D (5000 IU/d) on mood (Profile of Mood States) and psychological distress (Distress Thermometer).

Results: Vitamin C provided for a mean of 8.2 d increased plasma vitamin C concentrations to normal ($P < 0.0001$) and was associated with a 71% reduction in mood disturbance ($P = 0.0002$) and a 51% reduction in psychological distress ($P = 0.0002$). High-dose vitamin D provided for a mean of 8.1 d increased plasma 25-hydroxyvitamin D [25(OH)D] concentrations ($P < 0.0001$), but not into the normal range, and had insignificant effects on mood ($P = 0.067$) and distress ($P = 0.45$). The changes in mood and distress in the vitamin C group were greater than those in the vitamin D group ($P = 0.045$ for mood; $P = 0.009$ for distress).

Conclusions: Short-term therapy with vitamin C improves mood and reduces psychological distress in acutely hospitalized patients with a high prevalence of hypovitaminosis C and D. No conclusion is possible regarding the effects of vitamin D because the dose and duration of therapy were insufficient to raise 25(OH)D concentrations into the normal range. This trial was registered at clinicaltrials.gov as NCT01630720. *Am J Clin Nutr* 2013;98:705–11.

INTRODUCTION

Hypovitaminosis C and D are highly prevalent in acute-care hospitals (1–10), but their clinical consequences have rarely been studied (1, 11) and remain almost completely unknown (6). Currently, very few hospitalized patients are prescribed vitamin supplements.

Vitamin C and D play important roles in brain metabolism (12–20). Subclinical vitamin C deficiency induces fatigue and mood disturbance (6), whereas hypovitaminosis D has been linked to cognitive dysfunction (19, 21–25) and depression (16, 26–29). Small randomized clinical trials in the ambulatory setting suggest that vitamin D therapy can improve mental well-being (30, 31) and alleviate depression in people who are vitamin D deficient (29, 32, 33). We observed earlier that appropriate provision of vitamin C improved the mood state of acutely hospitalized patients, whereas vitamin D administration at the upper tolerable dose of 2000 IU/d had no effect (8). No conclusion was possible regarding the benefit of correcting in-hospital hypovitaminosis D insufficiency, however, because the administered dose only slightly increased plasma 25-hydroxyvitamin D [25(OH)D][5] concentrations during the short time course of the trial (8). The tolerable upper level of vitamin D intake was recently increased to 4000 IU/d (34). Accordingly, we carried out a randomized clinical trial to compare the effects of vitamin C and a very high dose of vitamin D on the psychological well-being of acutely hospitalized patients. The clinical hypothesis was that either vitamin C or high-dose vitamin D administration improves mood and reduces psychological distress in a population of acutely hospitalized patients with a high prevalence of hypovitaminosis C and D.

SUBJECTS AND METHODS

Clinical trial design

The design of the clinical trial was dictated by ethical and practical considerations regarding the use of active treatments compared with inactive placebos. The Canadian government's Interagency Advisory Panel on Research Ethics requires that, before a placebo control is used in a clinical trial, researchers must provide compelling justification for rejecting other valid methods of achieving internal validity, such as an active treatment control (35). Our previous research in this population indicated that hypovitaminosis C represents a true nutritional deficiency state (6) that can be easily corrected (6) and that such

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[5] Abbreviations used: DT, Distress Thermometer; POMS, Profile of Mood States; TMD, total mood disturbance; 25(OH)D, 25-hydroxyvitamin D.

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correction might improve mood state (8). We could not ethically justify using a placebo group in this situation, because high-dose vitamin D represents a safe and plausible active comparison treatment. This use of an active comparison treatment is consistent with recommendations in the medical literature regarding the pros and cons of placebo compared with active control subjects (36–38). Also consistent with the literature (39), our previous experience with this population indicated a strong disinclination to participate in a clinical trial that requires participants to take inactive placebos when the active treatment is known to be simple, safe, sensible, and plausible. It therefore served the ethical and scientific goals of this study to design it as a randomized, double-blind, active-control clinical trial. In addition, the use of high-dose vitamin D as an active control treatment provided an efficient way to obtain new information about the immediate therapeutic benefit of high-dose vitamin D provision in a population with a high prevalence of hypovitaminosis D.

Setting and participants

Over an 8-wk period from 9 June to 3 August 2011, all the patients on 8 active medical and surgical units of a university teaching hospital were approached for enrollment if their treatment team approved and they were judged to be mentally competent and fluent in French or English. Patients in the intensive care unit (or being considered for transfer there) or receiving renal replacement therapy were not eligible. Eligible patients were informed that they could be at risk of vitamin C and D deficiency and invited to participate in the study, which involved daily administration of vitamin C or vitamin D for a maximum of 10 d. Participating patients were examined for potential signs of scurvy (skin bruising or hemorrhagic gingivitis), and their BMI was visually estimated (5, 40).

Randomization and interventions

After enrollment, patients were randomly assigned in pairs to vitamin C or D therapy by a senior investigator who had no contact with them. The investigators who enrolled and followed the patients were blinded as to the treatment assignment. All the participants were carefully informed, first, of the blinded nature of the study, and second, that both treatments were active. The nurses refrained from telling their patients which vitamin was prescribed. Whereas it is possible that patients could determine their treatment assignment from the frequency of supplementation (twice daily for vitamin C, once daily for vitamin D), the large number of routine medications patients were already being administered would make such a determination difficult. Even if some patients did make such a determination, it would not bias their response because both treatments were active. Our experience with this patient population—confirmed in the current study—was that one of the commonest reasons why patients decline to participate is the burden of adding more pills to the large number of medications they are already prescribed. Because the treatment arms were in psychological equipoise, we determined that asking patients to take double-dummy placebo tablets would discourage participation and impose an unnecessary burden on the patients and their nurses. Therapy was 500 mg vitamin C twice daily or 5000 IU vitamin D once daily for a maximum of 10 d. This dose of vitamin D slightly exceeded the tolerable upper level of 4000 IU, but was used because a single dosage unit was conveniently available. The protocol stipulated that a treatment course was complete if $\geq$5 d of the 10-d course of vitamin therapy was completed. Before and after 5–10 d of vitamin administration, participants completed a mood-assessment questionnaire, indicated their level of psychological distress, and had a blood sample drawn for the analyses described below. The study protocol was approved by the Research Ethics Committee of Montreal's Jewish General Hospital.

Sample handling and laboratory procedures

Morning fasting blood samples were drawn before any vitamin administration and immediately pushed into crushed ice in a light-protected box in which they remained $<$2 h before being hand delivered to the research laboratory by one of the investigators. Immediately after separation in a refrigerated centrifuge, plasma samples were deproteinized, flash frozen, and stored at -80°C and analyzed for reduced ascorbic acid and total vitamin C by electrochemical detection HPLC, as previously described (8). A plasma total vitamin C concentration $<$28.4 μmol/L is regarded as vitamin C depletion and a concentration $<$11.4 μmol/L is regarded as frankly deficient (5, 6). Plasma 25(OH)D was analyzed by radioimmunoassay (Immunodiagnostic Systems). A concentration $<$75 nmol/L is considered subnormal (34). Intact parathyroid hormone (reference range: 10–70 ng/L) was measured in plasma by electrochemiluminescence immunoassay on a Modular Analytics E-Module (Roche). Plasma C-reactive protein (reference range: 1–10 mg/L) was measured by latex particle-enhanced immunoturbidimetry on a Cobas Integra 800 analyzer (Roche).

Analysis of mood and distress

The Profile of Mood States (POMS) is a widely used 65-item questionnaire that measures mood in healthy, physically ill, and psychiatric populations; the instrument generates a total mood disturbance (TMD) score (41–43). The 30-item POMS-B, a briefer version of the POMS, has been developed to accommodate the limited reserve of physically ill patients (42, 44, 45). The English Canadian and Canadian French versions of the POMS-B (MultiHealth Systems Inc) were used for this study because it is a validated and widely used broad spectrum tool that can be administered even to sick, hospitalized patients. TMD scores range from $-$20 to 100; higher scores indicate more severe mood disturbance. The Distress Thermometer (DT) is a validated one-item measure of psychological distress that directs the patient to circle a number between 0 and 10 that indicates their level of distress, alongside an image of a thermometer; a higher score indicates more intense distress (46, 47). The DT is strongly recommended as a valid and easy-to-use tool for measuring distress in people with cancer (46). It was administered at the same time as the POMS-B. The same investigator carried out each assessment; neither assessors nor patients knew their treatment assignment or biochemical vitamin status. Patients completed the questionnaires by hand or had them read to them without interference. The assessment was explicitly based on how they felt on the day of measurement. Initial and final assessments were always carried out in the same manner and at the same time of day.

Statistical analysis

The analysis was carried out with GraphPad Prism version 5.04 (GraphPad Software). Descriptive statistics were used to estimate the frequencies, means, and SDs of the study variables. Because the distributions of several variables did not fully meet the criteria for normality, significant differences between unpaired samples were routinely tested for by using the Mann-Whitney *U* or Fisher's exact test as appropriate ($P < 0.05$), and the Wilcoxon's matched-pairs test was used to detect significant differences in paired comparisons. Except where otherwise indicated, the results are expressed as means ± SDs.

RESULTS

Of the 153 patients considered for enrollment, 88 were mentally competent, were fluent in French or English, understood the nature of the research, signed the informed consent document, and commenced the study; they are referred to as the initial study group (**Figure 1**). Reasons for declining to participate included an unwillingness to take more pills, mistrust of research, feeling overwhelmed, and fear that vitamins might interact with their ongoing treatment. In this group, 75% of patients had subnormal plasma total vitamin C concentrations, and 30% had frankly deficient concentrations (<11.4 μmol/L); 85% of patients had subnormal plasma 25(OH)D concentrations. Skin bruising was observed in 20 patients and gingival bleeding in 2 patients. The mean plasma vitamin C concentration of these patients, while subnormal (26.8 ± 22.0 μmol/L), was not significantly different from those of patients without these physical findings (22.6 ± 18.8 μmol/L); 18% of patients with skin bruising or gingival bleeding had a plasma vitamin C concentration compatible with scurvy (<11.4 μmol/L), whereas 33% of patients without these findings had a plasma vitamin C concentration in the scorbutic range ($P = 0.28$). Of the initial study group, 36 did not complete the study (18 in each treatment group), because of hospital discharge before completing 5 d of therapy (9 in each group), withdrawal of consent (8 in the vitamin C group and 6 in the vitamin D group), or death (1 in the vitamin C group and 3 in the vitamin D group). The main reasons for withdrawing consent were the burden of taking extra pills and undergoing an additional blood test.

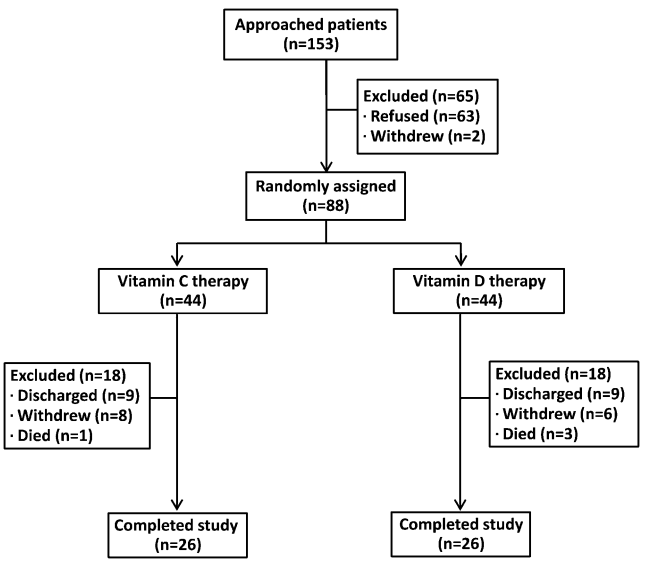

FIGURE 1. Flow diagram.

The 52 participants in the 2 study completed groups were similar to the initial study group in age, sex, and other variables (**Table 1**). In particular, 73% had plasma vitamin C concentrations <28.4 μmol/L, 29% had plasma vitamin C concentrations <11.4 μmol/L, and 79% had plasma 25(OH)D concentrations <75 nmol/L. The clinical diagnoses were as follows: solid tumor or hematologic malignancy (46.2% of patients), cardiovascular disease (13.5%), diabetes mellitus (11.5%), infectious disease (17.3%), gastrointestinal disease (17.3%), and other (21.2%). The distribution of these diagnoses was similar in the 2 study completed groups (data not shown). At the time of enrollment, one patient in the vitamin C group had previously been prescribed a daily multivitamin containing 90 mg vitamin C and 400 IU vitamin D, and 2 other patients were prescribed 400 IU vitamin D/d. One patient in the vitamin D group had already been prescribed the same multivitamin, and 3 others were prescribed an average of 1100 IU vitamin D/d.

The patients in the vitamin C group were treated for an average of 8.2 ± 1.8 d (range: 5–11 d). By the end of treatment, their mean plasma total vitamin C concentration increased into the normal range ($P < 0.0001$; **Table 2**). Their mean TMD score decreased by 71% from 24.0 ± 18.2 (median and range: 23.5; −10 to 54) to 6.92 ± 14.4 (median and range: 4.5; −20 to 49; $P = 0.0002$), and their mean DT score decreased by 51% from 4.5 ± 2.9 (median and range: 4.0; 0–9) to 2.2 ± 2.2 (median and range: 2.0, 0–8; $P = 0.0002$). The patients in the vitamin D group were treated for an average of 8.1 ± 1.7 d (range: 5–11 d). By the end of treatment, their mean plasma 25(OH)D concentration increased by 22% ($P < 0.0001$) but remained below normal. Their mean TMD score decreased by 33% from 21.7 ± 17.3 (median and range: 19.0; −9 to 65) to 14.6 ± 17.7 (median and range: 12.0; −12 to 59; $P = 0.067$), and their mean DT score decreased by 8% from 3.7 ± 2.6 (median and range: 3.5; 1–8) to 3.4 ± 2.8 (median and range: 3.0; 0–8; $P = 0.45$). Plasma parathyroid hormone concentrations were insignificantly higher in the vitamin C group at baseline and decreased significantly after vitamin C therapy but not after vitamin D therapy (Table 2).

As illustrated in **Figure 2**, the change in TMD score after vitamin treatment was significantly greater after vitamin C (−17.0 ± 17.8; range: −59 to 11) than after vitamin D (−7.1 ± 18.2; range: −58 to 26; $P = 0.045$). Similarly, the change in DT score was significantly greater after vitamin C (−2.3 ± 2.3; range: −6 to 1) than after vitamin D (−0.35 ± 2.7; range: −6 to 7; $P = 0.009$).

In a secondary analysis, we tested the hypothesis that beneficial changes in mood and distress were related on an individual basis to changes in plasma total vitamin C concentrations in all 52 patients. The correlation between improvement in TMD score and increase in plasma total vitamin C concentration was significant (Spearman $P = 0.0025$), whereas the correlation between reduction in distress and increase in plasma total vitamin C was nearly significant (Spearman $P = 0.064$).

DISCUSSION

This clinical trial was carried out to determine whether an improvement in mood after vitamin C (but not vitamin D) therapy observed in a previous trial (8) would be reproduced in a new clinical trial that enrolled more participants, used 2 different

TABLE 1
Baseline characteristics[1]

Variable	Initial study group (n = 88)	Study-completed group	
		Vitamin C (n = 26)	Vitamin D (n = 26)
Age (y)	64.5 ± 15.4[2]	65.5 ± 15.4	67.0 ± 14.1
Male sex (%)	53.4	57.7	50.0
Smoker (%)	13.6	7.7	23.1
Time in hospital at enrollment (d)	16 ± 23	15 ± 21	12 ± 11
Body weight (kg)	72.4 ± 17.0	70.0 ± 14.8	73.5 ± 18.8
BMI (kg/m^2)	25.8 ± 5.7	25.3 ± 5.0	25.6 ± 5.7
Blood hemoglobin (g/L)[3]	108 ± 18.3	109 ± 17.1	108 ± 13.6
Serum albumin (g/L)[3]	32.0 ± 7.1	32.2 ± 6.9	31.5 ± 6.9
Plasma C-reactive protein (mg/L)[3]	60.3 ± 74.1	74.9 ± 97.0	39.0 ± 44.2
Plasma parathyroid hormone (ng/L)[3]	44 ± 42	52 ± 66	36 ± 23
Plasma ascorbic acid (μmol/L)	20.6 ± 17.3	21.0 ± 17.4	18.7 ± 13.7
Plasma total vitamin C (μmol/L)[3,4]	23.6 ± 19.6	25.6 ± 22.3	21.7 ± 15.6
Patients with subnormal values (%)	75	73	73
Plasma 25-hydroxyvitamin D (nmol/L)[3]	51 ± 22	52 ± 24	54 ± 24
Patients with subnormal values (%)	85	81	77
Total mood disturbance score[5]	21.1 ± 18.7	24.0 ± 18.2	21.7 ± 17.3
Distress Thermometer score[6]	3.7 ± 2.7	4.5 ± 2.9	3.7 ± 2.6

[1] There were no significant differences between the initial study group and the study-completed group as a whole or between the vitamin C and vitamin D groups with the Mann-Whitney U test or Fisher's exact test for categorical values.
[2] Mean ± SD (all such values).
[3] Reference ranges are as follows: albumin (35–50 mg/L), parathyroid hormone (10–70 ng/L), C-reactive protein (<10 mg/L), hemoglobin (120–150 g/L), total vitamin C (>28.4 μmol/L), and 25-hydroxyvitamin D (75–250 nmol/L).
[4] Total vitamin C is the sum of ascorbic acid and dehydroascorbic acid.
[5] The total mood disturbance score ranges from −20 to 100.
[6] The Distress Thermometer score ranges from 0 to 10.

measures of psychological status, and used a much higher dose of vitamin D. On average, patients who received vitamin C experienced a large and statistically significant reduction in mood disturbance (TMD score) and distress (DT score), whereas those who received vitamin D did not.

Acutely hospitalized patients experience emotional distress for many reasons; therefore, it may seem unexpected that simple correction of their vitamin C deficiency could account for such rapid and dramatic improvements in psychological well-being. There are several reasons why this possibility merits serious consideration. First, the result is biologically plausible. Psychological dysfunction is known to occur in vitamin C deficiency (48–50), presumably because of the involvement of ascorbate in neuronal transmission and in brain neurotransmitter and fuel metabolism (12, 13, 15). Vitamin C concentrations in the cerebrospinal fluid are approximately 3-fold higher than in the plasma. These concentrations remain constant and normal over a wide physiologic range of plasma concentrations, but rapidly decrease as plasma concentrations fall below normal (14). If a subnormal cerebrospinal fluid vitamin C concentration leads to abnormal brain function, normalizing it might well improve mood or increase a person's emotional tolerance to a given level of physiologic stress. The rapid improvement in psychological well-being observed in this study is in keeping with the rate at which patients with known vitamin C deficiency improve clinically after appropriate vitamin C therapy. It cannot be determined from this trial whether the improvements in well-being that occurred were a result of the correction of cerebral vitamin C

TABLE 2
Metabolic and psychological effects of vitamin C and D therapy[1]

Variable[2]	Vitamin C–treated patients (n = 26)			Vitamin D–treated patients (n = 26)		
	Initial	Final	P[3]	Initial	Final	P[3]
Plasma ascorbic acid (μmol/L)	21.0 ± 17.4	69.1 ± 34.9	<0.0001	18.7 ± 13.7	20.4 ± 17.6	0.286
Plasma total vitamin C (μmol/L)	25.6 ± 22.3	79.5 ± 39.1	<0.0001	21.7 ± 15.6	23.0 ± 19.2	0.980
Plasma 25-hydroxyvitamin D (nmol/L)	52 ± 24	54 ± 26	0.382	54 ± 24	68 ± 26	<0.0001
Plasma C-reactive protein (mg/L)	74.9 ± 97.0	50.9 ± 71.3	0.247	39.0 ± 44.2	39.0 ± 47.2	0.780
Plasma parathyroid hormone (ng/L)	52 ± 66	38 ± 28	0.0099	36 ± 23	35 ± 20	0.809
Total mood disturbance score	24.0 ± 18.2	6.9 ± 14.4	0.0002	21.7 ± 17.3	14.6 ± 17.7	0.067
Distress Thermometer score	4.5 ± 2.9	2.2 ± 2.2	0.0002	3.7 ± 2.6	3.4 ± 2.8	0.454

[1] All values are means ± SDs.
[2] Details about the variables and their reference ranges are shown in Table 1.
[3] Wilcoxon's matched-pairs test.

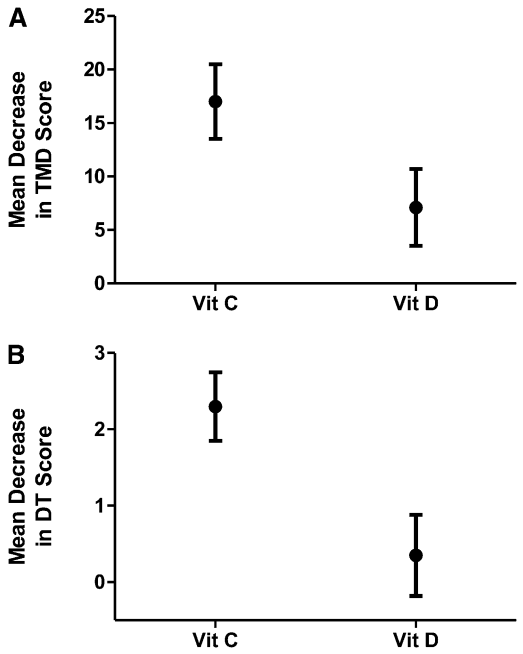

FIGURE 2. Mean decreases in mood disturbance and psychological distress after treatment with Vit C or Vit D. Mood disturbance was measured with the use of the POMS-B scale, on which the TMD score ranges from −20 to 100; lower scores indicated improved mood disturbance. Psychological distress was measured by using the DT scale, which ranges from 0 to 10; lower scores indicated less distress. A: Mean (±SEM) changes in TMD score in the 2 treatment groups (17.0 ± 3.5 for Vit C and 7.1 ± 3.6 for Vit D; $n = 26$ for both groups). The Mann-Whitney U test indicated that the decrease in TMD score was significantly greater in the Vit C group than in the Vit D group ($P = 0.045$). B: Mean (±SEM) changes in DT score (2.3 ± 0.45 for Vit C and 0.35 ± 0.53 for Vit D; $n = 26$ for both groups). The Mann-Whitney U test indicated that the decrease in DT score was significantly greater in the Vit C group than in the Vit D group ($P = 0.009$). DT, Distress Thermometer; POMS-B, Profile of Mood States–B; TMD, total mood disturbance; Vit C, vitamin C; Vit D, vitamin D.

deficiency or to a more general improvement in physiologic function.

Second, the clinical trial has internal validity. Baseline and posttreatment vitamin status were determined by using rigorous procedures for sample handling, storage, and analysis—important strengths that are lacking in most nutritional intervention studies (51). The 2 different, validated, and widely used instruments for measuring psychological well-being were in close agreement as to the direction and magnitude of the treatment effect. The characteristics of the patients who completed treatment were similar to the ones who began the study, and the comparison groups who completed the study were similar to one another (Table 1), including in their diagnostic mix, length of hospital stay at the time of enrollment, and duration of treatment. Some dropout is inevitable with in-hospital pragmatic clinical trials. It was prespecified in the protocol that a treatment was complete if 5 d of therapy were completed. The number of patients who did not complete 5 d of treatment was small in relation to the number enrolled and similar in number and reason in the 2 treatment groups, the most frequent reason being early discharge from hospital. It is unlikely, therefore, that participant dropout or another source of internal bias could have distorted the results enough to account for the large differences in outcome between the 2 treatment arms.

In addition, the large improvements in psychological well-being in the vitamin C–treated patients could not be explained by improvements in their general clinical condition. When untreated, hypovitaminosis C persists indefinitely in hospitalized patients (5), and any improvement in general clinical condition would not be restricted to the vitamin C group, unless correction of vitamin C deficiency itself caused a general physiologic improvement.

This pragmatic clinical trial also has external validity. The participants were typical of the heterogeneous mix of patients admitted to modern tertiary acute care hospitals, and the treatment was simple, safe, and applicable to everyday clinical practice (52, 53). The high prevalence of hypovitaminosis C among these patients, and the large magnitude of the beneficial effect of correcting it, makes these findings highly clinically relevant because alleviation of distress is a major goal of patient-centered care (46, 54, 55).

It is of potential interest that baseline plasma parathyroid hormone concentrations, which were modestly but insignificantly higher at baseline in the vitamin C group, decreased after vitamin C (but not after vitamin D) therapy (Table 2). We cannot explain this observation. In our view the higher baseline parathyroid hormone concentration in this group is most likely a chance finding with subsequent regression to the mean. Nonetheless, it is of some interest, because plasma vitamin C and parathyroid hormone concentrations are seldom measured together. An inverse association between them has been reported in hemodialysis patients (56), and preliminary evidence suggests that vitamin C therapy reduces parathyroid hormone concentrations in these patients (57).

This study had several weaknesses. It was relatively small and hence needs to be replicated in other centers (58). Small trials can be valuable when they test a novel important question, are carefully designed and executed, and the treatment effect is large, robust, and clinically relevant (59). The 71% improvement in mood disturbance after vitamin C therapy is similar to our observations in 2 earlier clinical trials that involved the same treatment in precisely similar patients (6, 8). Importantly, it remains to be determined whether the beneficial effects of normalizing vitamin C status last beyond the 5–10-d duration of this clinical trial.

Finally, it may be considered a weakness that, when the study was designed, the authors failed to adequately consider the possibility that the chosen dose of vitamin D, even though greater than the tolerable upper limit (34), would be insufficient to increase plasma 25(OH)D concentrations into the normal range within 5–10 d. Because of this design weakness, no conclusion is possible regarding the potential effectiveness of vitamin D therapy in hospitalized patients with hypovitaminosis D. The biological half-life of vitamin D appears to be long and variable (60, 61). Our results confirm what other recent reports (62–64) also indicate, namely, that several weeks of continuous high-dose vitamin D therapy would be necessary to normalize plasma 25(OH)D concentrations in this population. These findings strongly suggest the merit of developing and validating a safe and effective ultrahigh vitamin D loading and maintenance dose protocol for situations in which prompt clinical improvement is deemed to be in the patient's interest (64–66).

In conclusion, this research confirms several earlier reports that document an extremely high prevalence of hypovitaminosis C and D in acutely hospitalized patients. Because this information has been restricted almost entirely to nutrition journals, it remains

unknown to most physicians. In this randomized clinical trial, vitamin C administration normalized plasma vitamin C concentrations and substantially reduced mood disturbance and psychological distress in acutely hospitalized patients—a novel finding with important clinical implications in light of the goals of patient-centered care. No conclusion can be drawn regarding the potential benefits of vitamin D therapy in this patient population. Because of its long and variable half-life, future clinical trials of in-hospital vitamin D therapy will require the development and validation of a safe and effective ultrahigh loading dose protocol.

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