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Hemoglobin and Plasma Vitamin C Levels in Patients on Peritoneal Dialysis

Fredric O. Finkelstein[1,2,3], **Peter Juergensen**[1], **Suxin Wang**[4], **Sally Santacroce**[1], **Mark Levine**[5], **Peter Kotanko**[6], **Nathan W. Levin**[6], and **Garry J. Handelman**[4,6]

Garry J. Handelman: garry_handelman@uml.edu

[1]New Haven CAPD, New Haven, Connecticut [2]Hospital of St. Raphael, New Haven, Connecticut [3]Yale University, New Haven, Connecticut [4]University of Massachusetts, Lowell, Massachusetts [5]NIDDK, NIH, Bethesda, Maryland [6]Renal Research Institute, New York, USA

Abstract

Objective—To determine the contribution of vitamin C (Vit C) status in relation to hemoglobin (Hb) levels in patients on long-term peritoneal dialysis (PD).

Methods—56 stable PD patients were evaluated in a cross-sectional survey. Plasma samples were collected for Vit C (analyzed by HPLC with electrochemical detection) and high-sensitivity C-reactive protein (hs-CRP) determinations. Clinical records were reviewed for Hb, transferrin saturation (TSAT), ferritin, erythropoietin (EPO) dose, and other clinical parameters. Dietary Vit C intake was evaluated by patient survey and from patient records. Total Vit C removed during PD treatment was measured in 24-hour dialysate collections.

Results—Patients showed a highly skewed distribution of plasma Vit C levels, with 40% of patients below normal plasma Vit C levels (<30 μmol/L) and 9% at higher than normal levels (>80 μmol/L). Higher plasma Vit C levels were associated with higher Hb levels (Pearson $r = 0.33$, $p < 0.004$). No direct connection between Vit C levels and reported dietary intake could be established. In stepwise multiple regression, plasma Vit C remained significantly associated with Hb ($p = 0.017$) but there was no significant association with other variables (dialysis vintage, age, ferritin, TSAT, hs-CRP, residual renal function, and EPO dose). In 9 patients that were evaluated for Vit C in dialysate, plasma Vit C was positively associated (Spearman $r = 0.85$, $p = 0.01$) with the amount of Vit C removed during dialysis treatment.

Conclusions—These data indicate that plasma Vit C is positively associated with higher Hb level. Vit C status could play a major role in helping PD patients to utilize iron for erythropoiesis and achieve a better Hb response during anemia management.

Keywords

Vitamin C; hemoglobin; anemia

Vitamin C plays an important role in the kinetics of iron metabolism and the utilization of iron for red blood cell formation. Vitamin C added to cultured cells of the erythrocyte lineage increases the fraction of bioavailable iron that can be utilized for biochemical

Correspondence to: G.J. Handelman, Clinical Lab Sciences and Nutrition, University of Massachusetts, 3 Solomont Way, Lowell, MA 01854 USA.

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processes (1). Vitamin C-deficient guinea pigs accumulate iron in hepatic storage sites, and vitamin C promotes the release of stored iron from the highly insoluble he-mosiderin form for use in erythropoiesis in the guinea pig (2). Vitamin C may stimulate the release of iron from storage in ferritin deposits within reticuloendothelial cells (3), enabling iron to be used for erythropoiesis.

Vitamin C enhances the absorption of dietary iron; in the mildly alkaline environment of the duodenum, the ferrous form (Fe^{2+}) is soluble whereas the ferric form (Fe^{3+}) has poor solubility at duodenal pH (4). Maintenance of iron in solution assists uptake by duodenal transporters (5,6) and promotes bioavailability (7). Consistent with this mechanism, dietary vitamin C enhances absorption of dietary iron salts more effectively than EDTA (8), indicating that reduction to the ferrous state is more important than chelation.

Low plasma vitamin C levels have been documented in hemodialysis (HD) patients, who show a broad range of plasma vitamin C, from very low (<5 μmol/L) to very high (>200 μmol/L) (9), and studies indicate that dietary supplementation is generally indicated (10,11). Studies of vitamin C status have been conducted on peritoneal dialysis (PD) patients and indicate that some patients have very low plasma vitamin C levels (<5 μmol/L) (12–14). Deficiency in PD can be very common and may respond well to supplementation (14). Low levels of plasma vitamin C in PD patients may by exacerbated by losses during dialysis because vitamin C has a low molecular weight (176 Da) and thus readily appears in the dialysate (15–18). In a study where patients on long-term PD therapy were prescribed 200 mg/day supplemental vitamin C, plasma vitamin C was maintained at normal levels (19) despite substantial losses during PD treatment.

The diet of PD patients may restrict the intake of vitamin C but these restrictions are usually less marked than for HD patients. The vitamin C status of patients on dialysis has received increased attention with the introduction of measurement by HPLC with electrochemical detection, which allows measurements over a broad range: from 1 to several hundred micromoles per liter (20–24).

In several trials with HD patients, intravenous (IV) vitamin C decreased erythropoietin (EPO) requirements in EPO-resistant patients (25–27), indicating that vitamin C supports Hb production and new red blood cell formation. The mechanism is not clear but may arise from the ability of vitamin C to promote the release of iron from ferritin deposits within the reticuloendothelial system (3) or to mobilize iron administered as carbohydrate complexes (28). Deicher *et al.* (24), in a cross-sectional study of HD patients with different plasma vitamin C levels, reported that very high plasma levels of vitamin C were associated with decreased EPO requirements.

There is limited information examining the relationship of plasma vitamin C to Hb levels in PD patients; therefore, we conducted a cross-sectional study of patients at the New Haven PD unit to gain guidance for better management of Hb-related indicators for all PD patients in our clinic.

Methods

We evaluated plasma vitamin C levels and several other clinical parameters in patients receiving long-term PD (Baxter Healthcare cycler system; Deerfield, IL, USA) at New Haven CAPD in New Haven, CT. The 56 patients in the study included all adult patients (≥18 years of age) that were willing to participate, recruited from a clinic population of 84 eligible patients. All patients were medically stable and had no acute medical illnesses during the 3 months prior to obtaining vitamin C levels. All patients were prescribed vitamin supplements containing 60 – 100 mg vitamin C/day. For 23 patients, dietary vitamin C

intake was determined with a 3-day diet history. Basic demographic data were collected on all patients. Ten of the 56 patients had received IV iron during the preceding 6 months before sample collection. The protocol was approved by the Human Subjects Institutional Review Board, St. Raphael's Hospital, New Haven, CT, USA.

All blood samples were obtained during a routine clinic visit. At the time of the visit, daily vitamin C intake (including the vitamin supplement) was estimated by a dietitian. For measurement of vitamin C, venous blood was drawn using EDTA anticoagulant. The sample was centrifuged and mixed with an equal volume of 10% metaphosphoric acid to stabilize the vitamin C (21). Samples were frozen at −80°C until analysis. Plasma samples were processed within 1 hour; however, recent data indicate that heparin anticoagulant provides better stability than EDTA anticoagulant if plasma processing is delayed (Handelman, manuscript in preparation), as may occur if samples are shipped overnight to a testing laboratory.

Vitamin C was measured by HPLC following the protocol of Levine *et al.* (22). This method uses HPLC on a C18 column with octylamine ion-pairing reagent, with electrochemical detection (Coulochem; ESA – A Dionex Company, Chelmsford, MA, USA), and has to been shown to be linear over the range of 1 – 300 μmol/L plasma vitamin C. Our vitamin C calibration values agree within 2% with levels established for Standard Reference Material #970 (from NIST; Gaithersburg, MD, USA) (29).

C-reactive protein (CRP) was determined in plasma with the Dade Behring BN100 nephelometer (Dade Behring, Newark, DE, USA); this high-sensitivity method (30) has a lower detection limit of 0.12 mg/L. Other laboratory parameters [Hb, ferritin, and transferrin saturation (TSAT)] were determined by standard methods at Spectra-East Laboratories, Rockleigh, NJ, USA.

The entire 24-hour peritoneal dialysate volume was collected in a large plastic bag to which had been added 100 g citric acid to prevent vitamin C degradation in the sample. The volume of dialysate drainage was noted from the cycler. The bag was vigorously mixed and a 100 mL aliquot immediately brought to the clinic, where it was frozen at −80°C and analyzed for vitamin C within 14 days of collection. Control experiments indicated that this methodology would provide full recovery of added vitamin C for up to 8 hours of storage at ambient temperature.

The EPO dose used by each patient was the average weekly dose administered during the month prior to collection of whole blood for vitamin C measurement.

The clinic adjusts each patient's EPO dose on a monthly basis to maintain patients within the Hb range of 11.0 – 12.5 g/dL, which was the target Hb range in use at the time of the investigation. Determination of total weekly Kt/V urea was performed using standard methodology. Residual renal function, as a component of Kt/V urea, was determined for all patients.

Data analysis, including Pearson correlation, Spearman correlation, and stepwise multiple regression, was accomplished using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics and hematology indicators are reported in Tables 1 and 2.

Distribution of Plasma Vitamin C Levels

Plasma vitamin C levels were highly skewed in these patients (Figure 1). The mean was 33 μmol/L, with standard deviation of 34 μmol/L and median of 22 μmol/L. Plasma vitamin C levels in this patient group could not be explained by dietary evaluation, which found that intake ranged from 60 to 400 mg of vitamin C/day, including vitamin C from prescribed vitamin supplements. When vitamin C obtained from diet alone was evaluated, it also was not able to explain differences in plasma levels.

Hemoglobin and Plasma Vitamin C Level

The 56 patients were evaluated for Hb in relation to plasma vitamin C (Figure 2). Total Hb levels were positively correlated with plasma vitamin C levels (Pearson $r = 0.33$, $p < 0.004$).

Effects of Vitamin C and Other Variables on Hb Levels

Using stepwise regression, we examined for influence on Hb of age, time on PD, TSAT, high-sensitivity CRP (hs-CRP), ferritin, residual renal function, $\log_{10}$(EPO) dose, and plasma vitamin C. In the regression, vitamin C level was the only factor to significantly affect Hb level (Table 3).

Vitamin C in Peritoneal Dialysate

We selected 9 patients at random to collect PD fluid for vitamin C analysis. Vitamin C was determined in a 24-hour PD fluid collection, as described in the Methods. The volume of PD fluid varied from 10 to 20 L for each patient. The total amount of vitamin C measured in the PD fluid ranged from 8 to 300 mg (average 45 mg). Four patients had 40 mg or more of vitamin C in the PD fluid. The data were analyzed by a nonparametric regression (Spearman) based on ranks; the results are shown in Figure 3. The correlation coefficient by nonpara-metric analysis was $r = 0.85$, $p < 0.01$.

Discussion

This population of patients on PD shows a highly skewed distribution of plasma vitamin C (Figure 1). This same pattern has been observed in our previous studies of HD patients (9).

Our findings indicate that plasma vitamin C is associated with higher Hb level in patients on long-term PD ($r = 0.33$, $p < 0.004$; Figure 2). In stepwise multiple regression, we examined the relation of Hb levels to iron indicators (ferritin and TSAT), clinical variables (age, dialysis vintage, and residual renal function), inflammation (hs-CRP), $\log_{10}$(EPO) dose, and vitamin C. In the regression, vitamin C was the only variable to achieve significance.

The ability of vitamin C to support Hb production can be linked to effects of vitamin C on the metabolism of iron. The restriction of iron delivery from the tissues for erythropoiesis has been documented as a common feature of patients with renal disease and is frequently manifested as hypochromic reticulocytes or hypochromic red blood cells (31–33). Vitamin C could improve red cell production by mobilizing storage iron, including especially that portion of tissue iron that accumulates as hemosid-erin (2).

Another effect of vitamin C may be on the absorption of dietary iron, which was the predominant source of iron in these patients. Iron salts are absorbed more efficiently in the presence of dietary vitamin C, as was demonstrated in a recent study evaluating ascorbate effects on iron absorption (8). In that study (8), co-administration of an excess of vitamin C with ferrous fumarate was able to bring about 10% absorption of inorganic iron, a very large percentage compared to the normal absorption range of 2% – 4%. Although 10 patients (of a

total of 56) in the present study had received IV iron, there was no association between IV iron dose and achieved Hb level.

Plasma vitamin C levels in the present patient group could not be explained by dietary evaluation. In 23 patients where diet history was obtained, vitamin C intake ranged from 60 to 400 mg/day and included vitamin C from prescribed vitamin supplements. (All patients were prescribed a supplement containing 60 – 100 mg vitamin C/day and additional dietary vitamin C was obtained from food sources.) However, we could not establish a relation between dietary intake and plasma levels. Patients in this cohort did not report taking high-vitamin C supplements. Potassium restriction was not a general feature of this group of patients and they were usually allowed free access to fruits and vegetables. The reason for the variation in plasma vitamin C levels in patients is not clear. Low dietary vitamin C intake or poor compliance with supplemental vitamins may play a role.

Vitamin C has a low molecular weight and will freely diffuse into the dialysate. There may be significant losses into the dialysate: several patients lost 40 mg or more of vitamin C in their dialysate daily (Figure 3). Losses of this magnitude during PD treatment have been reported previously (16) and are a contributing factor in low plasma levels of vitamin C. But losses during PD treatment cannot fully account for low plasma levels, since losses in the dialysate decrease as plasma levels decline (Figure 3). Internal catabolism as a result other health problems may be a factor. Low vitamin C levels have been noted in a variety of other patients with major illnesses (34–36), in whom large dietary supplements were usually needed to return vitamin C to normal levels consistent with increased catabolism. In studies with HD patients (Handelman, Levin, and Kotanko, in preparation) we have observed that even patients that take substantial vitamin C supplements (500 mg/day) can have plasma vitamin C in the range of 10 – 20 μmol/L, which is below the limit of normal values in the non end-stage renal disease population.

Vitamin C is generally well absorbed into the mucosa of the small intestine but might be degraded from its interaction with elevated iron stored in the intestinal cells of end-stage renal disease patients (37,38). Upon contact with these iron deposits, vitamin C could be degraded to dehydroascorbate and diketogulonate and excreted in the stool. This degradation upon contact with stored mucosal iron could also lead to lower plasma vitamin C levels despite adequate dietary intake.

Our results justify investigation of the relation between plasma vitamin C and iron parameters (total Hb, reticulocyte Hb, ferritin, and TSAT) since vitamin C may mobilize storage iron for erythropoiesis. However, until the risks of hyperoxalemia can be addressed, we do not recommend vitamin C supplementation beyond current clinical guidelines.

We are planning an intervention with those patients with low plasma vitamin C who do not achieve clinical hemoglobin target levels, with the goal of testing the hypothesis that increased intake will lead to better achievement of hemoglobin levels and corresponding reduction in EPO requirements.

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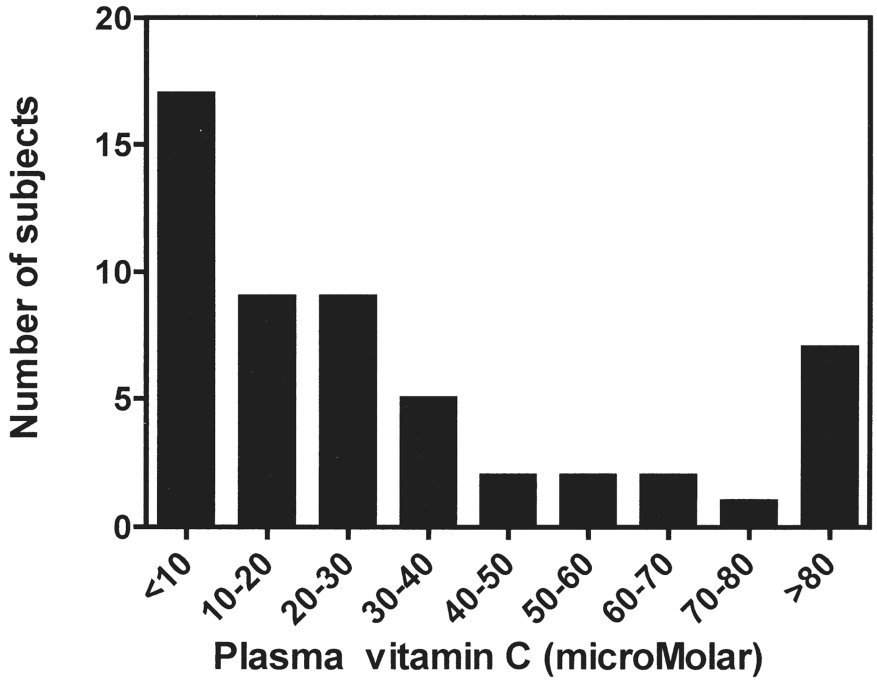

Figure 1.
Distribution of plasma vitamin C levels in 56 peritoneal dialysis patients.

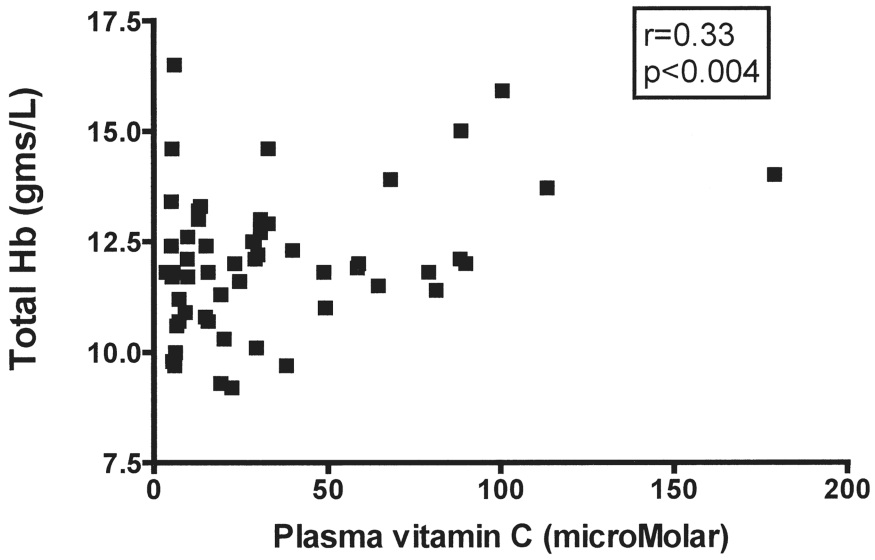

Figure 2.
Total hemoglobin in relation to plasma vitamin C levels.

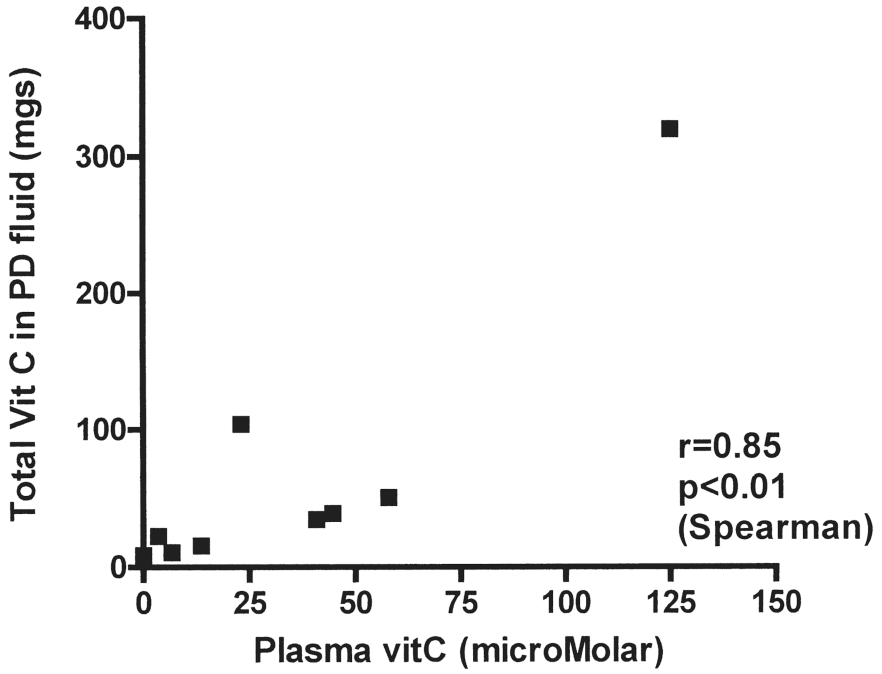

Figure 3.
Vitamin C in 24-hour peritoneal dialysate collections from 9 patients, in relation to plasma vitamin C. Spearman correlation, based on ranks. PD = peritoneal dialysis.

Table 1

Patient Characteristics

Gender	24 female/32 male
Age	57±16 years
Race (*n*)	
Caucasian	32
Black	22
Asian	2
Body mass index	29±8
Time on dialysis	
Average	28 months
Range	1–240 months
Weekly Kt/V	2.25±0.52

Table 2

Hematology Indicators

Hemoglobin	12.0±1.5 g/dL
Hematocrit	36.2%±4.5%
EPO dose	16 300±10 600 units/week
Ferritin	212±190 μg/L
TSAT	26.8%±10.3%

EPO = erythropoietin; TSAT = transferrin saturation.

Table 3

Stepwise Regression: Vitamin C And Other Variables' Effects On Hemoglobin

Variable	B	SE	Beta	T	*p* Value
(Constant)	13.163	1.730		7.609	0.000
Age (by decade)	−0.012	0.135	−0.014	−0.092	0.927
Dialysis vintage	0.047	0.074	0.098	0.629	0.533
TSAT	0.013	0.020	0.096	0.648	0.521
hs-CRP	0.006	0.006	0.165	1.129	0.266
Ferritin	−0.143	0.111	−0.213	−1.281	0.208
RRF	0.711	0.441	0.241	1.611	0.116
Log_{10}(EPO)	−1.042	0.630	−0.248	−1.654	0.107
Plasma vitamin C	0.017	0.006	0.420	2.876	0.007

TSAT = transferrin saturation; hs-CRP = high-sensitivity C-reactive protein; RRF = residual renal function; EPO = erythropoietin.