

Original article

Hypovitaminosis C in hospitalized patients

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Abstract

Background: In recent years, cases of scurvy have mainly been described in populations at risk. The prevalence and risk factors for hypovitaminosis C among hospitalized patients in a department of internal medicine are largely unknown. **Methods:** We determined serum ascorbic acid level (SAAL) and searched for clinical and biological signs of scurvy in 184 patients hospitalized during a 2-month period. **Results:** The prevalence of hypovitaminosis C (depletion: SAAL < 5 mg/l or deficiency: SAAL < 2 mg/l) was 47.3%. Some 16.9% of the patients had vitamin C deficiency. There was a strong association between hypovitaminosis C and the presence of an acute phase response ($p=0.002$). Other univariate risk factors for vitamin C depletion were male sex ($p=0.02$), being retired ($p=0.037$), and infectious diseases ($p=0.002$). For vitamin C deficiency, the significant univariate risk factors included the same ones found for vitamin C depletion, plus being unemployed ($p=0.003$) and concomitant excessive alcohol and tobacco consumption ($p<0.0001$). Logistic regression showed that being retired ($p=0.015$) and concomitant excessive alcohol and tobacco consumption ($p=0.0003$) were significant independent risk factors. Hemorrhagic syndrome and edema were described more often in patients with vitamin C deficiency than in those with vitamin C depletion or without hypovitaminosis. Clinical signs were more frequent for an ascorbic acid level below 2.5 mg/l. **Conclusion:** Hypovitaminosis C is frequent in hospitalized patients but should be interpreted according to the presence or absence of an acute phase response. The main risk factors are living conditions and excessive alcohol and tobacco consumption.

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Keywords: Vitamin C; Scurvy; Vitamin deficiency; Hypovitaminosis; Acute phase response

1. Introduction

Scurvy has been reported since antiquity and used to constitute a major health problem for long ocean voyages until James Lind showed that this disease could be prevented by eating citrus fruits. In recent years, cases of scurvy have been described in patients at risk due to a peculiar diet and especially in alcoholics, the elderly, men living alone, food faddists, the mentally ill, patients with intestinal diseases who suffer from malabsorption, and those undergoing peritoneal dialysis or hemodialysis. The symptoms of scurvy appear after 1–3 months of absolute

vitamin C deficiency, when the total ascorbic pool drops below 300 mg. Clinical manifestations include a hemorrhagic syndrome due to capillary fragility (purpuric lesions with perifollicular hemorrhage, ecchymosis, intramuscular hemorrhage), stomatologic signs (swollen and bleeding gums), weakness, anorexia, depression, myalgia, arthritis, and edema. Anemia, low serum cholesterol, and albumin are common. The diagnosis is established by clinical findings and a low serum ascorbic acid level (SAAL). Treatment with 1000 mg/day of ascorbic acid is fast and effective [1–10].

Scurvy was still prevalent in the 1990s [2,5–10]. We sought to ascertain the prevalence of hypovitaminosis C in hospitalized patients by conducting a prospective study in a department of internal medicine in the Paris suburbs.

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2. Methods

2.1. Patients

We studied all patients hospitalized in our department between 1 September 1997 and 31 October 1997 ($n=184$) after receiving their oral consent. We noted their living situation (living alone or not), social status (active, retired, unemployed), major medical problem, alcohol and tobacco consumption (excessive alcohol >80 g/day and excessive tobacco = 20 pack/year), and the presence or absence of an acute phase response. We classified patients into seven categories according to their major medical diseases (196 in 184 patients). These included infectious disease, diabetes mellitus, neoplasia, neurological and psychiatric disorders, inflammatory diseases, metabolic disorders (obesity and other endocrinological diseases), and acute phase response (Tables 1, 2). The presence of an acute phase response (APR) was defined as an erythrocyte sedimentation rate above 20 mm and an increase in acute phase reactants (C-reactive protein >10 mg/l and/or fibrinogen >4 g/l) [11]. A systematic search was done for the clinical signs of scurvy [purpuric lesions and/or hemorrhagic syndrome, arthralgia, dry (mouth and eye) syndrome, edema of the legs, gingivitis] by two investigators (BJ, OF). Clinical signs that pointed to a disorder other than scurvy were excluded secondarily. We also searched for biological signs of vitamin C deficiency by measuring hemoglobin, mean corpuscular volume (MCV), cholesterol, and serum albumin level. Within 24 h after admission, serum ascorbic acid level (SAAL) was measured.

Ascorbic acid level determination was done with high-performance liquid chromatography (HPLC) according to Speek's method [12]. Blood samples were rapidly transferred to the laboratory, stored at 4 °C in the dark, quickly pretreated with 5% metaphosphoric acid, centrifuged, and stored at -80 °C until HPLC analyses. The usual values for healthy French men and women ($n=20$) are 5–15 mg/l. According to Johnston's criteria [13], we defined serum ascorbic acid values below 2 mg/l (11.4 μ mol/l) as vitamin C deficiency and values below 5 mg/l (28.4 μ mol/l) as vitamin C depletion. Serum ascorbic acid values below 2 mg/l were defined as constituting a high risk for the development of scurvy [14].

2.2. Statistical analysis

Statistical analysis was performed using SPSS [15] and StatXact [16]. Data were expressed as means \pm S.E.M. and percentages. All means were compared using the Mann–Whitney (M-W) rank-sum test or the Kruskal–Wallis (K-W) nonparametric analysis of variance. After checking the assumption concerning the equality of variances (Levene test), we computed multiple comparisons of means for ascorbic acid using a one-way ANOVA with a post hoc Bonferroni test. The associations were tested in 2×2

cross-tabulations using Fisher's exact test. In the case of larger cross-tabulations, we tested the liaisons by computing Pearson's chi-square or by computing either the exact probability value or the Monte Carlo estimate of the exact probability value [17]. Risk was evaluated according to the prevalence of hypovitaminosis and the strength of the association of hypovitaminosis with epidemiological factors was measured by odds ratios with 95% confidence intervals. We computed stratified odds according to the presence or absence of acute inflammation, and we tested the homogeneity of odds with the Breslow–Day test. Logistic regressions, including all of the predictors (age as quantitative data) and stratified if the heterogeneity was significant, were then performed to identify the significant

Table 1
Characteristics of the 184 patients and their serum ascorbic acid levels

		(%)	Serum ascorbic acid (mg/l)	Comparison of means
			Means \pm S.E.M.	<i>p</i>
<i>Basic characteristics</i>				
20-year age	≤ 35	17.9	5.59 \pm 0.53	0.07
categories	36–55	39.7	6.33 \pm 0.46	
	56–75	26.6	6.00 \pm 0.70	
	>75	15.8	4.12 \pm 0.53	
Cutoff point for age	≤ 71.5	81.52	6.15 \pm 0.34	0.005
	>71.5	18.48	4.03 \pm 0.48	
Sex	M	47.3	4.80 \pm 0.37	0.003
	F	52.7	6.62 \pm 0.43	
Living situation	not alone	76.6	5.88 \pm 0.32	0.18
	living alone	23.4	5.37 \pm 0.71	
Social status	active*	39.1	7.01 \pm 0.42	0.0004
	retired	38.6	4.91 \pm 0.51	
	unemployed	22.3	5.05 \pm 0.56	
Dependence status	without any	69.0	6.20 \pm 0.34	<0.0001
	alcohol	8.20	6.57 \pm 1.37	
	tobacco	13.0	5.73 \pm 0.70	
	A + T [#]	9.80	1.98 \pm 0.52	
<i>Main diseases</i>				
Infectious	–	76.1	6.24 \pm 0.34	0.002
	+	23.9	4.23 \pm 0.50	
Diabetes mellitus	–	78.3	5.73 \pm 0.35	0.39
	+	21.7	5.85 \pm 0.48	
Neoplastic	–	83.7	5.81 \pm 0.32	0.77
	+	16.3	5.50 \pm 0.70	
Neurological and psychiatric	–	89.1	5.82 \pm 0.32	0.82
	+	10.9	5.30 \pm 0.64	
Inflammatory	–	89.1	5.62 \pm 0.31	0.21
	+	10.9	6.92 \pm 1.00	
Metabolism (diabetes excluded)	–	91.8	5.53 \pm 0.31	0.004
	+	8.20	8.35 \pm 0.84	
Acute phase response	–	69.6	6.38 \pm 0.34	<0.0001
	+	30.4	4.33 \pm 0.54	
Total		100.0	5.76 \pm 0.29	

* Active patients were significantly different from retired and unemployed; $p=0.0004$ and 0.03, respectively.

[#] Patients with concomitant excessive alcohol and tobacco consumption were significantly different from those with no dependence, only excessive alcohol consumption or only excessive tobacco consumption ($p=0.0001$, 0.004, and 0.01, respectively).

Table 2
Characteristics of infectious and neoplastic diseases

	<i>n</i>	%
Infectious diseases	44	23.9
HIV	8	4.3
Bronchitis and pneumonia	6	3.3
Pyelonephritis	5	2.7
Septicemia	6	3.3
Hepatitis C	6	3.3
Tuberculosis	5	2.7
Rickettsiosis	1	0.5
Infectious mononucleosis	1	0.5
Infectious diarrhea	2	1.1
Prostatitis	1	0.5
Meningitis	1	0.5
Leishmaniasis	1	0.5
Erysipelas	1	0.5
Neoplastic diseases	30	16.3
Non-Hodgkin's lymphoma	11	5.9
Chronic lymphocytic leukemia	4	2.2
Myeloma	3	1.6
Myelodysplastic syndrome	4	2.2
Lung carcinoma	4	2.2
Pancreatic carcinoma	1	0.5
Larynx carcinoma	1	0.5
Ovarian carcinoma	1	0.5
Ewing sarcoma	1	0.5

and independent risk factors for vitamin C deficiency. All of the predictors were included in the models. We used a chi-squared automatic interaction detection algorithm [18] to determine the cutoff point of SAAL, obtaining two independent samples having the optimum homogeneity with respect to manifestations of scurvy. We used the same method to determine the cutoff point of age with respect to categories of hypovitaminosis. All probabilities were two-sided and a *p* value below 0.05 was considered statistically significant.

3. Results

A total of 184 patients were studied (Tables 1, 2). The prevalence of hypovitaminosis C was 47.3% (87 patients). Thirty-one patients (16.9%) had a SAAL strictly below 2 mg/l (deficiency), 56 (30.4%) between 2 and 5 mg/l (depletion), and 97 (52.7%) equal to or above 5 mg/l (normal). The risk factors for hypovitaminosis are shown in Table 3. The global mean SAAL was 5.76 ± 0.29 mg/l. Comparative analysis (Table 1) showed that mean SAAL was lower in men than in women ($p=0.003$), in patients over 71.5 years than in those below ($p=0.005$), in retired or unemployed patients than in active patients ($p=0.0004$ and 0.032 , respectively), in patients without dependence and with excessive alcohol or tobacco consumption than in those with concomitant alcohol and tobacco consumption ($p=0.0001$, 0.004 , and 0.011 , respectively), in patients with infectious disease ($p=0.002$), and in patients with an acute phase response ($p<0.0001$). The lowest mean SAAL was observed in patients with excessive alcohol and tobacco consumption (1.98 mg/l).

3.1. Predictors of vitamin C depletion (<5 mg/l)

The presence of an acute phase response ($p=0.002$), male sex ($p=0.02$), being retired ($p=0.037$), and infectious disease were significant univariate predictors. The risk attached to infectious disease (OR:12.44) in the presence of an acute phase response was greater than in its absence (OR:1.24; $p=0.019$). Logistic regression in the presence of an acute phase response showed that infectious disease was an independent and significant predictor ($p=0.01$). In the absence of an acute phase response (112 patients), we found no significant univariate or multivariate predictor (Table 3).

Table 3
Risk factors for hypovitaminosis C (mg/l): univariate analysis

		Normal: (SAAL \geq 5) (%)	(2 \leq SAAL < 5) versus normal			(SAAL < 2) versus normal		
			2 \leq SAAL < 5 (%)	OR \pm 95%CI	<i>p</i>	SAAL < 2 (%)	OR \pm 95%CI	<i>p</i>
Sex	female	62.9	25.8	1		11.3	1	
	male	41.4	35.6	2.10 [1.08; 4.10]	0.02	23.0	3.08 [1.33; 7.16]	0.012
Social status	active	69.4	26.4	1		4.2	1	
	unemployed	46.3	31.7	1.80 [0.75; 4.35]	0.25	22.0	7.90 [1.93; 32.32]	0.003
	retired	39.4	33.8	2.26 [1.06; 4.82]	0.037	26.8	11.31 [3.07; 41.61]	<0.0001
Dependence status	no dependence	58.3	31.5	1		10.2	1	
	alcohol	60.0	20.0	0.62 [0.16; 2.41]	0.75	20.0	1.90 [0.45; 7.96]	0.41
	tobacco	50.0	33.3	1.23 [0.47; 3.27]	0.8	16.7	1.90 [0.53; 6.80]	0.3
Infectious status	alcohol + tobacco	11.1	27.8	4.63 [0.86; 24.92]	0.1	61.1	31.31 [6.21; 157.86]	<0.0001
	–	59.3	25.7	1		15.0	1	
Acute phase response	+	31.8	45.5	3.29 [1.50; 7.24]	0.002	22.7	2.82 [1.10; 7.24]	0.036
	–	61.7	25.8	1		12.5	1	
	+	32.1	41.1	3.06 [1.46; 6.40]	0.002	26.8	4.12 [1.72; 9.83]	0.002

SAAL: serum ascorbic acid level.

Table 4
Clinical manifestations according to serum ascorbic acid levels (SAAL)

Clinical manifestations		Serum ascorbic acid (mg/l)	SAAL			<i>p</i>		
			(%)	Means ± S.E.M.	<i>p</i>		Normal (%)	Depletion (%)
Arthralgia	–	78.3	5.77 ± 0.33	0.87	78.4	80.4	74.2	0.83
	+	21.7	5.74 ± 0.64		21.6	19.6	25.8	
Lower limb edema	–	92.4	5.88 ± 0.29	0.04	94.8	94.6	80.6	0.03
	+	7.6	4.34 ± 1.44		5.2	5.4	19.4	
Gingivitis	–	97.3	5.85 ± 0.30	0.04	99.0	96.4	93.5	0.19
	+	2.7	2.40 ± 0.95		1.0	3.6	6.5	
Dry syndrome	–	96.7	5.76 ± 0.29	0.36	97.9	96.4	93.5	0.47
	+	3.3	5.63 ± 2.75		2.1	3.6	6.5	
Hemorrhagic syndrome or purpura	–	94.6	5.91 ± 0.29	0.006	97.9	94.6	83.9	0.01
	+	5.4	3.22 ± 1.57		2.1	5.4	16.1	
Total		100.0	5.76 ± 0.29		100.0	100.0	100.0	

3.2. Predictors of vitamin C deficiency (<2 mg/l)

The presence of an acute phase response ($p=0.002$), male sex ($p=0.012$), being unemployed ($p=0.003$) or retired ($p<0.0001$), concomitant excessive alcohol and tobacco consumption ($p<0.0001$), and infectious disease ($p=0.036$) were significant univariate risk factors (Table 2).

The risk attached to infectious disease was not different in the presence or absence of an acute phase response ($p=0.90$). Logistic regression (including acute phase response) showed that being retired ($p=0.015$) and concomitant excessive alcohol and tobacco consumption ($p=0.0003$) were independent and significant risk factors.

When comparing patients with vitamin C deficiency ($n=31$) with those with depletion ($n=56$), we found that being retired ($p=0.015$) and concomitant excessive alcohol and tobacco consumption ($p=0.002$) were significant uni-

variate risk factors. The presence of an acute phase response was not significant ($p=0.65$). Logistic regression (including an acute phase response) determined the role of concomitant excessive alcohol and tobacco consumption ($p=0.003$) (Table 3).

3.2.1. Clinical manifestations

We searched for associations between clinical or biological signs observed in scurvy and mean SAAL (Table 4). Mean SAAL was lowest (<5 mg/l) in patients who had hemorrhagic syndrome ($p=0.006$), lower limb edema ($p=0.04$), and gingivitis ($p=0.04$). Hemorrhagic syndrome and edema were described more often in patients with vitamin C deficiency (16.1% and 19.4%, respectively) than in depleted patients (5.4% and 5.4%, $p=0.12$ and 0.063 , respectively) and nondepleted ones (2.1% and 5.2%, $p=0.009$ and 0.024 , respectively; Fig. 1).

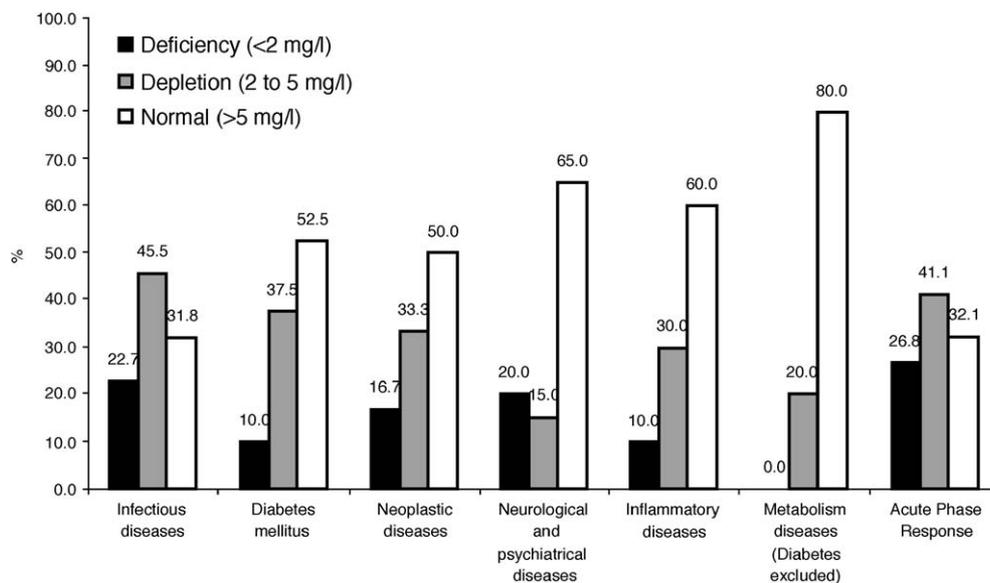


Fig. 1. Serum ascorbic acid levels (SAAL) according to main diseases.

Table 5

Biological data according to serum ascorbic acid levels (SAAL) and acute phase response (APR)

Categories of patients		n	Hemoglobin (g/dl)		Mean corpuscular volume (μ^3)		Albumin (g/l)		Cholesterol (mmol/l)	
			Mean \pm S.E.M.	P	Mean \pm S.E.M.	P	Mean \pm S.E.M.	P	Mean \pm S.E.M.	P
mg/l	SAAL < 2	31	11.55 \pm 0.46	0.03	93.17 \pm 2.13	0.43	36.06 \pm 1.33	< 0.0001	4.07 \pm 0.26	0.02
	2 < SAAL < 5	56	12.29 \pm 0.32		92.93 \pm 1.47		40.07 \pm 0.74		4.49 \pm 0.13	
	SAAL \geq 5	97	12.75 \pm 0.17		93.18 \pm 0.80		42.65 \pm 0.42		4.87 \pm 0.12	
APR	–	128	12.68 \pm 0.18	0.002	93.60 \pm 0.86	0.52	42.02 \pm 0.44	< 0.0001	4.73 \pm 0.097	0.02
	+	56	11.77 \pm 0.28		91.97 \pm 1.26		37.86 \pm 0.86		4.37 \pm 0.18	
Total		184	12.41 \pm 0.16		93.10 \pm 0.71		40.76 \pm 0.42		4.62 \pm 0.088	

Using a classification and regression decision tree, we determined that the SAAL below which the clinical associations of signs were significantly more frequent was 2.5 mg/l; 68.9% of patients (31/45) with a SAAL below 2.5 mg/l had no manifestation of scurvy and 94.2% of patients (131/139) with a SAAL above 2.5 mg/l had no manifestation of scurvy ($p=0.0001$). Hemorrhagic syndrome and edema were not significantly associated with different categories of major medical problems, and there was no association between edema and serum albumin level ($p=0.39$).

3.2.2. Biological results

Biological results analysis (Table 5) showed that hemoglobin ($p=0.03$), serum albumin ($p<0.0001$), and cholesterol level ($p=0.02$) were significantly related to ascorbic acid levels. Mean corpuscular volume (MCV) was not significantly different ($p=0.43$). However, patients who presented an acute phase response had significantly lower hemoglobin ($p=0.002$), albumin ($p<0.0001$), and cholesterol levels ($p=0.02$). In patients who did not have an acute phase response (128 patients), serum albumin differed between those who were depleted ($n=33$, mean 41.3 g/l) and those with deficiencies ($n=16$, mean 37.7 g/l; $p=0.034$), and between patients with deficiencies and those without hypovitaminosis C ($n=79$, mean 43.2 g/l; $p<0.0001$). Mean hemoglobin was lower in patients with deficiencies than in those without hypovitaminosis ($p=0.024$); mean serum cholesterol did not differ between these groups.

4. Discussion

Our study showed a high prevalence of low SAAL (47.3%) in patients hospitalized in a department of internal medicine in the Paris suburbs. Acute diseases, mainly when an acute phase response is present, may produce a temporary decrease in circulating vitamin C [19]. Vitamin C is taken up from plasma by granulocytes [20]. We showed in our study that an acute phase response is a risk factor for a low SAAL ($p=0.002$), but also that an acute phase response accentuates the role, in vitamin C depletion, of commonly associated infectious diseases ($p=0.019$). The problem is knowing whether there is a real hypovitaminosis or a redistribution of vitamin C toward granulocytes. Mea-

surement of leukocyte vitamin C provides a better index of ascorbic acid stores, but it is not usually done. Moreover, in our patients without an acute phase response, hypovitaminosis C was not negligible: 38.28% of patients had a low SAAL.

Our hospital is situated in an area near Paris where the incidence of unemployment and homelessness is greater than in other regions of France. This fact may partly explain this high prevalence. In a study of 1108 non-hospitalized subjects in another Paris suburb (Val de Marne), Hercberg et al. [21] also showed that 5% of women and 12% of men had a SAAL below 2 mg/l (11.4 $\mu\text{mol/l}$); this percentage rose to 15% of women and 20% of men over the age of 65. Surveys from the United Kingdom in the early 1970s reported that more than 50% of elderly people living in their own homes had a SAAL below 2 mg/l (11.4 $\mu\text{mol/l}$) [22]. Johnston and Thompson [13] found 6% of subjects with vitamin C deficiency (<2 mg/l) and 30.4% who were vitamin C depleted (2–5 mg/l) among generally healthy middle-class patients. Our study was conducted in September and October, when it is relatively easy to find fruit and vegetables; the percentage of hypovitaminosis would have been higher if the same study had been done in the winter. A clear seasonal variation in plasma ascorbic acid levels was found in a Finnish study [23]; the highest values were detected in August, September, and April and the lowest in November–January and June.

We found several univariate risk factors that predispose to vitamin C deficiency: male sex, being retired or unemployed, and especially excessive alcohol and tobacco consumption. Previous case reports [9,10] described scurvy in this selected population. Although Johnston and Thompson [13] did not find any variation in vitamin C status according to sex in an outpatient population, Jacob et al. [24] showed in a healthy elderly population that SAAL was higher in females than in males. As for tobacco, Schectman [25] showed that smokers had a threefold higher incidence of low SAAL than nonsmokers and that they should have a daily ascorbic acid intake above 200 mg. However, for Lowik et al. [26], smoking status did not affect the vitamin C blood level in a selected population (elderly women). In our study, we observed that concomitant excessive tobacco and alcohol consumption was associated with hypovitaminosis C, but this was not the case with tobacco alone. We did not show that cancer predisposed to hypovitaminosis C;

however, malnutrition and malabsorption are common in these diseases, and scurvy has been described in patients affected by neoplasia [27]. The low number of patients affected by cancer in our study and the heterogeneity of the same disease at different stages could explain this fact. Deficiency is probably more frequent during the terminal state of these diseases. In our study, diabetes mellitus did not appear to constitute a risk factor either, whereas Cunningham et al. [28] showed that the leukocyte ascorbic content was lower in insulin-dependent diabetic patients, even when consuming adequate dietary vitamin C, and Johnston and Thompson [13] observed that diabetics had significantly lower mean plasma vitamin C concentrations (4.5 ± 1.9 mg/l). The latter was perhaps due to the fact that the study included both insulin-dependent and insulin-independent diabetic patients. In a large population, we showed that clinical manifestations described in scurvy occurred most often when the SAAL was below 2.5 mg/l. This value was comparable to that usually reported (2 mg/l) [13]. Hodges et al. [29], in a study of five patients presenting experimental scurvy, showed that the first signs of scurvy appeared when the plasma ascorbic acid level was between 1.3 and 2.4 mg/l. In our study, vitamin C depletion was frequent but scurvy was rarer. However, vitamin C depletion must be taken into consideration as it is responsible, before the emergence of scurvy, for such deleterious effects as an increased risk of myocardial infarction [30], an increased severity of infection [31,32], and by diminishing the vitamin C antioxidant effect, an increased risk of cancer [33], cataracts [34], and mortality among men [35]. Hemoglobin was lower in depleted and deficient patients, as vitamin C favors iron absorption and folates originate from the same foods as vitamin C. However, when we analyzed the patients without an acute phase response, hemoglobin, like cholesterol, was not different from that in patients with hypovitaminosis. In these same patients without an acute phase response, the serum albumin level was significantly lower in depleted and deficient patients; it was a nonspecific sign but a stigma of global malnutrition and not secondary to an acute phase response.

Although our study showed that SAAL was frequently low in hospitalized patients, this result should be interpreted according to the presence or absence of an acute phase response. Nonetheless, a low SAAL was observed in patients without an acute phase response, and in this case, this low level was associated with living conditions and excessive alcohol and tobacco consumption.

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