Vitamin E Status in Patients With Liver Cirrhosis: Normal or Deficient?

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The study aim was to compare the ratio of vitamin E to serum cholesterol with the serum vitamin E level alone as a measure of vitamin E status in patients with different degrees of liver dysfunction. Assessment of serum vitamin E and total serum cholesterol was performed in 85 patients with liver cirrhosis at Child's stage A (n = 26), B (n = 26), and C (n = 33) and 50 patients with noncirrhotic liver disease. As surrogate markers of liver function, 7α-hydroxycholesterol and prealbumin concentrations and the plasma prothrombin time were determined. Mean serum vitamin E concentrations in Child A, B, and C patients were 27.4%, 36.9%, and 37.3% lower, respectively, than in healthy controls ($P < .01$). Twelve of 26 Child A, 14 of 26 Child B, and 14 of 33 Child C patients had vitamin E deficiency with respect to the absolute values, ie, serum levels less than 13.76 μmol/L (5% percentile of healthy controls). In contrast, only two of 26 Child A, five of 26 Child B, and five of 33 Child C patients ($P < .01$ for Child A/B and $P < .05$ for Child C) were vitamin E–deficient according to the serum vitamin E to cholesterol ratio, ie, less than 2.86 μmol/mmol. Serum vitamin E was correlated significantly with prealbumin, 7α-hydroxycholesterol, and the plasma prothrombin time, but the vitamin E to cholesterol ratio was not. Correcting serum vitamin E for total serum cholesterol in patients with liver cirrhosis leads to the phenomenon of reduced serum vitamin E levels inadvertently shifted toward normal values. In patients with liver cirrhosis, the absolute vitamin E concentration correlates better with the typical clinical and biochemical findings of the disease than the vitamin E to cholesterol ratio. Therefore, a considerable number of patients with advanced liver cirrhosis might actually be vitamin E–deficient.

VITAMIN E SPECIES (ie, α-, β-, δ-, and γ-tocopherol and tocotrienols) act as important lipid-soluble antioxidants in cell membranes by inhibiting lipid peroxidation and subsequent free-radical chain reactions.[1,2] Although γ-tocopherol is the predominant vitamin E form in the human diet, α-tocopherol accounts for about 90% of the vitamin E found in tissues. Therefore, in this study, the term vitamin E generally refers to α-tocopherol. Vitamin E deficiency, rarely found in healthy humans, is characterized by neurological symptoms, eg, spinocerebellar ataxia, posterior column dysfunction and peripheral neuropathy, muscular dystrophy, and increased erythrocyte hemolysis. These symptoms, along with low vitamin E status, were observed in patients with chronic cholestatic liver disease, cystic fibrosis, abetalipoproteinemia, or ileal resection.[3-7] Vitamin E status in humans depends on the amount of intake, absorption, intrinsic consumption (owing to oxidative stress), and excretion of the vitamin. Hepatic tocopherol binding protein has been identified as a genetically determined sentinel of serum vitamin E concentrations.[6] The protein preferentially incorporates α-tocopherol and—with much less affinity—γ-tocopherol into nascent very–low-density lipoprotein (VLDL). After catabolism of VLDL to low-density lipoprotein (LDL), most of the vitamin E is delivered to the peripheral cells mainly via the LDL receptor.[1] Vitamin E in serum declines progressively with increasingly impaired liver function.[8-15] On the other hand, serum concentrations of vitamin E correlate with the concentrations of serum lipids such as cholesterol, triglycerides, and/or phospholipids.[7,8,16-19] This is the reason that several investigators recommend the ratio of vitamin E to cholesterol or vitamin E to total lipids as a better reflection of an individual's vitamin E status.[5,8-10,19-21] This proposal was corroborated by measuring erythrocyte hemolysis after exposing erythrocytes to different dilutions of hydrogen peroxide and relating the degree of hemolysis to the vitamin E concentration and to the vitamin E to lipid ratio.[7,22] However, the hemolysis assay is not useful for assessing vitamin E status in cirrhotics, since it has been shown that erythrocyte resistance to hemolysis was even increased, owing to changes in membrane lipid composition in patients with alcoholic cirrhosis.[23]

Hepatic fibrosis is a common response to chronic inflammation or intoxication caused by viral infection, autoimmune disorders, transition metal overload, or alcohol abuse; in almost all instances, liver cirrhosis is the sequela. Hepatic lipid peroxidation accelerates progression to cirrhosis by activating hepatic stellate cells to increase the production of extracellular matrix proteins.[24-29] In turn, vitamin E effectively interferes with the molecular mechanisms of fibrosis.[30-33] Hence, liver fibrosis may exacerbate under conditions of decreased vitamin E availability. Partially, these effects may be mediated even beyond the antioxidant function of vitamin E.[34] Moreover, some investigators today consider the use of tocopherols to counteract hepatofibrosclerosis in progressive liver disease.[9,35-37]

While correcting vitamin E levels for lipid and cholesterol concentrations has proven useful in healthy individuals and in hyperlipidemic states, eg, nonparenchymal cholestatic liver disease,[5] it is not clear whether this correction makes sense when parenchymal liver cirrhosis is present and both vitamin E and lipids[38] decline with decreasing liver function. Therefore, we compared the incidence of vitamin E deficiency in patients with liver cirrhosis, with either the absolute serum concentration or the vitamin E to cholesterol ratio as the basis. We further investigated whether serum vitamin E correlates with parameters that reflect liver (dys)function, ie, serum bilirubin, 7α-hydroxycholesterol,[39] and prealbumin concentrations[40] and the

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plasma prothrombin time, and if so, whether these correlations hold true if the vitamin E to cholesterol ratio is applied.

SUBJECTS AND METHODS

Subjects

The study group consisted of 144 consecutive patients with liver disease. The patients were treated at the Department of General Internal Medicine at the University of Bonn in 1996 for complications of liver disease (variceal bleeding, ascites, and/or encephalopathy) or for elective diagnostic and therapeutic measures such as insertion of a transjugular intrahepatic portosystemic shunt or upper gastrointestinal endoscopy. Eighty-five patients had cirrhosis of the liver (histologically proven, n = 45; according to laboratory, clinical, endoscopic, and ultrasound signs, n = 40) and were classified into three groups, A (n = 26), B (n = 26), and C (n = 33), according to the Child-Pugh classification system.[41] The Child-Pugh classification system is commonly used to estimate the severity of liver cirrhosis based on biochemical serum parameters (bilirubin, albumin, and prothrombin time) and clinical parameters (degree of hepatic encephalopathy or ascites). Fifty patients with chronic liver disease but without histological (n = 40) and/or biochemical (n = 10) evidence of liver cirrhosis (chronic hepatitis B, n = 5; chronic hepatitis C, n = 30; alcoholic liver disease, n = 7; cryptogenic/autoimmune hepatitis, n = 6; hemochromatosis, n = 1; Wilson's disease, n = 1) were designated as disease controls. The group of healthy controls consisted of 48 subjects without clinical or biochemical evidence of liver disease with a median age of 43.3 years (range, 24 to 64; 33 males and 15 females). None of the patients or healthy subjects had taken vitamin E supplements during the year before the study. Demographic characteristics of the patients are summarized in Table 1. Informed consent for blood sampling was obtained from all individuals.

Sample Collection

Blood was drawn from patients and healthy individuals after overnight fasting. Serum was obtained by centrifuging the blood samples at 4,000 × *g* for 10 minutes at 4°C. Suitable aliquots were placed in Eppendorf tubes, immersed in liquid nitrogen for 2 minutes, and stored at −20°C. The serum samples were analyzed within 6 months.

Analysis of Serum

The vitamin E concentration in serum was determined by reverse-phase high-performance liquid chromatography with a Nucleosil C_{18} column on Millipore-Waters (Bedford, MA) equipment. Elution was achieved by methanol:water (96:4), detection was made by UV absorption at 294 nm, and quantitation was performed by a standard curve of peak height ratios with retinyl acetate as the internal standard. Values for the serum vitamin E concentration and the serum vitamin E to cholesterol ratio less than the 5% percentile of the group of healthy controls were considered deficient. The prealbumin concentration was determined by nephelometry on an Array 360 photometer (Beckmann, Munich, Germany). Serum cholesterol was determined by a standardized enzymatic method with a commercially available kit from Boehringer (Mannheim, Germany). 7α-Hydroxycholesterol concentrations were determined by gas chromatography–mass spectrometry according to a recently published method.[42] Prothrombin time was assessed on an Electra 1000 C analyzer with a commercial kit from Baxter (Pleasantville, FL). Serum bilirubin concentrations were determined on a Synchron CX 7 analyzer using a commercially available kit supplied by Beckman (Fullerton, CA) in the university core laboratory.

Table 1. Demographic and Clinical Characteristics of the Study Population

Parameter	No Cirrhosis	Liver Cirrhosis		
		Child A	Child B	Child C
Median age, yr (range)	38 (19-71)	54 (36-72)	57 (32-72)	55 (36-66)
No. of subjects (male/female)	50 (31/19)	26 (16/10)	26 (15/11)	33 (20/13)
Chronic hepatitis B	5	4	2	6
Chronic hepatitis C	30	5	5	5
Alcoholic liver disease	7	15	15	17
Cryptogenic cirrhosis	6	1	4	5
Hemochromatosis	1	1	—	—
Wilson's disease	1	—	—	—

Statistical Analyses

All data are reported as the mean (95% confidence interval of the mean) except for the age of the subjects, which is the median and range. One-way ANOVA with Student-Newman-Keuls post hoc adjustment was used for group comparisons, and the Pearsson coefficient for linear regression analysis. Multiple and partial regression analyses were performed to evaluate the colinearity of serum vitamin E concentrations with cholesterol, 7α-hydroxycholesterol, prealbumin, or plasma prothrombin time. The frequencies of vitamin deficiency with respect to the serum vitamin E concentration and the serum vitamin E to serum cholesterol ratio were compared by Fisher's exact test. For all tests, a P value less than .05 was considered statistically significant. The SPSS software package (SPSS, Chicago, IL) was used.

RESULTS

Serum Vitamin E Concentration Versus Serum Vitamin E to Cholesterol Ratio

Serum vitamin E concentrations clearly declined with increased liver dysfunction. However, the decrease was not significant in a multivariate analysis when the vitamin E to cholesterol ratio was considered. The mean serum vitamin E concentration in Child A, B, and C patients was 27.4%, 36.9%, and 37.3% lower, respectively, than in healthy controls (Table 2). Twelve of 26 Child A, 14 of 26 Child B, and 14 of 33 Child C patients were vitamin E–deficient, ie, they had levels lower than 13.77 μmol/L (5% percentile of healthy controls). Only two of 26 Child A, five of 26 Child B, and five of 33 Child C patients ($P < .01$ for Child A/B and $P < .05$ for Child C, respectively) were found to be vitamin E–deficient when the serum vitamin E to serum cholesterol ratio was considered, ie, less than 2.86 μmol/mmol (Figs 1 and 2).

Liver Biosynthesis Capacity

The serum concentrations of prealbumin, total cholesterol, and 7α-hydroxycholesterol and the plasma prothrombin time decreased with an increased severity of liver disease. Notably, the total serum cholesterol level in Child B and C patients was significantly lower than in disease controls and healthy controls (Table 2).

Vitamin E Status in Relation to Parameters of Liver Function

Serum vitamin E was found to be significantly correlated with the Child score, serum albumin, prealbumin, total cholesterol, 7α-hydroxycholesterol, and prothrombin time. These correlations were not found when the vitamin E to cholesterol

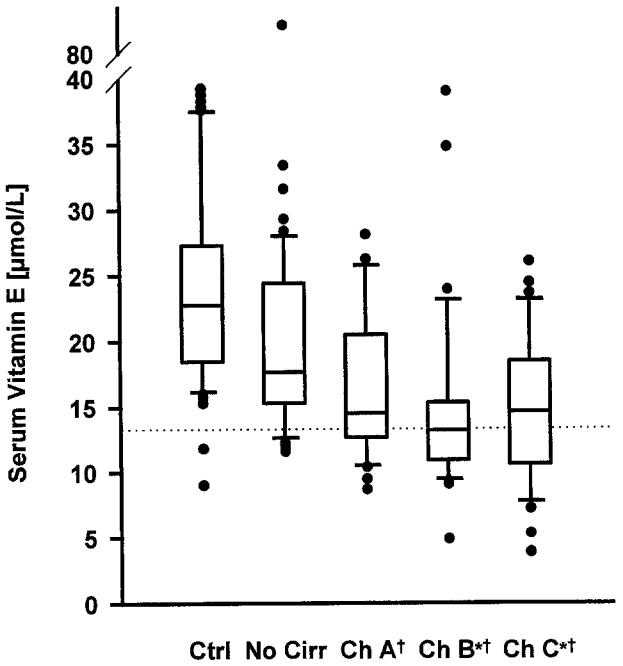

Fig 1. Serum vitamin E levels. The lower boundary of the box indicates the 25th percentile, the line within the box marks the median, and the upper boundary of the box indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles. In addition, the outlying points are graphed. The dotted line indicates the lower threshold (5% percentile of healthy controls) of serum vitamin E concentrations. Child A, B, and C patients (Ch A, Ch B, and Ch C) had significantly lower serum vitamin E levels compared with healthy controls (ctrl). One markedly high outlayer in the no-cirrhosis group (No Cirr) was a patient presenting with Zieve's syndrome and extremely high serum vitamin E and cholesterol concentrations. †Significantly different *v* Ctrl, $P < .05$; *significantly different *v* No Cirr, $P < .05$.

ratio was applied (Table 3). Stepwise multiple regression analysis of vitamin E versus cholesterol, 7α-hydroxycholesterol, and prealbumin in a randomly selected subset of 74 subjects showed that only serum cholesterol levels predicted serum vitamin E concentrations (multiple $r = .76$, $P < .01$; n = 74). Concordantly, the partial correlation of vitamin E and 7α-hydroxycholesterol versus total cholesterol showed that the correlation between vitamin E and 7α-hydroxycholesterol depended entirely on the colinearity of cholesterol and 7α-hydroxycholesterol, whereas 7α-hydroxycholesterol and prealbumin were not independently correlated with serum vitamin E. The correlation between serum vitamin E and total cholesterol is shown in Fig 3.

Correlations Among Parameters of Liver Function

Plasma prothrombin time was significantly correlated with prealbumin ($r = .71$, $P < .001$) and 7α-hydroxycholesterol ($r = .68$, $P < .001$). Serum albumin was significantly correlated with prealbumin ($r = .67$, $P < .001$) and 7α-hydroxycholesterol ($r = .56$, $P < .001$). Total serum cholesterol was significantly correlated with prealbumin ($r = .57$, $P < .001$) and 7α-hydroxycholesterol ($r = .68$, $P < .001$). There was a strong correlation between prealbumin and 7α-hydroxycholesterol ($r = .77$, $P < .001$).

DISCUSSION

The present study indicates that correcting serum vitamin E for total serum cholesterol in patients with liver cirrhosis leads to the phenomenon that decreased serum vitamin E levels are significantly increased toward normal. A novel aspect of this survey concerning the basic debate as to the best way to evaluate the effective vitamin E status in humans is that the difference between the two methods of expression, ie, absolute vitamin E concentration versus vitamin E to cholesterol ratio, proved to be statistically significant. Hence, a considerable number of liver cirrhosis patients who might benefit from vitamin E supplementation may be inadvertently judged to be not vitamin E–deficient. Some investigators state that a decreased liver synthesis capacity cannot account for vitamin E deficiency because tocopherols are vitamins.[9] This should be reconsidered, since we found significant correlations between parameters of liver function and serum vitamin E concentrations. These correlations were lost if the vitamin E to cholesterol ratio was applied, supporting the view that liver dysfunction, reflected in the impairment of lipoprotein, bile acid, and synthesis of tocopherol binding protein (not studied), actively influences the vitamin E status in healthy individuals and cirrhotics.

Advanced liver cirrhosis is characterized by multilevel impairment of almost all synthetic and metabolic functions, including the synthesis of apolipoproteins and the assembly of nascent VLDL. The view that lipoprotein synthesis has a major role in governing serum vitamin E levels is further supported by

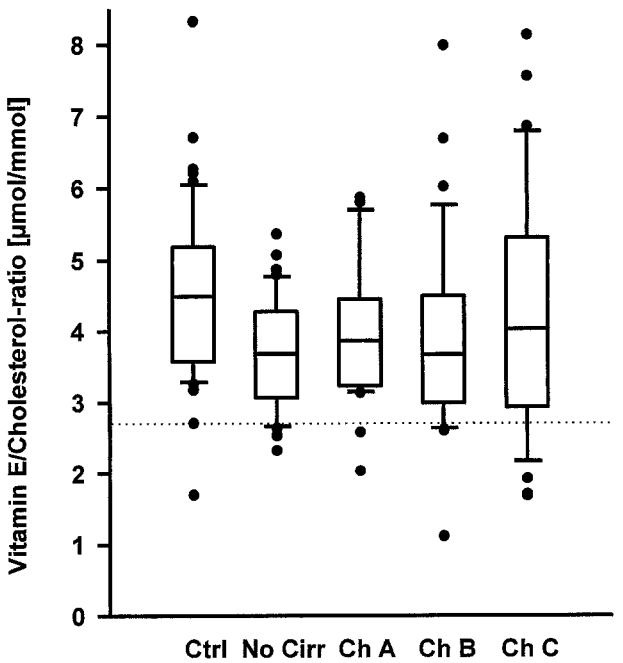

Fig 2. Vitamin E to cholesterol ratio. The dotted line indicates the lower threshold (5% percentile of healthy controls) of serum vitamin E concentrations. There were no longer significant differences between the 5 groups following cholesterol adjustment.

Table 2. Serum Vitamin E, Vitamin E to Cholesterol Ratio, and Parameters of Liver Function

	Healthy Controls			No Cirrhosis			Liver Cirrhosis								
							Child A			Child B			Child C		
Parameter	No.	Mean	95% CI	No.	Mean	95% CI	No.	Mean	95% CI	No.	Mean	95% CI	No.	Mean	95% CI
Vitamin E (μmol/L)	48	23.6	21.6-25.5	50	20.6	17.9-23.7	26	17.3†	14.4-20.2	26	14.8*†	12.1-17.6	33	14.7*†	12.8-16.7
Vitamin E/cholesterol ratio (μmol/mmol)	48	4.6	4.2-4.9	50	3.7	3.5-3.9	26	3.91	3.6-4.4	26	3.9	3.5-4.6	33	4.3	3.7-4.9
Total cholesterol (mmol/L)	48	5.3	5-5.5	50	5.5	4.8-6.4	26	4.7	3.3-6.3	26	3.8*	3.3-4.4	33	3.7*	3.2-4.2
Prealbumin (mg/dL)	22	27	24-29	27	21.7†	19.5-23.8	17	12.6*‡	10-15.1	23	8.8*‡	7.4-10.2	29	8.2*‡	8.8-14.6
7α-Hydroxycholesterol (mg/dL)	12	50	38-61	18	70.8†	58-83.3	14	28*	19.3-36.8	14	23.6*	14.5-32.7	18	19.1*	15.1-23
Bilirubin (μmol/L)	21	12	8.6-15.4	50	27.4	17.1-37.6	26	20.5	15.4-23.9	26	44.5*	29.1-61.6	33	83.8*	54.7-88.9
Prothrombin time (fraction of 1.0)	32	1.04	1-1.09	50	1.06	1-1.1	26	0.86*	0.79-0.93	26	0.70*	0.63-0.78	33	0.59*	0.53-0.64

NOTE. The number of cases varies due to the availability of suitable samples.
*$P < .05$ *v* healthy controls and no cirrhosis.
†$P < .05$ *v* healthy controls.
‡$P < .05$ *v* no cirrhosis.

the stepwise multiple regression analysis of serum vitamin E with 7α-hydroxycholesterol, prealbumin, and cholesterol concentrations in our patients. It clearly showed that only serum cholesterol was independently correlated with serum vitamin E.

In this regard, a study involving 15 individuals (13 children and two adults) with inherited cholestatic disorders, eg, extrahepatic biliary atresia, neonatal intrahepatic cholestasis, α_1-antitrypsin deficiency, biliary cirrhosis, and arteriohepatic dysplasia, is frequently cited.[5] Three of the children showed symptoms of vitamin E deficiency despite normal serum vitamin E concentrations; notably, lipid levels were elevated as a feature of their inherited diseases. Hence, the investigators postulated that low serum concentrations of vitamin E generally reflect deficiency, provided that the levels of circulating lipoproteins are not decreased. In turn, this would mean that patients with liver cirrhosis and both low serum cholesterol and low serum vitamin E would no longer be considered vitamin E–deficient. We believe that the absolute serum concentration better describes an individual's vitamin E status than the vitamin E to cholesterol ratio, when lipoprotein synthesis deteriorates during progressive liver cirrhosis. We also emphasize that we studied adult patients with parenchymal liver disease (viral, autoimmune, or toxic), in whom the alterations of lipid metabolism are different from those found in children with inherited cholestatic disorders.[5,20] Since the principal biological action of vitamin E is antioxidant, the most concise expression of its status may be a relative one, ie, the vitamin E amount per oxidative hits per unit of time.

One might argue that it is preferable to determine tissue vitamin E levels. However, data from the literature show that there is only a weak correlation between serum or red blood cell concentrations and vitamin E levels in liver tissue.[8,12,43] In particular, the vitamin E to lipid ratio in serum did not correlate with the vitamin E content in liver tissue.[43] Most recently, Nagita and Ando[43] suggested that the hepatic vitamin E to lipid ratio describes the liver vitamin E content; however, only 17 of

Table 3. Comparison of the Correlation of Serum Vitamin E and the Vitamin E to Cholesterol Ratio With Parameters of Liver Function

	Vitamin E			Vitamin E to Cholesterol Ratio		
Parameter	No.	*r*	*P*	No.	*r*	*P*
Prealbumin	118	.47	<.001	118	.038	NS (.7)
Total cholesterol	183	.76	<.001	183	−.18	.017
7α-Hydroxycholesterol	74	.57	<.001	74	−.08	NS (.5)
Bilirubin	156	−.08	NS (.29)	156	.04	NS (.6)
Prothrombin time	167	.20	.017	167	−.24	.009
Child points	183	.30	<.001	183	.1	NS (.2)

NOTE. Data include healthy controls, disease controls, and Child A, B, and C patients. The number of cases varies with the availability of suitable samples for assessment of the respective parameters. Five Child points were allocated to healthy controls and to patients from the no cirrhosis group to perform regression analyses.

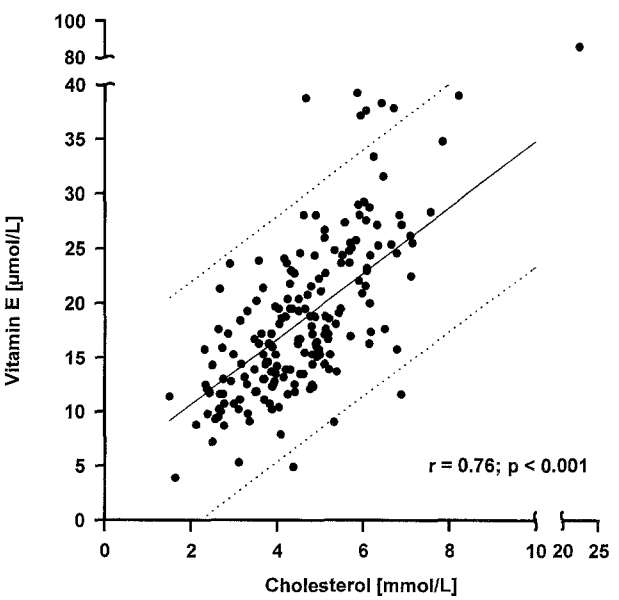

Fig 3. Linear regression between serum vitamin E and cholesterol concentrations for all 5 groups studied. Dotted lines indicate the 95% prediction interval, ie, the confidence interval for the population that describes the range of values that will occur a percentage of the time for repeated measurements.

66 patients with liver disease had liver cirrhosis, and Child's stage was not indicated. These observations confirm our study and others showing that the serum cholesterol level and total lipid concentration in the liver tissue of cirrhotics decrease.[8,12,44,45] Thus, the question as to whether there is a relative hepatic vitamin E deficiency in progressive cirrhosis is still open. Furthermore, it is important to determine whether and to what extent the hepatic vitamin E content is increased by daily vitamin E supplementation.

The intake of vitamin E in alcoholic liver cirrhotics may be low owing to their life-style. However, this can only partially explain the low vitamin E levels in these patients, since vitamin E stores last for several years and only a long period of dietary deprivation will deplete them.[8,46] A further mechanism might be an impaired absorption of vitamin E, which requires a luminal bile salt concentration that allows the formation of micelles. In our patients, serum vitamin E appeared to be closely correlated with the serum level of 7α-hydroxycholesterol. Using the fecal balance method, Hahn et al[42] have shown that a low serum concentration of 7α-hydroxycholesterol adequately predicts impairment of de novo synthesis of bile acids. Low bile acid synthesis in patients with cholestatic liver disease[47] leads to vitamin E malabsorption.[11] This may also be the case in the patients of the present study at Child stages B and C who have both low serum vitamin E and low 7α-hydroxycholesterol concentrations.

The consequence of misinterpreting vitamin E status in cirrhotics with low serum lipids has not yet been sufficiently discussed considering the potential of vitamin E to counteract hepatic fibrosis.[24,26-30,37] In patients with alcoholic liver cirrhosis, plasma lipid peroxides were elevated and the vitamin E concentration was reduced, a condition that is likely to increase oxidative stress.[48] An overt antioxidant (eg, vitamin E) deficiency may lead to a faster progression of cirrhosis to end-stage liver failure by creating a permissive milieu for fibrotic processes.[24,25,34,49] To prevent this, it might be effective to supplement patients with chronic liver disease with antioxidants such as vitamin E species to counteract pro-oxidative conditions. However, in a placebo-controlled trial in alcoholics with decompensated cirrhosis, vitamin E treatment (500 mg/d orally for 1 year) did not lead to a better outcome in comparison to the control group.[35]

It might also be of interest to investigate serum γ-tocopherol concentrations in cirrhotics. γ-Tocopherol, accounting for only 10% of total tocopherols in tissue, has a unique chemistry, since it quenches the toxic metabolite peroxynitrite.[50] The latter might be increasingly formed during cirrhosis by the reaction of nitric oxide (NO) with the superoxide anion, and it is known that NO generation is often increased in patients with advanced liver cirrhosis.

In conclusion, our data show that in patients with liver cirrhosis, the absolute vitamin E concentration correlates better with the typical clinical and biochemical findings of the disease than the vitamin E to cholesterol ratio. We furthermore emphasize that in recently published in vitro and animal studies showing that vitamin E protects against fibrosclerosis induced by various challenges, the results were presented by relating this effect to the absolute vitamin E level in the respective experimental condition.[26,29-31,33,37] Therefore, it might be better not to use a strict lipid adjustment to assess the effective vitamin E status in normolipidemic and hypolipidemic patients with parenchymal liver cirrhosis.

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