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Vitamin E Treatment in Patients with Nonalcoholic Steatohepatitis: A Six-Month, Open-Label Study of Sixteen Patients

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ABSTRACT

Background: Free radicals have a pivotal role in the pathogenesis of nonalcoholic steatohepatitis (NASH). Decreasing oxidative stress might have beneficial effects on the biochemical and histologic progression of this disease.

Objective: We aimed to determine the therapeutic effect of vitamin E, a potent antioxidant, on liver enzymes and histology in NASH.

Methods: This 6-month, open-label study was conducted at the Departments of Gastroenterology and Pathology, Gazi University School of Medicine (Ankara, Turkey). Patients aged 18 to 70 years with biopsy-proven NASH were included in the study. All patients received vitamin E 800 U/d in 2 divided doses, orally (capsules) for 6 months. Patients were not advised to change their exercise or dietary habits. Body mass index (BMI) was calculated at months 0 (baseline) and 6. Histologic scoring of steatosis, necroinflammatory grade, and fibrosis stage was performed at 0 and 6 months. Liver enzyme activities (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and gamma-glutamyltransferase [GGT]) were monitored monthly. Control biopsy specimens were obtained at the end of the treatment. All of the liver biopsies were read by a single pathologist (G.A.) who was blinded to the clinical, laboratory, and histopathologic data, as well as the sequence of liver biopsies. Assessments of compliance and tolerability of treatment were performed using a pill count and patient interview, respectively, at the end of each month.

Results: Sixteen patients (12 men, 4 women; mean [SD] age, 45.5 [6.9] years [range, 37–60 years]) were enrolled. All patients completed 6 months of treatment. Mean BMI did not change significantly from baseline. Significant improvements in mean (SD) serum liver enzyme activities were observed at 6 months

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compared with baseline (ALT: 38.6 [16.3] U/L vs 84.8 [22.1] U/L, respectively, $P = 0.001$; AST: 29.8 [15.4] U/L vs 46.0 [16.0] U/L, respectively, $P = 0.001$; ALP: 154.6 [64.1] U/L vs 211.5 [70.4] U/L, respectively, $P = 0.011$; and GGT: 49.8 [38.5] U/L vs 64.7 [54.4] U/L, respectively, $P = 0.002$), as well as in total cholesterol level (176.2 [42.0] mg/dL vs 199.6 [60.6] mg/dL; $P = 0.02$). Posttreatment liver biopsy was available in 13 patients (81%). Significant improvements in the mean (SD) scores of steatosis (1.46 [0.66] vs 2.43 [0.62]; $P = 0.002$) and necroinflammatory grade (0.84 [0.24] vs 1.31 [0.51]; $P = 0.006$) were observed at 6 months compared with baseline, respectively. However, no significant change was noted in the mean (SD) score of fibrosis stage (0.77 [0.33] vs 1.12 [0.59], respectively). None of the patients reported any adverse effects.

Conclusion: In this small, 6-month, open-label study, vitamin E treatment was safe and well tolerated and led to potential biochemical and histologic improvements (except in fibrosis) in patients with NASH. (*Curr Ther Res Clin Exp.* 2004;65:266–277) Copyright © 2004 Excerpta Medica, Inc.

Key words: nonalcoholic steatohepatitis, vitamin E, treatment, antioxidant.

INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is a condition characterized by hepatomegaly, elevated serum aminotransferase activities, and a histologic picture similar to alcoholic hepatitis in the absence of significant consumption of alcohol (typically >20 g/d in women and >40 g/d in men).[1,2] Clinical conditions commonly associated with NASH include obesity, insulin resistance syndromes, and hyperlipidemia.[1,2] Commonly, the disease is noted incidentally, with elevated liver enzyme activities in routine laboratory studies, or with hepatomegaly during examination.[1,2] NASH has been described as a clinically mild disease and a biologically low-grade condition, but a disease that has the potential to progress and evolve into cirrhosis in some patients.[3,4] Progression to cirrhosis is noted in ~5% to 15% of patients.[5–7] This may be an underestimate of its severity because the disorder may underlie many cases of cryptogenic cirrhosis.[8–10]

A 2-hit theory best describes the progression from simple steatosis to NASH. These 2 hits consist of the accumulation of excessive hepatic fat primarily due to insulin resistance, and oxidative stress due to reactive oxygen species (ROS). Mitochondria are the main cellular source of ROS in cases of NASH. In the presence of steatosis, mitochondrial ROS oxidize accumulated hepatic fat, causing lipid peroxidation. Lipid peroxidation causes cell death, which leads to cell necrosis and increases collagen synthesis, which in turn leads to fibrosis. ROS also induce the secretion of cytokines, such as tumor necrosis factor-alpha (TNF-alpha), transforming growth factor-beta (TGF-beta), and interleukin (IL)-8.[11,12]

Gradual and sustained weight loss is the classic therapy for the disease, but rapid weight reduction or starvation may precipitate worsening of NASH.[13] Use

of medications that can directly reduce the severity of liver damage independent of weight loss is a reasonable alternative treatment.[13] For this purpose, various agents, such as bile acids,[14,15] lipid-lowering drugs,[14,16] insulin-sensitizing drugs,[17,18] and antioxidants,[19–23] have been studied in the treatment of NASH.

Because increased oxidative stress, increased lipid peroxidation, and impaired ROS inactivation by antioxidant depletion have a pivotal role in NASH pathogenesis,[11,12] the use of exogenous antioxidants may be beneficial in the treatment of NASH. We aimed to determine the therapeutic effect of vitamin E, a potent and well-tolerated antioxidant, on liver function tests (LFTs) and histology in patients with NASH.

PATIENTS AND METHODS

Patient Selection and Assessment

This study was conducted between February 2001 and November 2002 at the Departments of Gastroenterology and Pathology, Gazi University School of Medicine (Ankara, Turkey). Patients with biopsy-proven NASH were recruited from the gastroenterology outpatient clinic because elevated liver enzyme activities were included in this study. In addition, patients were asked to discontinue any multivitamin preparations or herbal/alternative medicines. Patients were enrolled in this study after a complete clinical history, physical examination (including calculation of body mass index [BMI]), and baseline laboratory investigation (including serum liver enzyme activities and serum lipid levels).

Inclusion criteria were age 18 to 70 years; persistent elevation of aminotransferase activities to $\geq$1.5 times the upper limit of normal for $\geq$3 months; liver histology compatible with the diagnosis of NASH (steatosis plus lobular necroinflammatory activity, regardless of the presence of Mallory hyaline or abnormal fibrosis); and appropriate exclusion of other liver diseases, including alcoholic liver disease, primary biliary cirrhosis, biliary obstruction, autoimmune or viral hepatitis, and metabolic/hereditary liver disease. For this purpose, serum alpha$_1$-antitrypsin, ceruloplasmin, iron, and ferritin levels; total iron-binding capacity; copper and glucose levels; total protein level; albumin level; prothrombin time; complete blood count; and erythrocyte sedimentation rate were assessed. Abdominal sonography was performed to assess liver parenchyma, biliary tree, vascular patency, and the presence of ascites or portal hypertension, and to exclude the possibility of underlying hepatocellular carcinoma. Hepatitis B surface antigen, antibodies against hepatitis C virus (HCV) or undetectable HCV RNA, HIV antibodies, and panels to exclude TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) and Epstein-Barr virus were investigated for the exclusion of viral hepatitis. Autoimmune causes were precluded by assessment of serum levels of anti–smooth muscle antibody, antinuclear antibody, antiliver/kidney microsomal antibody, and antimitochondrial antibody.

Patients with a history of excessive alcohol consumption were excluded. The other exclusion criteria were a history of having received total parenteral nutrition, a history of abdominal surgery, or a history of using drugs known to cause steatohepatitis (eg, valproate sodium, amiodarone, perhexiline maleate, methotrexate sodium, estrogens, tamoxifen citrate, nifedipine, diltiazem hydrochloride, chloroquine hydrochloride, prednisone sodium). Eligible patients had compensated liver disease, serum creatinine concentration <1.5 mg/dL, and normal serum creatine phosphokinase activity and thyroid-stimulating hormone levels. Women who were pregnant, possibly pregnant, planning a pregnancy or breastfeeding were excluded from the study. Patients who had received any prior medical treatment for NASH also were excluded.

All patients provided written informed consent to participate in the study, and the local ethics committee approved the study protocol.

Histologic Assessment

Liver biopsy specimens were collected by 2 of the authors (F.Y. and S.G.) and examined by a pathologist (G.A.) before (month 0 [baseline]) and after 6 months of treatment with vitamin E. Histologic scoring of steatosis, necroinflammatory grade, and fibrosis stage was performed at 0 and 6 months according to the method defined by Brunt et al.[24] Steatosis was graded as follows: 1 = 10% to 30%, 2 = 30% to 70%, 3 = 70% of hepatocytes affected. Necroinflammatory grade and fibrosis stage were scored from 0 to 3 in increasing severity. Each biopsy specimen was analyzed and graded by a single pathologist (G.A.), who was blinded to clinical, laboratory, and histopathologic data; vitamin E supplementation; and liver biopsy sequence.

Treatment and Follow-Up

Patients were given oral vitamin E capsules, 800 U/d in 2 divided doses self-administered for 6 months. Patients were not advised to change their exercise or dietary habits. During the 6-month follow-up period, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT) activities, and levels of total bilirubin (BIL), total cholesterol (TC), and triglyceride (TG) were assessed monthly. Assessments of compliance and tolerability of treatment were performed using pill count and patient interview, respectively, at the end of each month.

Statistical Analysis

Results of the study are expressed as mean (SD). The Wilcoxon signed-rank test was used to compare biochemical and liver biopsy results. $P \leq 0.05$ was considered statistically significant. Data were analyzed with SPSS software version 10.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Sixteen patients (12 men, 4 women) were enrolled. The mean (SD) age of the patients was 45.5 (6.9) years (range, 37–60 years), and the mean (SD) BMI was 26.1 (1.2) kg/m^2 (range, 24.1–30.2 kg/m^2). Two patients had type 2 diabetes mellitus, and 1 of them was undergoing oral antidiabetic (sulfonylurea group) treatment. The laboratory findings and clinical characteristics before and after treatment with vitamin E are shown in **Table I**.

Therapeutic Effect

All patients completed 6 months of treatment. No significant changes occurred in mean (SD) BMI at 6 months compared with baseline (26.0 [1.2] kg/m^2 vs 26.1 [1.2] kg/m^2). At 6 months, significant improvements were found in mean (SD) serum enzyme activities from baseline (ALT: 38.6 [16.3] U/L vs 84.8 [22.1] U/L, respectively, $P = 0.001$; AST: 29.8 [15.4] U/L vs 46.0 [16.0] U/L, respectively, $P = 0.001$; ALP: 154.6 [64.1] U/L vs 211.5 [70.4] U/L, respectively, $P = 0.011$; and GGT: 49.8 [38.5] U/L vs 64.7 [54.4] U/L, respectively, $P = 0.002$), as well as in serum TC level (176.2 [42.0] mg/dL vs 199.6 [60.6] mg/dL, respectively; $P = 0.02$) (Table I, **Table II**, **Figure 1**, and **Figure 2**). All patients had elevated serum ALT activity before treatment. ALT activity returned to normal range (0–40 U/L) in 8 patients (50%) but remained elevated with decreasing levels in the other 8 patients (50%) at the end of the treatment. Nine patients (56%) had elevated AST activity before treatment, which returned to normal range (0–40 U/L) in 7 patients (78%) but remained elevated in 2 patients (22%). No significant changes occurred in serum BIL or TG levels during the treatment period.

Because 3 patients (19%) refused control biopsy, paired liver histologic assessment was available for 13 of 16 patients (81%). The degree of steatosis and necroinflammatory grade decreased significantly but the fibrosis score did not change significantly (**Table III**). Significant improvements in the mean (SD) scores of steatosis (1.46 [0.66] vs 2.43 [0.62]; $P = 0.002$) and necroinflammatory grade (0.84 [0.24] vs 1.31 [0.51]; $P = 0.006$) were observed at 6 months compared with baseline, respectively. However, no significant change was noted in the mean (SD) fibrosis score (0.77 [0.33] vs 1.12 [0.59], respectively). Steatosis score decreased in 11 of 13 patients (85%) and remained unchanged in 2 patients (15%). Necroinflammatory grade score decreased in 9 patients (69%) and remained unchanged in 4 patients (31%). Fibrosis score decreased in only 4 patients (31%) and remained unchanged in 8 patients (62%). Progression in fibrosis stage was noted in 1 patient (8%). **Figure 3** and **Figure 4** show the beneficial effects of vitamin E on liver histology in 1 patient.

Compliance and Tolerability

Vitamin E was well tolerated; none of the patients reported any adverse effects.

Table I. Laboratory findings and clinical characteristics of patients with nonalcoholic steatohepatitis before (month 0) and after (month 6) vitamin E treatment. (Values are expressed as data at 0/6 months.)

	Laboratory Variable (Normal Range)								
Patient No.	ALT, U/L (0–40)	AST, U/L (0–40)	ALP, U/L (53–119)	GGT, U/L (0–50)	BIL, mg/dL (0.2–1.3)	TC, mg/dL (110–200)	TG, mg/dL (50–200)	DM-2	BMI, kg/m^2
1	87/32	35/22	190/191	71/51	0.9/1.0	298/247	217/209	No	26.2/26.2
2	70/52	18/19	176/154	22/24	0.9/1.2	149/154	169/114	No	26.3/25.4
3	96/27	59/25	266/206	43/28	0.5/0.4	211/193	133/178	No	25.4/25.2
4	86/34	32/37	126/155	135/96	0.8/0.7	169/186	324/196	No	26.3/25.9
5	68/43	34/28	200/160	38/26	0.8/1.9	164/188	147/84	No	25.3/25.2
6	89/64	46/36	319/206	80/37	0.7/1.0	238/182	206/145	No	26.1/25.4
7	80/25	43/23	127/87	63/35	0.7/0.8	91/85	179/59	No	26.1/26.0
8	62/17	36/15	125/125	32/28	1.5/1.6	164/160	125/111	No	26.1/26.4
9	91/14	55/17	146/205	28/16	0.9/0.9	153/126	193/213	No	26.2/26.1
10	92/45	51/29	146/72	89/70	0.7/0.9	216/180	167/99	No	26.2/26.1
11	144/58	67/38	234/251	34/18	1.1/1.0	213/215	126/176	No	25.2/25.1
12*	96/58	81/78	316/152	143/41	0.7/0.7	297/172	231/105	Yes	26.4/26.4
13*	63/51	62/42	304/271	176/141	0.6/0.7	197/140	143/92	No	26.1/26.3
14	77/54	39/33	183/74	29/31	1.3/0.7	264/229	139/239	No	24.1/24.2
15	108/22	49/16	290/98	19/29	0.4/0.6	253/224	95/121	No	26.3/26.2
16*	48/23	30/19	237/67	176/126	0.7/0.7	117/139	93/113	Yes	30.2/30.2

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyltransferase; BIL = total bilirubin; TC = total cholesterol; TG = triglycerides; DM-2 = type 2 diabetes mellitus; BMI = body mass index.
*Control liver biopsy was not performed in this patient.

Table II. Biochemical findings in the patients with nonalcoholic steatohepatitis before (month 0) and after (month 6) vitamin E treatment (N = 16). (Values are expressed as mean [SD].)

Biochemistry (Normal Range)	Month 0	Month 6	*P*
ALT, U/L (0–40)	84.8 (22.1)	38.6 (16.3)	0.001
AST, U/L (0–40)	46.0 (16.0)	29.8 (15.4)	0.001
ALP, U/L (53–119)	211.5 (70.4)	154.6 (64.1)	0.011
GGT, U/L (0–50)	64.7 (54.4)	49.8 (38.5)	0.002
BIL, mg/dL (0.2–1.3)	0.8 (0.3)	0.9 (0.4)	NS
TC, mg/dL (110–200)	199.6 (60.6)	176.2 (42.0)	0.02
TG, mg/dL (50–200)	167.9 (58.0)	140.9 (53.7)	NS

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyltransferase; BIL = total bilirubin; NS = nonsignificant; TC = total cholesterol; TG = triglycerides.

DISCUSSION

Treatment of patients with NASH has typically been focused on the management of associated conditions, such as obesity, diabetes mellitus, and hyperlipidemia. Based on the fact that rapid weight loss may worsen the liver disease, pharmacologic therapy with agents that can directly reduce the severity of liver damage independent of weight loss has been a field of interest in the treatment of NASH.[13] Most of these studies were uncontrolled, open-label, and had a duration of ≤1 year,[14–22] and only a few of them[14,18,19,22] assessed the effects of treatment on liver histology.

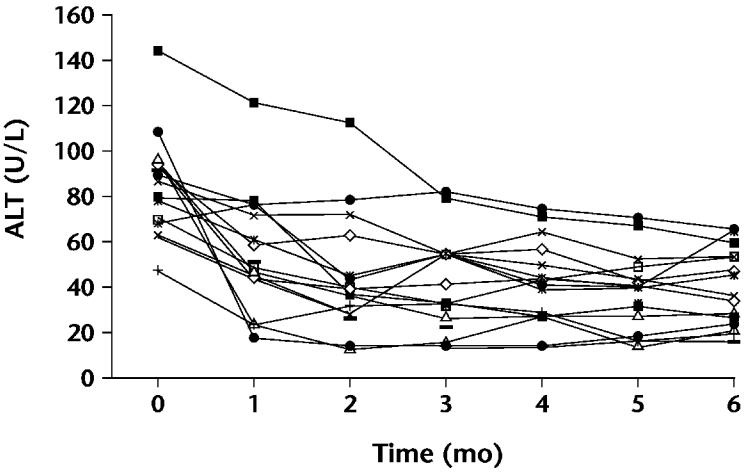

Figure 1. Serum alanine aminotransferase (ALT) activity in each patient during a 6-month treatment period with vitamin E.

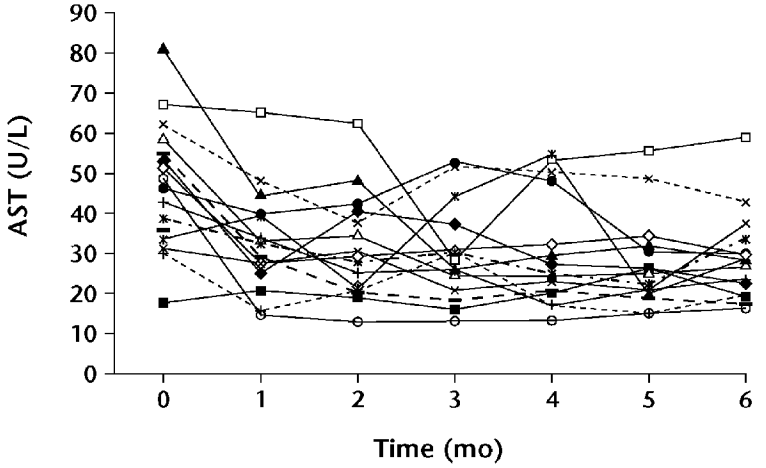

Figure 2. Serum aspartate aminotransferase (AST) activity in each patient during a 6-month treatment period with vitamin E.

Ursodeoxycholic acid (UDCA), a nonhepatotoxic bile acid, has membrane-stabilizing and cytoprotective effects.[25] The effects of UDCA on NASH were assessed in some studies.[14,15] In 1 of these,[14] UDCA (13–15 mg/kg·d) was given to 24 patients for 12 months, and significant improvements in LFTs and in the degree of steatosis were observed (all, $P < 0.05$). In another study,[15] LFTs significantly improved after 6 months of treatment with UDCA (10 mg/kg·d) in 13 patients.

In some studies,[14,16] lipid-lowering drugs have been assessed in the treatment of NASH. Clofibrate was not found to be beneficial,[14] but gemfibrozil was found to have beneficial therapeutic effects in NASH.[16] Two studies have demonstrated that insulin-sensitizing medications, such as metformin[17] and thiazolidinedione derivatives,[18] have beneficial effects in NASH.

Based on the fact that increased oxidative stress and lipid peroxidation have a pivotal role in NASH pathogenesis,[11,12] various antioxidants (eg, betaine anhydrous,[19] *N*-acetylcysteine,[20] vitamin E,[21,22] and probucol[23]) have been ana-

Table III. Histologic scores in patients with nonalcoholic steatohepatitis before (month 0) and after (month 6) vitamin E treatment (N = 16). (Values are expressed as mean [SD].)

Histologic Feature	Month 0	Month 6	*P*
Steatosis*	2.43 (0.62)	1.46 (0.66)	0.002
Necroinflammatory grade†	1.31 (0.51)	0.84 (0.24)	0.006
Fibrosis stage†	1.12 (0.59)	0.77 (0.33)	NS

NS = nonsignificant.
*Steatosis was graded as follows: 1 = 10% to 30%, 2 = 30% to 70%, 3 = >70% of hepatocytes affected.
†Necroinflammatory grade and fibrosis stage were scored from 0 to 3 in increasing severity.

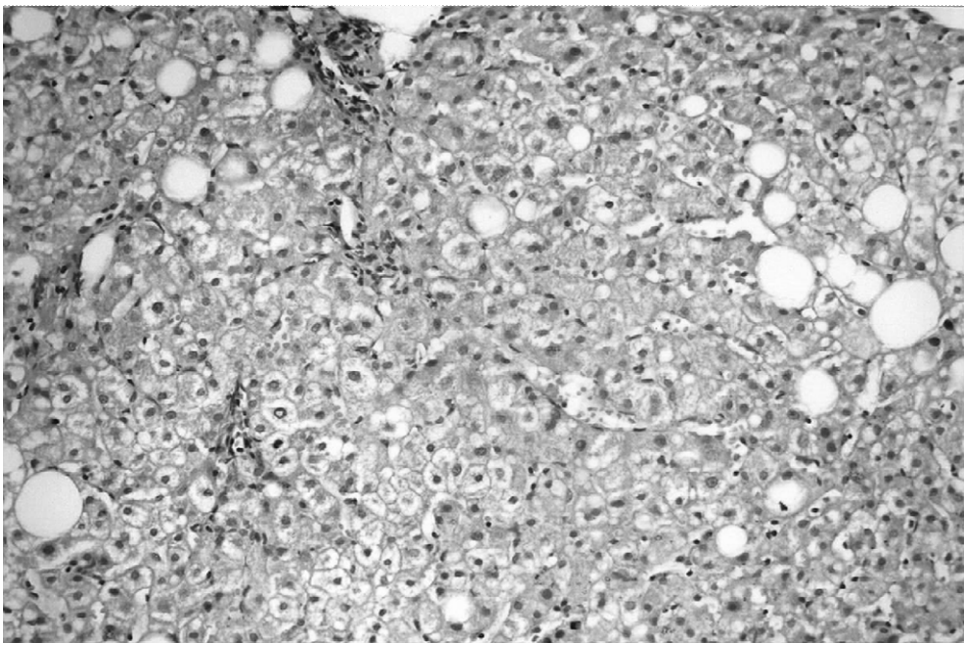

Figure 3. Liver biopsy in a patient before vitamin E therapy, showing steatohepatitis with marked steatosis (hematoxylin and eosin, magnification ×200).

lyzed in small pilot studies, without satisfactory results. Betaine treatment was associated with a significant improvement in serum aminotransferase activities (ALT, $P = 0.007$; AST, $P = 0.02$). Similarly, they found marked improvements in the degree of steatosis, necroinflammatory grade, and fibrosis stage at 1 year of treatment.[19] Another antioxidant, *N*-acetylcysteine, when administered 1 g/d for 3 months, was found to significantly improve aminotransferase activities.[20] Merat et al[23] found that probucol, a potent antioxidant, was effective in decreasing liver enzyme activities.

Vitamin E, a potent and well-tolerated antioxidant, is particularly effective against membrane lipid peroxidation and suppresses TNF-alpha, IL-1, IL-6, and IL-8 expression by monocytes and/or Kupffer cells and inhibits liver collagen alpha-1 gene expression.[26] In a pilot study[21] of 11 pediatric patients, oral vitamin E (400–1200 U/d for 4–10 months) was associated with improved LFTs. However, the potential weakness of that study was a lack of histologic confirmation. In another study,[22] vitamin E at a dosage of 300 mg/d was given for 1 year to 12 patients with NASH. After treatment, LFTs had improved significantly compared with baseline. Likewise, the degrees of steatosis, necroinflammatory grade, and fibrosis stage were improved in 9 patients (75%).

In the present study, significant improvements in LFTs, steatosis, and necroinflammatory grade scores were observed with vitamin E treatment. However,

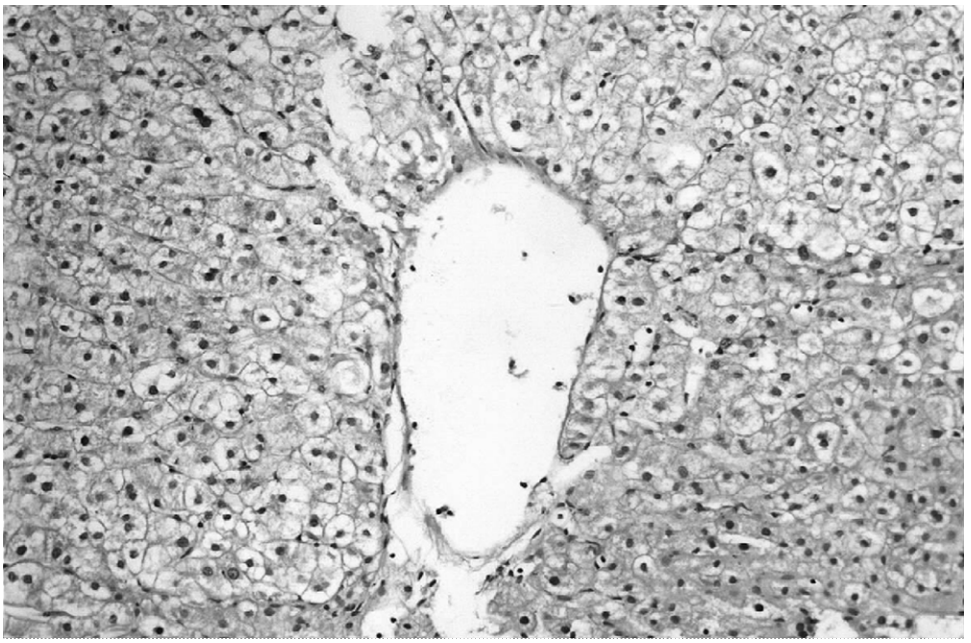

Figure 4. Hydropic degeneration in hepatocytes, loss of steatosis, and reduction of inflammation in the same patient following treatment with vitamin E (hematoxylin and eosin, magnification $\times 200$).

no significant change in fibrosis stage score was noted. Normalization of serum aminotransferase activities may be related to the decreased oxidative stress and the resultant decrease in the inflammatory process. Although vitamin E has antifibrotic properties,[26] the lack of antifibrotic response in our series might be attributable to the short duration of the treatment period. Because the fibrotic process is rather slow and progressive, a longer duration of therapy might be beneficial.

Although our pilot study histologically showed the potential beneficial effect of vitamin E treatment in patients with NASH, the weak points in our study include the open-label design, the small study population, and the short duration of the follow-up period. We believe that vitamin E deserves further assessment in a large-scale, randomized, placebo-controlled study as therapy for patients with NASH.

CONCLUSION

In this small, 6-month, open-label study, vitamin E treatment was safe and well tolerated and led to potential biochemical and histologic improvements (except in fibrosis) in patients with NASH.

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