Turk J Gastroenterol 2005; 16 (3): 124-128

Management of fatty liver disease with vitamin E and C compared to ursodeoxycholic acid treatment

Yağlı karaciğer hastalığının ursodeoksikolik asit ile karşılaştırmalı olarak E ve C vitamini ile tedavisi

Galip ERSÖZ, Fulya GÜNŞAR, Zeki KARASU, Sinan AKAY, Yücel BATUR, Ulus Salih AKARCA

Department of Gastroenterology, Ege University Medical School, Izmir

Background/aims: *Despite a proposed role of oxidative stress in the pathogenesis of nonalcoholic steatohepatitis, antioxidant approaches have not been investigated sufficiently in the therapy of nonalcoholic steatohepatitis. Our aim was to determine whether vitamin E plus C therapy is effective in normalization of liver enzymes compared to ursodeoxycholic acid treatment in patients with fatty liver disease.* ***Methods:*** *This was an open-labeled, prospective, randomized study enrolling patients with histologically proven fatty liver disease who had chronically elevated alanine aminotransferase, despite a three-month reducing diet. Patients consuming alcohol (more than 20 g/day) were excluded. The patients were randomly prescribed either oral vitamin E (600 IU/day) plus vitamin C (500 mg/day) or ursodeoxycholic acid (10 mg/kg/day). Patients were randomized as two groups to receive vitamin E plus vitamin C combination (28 patients, 10 F) or ursodeoxycholic acid treatment (29 patients, 13 F).* ***Results:*** *There was no significant change in body mass index before and after the treatment in both groups. At the end of six months of therapy, serum aspartate aminotransferase and aminotransferase levels significantly decreased in both treatment options. Vitamin E and C combination was more efficacious on serum aminotransferase levels than ursodeoxycholic acid, but the difference was not significant. Alanine aminotransferase decreased to normal levels in 17 of 27 (63%) and in 16 of 29 patients (55%), respectively, in the two groups. Gamma-glutamyl transpeptidase decreased in patients receiving ursodeoxycholic acid, but no change was obtained in the vitamin-treated patients.* ***Conclusions:*** *Vitamin E plus C combination treatment is a safe, inexpensive and effective treatment option in patients with fatty liver disease, with results comparable to those obtained with ursodeoxycholic acid. Since more effective new therapeutic options are lacking, patients with fatty liver disease should be encouraged to take vitamin E and C supplements, which are safe and affordable.*

Key words: Fatty liver, steatohepatitis, vitamin C, vitamin E, ursodeoxycholic acid

Amaç: *Nonalkolik steatohepatit patogenezinde oksidatif stres öne sürülmesine karşın antioksidan tedavi yaklaşımları nonalkolik steatohepatit tedavisinde yeterince araştırılmamıştır. Yağlı karaciğer hastalığında karaciğer enzimlerinin normalleşmesinde vitamin E ve C tedavisinin etkisini ursodeoksikolik asit tedavisi ile karşılaştırarak değerlendirmek amaçlanmıştır.* ***Yöntem:*** *Bu araştırma açık etiketli, prospektif, randomize bir çalışma olup araştırmaya histolojik olarak ispatlanmış yağlı karaciğer hastalığı olan ve 3 aydır zayıflatıcı diyet almasına rağmen ALT yüksekliği sebat eden hastalar dahil edilmiştir. Alkol kullanımı 20gr/gün üzeri olan hastalar çalışma dışı bırakılmıştır. Hastalar vitamin E (600IU/gün) ve vitamin C (500mg/gün) veya ursodeoksikolik asit (10mg/kg/gün) alacak şekilde randomize edildi. Hastalar vitamin E+vitamin C kombinasyonu (28 hasta, 10 kadın) veya ursodeoksikolik asit (29 hasta, 13 kadın) alacak üzere randomize edildi.* ***Bulgular:*** *Her iki grupta vücut kitle indeksinde tedavi öncesi ve sonrası olarak belirgin bir değişiklik saptanmadı. Her iki tedavi grubunda da 6. ayın sonunda AST ve ALT seviyeleri belirgin olarak azaldı. Serum ALT düzeylerinde vitamin E ve C kombinasyon tedavisi ursodeoksikolik asit tedavisine göre daha etkili idi, fakat fark istatiksel olarak anlamlı değildi. Sırası ile ALT'nin normal seviyelere düşmesi 27 hastanın 17'sinde (%63) ve 29 hastanın 16'sında (%55) olmuştur. Ursodeoksikolik asit alan hastalarda GGT azalmış olup vitamin tedavisi alan grupta GGT'de herhangi bir değişiklik olmamıştır.* ***Sonuç:*** *Yağlı karaciğer hastalığında vitamin E ve C kombinasyon tedavisi ursodeoksikolik asite benzer şekilde güvenli, ucuz ve etkili bir seçenektir. Yağlı karaciğer hastalığı olanlar daha etkili yeni tedavi seçenekleri olmadığı için ucuz ve güvenli olan E ve C vitamini preperatlarını almaya teşvik edilmelidir.*

Anahtar kelimeler: Yağlı karaciğer, steatohepatit, vitamin C, vitamin E, ursodeoksikolik asit

Address for correspondence: Fulya GÜNŞAR
Ege University Medical School, Department of Gastroenterology,
35100 Bornova, İzmir, Turkey
Phone: +90 232 388 19 69 • Fax: +90 232 374 57 61
E-mail: fulyagunsar@hotmail.com

Manuscript received: 20.05.2004 **Accepted:** 17.05.2005

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized condition that may progress to end stage liver disease (1, 2). The spectrum of NAFLD is wide and ranges from simple fat accumulation in hepatocytes (fatty liver) without biochemical or histological evidence of inflammation or fibrosis, to fat accumulation plus necroinflammatory activity with or without fibrosis (steatohepatitis), and to the development of advanced liver fibrosis or cirrhosis (cirrhotic stage). Nonalcoholic steatohepatitis (NASH) is believed to be an intermediate stage in the progression from steatosis to cirrhosis. The probability of developing advanced hepatic fibrosis is significantly greater in individuals with steatohepatitis than in those with simple steatosis (3-5).

Because the pathogenesis of NAFLD remains unknown, the management of this condition is empirical. NAFLD may resolve with weight loss, although the benefits of weight loss have been inconsistent (6-9). Since a considerable number of patients with NAFLD are not obese, or do not benefit from weight loss, use of medication that can directly reduce the severity of liver damage independent of weight loss is a reasonable alternative.

In NAFLD, two different pathogenetic mechanisms are thought to lead to steatohepatitis and progressive liver fibrosis from simple steatosis. First, insulin resistance leads to accumulation of fat within the hepatocytes, and second, mitochondrial reactive oxygen radicals cause lipid peroxidation, cytokine induction, and the induction of apoptotic or necrotic signals (10). Despite a proposed role of oxidant stress in the pathogenesis of NAFLD, antioxidant approaches have not been investigated sufficiently in NAFLD therapy (11-13).

Ursodeoxycholic acid (UDCA) is the epimer of chenodeoxycholic acid and appears to replace endogenous bile acids, some of which may be hepatotoxic. UDCA has cytoprotective and immunomodulatory effects. It has been used in the treatment of cholestatic liver disease (autoimmune hepatitis), and its efficacy in patients with NAFLD has been evaluated in several studies (14-16). In these studies, it is reported that UDCA leads to improvement in biochemical tests, but the findings for histological improvements are inconsistent.

Vitamin C and E combination therapy has been investigated in NAFLD in some studies, which revealed improvements in fibrosis and ALT levels with this therapy (17-18). Therefore vitamin C and E combination therapy could be used as an alternative therapy to UDCA, which is an expensive drug.

Here we report the results of six months of therapy with UDCA or with vitamin C plus vitamin E combination in the treatment of NAFLD.

MATERIALS AND METHODS

This is an open-label, prospective, randomized study. Sixty-four patients with NAFLD were evaluated. Patients were excluded if they had an intake of ethanol (more than 20 g/day) or of known associated medications. Viral hepatitis B and C were excluded by HBsAg and anti HCV tests. Other hepatic diseases including autoimmune hepatitis, Wilson's disease, hemochromatosis and alpha-1 antitrypsin deficiency were also ruled out. Patients with severe comorbid medical conditions (such as severe cardiac, pulmonary, renal or psychological problems) or those not consenting to participate in the study were also excluded. The patients were followed up with a weight-reducing diet at least three months by checking alanine aminotransferase (ALT) levels. In this screening period, liver biopsies were performed in order to rule out other causes of liver diseases and to prove the histologic diagnosis of NAFLD. At the end of this period, 57 patients having ALT levels at least 1.2 times the upper limit of normal, despite a three-month weight-reducing diet, were included in the study. Patients were randomized to two groups to receive vitamin E plus vitamin C combination (28 patients) or UDCA treatment (29 patients). One of the patients in the vitamin-treated group discontinued participation after the screening period and was not evaluated in the study. Demographic data of the patients is given in Table 1.

Table 1. Demographic data of the cases

		Vit E+Vit C	UDCA
Age		46.3±9.4	47.9±10.6
Sex		10F/17M	13F/16M
NASH n (%)		15 (55.5)	15 (51.7)
Steatosis n (%)		12 (44.5)	14 (48.3)
BMI	<25	6 (22.2)	4 (13.8)
	25-29.9	12 (44.4)	15 (51.7)
	30-39.9	9 (33.3)	10 (34.5)
Diabetes mellitus n (%)		7 (25.9)	7 (24.1)
Hyperlipidemia n (%)		11 (40.7)	7 (24.1)
Primary NASH n (%)		2 (7.4)	4 (13.8)
BMI (Before therapy)		28±3.3	28.8±3.4
BMI (After therapy)		27.1±3.0	28.0±3.4

BMI: Body mass index

The diagnosis of steatohepatitis was based on histological examination. Cases were identified as steatohepatitis if macrovesicular fat was observed as greater than 5% of hepatocytes accompanied by any degree of portal lobular inflammation and fibrosis, and as steatosis if macrovesicular fat was observed as more than 5% of hepatocytes without accompanying inflammation and/or fibrosis.

Oral vitamin preparations were prescribed as vitamin E 600 IU (Ephynal 300 IU, Roche) per day plus vitamin C 500 mg (Redoxan tbl, Roche) per day. UDCA was given at a dose of 10 mg/kg/day in divided doses with meals. Treatment was continued for six months and cases were evaluated every two months in the out-patient clinic. Serum levels of ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), serum triglycerides, and cholesterol values were monitored at each visit during treatment. Ultrasonographic evaluations of the liver were performed at the entry of the study and at the end of the treatment, and liver steatosis scores were compared between the two treatment groups. In the ultrasonographic examination, fatty liver was diagnosed according to the modified criteria of Kurtz et al. (19). The four parameters used in this criteria are brightness of the liver, attenuation of echogenicity, blurred vessels, and the contrast ratio of the liver-to-kidney on ultrasonography (US) (General Electric LOGIQ 400 CL). We also evaluated the grade of fatty liver according to the echogenecity as follows: Grade 1: A slight diffuse increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel border. Grade 2: A moderate diffuse increase in fine echoes with slightly impaired visualization of the diaphragm and intrahepatic vessels. Grade 3: A marked increase in fine echoes with poor or no visualization of the intrahepatic vessel border, diaphragm, and posterior portion of the right lobe of the liver (20). To avoid inter-rater differences in the grading of US, only one hepatologist performed and evaluated US images based on the above criteria.

Hyperlipidemia was considered when the serum cholesterol level was higher than 200 mg/dl (normal value 100-200 mg/dl) and/or serum triglyceride level was over 170 mg/dl (normal value 30-150 mg/dl).

In the treatment period, none of the patients was on a diet for weight loss nor consumed lipid-lowering medication.

Decreases in enzyme levels were compared using Wilcoxon rank sum test. The chi-square test was used to compare the number of patients whose enzyme levels normalized at the end of the study in each group.

RESULTS

Eighty-two percent of the NAFLD patients included in the study had body mass indexes (BMI) greater than 25. However, there was no patient with a BMI greater than 40 in our study. In the whole treatment group there were 14 patients with diabetes mellitus who were on diabetic diet without antidiabetic medication (25%) and 17 patients with hyperlipidemia (30%). There was no significant difference in age, gender, BMI, and frequency of diabetes mellitus and hyperlipidemia between the two treatment groups (Table 1). Primary NAFLD patients who were characterized by absence of obesity, diabetes mellitus and hyperlipidemia constituted a small percentage of our patients (Table 1). When the patients were separated into two groups as fatty liver or steatohepatitis, there was no difference in terms of therapy responses in these two groups. BMI did not change significantly before and after treatment in either treatment group. There was a significant decrease in the serum AST and ALT levels in both treatment groups. The percentage of patients with ALT normalization was 63% (17 of 27 patients) in the vitamin-treated group and 55% (16 of 29 patients) in the UDCA-treated group, but the difference between them was not significant (Table 2). Decreases in GGT levels were significant in the UDCA-treated group, but not significant in the vitamin-treated group (Table 2).

There was no change in the liver echogenicity of patients as detected with US in either treatment group (Table 2).

Table 2. Laboratory values and ultrasound score before and after therapy

	Vit E+Vit C		UDCA	
	Before Therapy	**After Therapy**	**Before Therapy**	**After Therapy**
AST	49.6±22.7	29.1±8.6*	56.1±23.8	36.0±21.3*
ALT	91.9±47.8	39.1±16.4*	93.7±52.5	49.1±40.4*
GGT	61.5±48.9	40±39.7	76.7±73.3	36.1±31.1*
ALP	196.7±84.1	188.2±76.4	271.4±87.3	232.8±92.6
US Score	1.41±0.57	1.41±0.57	1.48±0.65	1.48±0.58

*p<0.05, AST: Aspartate aminotransferase (normal: 5-35 U/L) ALT: Alanine aminotransferase (normal: 5-40 U/L), GGT: Gamma-glutamyl transpeptidase (normal: 7-32 U/L), ALP: Alkaline phosphatase (normal: 90-260 U/L), US: Ultrasound

Side effects in three patients in the UDCA treatment group included epigastric pain, nausea and diarrhea. No side effects were reported in the vitamin-treated group.

DISCUSSION

Non-alcoholic fatty liver disease is commonly associated with obesity, hyperlipdemia and type II diabetes mellitus (21-23). Most of our patients were middle-aged and obese (82%). In the course of NAFLD, there are two important steps. The first is characterized by lipid accumulation in the hepatocyte without inflammation and fibrosis. In most patients insulin resistance is thought to be the cause of lipid accumulation in the hepatocytes. In the second step, steatohepatitis, oxidative stress is cited as responsible for the hepatic inflammation and fibrosis (10). Thus, it may be appropriate to use drugs that overcome insulin resistance in the first step and antioxidant treatment in the second step of this disease process. In this study, we evaluated the efficacy of oral vitamin E plus vitamin C as an anti-oxidant combination that is available at affordable prices and carries negligible side effects, and we compared this combination with UDCA treatment.

We noted that vitamin E plus vitamin C combination treatment is as effective as UDCA in normalization of ALT in NAFLD patients. In NAFLD, in which oxidative stress is thought to be the main pathogenic mechanism, the two treatments had the same efficacy in normalization of ALT.

There are not sufficient studies about the treatment of NAFLD. In most of the publications about the treatment of NAFLD, focus is on improvement of associated conditions like obesity, diabetes mellitus and hyperlipidemia. Weight loss is known to be effective in many obese NAFLD patients (24-26). However, adverse effects on liver histology, such as progression of fibrosis, have been noted as well (9, 27, 28). Furthermore, most of the obese patients find it virtually impossible to maintain weight loss (29).

Probucol, a drug with lipid-lowering and antioxidant effects, has been shown to be significantly effective in decreasing ALT levels in patients with NASH. In that study, it was reported that it is the antioxidant and not the lipid-lowering effect of probucol that was the responsible mechanism for the normalization of ALT levels. Researchers had interpreted this finding as an evidence of oxidative stress as a responsible mechanism in the pathogenesis of NASH (26).

Three open-label studies were performed to evaluate the therapeutic benefits of UDCA in patients with NAFLD. In one of these studies, 24 patients with NAFLD received UDCA for 12 months. UDCA led to a significant improvement in liver tests and the degree of hepatic steatosis when compared with baseline (14). In another study, liver tests normalized or were significantly improved after six months of treatment with UDCA (15). In the study by Ceriani et al. (16), UDCA plus low-fat diet was compared with low-fat diet given for six months in 31 patients with NASH. Normalization of ALT was reported in 87% of 16 patients receiving UDCA plus low-fat diet and in 26% of 15 patients receiving low-fat diet alone. However, in the three- month follow-up period without treatment, 42.8% of patients with normal liver function tests had a relapse with an increase in serum liver tests. In that study, the ratio of patients with normalization of ALT provided with UDCA was higher than our results. A possible reason may be the low-fat diet prescribed to the patients in addition to the UDCA treatment.

In another study, treatment of NASH for 12 months with UDCA resulted in significant improvement in hepatic steatosis and ALP, ALT, and GGT levels. At the end of the 12-month treatment, it was reported that the liver function tests had normalized in 20.8% of patients (14). The proportion of patients who had normalization of liver function tests after therapy was lower than our results, possibly due to the inclusion in that study of only the cases with steatohepatitis, who may have had histologically more severe lesions than our patients. In our study, we did not grade the histologic lesions so we cannot comment with certainty about the severity of steatohepatitis. Recently Lindor et al. (30), in a randomized trial, revealed that two years of UDCA therapy was no more efficient than placebo in patients with NASH. Therefore, the effect of UDCA in NAFLD is quite controversial. In patients receiving UDCA in our study, there was a significant decrease in GGT levels, which was not observed in the vitamin-treated group. This result may be related to the choleretic effect of UDCA.

In adults with NAFLD, N-acetyl cysteine as an antioxidant treatment significantly decreased ALT, AST and GGT levels (31). In obese children with NASH, vitamin E has been demonstrated to significantly decrease the serum ALP, AST and ALT

levels (32). Harrison et al. (17) revealed that vitamin E and vitamin C treatment improves fibrosis in adult patients with NASH.

In NAFLD patients, we investigated the effect of vitamin E plus vitamin C combination and UDCA on biochemical tests. We could not reach a conclusion about the histologic change because we did not re-biopsy the patients after the treatment period. Transaminase levels are generally accepted as the reflection of liver injury, and decrease in transaminase levels generally accompanies histologic healing.

The study with higher dosages of vitamin E (1000 IU/day) and vitamin C (1000mg/day) showed that the therapy improved the fibrosis, but its effect was not different from placebo in terms of ALT levels (17). In another study, vitamin E was detected to have no effect on cytokine profile and levels of hyaluronic acid, one of the fibrosis markers (33).

In conclusion, in terms of biochemical improvement, vitamin E plus vitamin C combination treatment is as effective as UDCA in the treatment of NAFLD, for which there is not yet an existing proven treatment. Treatment with vitamins costs less than any other treatment and there are negligible side effects. In the future, our data must be confirmed in larger scale studies with pre- and post-treatment biopsies.

REFERENCES

1. Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000; 132: 112-7.
2. Nomura H, Kashiwagi S, Hayashi J, et al. Prevalence of fatty liver in a general population of Okinawa, Japan. Jpn J Med 1988; 27: 142-9.
3. Matteoni C, Younossi ZM, McCullough A. Nonalcoholic fatty liver disease: a spectrum of clinical pathological severity. Gastroenterology 1999; 116: 1413-9.
4. Pares A, Caballeria J, Brugera M. Histologic course of alcoholic hepatitis: influence of abstinence, sex, and extent of hepatic damage. J Hepatol 1986; 2: 33-8.
5. Galambos J. Natural history of alcoholic hepatitis III: histologic changes. Gastroenterology 1972; 56: 515-22.
6. Eriksson S, Eriksson KF, Bondesson L. Nonalcoholic steatohepatitis in obesity: a reversible condition. Acta Med Scand 1986; 220: 83-8.
7. Rozental P, Biava C, Spencer H, et al. Liver morphology and function tests in obesity and during total starvation. Am J Dig Dis 1967; 12: 198-208.
8. Drenick EJ, Simmons F, Murphy J. Effect on hepatic morphology of treatment of obesity by fasting, reducing diets, and small bowel bypass. N Engl J Med 1970; 282: 829-34.
9. Palmer M, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. Gastroenterology 1990; 99: 1408-13.
10. Day CP, James OFW. Steatohepatitis: a tale of two "hits" ?. Gastroenterology 1998; 114: 842-5.
11. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 346: 1221-31.
12. Chitturi S, Farrell GC. Etiopathogenesis of nonalcoholic steatohepatitis. Semin Liver Dis 2001; 21: 27-41.
13. Reid AE. Nonalcoholic steatohepatitis. Gastroenterology 2001; 121: 710-23.
14. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of nonalcohol-induced steatohepatitis: a pilot study. Hepatology 1996; 23; 1464-7.
15. Guma C, Viola L, Thome M, et al. Ursodeoxycholic acid in the treatment of nonalcoholic steatohepatitis: result of a prospective clinical controlled trial (Abstract). Hepatology 1997; 26: 387A.
16. Ceriani R, Bunati S, Morini L, et al. Effect of ursodeoxycholic acid plus diet in patients with non-alcoholic steatohepatitis (Abstract). Hepatology 1998; 28: 386A.
17. Harrison SA, Torgerson S, Hayashi P, et al. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2003; 98: 2485-90.
18. Patrick L. Nonalcohoic fatty liver disease: relationship to insulin sensitivity and oxidative stress. Treatment approaches using vitamin E, magnesium and betaine. Altern Med Rev 2002; 7: 276-91.
19. Kurtz AB, Dubbins PA, Rubin CS, et al. Echogenicity: analysis, significance, and masking. AJR 1981; 137: 471-6.
20. Hagen-Ansert SL. Textbook of Diagnostic Ultrasonography. 5th ed. St Louis, Missouiri: Mosby, 2001; 134-63.
21. Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980; 55: 434-8.
22. Powell EE, Cooksley WG, Hanson R, et al. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. Hepatology 1990; 11: 74-80.
23. Bacon BR, Farahvash MJ, Janney CG, et al. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology 1994; 107: 1103-9.
24. Knobler H, Schattner A, Zhornicki T, et al. Fatty liver - an additional and treatable feature of the insulin resistance syndrome. Q J Med 1999; 92: 87-96.
25. Ueno T, Sugawara H, Sujaku K, et al. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. J Hepatol 1997; 27: 103-7.
26. Merat S, Malekzadeh R, Sohrabi MR, et al. Probucol in the treatment of non-alcoholic steatohepatitis: a double-blind randomized controlled study. J Hepatol 2003; 38: 414-8.
27. Angulo P, Lindor KD. Treatment of nonalcoholic fatty liver: present and emerging therapies. Semin Liver Dis 2001; 21: 81-8.
28. Andersen T, Gluud C, Franzmann MB, et al. Hepatic effects of dietary weight loss in morbidly obese subjects. J Hepatol 1991; 12: 224-9.
29. MacCuish AC, Munro JF, Duncan LJ. Follow-up study of refractory obesity treated by fasting. Br Med J 1968; 1(584): 91-2.
30. Lindor KD, Kowdley KV, Heathcote EJ, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of randomized trial. Hepatology 2004; 39: 770-8.
31. Gulbahar O, Karasu ZA, Ersoz G, et al. Treatment of nonalcoholic steatohepatitis with N-acetyl cysteine. Gastroenterology 2000; 118: A1444.
32. Levine JE. Vitamin E treatment of nonalcoholic steatohepatitis in children: a pilot study. J Pediatrics 2000; 136: 734-8.
33. Ugelmas M, Hill DB, Vivian B. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. Hepatology 2003; 38: 413-9.