Vitamin E Treatment in Pediatric Obesity-Related Liver Disease: A Randomized Study


*Departments of Pediatrics and †Laboratory Medicine, University of Naples Federico II, and ‡European Laboratory for Food Induced Disease [ELFID], Naples, Italy.

ABSTRACT

Objective: A beneficial role of antioxidants in hepatopathic obese individuals has hitherto been inferred only from uncontrolled pilot studies. The authors compared the effect of vitamin E and weight loss on transaminase values and on ultrasonographic bright liver in a controlled group of children with obesity-related liver dysfunction.

Methods: Twenty-eight children with obesity-related hypertransaminasemia and bright liver were randomly allocated to two single-blind groups: group 1 (n = 14) treated with a low-calorie diet associated with oral placebo for 5 months, and group 2 (n = 14) treated with a low-calorie diet associated with oral vitamin E (400 mg/d × 2 months, 100 mg/d × 3 months). Transaminase values and ultrasonographic liver brightness along with weight loss and vitamin E levels were monitored.

Results: Variations in transaminase levels and percentage of patients with normalized transaminase values were comparable in the two groups. The disappearance of bright liver was observed only in patients who lost weight and was twice as common in patients from group 1. Two subgroups of patients with complete normalization of transaminase values emerged as a consequence of controlled adherence to diet alone (n = 6; significant decrease of percent overweight: \( P = 0.0019 \)) and to vitamin E alone (n = 7; unmodified percent overweight and significant increase of vitamin E/cholesterol ratio: \( P < 0.0001 \)). Changes in treatment-induced alanine aminotransferase levels in these two subgroups were comparable at month 2, whereas values at month 5 were significantly lower in the subgroup adherent to diet alone (\( P = 0.04 \)). In the subgroup adherent to vitamin E alone, after 2 months washout, transaminase remained stable in 5 patients and increased in 2; bright liver persisted in all.


INTRODUCTION

Obesity is one of the most common health problems among children and adolescents. It is well known that it has become more prevalent and has a significant impact on later mortality and morbidity in adulthood (1). It has psychologic, respiratory, orthopedic, biliary, and later in life, cardiovascular consequences. The liver recently has been recognized as a major target organ, and obesity has become a leading cause of elevated serum aminotransferases for all ages in industrialized countries (1–3). We previously have shown that as many as 50% of obese children have ultrasonographic (US) bright liver, and half of them (25% of all obese children) have hypertransaminasemia (4,5).

Obesity-related liver dysfunction falls within the abnormalities pertaining to the complex spectrum of nonalcoholic fatty liver disease (NAFLD) (6). These may range from simple hepatic steatosis, a common and putatively benign condition with an indolent natural history, to progressive necroinflammatory damage associated with a more severe condition that may develop into liver fibrosis and cirrhosis both in adults and in children (7–10). Although different studies on various aspects of NAFLD have been reported during the last few years, information on disease prevalence in pediatrics remains sparse, and management strategies are poor. Pending prospective studies linking natural histories of pediatric and adult liver disease of obese populations, all (even mild) liver abnormalities should be considered relevant medical problems when children are affected. As a matter of fact, with a long life expectancy at this age, the patients probably...
will be exposed to a variety of metabolic, toxic, or infectious agents that are likely to aggravate an underlying obesity-related liver steatosis, if the condition is left untreated.

Because early hepatic abnormalities normalize after gradual loss of weight, a prudent weight-reducing diet is the first line of treatment, but unfortunately the adherence rate is poor (4,5,11). We have shown that treatment with ursodeoxycholic acid in obese children with liver dysfunction who were unable to comply with a diet failed to correct hepatic abnormalities (12). Thus, our pediatric study could not confirm the optimistic results reported in a pilot, open-label study performed on a similar series of adults treated with ursodeoxycholic acid (13). All these considerations make it important to find more pathophysiologically based innovative treatments.

In the two-hit model of NAFLD pathogenesis, insulin resistance (IR) plays a pivotal role in determining the first hit: steatosis (14). This increases the sensitivity of the liver to the second hits responsible for progression of liver disease to hepatic necroinflammatory damage. Second hits involve oxidative stress resulting from an imbalance between pro-oxidant and antioxidant processes in the liver. This imbalance may be caused by any combination of the following: induction of microsomal p450 enzymes, mitochondrial release of reactive oxygen species, H$_2$O$_2$ release from peroxisomal beta-oxidation of fatty acids, and cytokines released from activated inflammatory cells. Oxidative stress can lead to peroxidation of membrane lipids, causing the production of malondialdehyde and 4-hydroxynonenal, which in turn induces the production of proinflammatory cytokines, stellate cell activation, and fibrogenesis, as well as direct hepatocyte damage. Mitochondrial reactive oxygen species release also may be increased with the expression of uncoupling protein 2, leading to adenosine triphosphate depletion. In addition, elevation of serum tumor necrosis factor $\alpha$ (TNF$\alpha$) can contribute to oxidative stress and apoptosis. There is still conflicting evidence regarding the role of hepatic iron deposition as a cofactor of progression of NAFLD in adults. Unlike animal models of fatty liver, leptin levels are increased in obese humans, and resistance at the receptor site has been documented (15). A significant role played by oxidative stress and lipid peroxidation in the cascade of events involved in hepatic necroinflammatory damage (3,16–18) is supported by a recent experimental study, which showed that antioxidant vitamin E reduces fatty liver in obese Zucker rats (19). However, despite these premises, the claimed beneficial effects of antioxidants upon obesity-related dysfunction in humans have been based on only a few uncontrolled pilot clinical studies (20–24). Therefore, we studied hypertransaminasemia and US bright liver changes in a controlled group of 28 obese children treated with vitamin E and a low caloric diet versus placebo and diet.

**MATERIALS AND METHODS**

Thirty-four consecutive obese (ideal body weight $\geq 120\%$ according to Tanner (25), and body mass index [BMI, Kg/m$^2$] (26 > 95th percentile) patients seen at our institution from January 1999 to June 2001 because of chronic (> 6 months’ duration) hypertransaminasemia (aspartate aminotransferase or alanine aminotransferase [ALT] $\geq 1.5$ times above normal values for more than 6 months) and US hepatic steatosis (bright liver) were considered eligible for the current study.

None of the patients had previously been treated with hepatotoxic drugs, undergone surgery, received blood or blood products, or had a history of alcohol consumption. No patient had a history of short gut syndrome, small bowel intestinal bypass, Cushing disease, or diabetes mellitus, which could have caused hepatic steatosis. All had asymptomatic disease. None had arterial hypertension. Sixteen patients had mild hepatomegaly of normal consistency. None had splenomegaly or other stigmata of portal hypertension.

Baseline serum lipid, blood glucose, and glycosylated hemoglobin levels, and usual liver function tests in addition to ALT and aspartate aminotransferase (alkaline phosphatase, gamma glutamyl transpeptidase, bilirubin, total protein, protein electrophoresis) also were performed.

Causes of chronic hypertransaminasemia other than obesity, such as muscular disease, viral hepatitis B and C, autoimmune hepatitis, $\alpha_1$-antitrypsin deficiency, cystic fibrosis, Wilson disease, hemochromatosis, hereditary fructose intolerance, amino acid disorders, malnutrition, and atypical celiac disease were investigated by appropriate tests.

Six of the 34 eligible patients refused to participate in the study. The remaining 28 patients (baseline demographic and clinical data are shown in Table 1) were randomly allocated to one of the two single-blind treatments: 14 were assigned to group 1 (placebo + diet) and group 2 (vitamin E + diet).

**TABLE 1. Baseline demographic, clinical, laboratory, and ultrasonographic data of patients before and after random allocation to group 1 (placebo + diet) and group 2 (vitamin E + diet)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 14)</th>
<th>Group 2 (n = 14)</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>9.88 ± 3.97</td>
<td>10.7 ± 3.45</td>
</tr>
<tr>
<td>Gender F/M</td>
<td>3/11</td>
<td>4/10</td>
</tr>
<tr>
<td>IBW (%)</td>
<td>141.40 ± 15.20</td>
<td>140.20 ± 16.99</td>
</tr>
<tr>
<td>BMI</td>
<td>24.82 ± 2.35</td>
<td>24.50 ± 2.78</td>
</tr>
<tr>
<td>Percent overweight*</td>
<td>143.90 ± 17.70</td>
<td>140.20 ± 17.00</td>
</tr>
<tr>
<td>ALT U/L (normal, &lt;40)</td>
<td>76.00 ± 23.45</td>
<td>72.58 ± 17.46</td>
</tr>
<tr>
<td>Vitamin E $\mu$mol/L (normal, 12–33)†</td>
<td>22.58 ± 5.80</td>
<td>24.30 ± 5.90</td>
</tr>
<tr>
<td>Cholesterol mmol/L (normal, &lt;4.4)</td>
<td>4.01 ± 1.05</td>
<td>4.00 ± 1.03</td>
</tr>
<tr>
<td>Vitamin E/Cholesterol ratio‡</td>
<td>5.85 ± 1.02</td>
<td>6.27 ± 1.10</td>
</tr>
<tr>
<td>Bright liver at ultrasonography</td>
<td>14/14</td>
<td>14/14</td>
</tr>
</tbody>
</table>

* Percent overweight based on comparisons between body mass index (BMI = kg/m$^2$) and the 50th percentile BMI for age and sex.
† Vitamin E serum levels and vitamin E/cholesterol ratio in a control group of 25 age- and gender-matched healthy children: 20.2 ± 5.2 $\mu$mol and 5.3 ± 2.3 $\mu$mol. Differences with our patient series were not statistically significant. Vitamin E serum levels and vitamin E/cholesterol ratio in a control group of 12 age- and gender-matched obese children without liver disease: 22.5 ± 5.4 $\mu$mol and 5.5 ± 1.4 $\mu$mol. Differences with our patient series were not statistically significant.
The primary aim of the study was to verify the efficacy of vitamin E and diet treatment versus placebo and diet in reducing aminotransferase values and liver echogenicity.

The number of cases untreated for each treated case (14 cases and 14 controls) required to complete the study was estimated by the Schlessmann formula (30).

The characteristics at baseline and after treatments (clinical features and laboratory/ultrasonographic results) were compared between the two groups by independent t tests or exact Fisher test, as appropriate.

To compare variable treatment-induced changes attributable to weight loss only, or to vitamin E, it was necessary to carry out an additional post-hoc analysis in subgroups of patients selected on the basis of verified compliance to diet alone and to vitamin E administration alone. In each subgroup, multiple comparisons between means of serum ALT levels, overweight, and vitamin E/cholesterol ratio were assessed by repeated measures ANOVA. Differences between the two means were evaluated by the paired Student t test.

The statistical significance level selected for all tests was P < 0.05.

The inclusion of the individual in group 2 who was exempted from the completion of the study in intention to treat (ITT) analyses is explicitly indicated.

All data are expressed as mean ± SD.

RESULTS

Baseline Characteristics

Baseline serum lipid levels, blood glucose, glycosylated hemoglobin levels, and results of usual liver function tests other than serum aminotransferase were within the normal range in all. In none of them did we find any causes of hypertransaminasemia other than obesity. No statistically significant differences existed between the baseline characteristics of the two groups, as shown in Table 1.

Only 10 patients (6 in group 1, and 4 in group 2) consented to basal liver biopsy, which showed comparable findings of typical mixed macro- and microvesicular hepatic steatosis, scattered lobular inflammation, and either absence of (n = 6) or mild (n = 4) fibrosis.

Treatment-induced Changes in the Two Study Groups

As shown in Table 2, there were statistically significant differences between groups 1 and 2 in vitamin E/cholesterol ratios at 2 and 5 months and in percent of weight lost at 5 months only, whereas ALT level changes were comparable.

There was no statistically significant difference between the number of patients who had normalized ALT values in the two groups (6/14 in group 1 and 7/13 or 7/14, ITT) in group 2, at both 2 and 5 months). Bright liver disappeared in six patients in group 1 and in three patients in group 2 (P = 0.41), and it was always associated with loss of weight.

Stratification of the Two Groups of Patients on the Basis of Effective Compliance to Diet and Vitamin E Therapy

Stratification of the two groups of patients on the basis of effective compliance to diet (thus achieving weight reduction) and vitamin E therapy (thus increasing serum vitamin E/cholesterol ratios) during the study yielded four subgroups (Fig. 1): patients compliant to diet (subgroup 1A, n = 6/14) and those noncompliant to diet (subgroup 1B, n = 8/14) in group 1, and patients compliant to vitamin E therapy (subgroup 2A, n = 10/13)
and those not compliant to vitamin E (subgroup 2B, n = 3/13) in group 2. Post-hoc analysis showed that the vitamin E levels of the three patients in subgroup 2B remained low despite that they were taking the same dose of oral vitamin E/kg body weight/d. Among the patients in subgroup 2A, seven remained weight-stable (subgroup 2A1) and three lost weight (subgroup 2A2).

It is noteworthy that compliance to diet was extremely low in both groups: 6 of 14 (43%) in group 1; 3 of 13 (23%; or 3 of 14 for 21% [ITT]) in group 2, with an overall compliance of 9 of 28 (32%; or 9 of 27 for 33% [ITT]). Figure 1 shows the initial and final allocation of the patients enrolled, according to real compliance to diet and/or vitamin E treatment. The baseline characteristics of the five patients’ subgroups were not statistically different.

Changes in Clinical and Laboratory Parameters During the Study of the Patients Reallocated to the Five Subgroups

Figure 2 depicts the variations in clinical and laboratory parameters during the study of the patients reallocated to the five post-hoc subgroups.

Subgroup 1A showed a statistically significant decrease in percent overweight and transaminase values, with normalization of ALT and liver brightness at ultrasonography in all.

Subgroup 1B did not lose weight, their ALT levels remained unchanged, and ultrasonographic liver brightness persisted.

Serum vitamin E and cholesterol levels, and ratios before and after diet remained fairly stable in subgroups 1A and 1B.

For subgroup 2A1, there was an approximately twofold increase in vitamin levels at a dosage of 400 mg/d of vitamin E, accompanied by a significant decrease in ALT levels ($P = 0.0019$) down to complete normalization in all patients, despite their unmodified weight. When the dosage was decreased to 100mg, ALT levels remained within the normal range, although five of them experienced a mild increase; moreover, their vitamin E serum levels decreased ($P = 0.0068$) but were still moderately higher ($P = 0.045$) than those of control subjects. During follow-up, at the end of the 2-month washout, ALT values remained stable in five but became frankly abnor-

<table>
<thead>
<tr>
<th>TABLE 2. Treatment-induced changes in the study groups</th>
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<tbody>
<tr>
<td><strong>Group 1</strong> placebo + diet (n = 14)</td>
</tr>
<tr>
<td>Evaluation at month 2 (vitamin E 400 mg/d)</td>
</tr>
<tr>
<td>Loss of weight (%)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
</tr>
<tr>
<td>Vitamin E/cholesterol ratio</td>
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<tr>
<td>Evaluation at month 5 (vitamin E 100 mg/d)</td>
</tr>
<tr>
<td>Loss of weight (%)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
</tr>
<tr>
<td>Vitamin E/cholesterol ratio</td>
</tr>
</tbody>
</table>

Changes were the difference between baseline values (before treatment) and values measured at months 2 and 5. Negative values indicate a decrease. Values are mean (SD).
* Student t test.
ALT, alanine aminotransferase; itt, intention to treat.

FIG. 1. Reallocation of the patients during the study from initial group 1 (placebo plus diet) and group 2 (vitamin E plus diet) to subgroup 1A (diet compliers), subgroup 1B (diet noncompliers), subgroup 2A (vitamin E compliers) (including: Subgroup 2A, of diet noncompliers and vitamin E compliers and subgroup 2A of diet and vitamin E compliers), and subgroup 2B (diet and vitamin E noncompliers).
mal in two. One experienced normalized transaminases when vitamin E treatment was resumed. Despite the normalization of ALT values, all seven patients continued to show ultrasonographic evidence of hepatic steatosis.

Patients in subgroup 2A2 also lost weight during the treatment with 400 mg vitamin E. Disappearance of liver brightness at US was observed. Although serum transaminases normalized in all, values before and during the treatment did not show a statistically significant difference. Data at 5 and 7 months (vitamin E 100 mg/d [T5]; during washout [WASH]) could not be included in the statistical analysis because of the inconstant compliance to diet or vitamin E in two of them.

In subgroup 2B, none of the three patients had statistically significant clinical, echographic, and laboratory changes during follow-up.

In the patient excluded from the study because of marked hypertransaminasemia after starting vitamin E supplementation, transaminase values returned to their usual pattern of chronic mild fluctuations (ranging from 1.5 to 2 times upper normal values), despite a successful weight loss. An assumed diagnosis of obesity-unrelated liver disease or vitamin E intolerance was taken into consideration.

### Comparisons of Treatment-induced Changes in the Two Subgroups of Patients with Controlled Adherence to Diet Alone or Vitamin E Alone

Comparisons of treatment-induced changes in the two subgroups of patients with controlled adherence to diet

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**FIG. 2.** Changes in alanine aminotransferase (ALT) levels, % overweight, and vitamin E/cholesterol (vit E/chol) ratio in the five subgroups of patients before (T0) and during diet ± placebo or vitamin E treatment (baseline [T0]; with vitamin E 400 mg/d [T2]; with vitamin E 100 mg/d [T5]; during washout [WASH]). Each value represents the mean ± SD. Subgroups: 1A diet compliers; 1B diet noncompliers; 2A1 diet noncompliers and vitamin E compliers; 2A2 diet and vitamin E compliers; 2B diet and vitamin E noncompliers. *P < 0.05; **P < 0.001; ***P < 0.0001; NS, not significant, compared with T0 (paired Student t test). P and F values refer to multiple comparisons between means assessed by repeated measure ANOVA.
alone (1A) and vitamin E alone (2A1) were performed to eliminate the respective treatment biases; they showed comparable decreases in ALT levels at 2 months and a more marked decrease in ALT in patients on diet alone at 5 months (Table 3).

With regard to the number of patients who experienced normalized ALT values, there were no statistically significant differences between subgroups 1A and 2A1 (6/6 and 7/7, respectively). Normalization of bright liver was observed only in patients who lost weight (subgroups 1A and 2A2) and never in those who did not (subgroups 1B, 2A1, and 2B), regardless of whether they received vitamin E treatment.

**Side Effects or Adverse Events**

Except for the one patient who experienced an increase in transaminase values after starting vitamin E, no side effects or adverse events were recorded in either group.

**DISCUSSION**

As with other reports dealing with individuals affected by obesity-related liver dysfunction (4,5,11), the current study showed an extremely small number of patients able to comply with the diet and lifestyle changes required for this therapy to be successful (approximately 1/3 of whole series). To the best of our knowledge, our work is the first controlled pediatric study to document a clear beneficial effect of vitamin E as a measure for reducing and normalizing aminotransferase values in this challenging group of individuals. However, vitamin E was not effective on US liver brightness.

It has been proposed that in obesity-related hepatic steatosis, lipid-laden hepatocytes act as a reservoir of hepatotoxic agents (e.g., free fatty acids) and thus are more susceptible to a second hit injury (31–33). Several reports suggest that vitamin E, vitamin alone or together with other antioxidants, protects tissues from reactive oxygen species damage in diseases involving some other organ (34). This background prompted Lavine (20) and Hasegawa et al. (21) to investigate the possible therapeutic role of vitamin E in two uncontrolled pilot groups of adolescents and adults with obesity-related liver dysfunction. The younger age of our patients represents an ideal model for studying the effects of treatment on this condition because of the probable absence of secret alcohol consumption or drug toxicity caused by the need for medical treatment for chronic associated diseases. There also is a lower incidence of comorbid metabolic abnormalities (e.g., diabetes or hypertriglyceridemia), as confirmed by baseline data reported in our previous (12) and current studies. Articles on vitamin E and other antioxidants (e.g., N-acetyl-cysteine (22), betaine (23), and a mixture of lecithin, vitamin C, low-dose vitamin E, beta carotene, selenium, and vitamin B complex (24)) also have reported variable success in reducing serum aminotransferases or improving histologic findings. These studies (20–24) were flawed because of the small sample size and the lack of a control population.

The rationale of vitamin E dosing in our study was based on published clinical trials performed on adults, in whom a dose of 300 to 400 mg/d was considered satisfactory to obtain an antioxidant effect (35–36). Pending the verification of data on the safety of high vitamin E doses for medium term treatments in children, we ensured that the drug was prescribed at a lower dosage after the first 2 months of treatment.

To compare the effects of vitamin E and diet separately, our study ideally should have had four arms: diet and placebo, no diet and vitamin E, diet and vitamin E, and no diet and placebo. However, once obesity has been recognized as a true medical problem, general practitioners and parents tend to promote healthy eating, which may lead to unpredictable weight loss, so a veritable “no diet” arm is difficult to obtain in a controlled study. Thus, in the current study we had to resort to a post-hoc

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**TABLE 3.** Treatment-induced changes in the two subgroups that allow direct comparison between vitamin E alone (vitamin E compliers-diet noncompliers) versus diet alone (diet compliers)

<table>
<thead>
<tr>
<th></th>
<th>Subgroup 1A</th>
<th>Subgroup 2A</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 6/14)</td>
<td>(n = 7/13); (n = 7/14, itt)</td>
<td></td>
</tr>
<tr>
<td><strong>Evaluation at month 2 (vitamin E 400 mg/d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of weight (%)</td>
<td>−16.20 (5.39)</td>
<td>−1.38 (2.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>−47.80 (9.52)</td>
<td>−37.63 (11.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Vitamin E/Cholesterol ratio</td>
<td>−0.16 (0.78)</td>
<td>+4.07 (2.38)</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>Evaluation at month 5 (vitamin E 100 mg/d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of weight (%)</td>
<td>−28.66 (13.26)</td>
<td>−2.70 (5.2)</td>
<td>0.0007</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>−51.00 (12.63)</td>
<td>−33.50 (15.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Vitamin E/Cholesterol ratio</td>
<td>−0.63 (1.26)</td>
<td>+1.23 (1.44)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Changes were the difference between baseline values (before treatment) and values measured at months 2 and 5. Negative values indicate a decrease. Values are mean (SD).

* Student t test.

ALT, alanine aminotransferase; itt, intention to treat.
analysis of small subgroups coming from the original group allocation.

The baseline levels of α-tocopherol in our obese patients with liver dysfunction were within the normal range yet moderately higher than those reported in older children (20), possibly reflecting an age-dependent effect (37). We did not find any differences in the vitamin E status before and after the low-calorie diet. It is unlikely that the reduction of liver damage was attributable to the changes in diet composition affecting vitamin E status (weight-reducing diets generally are richer in green and red vegetables but lower in sugar, starch, and fat); instead, it is more likely to be attributable to the weight loss.

If one considers only the subgroups of patients with controlled adherence to diet alone and vitamin E alone, it is evident that ALT reduction in diet-compliant children and in vitamin E-treated patients who did not lose weight initially was comparable and tended to be more consistent with time in those who lost weight. There was no apparent benefit of vitamin E supplementation in those who were able to comply with the diet.

The persistence of ultrasonographic hepatic steatosis in the group of children treated with vitamin E despite normalization of serum aminotransferases may be explained by the pathophysiological mechanism of the treatment. As a matter of fact, antioxidants do not remove lipids from hepatocytes but interrupt the vicious cycle leading to hepatocyte necroinflammation. It is unlikely that doses of vitamin E higher than those used by us will have an effect upon liver steatosis because adolescents treated by Lavine (20) with vitamin E doses ranging from 800 to 1200 mg/d also remained steatotic.

Other therapeutic strategies, e.g., those aiming to halt insulin resistance (a factor that seems to play an important role in the first steps toward fatty liver of obese individuals), recently have been suggested to have beneficial effects on the liver steatosis of obese patients (38). With regard to this, future studies combining these drugs and antioxidants might prove effective.

Our protocol did not consider the unwillingness to undergo needle liver biopsy as an exclusion criteria because of our patients’ minimal clinical liver disease, the usual slow progression of obesity-related liver disease at these ages, the existing risk of complications of liver biopsy, and the still limited treatment options for obesity-related liver disease that are unlikely to be altered by the histologic results (33,39). Indeed, the liver histologic findings of the patients examined showed only mild alterations that were quite homogeneously distributed among the groups. Although we do not make liver histologic analysis available to all patients, it is conceivable that the clear-cut normalization of aminotransferase values together with the disappearance of liver brightness in all patients who lost weight may suggest a probable resolution of existing steatosis or necroinflammation, without the need to resort to basal or repeat liver biopsy. Aminotransferase normalization with persisting bright liver in patients taking antioxidant oral vitamin E without losing weight may suggest the resolution of necroinflammation but not of steatosis. Follow-up liver biopsy might be necessary in these cases.

A final reflection concerns the unexplained increase in aminotransferase values observed after starting vitamin E treatment in one patient. Potential vitamin E hepatotoxicity is unlikely but still possible (40), so careful monitoring might be advisable when prescribing treatment based on high doses of vitamin E in future studies.

In conclusion, the current study strengthens the view that antioxidants may represent a relevant therapeutic tool for the treatment of children with obesity-related dysfunction who are unable to adhere to low-calorie diets. For additional confirmation of our results and delineation of the optimal daily dosage of vitamin E it may be necessary to carry out large-scale collaborative studies.

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