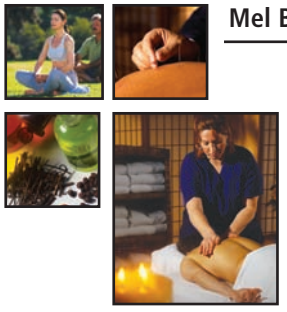
Vitamin E Treatment of NAFLD/NASH



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Non-alcoholic fatty liver disease (NAFLD)—as well as its more serious form, non-alcoholic steatohepatitis (NASH)—is a common liver disease that can progress to cirrhosis. There is no recognized effective therapy for either condition, except gradual weight loss. Insulin resistance and oxidative stress appear to contribute to the pathogenesis of NASH. In several studies, the antioxidant vitamin E improved liver biochemistry and histological lesions in this disease. It inhibited transforming growth factor-ß, a cytokine involved in liver fibrogenesis. Vitamin E has been shown to protect against liver damage induced by oxidative stress in animal experiments. In one randomized controlled trial, Vitamin E improved the aminotransferase status of patients suffering from viral hepatitis C.

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Positive research

In the trial conducted by Dufour *et al*,[1] 48 patients with elevated aminotransferases were randomly assigned to receive either:

- 12 mg/kg body weight q.d. to 15 mg/kg body weight q.d. of ursodeoxycholic acid (UDCA) with 400 IU q.d. of vitamin E (UDCA/VitE),
- UDCA with placebo (UDCA/P) or
- placebo with placebo (P/P).

At the end of the treatment period, which lasted two years, these patients underwent a second liver biopsy. BMI remained unchanged during the study. Neither the aspartate aminotransferase, nor the alanine aminotransferase (ALT) improved in the P/P group, but both enzymes improved significantly in the two other groups. The enzymes improved slightly more in the UDCA/VitE group than in the UDCA/P group. Histologically, the activity index was unchanged at the end of the study in the P/P and UDCA/P groups, but improved significantly in the UDCA/VitE group. Moreover, the fibrosis improved only in the UDCA/VitE group. The administration of 12 mg/kg body weight to 15 mg/kg body weight of UDCA q.d., with or without vitamin E, improved the serum aminotransferase levels in comparison to placebo. The combination of UDCA and vitamin E not only improves the laboratory values, but also the hepatic histology.

In a randomized prospective trial Sanyal *et al* gave 20 nondiabetic, noncirrhotic subjects with NASH either 400 IU of vitamin E q.d., or 400 IU of vitamin E and 30 mg of pioglitazone q.d.[2] Treatment with vitamin E only produced a significant decrease in steatosis. Combination therapy produced a significant decrease in:

- steatosis,
- cytologic ballooning,
- Mallory's hyaline and
- pericellular fibrosis.

Although vitamin E had no significant effects, combination therapy produced a significant increase in

metabolic clearance of glucose and a decrease in fasting free fatty acid (FFA) and insulin. The improvement in steatosis and cytologic ballooning are related to treatment-associated decreases in fasting FFA and insulin levels.

Harrison *et al* conducted a prospective, double-blind, randomized, placebo-controlled trial of 45 patients, who received either vitamins E and C (1000 IU and 1000 mg, respectively) or placebo q.d. for six months, based on their initial histologic diagnosis of NASH.[3] Additionally, all patients were given standard weight-loss counselling and encouraged to follow a low fat diet (< 30 g of fat per day). Vitamin treatment resulted in a statistically significant improvement in fibrosis score. No improvement in necroinflammatory activity or ALT was seen with this combination. Since there was improvement of fibrosis in the placebo group as well, other researchers evaluating the study felt that vitamin therapy was not better than placebo.

In another open-label, non-placebo-controlled trial, 11 obese children with NASH were given 400 IU to 1200 IU of vitamin E daily for four months to 10 months. Their BMI did not change significantly during treatment. There was a normalization of serum aminotransferase and a decrease in alkaline phosphates levels during treatment. Two children who discontinued treatment had a re-elevation of aminotransferase within two months.

Trials demonstrating no benefit

In the study by Kugelmas *et al*, 16 patients with biopsy-proven NASH were given a Step 1 American Heart Association diet, plus aerobic exercise, with or without 800 IU of vitamin E daily. Biochemical assessment of liver function, lipid profiles and BMI significantly improved during the first six weeks of therapy and remained stable during the following six weeks. Plasma hyaluronic acid (HA) concentrations and interleukin 6 decreased in parallel with weight loss.

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Lifestyle modifications (low-fat diet and exercise) were associated with improvement in liver enzymes, cholesterol and plasma HA levels in patients with NASH, whereas the level of vitamin E supplementation used in this short-term pilot study provided no apparent added benefit.[4]

In an open-label, randomized trial Bugianesi *et al* gave non-diabetic NAFLD patients metformin (2 g q.d.; n = 55) for 12 months. The control cases were given either vitamin E (800 IU q.d.; n = 28), or were treated by a prescriptive, weight-reducing diet (n = 27). Aminotransferase levels improved in all groups, in association with weight loss. NAFLD patients receiving nutritional counselling achieved better results with metformin treatment than with either a prescriptive diet or vitamin E.[5]

The Medical Research Council and British Heart Foundation's Heart Protection Study and the Womens' Angiographic Vitamin and Estrogen Study found that vitamin E did not improve cardiovascular risk for cardiovascular events. In the Heart Outcomes Prevention Evaluation (HOPE) and HOPE-2 trials, vitamin E had been associated with a higher risk of heart failure. A meta-analysis of vitamin E studies found that doses > 400 IU q.d. were associated with a increase in all-cause mortality. Most of these studies involved alpha-tocopherol, a synthetic form of vitamin E, as opposed to gamma-tocopherol, which is the main dietary form of tocopherol. This may explain why vitamin E from food is more effective than alpha-tocopherol in previous positive epidemiological heart protection studies. Dx

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