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Antioxidant treatment in nonalcoholic fatty liver disease

To the Editor,

We read with great interest the article recently published in Turkish Journal of Gastroenterology by Basaranoglu et al. (1), presenting the management of nonalcoholic fatty liver disease (NAFLD). They simply mentioned vitamin E as a pharmacotherapy option for NAFLD, which needs further clarification. We want to add some points that may take into consideration the antioxidant therapy of NAFLD.

Vitamin E is one of the most important lipid-soluble antioxidants, and it prevents lipid peroxidation and scavenges free radicals. As oxidative stress takes a role in the pathogenesis of nonalcoholic steatohepatitis (NASH), vitamin E supplementation acts as a promising therapeutic strategy. In a phase 3, multicenter, randomized, placebo-controlled, double-blind clinical trial (PIVENS) by Sanyal et al., vitamin E therapy (800 IU daily for 96 weeks) was associated with a significantly higher rate of improvement in nonalcoholic steatohepatitis, with reductions in both hepatic steatosis and lobular inflammation (2). They also conclude that serum alanine and aspartate aminotransferase levels were reduced with vitamin E treatment. A recent meta-analysis concluded that vitamin E treatment can optimize ALT and AST levels in patients with NASH (3). Another antioxidant, lycopene, which is responsible for the color of tomatoes and some vegetables, has the capacity to protect against diseases that are associated with oxidative stress and inflammation. Lycopene has a beneficial effect on obesity-related hepatic inflammation and carcinogenesis (4,5). Although lycopene studies come from experimental models, it promises future perspectives for human research.

We know that the current management of NAFLD relies on weight loss and exercise, and antioxidants, like vitamin E and lycopene, may be an important therapeutic option. The unknown long-term potential for adverse events with antioxidants should be taken into account regarding treatment decisions.

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Author's Reply

To the Editor,

Thank you for Çelikbilek et al.'s kind note. The current English literature shows 5 major studies regarding vitamin E (α-tocopherol) efficacy in patients with NAFLD (1-5). Four of them were randomized control studies. Comparison between these trials is difficult due to some limitations, such as varying entry criteria,

different doses and formulation of vitamin E, and additional use of other agents. Among them, Sanyal et al. performed the largest clinical study with the longest follow-up (24 months) so far (5). They included 84 patients in this study. Sanyal et al. showed that liver fat infiltration, lobular inflammation, and serum liver enzymes were all decreased during the study duration. However, there was no improvement in the fibrosis score or stage in the study, even after 24 months. Hasegawa et al. and Harrison et al. reported improvement in fibrosis score after 12 months and 6 months, respectively (1,2). Bugianesi et al., from Turine University, showed some degree of improvement in serum liver enzymes without histologic data (4).

On the other hand, new data indicated some concerns regarding vitamin E use (6,7). One concern is that vitamin E might increase all-cause mortality, particularly with high-dose vitamin E (> a dose of 400 IU/day) (6). A recently performed randomized control study also showed increased prostate cancer risk in relatively healthy men, even at a dose of 400 IU/day (7). In the light of this evidence, the AASLD recommendations are as follows: vitamin E administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH. Thus, vitamin E should be considered as a first-line pharmacotherapy in this group. However, until further data support its effectiveness, vitamin E is not recommended to treat NASH patients with diabetes or without liver biopsy or cirrhosis or cryptogenic cirrhosis (8).

Although oxidative stress is considered a key player in the molecular pathogenesis of NAFLD, particularly during the disease progression from simple steatosis to NASH with fibrosis, there is still no strict proof on this issue as a cause-result relationship (9,10). Almost all of the evidence so far has been gained from antioxidant therapy studies (1-5,11). Our group also tried to find some direct evidence regarding the role of oxidant stress in the pathogenesis of NASH but failed in ALIOS mice (12-14).

Briefly, we suggest that vitamin E supplements should be avoided or used cautiously, and several restrictions should be applied in patients with NAFLD.

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