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Letters to the Editor

Vitamin E therapy for NAFLD/NASH



To the Editor:

My colleagues and I read with great interest the recent article by Ji and colleagues reporting the effect of vitamin E on serum aminotransferase levels in patients with nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and chronic hepatitis C, evaluated by meta-analysis [1]. NAFLD is increasingly recognized as a common cause of chronic liver diseases in association with the current epidemic prevalence of obesity and diabetes mellitus in the general population. NAFLD is now regarded as a manifestation of metabolic syndrome and the link between obesity, diabetes mellitus, cardiovascular disease and NAFLD is likely to reflect shared pathogenic factors. The spectrum of NAFLD ranges from simple hepatic steatosis without associated necroinflammatory changes or fibrosis to NASH, which is characterized by necroinflammation, cytopathic changes in hepatocytes, such as ballooning degeneration and Mallory-Denk body, and various degrees of fibrosis [2,3]. Several studies have been aimed at discovering pharmacologic treatments for NAFLD/NASH; however, despite the clinical importance, unfortunately, there is still a lack of consensus for pharmacologic treatment of the diseases. Oxidative stress is considered to be one of the main players in the development and progression of NAFLD/NASH [4–6], and vitamin E is known as a free radical scavenger, acting on TGF- β 1, peroxisome proliferator-activated receptors, and apoptosis regulating genes [7,8]. Ji and colleagues tried to evaluate the efficacy of vitamin E on NAFLD/NASH by meta-analyzing previously published data through June 2013. They found that vitamin E has a preferred effect on NAFLD/NASH as well as chronic hepatitis C by improving serum aminotransferase levels. We initially reported the efficacy of vitamin E in adult patients with NASH [9]. We enrolled 12 patients with NASH and 10 with NAFLD. All patients were given dietary instruction for 6 mo, and thereafter vitamin E (300 mg/d; 100 mg is equivalent to 100 IU) was given to only patients with NASH for 1 y. In consequence, plasma aminotransferase levels were improved by diet in patients with NAFLD but not those with NASH, and then we gave vitamin E to only patients with NASH because serum biochemical markers in patients with NAFLD had been already improved by diet without medications. We greatly appreciate Ji and colleagues for referencing and including our data in their analysis; however, we did not examine the effect of vitamin E on NAFLD patients. We are concerned that the authors misread our data because they included our data in meta-analysis of vitamin E's effect on NAFLD though we did not give vitamin E to these patients. Moreover, as far as we know, still

several randomized controlled trials, which have higher evidence levels compared with our previous pilot study, do exist, but Ji and colleagues did not included these trials in their meta-analysis. For example, a Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis study dealt with a large population of NASH patients and observed them for 96 wks to evaluate the efficacy of vitamin E on NASH [10], and a Treatment of NAFLD in Children study also examined vitamin E's effect in child NASH patients [11]. Because we really cannot understand why Ji and colleagues excluded the data of these large randomized controlled trials, we strongly recommend Ji and colleagues reanalyze the efficacy of vitamin E on NAFLD/NASH by including large randomized controlled trial data and excluding our reported data from NAFLD meta-analysis. Otherwise, the readers of "Nutrition" may misunderstand their articles.

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Vitamin E therapy on aminotransferase levels in NAFLD/NASH patients



Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent diseases worldwide. In view of the widely accepted role of oxidative stress in the pathogenesis of NAFLD, many antioxidants have been widely used to treat the disease [1,2]. In recent years, the therapeutic effects of vitamin E for NAFLD have been widely studied. With the aim to evaluate the therapeutic efficacy, we performed a meta-analysis on the effects of vitamin E supplement in lowering the aspartate transaminase (AST) and alanine transaminase (ALT) levels in patients with NAFLD and nonalcoholic steatohepatitis (NASH) [3]. I appreciate Yoneda et al. for their interest in our study [4] and would like to provide more details about the reference selection criteria of our meta-analysis. Yoneda et al. discussed that several recent high-quality studies reporting the effects of vitamin E supplement on NASH were not included in our meta-analysis [5,6]. We certainly reviewed these studies during the data collection; however, they could not be included in our meta-analysis mainly for two reasons.

First, during the study selection process, we required that included studies must provide the exact mean and SD of the baseline (before treatment) and endline (after treatment) ALT and AST levels. However, there is lack of exact endline SD (after treatment) of ALT and AST levels in PIVENS (Pioglitazone or Vitamin E for NASH Study), which investigated the efficacy of vitamin E therapy on patients with NASH for 96 wk [5]. Similarly, the TONIC (Treatment of NAFLD in Children) trial, which investigated the efficacy of vitamin E therapy for patients with pediatric

NAFLD, did not provide endline SDs of ALT and AST levels [6]. Because SD is an important parameter to affect results, these studies were not included in our meta-analysis to ensure accuracy. Second, ALT and AST levels were reported in two sets of units in relative studies, U/L and IU/L, whereas the two units cannot be transferred and thus the studies in different units could not be divided in one group to perform meta-analysis, which further limits the number of included studies. Additionally, as a subtype of NAFLD, nonalcoholic fatty liver also can lead to fibrosis progression in patients, as suggested by emerging studies. Thus, the data in the paper by Hasegawa et al. was included in the NAFLD analysis, although exclusion of the data would not influence the conclusion [7].

There is only limited number of eligible studies that can be included in the meta-analysis at present. With more published studies providing detailed results, a more comprehensive conclusion can be drawn on the therapeutic effect of vitamin E on NAFLD and NASH in future.

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