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Meta-analysis

Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: A meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: Vitamin E is often used in the treatment of nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH); however, the magnitude of treatment response associated with vitamin E in improving liver function and histology in NAFLD/NASH has not, to our knowledge, been quantified systematically. Thus, we conducted a meta-analysis of randomized controlled trials (RCTs) using vitamin E in the treatment of NAFLD/NASH.

Methods: PubMed, Medline, and Cochrane Library Full Text Database, and Japan Medical-Literature Database (Igaku Chuo Zasshi) were searched until March 2014, and five RCTs were identified for meta-analysis.

Results: According to a random effect model analysis of the five studies, vitamin E significantly reduced aspartate transaminase (AST) by −19.43 U/L, alanine aminotransferase (ALT) by −28.91 U/L, alkaline phosphatase (ALP) by −10.39 U/L, steatosis by −0.54 U/L, inflammation by −0.20 U/L, and hepatocellular ballooning by −0.34 U/L compared with the control group. Vitamin E treatment with NASH adult patients showed obvious reductions in not only AST of −13.91 U/L, ALT by −22.44 U/L, steatosis of −0.67 U/L, inflammation of −0.20 U/L, but also fibrosis of −0.30 U/L compared to the control treatment.

Conclusions: Vitamin E significantly improved liver function and histologic changes in patients with NAFLD/NASH.

Introduction

With the increase in the prevalence of obesity and metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) has become one of the most important global public health issues of the twenty-first century [1,2]. NAFLD is a term used to describe liver diseases that express hepatic steatosis without excessive alcohol intake, and includes a wide spectrum of liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), which causes liver cirrhosis and may develop into hepatocellular carcinoma [3–5]. Although the pathogenesis of NASH remains obscure the, “two-hit theory” and the “multiple parallel hits hypothesis” have been proposed [6,7]. In both, oxidative stress is considered to be one of the key factors in the onset and development of NASH [7–9]. Antioxidant therapy has thus been considered to have the possibility of beneficial effects in the management of NASH. In particular, vitamin E has been thought to act as an antioxidant agent [10]. Since we reported the efficacy of vitamin E on adult patients with NASH [11], a number of clinical studies, including randomized control trials (RCTs), have been attempted to confirm the effect of vitamin E on NASH.

Although some meta-analyses on the efficacy of antioxidant agents was performed, and their usefulness was demonstrated [12,13], one systematic review, by Socha et al. [14] evaluated vitamin E therapy on NASH. Recently, Ji et al. [15] presented a meta-analysis demonstrating the effect of vitamin E on NAFLD and NASH; however, their analysis had some critical issues. For

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example, their most recent included data was published in 2008, even though two large RCTs on vitamin E and NAFLD/NASH were published in 2010 and 2011 [13,16]. Moreover, although they included our original pilot study [11], they misunderstood and misanalysed our data. Therefore, the aim of this study was to perform a meta-analysis to evaluate the efficacy of vitamin E on liver dysfunction, including biochemical and histologic indexes in patients with NAFLD/NASH. This study might assist clinicians in better assessing the benefits of vitamin E in treating NAFLD/NASH, and might help to draw up clinical guidelines for NAFLD/NASH backed by strong evidence.

Methods

Data sources and searches

We searched PubMed, Medline, the Cochrane Library Full Text Database, and the Japan Medical-Literature Database (Igaku Chuo Zasshi) up to March 2014. The search strategy used free-text words and MeSH terms to increase sensitivity, including NASH or NAFLD or "nonalcoholic steatohepatitis" or "nonalcoholic fatty liver disease" or "fatty liver" and "vitamin E" or "alpha-Tocopherol" or "α-tocopherol". Available abstracts from the Digestive Diseases Week and European United Gastroenterology Week Conferences were also screened, and full texts were requested if necessary. In addition, a manual literature search was conducted using the reference lists of identified original manuscripts and reviews. All searches were conducted independently by two investigators. The results were compared, and any questions or discrepancies were resolved through discussion and consensus.

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) patients of any sex or ethnic origin with NAFLD/NASH, 2) randomized controlled trials using vitamin E, and 3) diagnosis of NAFLD/NASH determined by histology or ultrasonography. Patients with other causes of hepatic steatosis or steatofibrosis, such as alcoholic fatty liver disease, viral hepatitis, autoimmune hepatitis, liver decompensation, or malignancy, were excluded. Case reports or series were excluded, as were review articles. Studies were also excluded if relevant data were not extractable, if the trial lacked interindependence with other trials or if it lacked peer review [17].

The trials needed to have at least one of the following characteristics: body mass index (BMI), alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and histologic changes at baseline and postbaseline visits. Studies had to have objective outcome measures, otherwise they were excluded from this analysis [18].

Statistical analysis

For absolute values of AST, ALT, γ-GTP, ALP, BMI, steatosis, lobular inflammation, fibrosis, and hepatocellular ballooning at last visit on treatment, we estimated the pooled mean differences between the two treatment groups (vitamin E and control) and the 95% confidence interval (CI). The pooled mean difference for each outcome measure was estimated by using the point estimates of the mean difference for each separate study weighted according to the reciprocal of their variance (calculated as the square of the standard error in the individual study).

Absolute values for the nine outcomes at the last visit on treatment were analyzed as a substitute for the change from baseline, because some studies did not show the variability parameter (i.e., standard deviation [SD], standard error [SE], or 95% CI) of the change from baseline. However, it is not necessary to consider the baseline differences between the two treatment groups, as only randomized controlled trials were selected in this meta-analysis and the baseline values of the outcomes were essentially not different between the two groups in the selected studies.

Statistical heterogeneity of the mean differences across studies was assessed by applying the chi-square test for Cochrane Q statistics and I^2 statistics [19]. The I^2 statistics are derived from the Q statistics ($I^2 = [Q–df]/Q \times 100$) and quantify heterogeneity on a scale of 0–100%, where *df* is a degree of freedom. If the *P* value for the chi-square test was lower than 0.10 or the I^2 statistics was higher than 75%, we considered it representative of heterogeneity [19,20]. The outcome measures with heterogeneity were analyzed using a mixed effect model including the treatment group as a fixed effect and the study as a random effect. This model is known as random effect model in meta-analyses (henceforth referred to as random effect model). Otherwise, the mean differences with the 95% CI were pooled using a fixed effect model including the treatment group and study as fixed effects.

To assess the influences of patient characteristics and the sensitivity of the meta-analysis, we performed two subgroup analyses with adult NASH patients, when there were two or more studies in the subgroup. Furthermore, the possibility of publication bias was assessed by using a funnel plot [21]. The mean differences for each outcome measure were plotted against the standard errors of the mean differences of the selected studies.

If the identified studies did not report the mean and SD, SE, or the 95% CI for the outcome measures on each treatment group in the text or tables, the figures were removed from the PDF files, and the mean and SD were digitally measured by a computer using Adobe Photoshop CS5 (Adobe Systems Inc., San Jose, CA, USA). When the SD at last visit on treatment was missing in the articles, we substituted for the missing value by using the SD at baseline for the outcome measures.

All *P* values were two-sided and $P < 0.05$ was considered statistically significant. All statistical analyses were done with the Review Manager 5.2 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark).

Results

Study selection

Our initial search identified 293 potentially relevant publications, of which 274 did not meet our inclusion criteria (Fig. 1), resulting in 19 papers, 14 of which could not be used effectively to evaluate the effect of vitamin E, and were excluded. Finally, we included only five studies that reported randomized controlled study data results with clear, concise methodology. Of the five studies included, two originated from North America [16,22], one from Asia [23], and two from Europe [24,25]. All searches were conducted independently by two investigators. The results were compared, and any questions or discrepancies were resolved through discussion and consensus.

Baseline characteristics

Data was analyzed for 401 patients (n = 190 in vitamin E group and n = 211 in control group) with NASH or NAFLD who participated in the selected five randomized trials. The study designs and baseline characteristics are summarized in Table 1. All of the studies comprised both men (n = 229, 57%) and women (n = 172, 43%). The pooled number of patients with NASH and NAFLD were 200 (50%) and 201 (50%), respectively. Among the five studies, two enrolled adult patients (range of the means across studies: 45–47 y) and three targeted children and adolescents with NAFLD

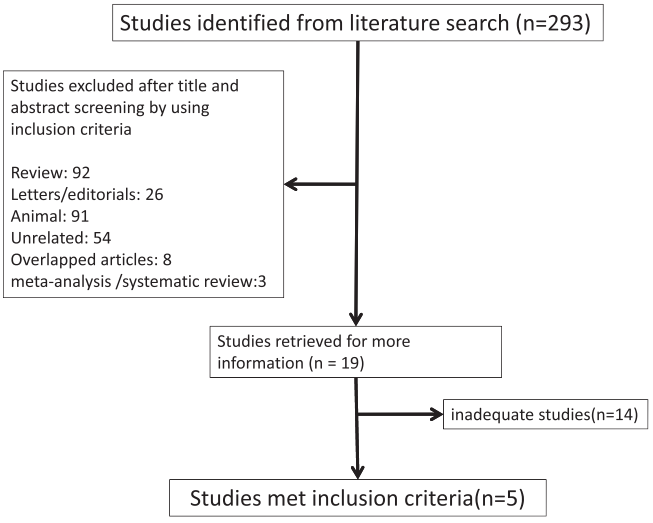

Fig. 1. Published work search and selection process.