

Abstract

JAMA. 2011 Apr 27;305(16):1659-68.

Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial.

Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, Abrams SH, Scheimann AO, Sanyal AJ, Chalasani N, Tonascia J, Ünalp A, Clark JM, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; Nonalcoholic Steatohepatitis Clinical Research Network.

Department of Pediatrics, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Columbia University, New York, New York, USA.

CONTEXT: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in US children and adolescents and can present with advanced fibrosis or nonalcoholic steatohepatitis (NASH). No treatment has been established.

OBJECTIVE: To determine whether children with NAFLD would improve from therapeutic intervention with vitamin E or metformin.

DESIGN, SETTING, AND PATIENTS: Randomized, double-blind, double-dummy, placebo-controlled clinical trial conducted at 10 university clinical research centers in 173 patients (aged 8-17 years) with biopsy-confirmed NAFLD conducted between September 2005 and March 2010. Interventions Daily dosing of 800 IU of vitamin E (58 patients), 1000 mg of metformin (57 patients), or placebo (58 patients) for 96 weeks.

MAIN OUTCOME MEASURES: The primary outcome was sustained reduction in alanine aminotransferase (ALT) defined as 50% or less of the baseline level or 40 U/L or less at visits every 12 weeks from 48 to 96 weeks of treatment. Improvements in histological features of NAFLD and resolution of NASH were secondary outcome measures.

RESULTS: Sustained reduction in ALT level was similar to placebo (10/58; 17%; 95% CI, 9% to 29%) in both the vitamin E (15/58; 26%; 95% CI, 15% to 39%; $P = .26$) and metformin treatment groups (9/57; 16%; 95% CI, 7% to 28%; $P = .83$). The mean change in ALT level from baseline to 96 weeks was -35.2 U/L (95% CI, -56.9 to -13.5) with placebo vs -48.3 U/L (95% CI, -66.8 to -29.8) with vitamin E ($P = .07$) and -41.7 U/L (95% CI, -62.9 to -20.5) with metformin ($P = .40$). The mean change at 96 weeks in hepatocellular ballooning scores was 0.1 with placebo (95% CI, -0.2 to 0.3) vs -0.5 with vitamin E (95% CI, -0.8 to -0.3; $P = .006$) and -0.3 with metformin (95% CI, -0.6 to -0.0; $P = .04$); and in NAFLD activity score, -0.7 with placebo (95% CI, -1.3 to -0.2) vs -1.8 with vitamin E (95% CI, -2.4 to -1.2; $P = .02$) and -1.1 with metformin (95% CI, -1.7 to -0.5; $P = .25$). Among children with NASH, the proportion who resolved at 96 weeks was 28% with placebo (95% CI, 15% to 45%; 11/39) vs 58% with vitamin E (95% CI, 42% to 73%; 25/43; $P = .006$) and 41% with metformin (95% CI, 26% to 58%; 16/39; $P = .23$). Compared with placebo, neither therapy demonstrated significant improvements in other histological features.

CONCLUSION: Neither vitamin E nor metformin was superior to placebo in attaining the primary outcome of sustained reduction in ALT level in patients with pediatric NAFLD.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00063635.

PMID: 21521847

