SUPPLEMENTARY DATA

Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients with Type 2 Diabetes: A Randomized Controlled Trial

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List of investigators

Fernando Bril, MD[1]; Diane M. Biernacki, RN[1]; Romina Lomonaco, MD[1]; Srilaxmi Kalavalapalli, MS[1]; Sreevidya K. Subbarayan, MD[1]; Jinping Lai, MD[2]; Fermin Tio, MD[3]; Amitabh Suman, MD[4]; Beverly K. Orsak, RN[5]; Joan Hecht, RN[6]; Kenneth Cusi, MD[1,7].

From: [1]Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, Florida; [2]Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, Florida; [3]Department of Pathology, University of Texas Health Science Center at San Antonio (UTHSCSA), San Antonio, Texas; [4]Division of Gastroenterology, Hepatology, and Nutrition, Malcom Randall VA Medical Center, Gainesville, Florida; [5]Division of Diabetes, University of Texas Health Science Center at San Antonio (UTHSCSA), San Antonio, Texas; [6]Division of Diabetes, Audie L. Murphy Memorial VA Hospital, San Antonio, Texas; [7]Division of Endocrinology, Diabetes and Metabolism, Malcom Randall VA Medical Center, Gainesville, Florida.

Address for correspondence:
Kenneth Cusi, M.D., F.A.C.P., F.A.C.E., Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Florida
1600 SW Archer Road, room H-2. Gainesville, Florida 32610
Phone: 352-273-8662
Email: Kenneth.Cusi@medicine.ufl.edu

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Complete inclusion and exclusion criteria

A total of 288 patients were recruited, and 105 patients were randomized after initial screening. Inclusion and exclusion criteria were evaluated by the investigators.

Patients had to complete the following inclusion criteria:

1. Had to been able to communicate meaningfully with the investigator and be legally competent to provide written informed consent.
2. Age range between 18 to 70 years (inclusive).
3. Caucasian, African-American, or Hispanic ethnicity.
4. Diagnosis of type 2 diabetes mellitus, based on prior medical history, results from prior laboratories (hemoglobin A1c or fasting plasma glucose), results from the oral glucose tolerance test performed during the study, or use of glucose-lowering medications (use of thiazolidinediones, GLP-1 agonists and SGLT-2 inhibitors was not allowed).
5. Diagnosis of definite NASH based on a liver biopsy, and defined as: zone 3 accentuation of macrovesicular steatosis (any grade), hepatocellular ballooning (any degree) and lobular inflammatory infiltrates (any amount).
6. Female patients that were at least one year post-menopausal, or were using adequate mechanical contraceptive precautions (i.e. intrauterine device, diaphragm with spermicide, condom with spermicide), history of surgically sterilized (i.e. bilateral tubal ligation, bilateral oophorectomy), or had undergone a hysterectomy.
7. Female patients (except for those patients who had undergone a hysterectomy or a bilateral oophorectomy) were eligible if they had a negative pregnancy test throughout the study period.
8. Participants had to fulfill the following laboratory values: hemoglobin $\geq$ 12 g/dl in males, or $\geq$ 11 g/dl in females, white blood count $\geq$ 3,000/mm3, neutrophil count $\geq$ 1,500/mm3, platelets $\geq$ 100,000/mm3, albumin $\geq$3.0 g/dl, serum creatinine $\leq$ 1.8 mg/dl, AST and ALT $\leq$ 3 times the upper limit of normal (if only AST or ALT $\geq$3, it did not definitively excluded the patient, but plasma aminotransferases were repeated to confirm that they were $\leq$3 to enter the study within 1-8 weeks).

Individuals that met the following exclusion criteria were not included in the study:

1. No past or current history of alcohol abuse (alcohol consumption greater than 20 grams of ethanol per day). Alcohol abuse was ruled out based on the physicians' judgment, self-reported usage of alcohol, and family members' report of patient's alcohol use. In addition, the Alcohol Use Disorders Identification Test (AUDIT) questionnaire was used to assess alcohol use.
2. Patients that received chronically medications known to have adverse effects on glucose tolerance levels, unless the patient had been on a stable dose of such agents for 4 weeks prior to study entry.
3. Patients that were taking medications that could induce steatosis, such as estrogens or other hormonal replacement therapy, tamoxifen, raloxifene, oral glucocorticoids or chloroquine.
4. Any cause of chronic liver disease other than NASH (such as –but not restricted to– alcohol or drug abuse, medication, chronic hepatitis B or C, autoimmune, hemochromatosis, Wilson's disease, α1-antitrypsin deficiency). The following tests were done to rule out these differential diagnosis:

- Hepatitis B: positive hepatitis B surface antigen (HBsAg).
- Hepatitis C: positive hepatitis C antibody (anti-HCV).
- Autoimmune liver disease: positive ANA, anti-smooth muscle ab, anti-mitochondrial ab, anti-LKM antibodies or previous histologic features consistent with autoimmune hepatitis.
- Wilson's disease: ceruloplasmin levels below the limits of normal.
- α1- antitrypsin (A1AT) deficiency: α1-antitrypsin level below normal level.
- Hemochromatosis or history of iron overload: Presence of 3+ or 4+ stainable iron on liver biopsy, history of iron overload.
- Drug-induced liver disease: History of exposure.
- History of primary or metastatic liver cancer.

5. Subjects were excluded if they had other medical conditions known to cause fatty liver disease.
6. Any clinical evidence of hepatic decompensation such as history of ascites, esophageal bleeding varices, or spontaneous encephalopathy.
7. Prior or scheduled surgical procedures to include gastroplasty, jejuno-ileal or jejunocolic bypass.
8. Prior exposure to organic solvents such as carbon tetrachloride.
9. Total parenteral nutrition (TPN) within the past 6 months.
10. Subjects with type 1 diabetes mellitus.
11. Patients with a history of clinically significant heart disease (New York Heart Classification greater than grade II), peripheral vascular disease (history of claudication), or diagnosed pulmonary disease (dyspnea on exertion of one flight or less; abnormal breath sounds on auscultation).
12. Patients with severe osteoporosis (T-score -3.0 at the level of spine and hip) were excluded from participating.
13. Pregnant or lactating women.

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Supplementary Table S1. Adverse events

	Placebo (n=32)	Vitamin E (n=36)	Vitamin E and pioglitazone (n=36)
Cardiovascular			
Death	0	2	2
Atypical chest pain or epigastralgia	3	4	6
Arrhythmia	1	1	1
Orthostatic hypotension	0	1	0
Hypertensive crisis	0	0	1
Patients with lower limb edema leading to pioglitazone down-titration	1	0	5*
Gastrointestinal			
Pancreatitis	1	0	0
Diverticulitis	0	0	1
Diarrhea/constipation	6	6	4
ALT/AST elevations	3	1	0
Respiratory			
Upper respiratory infection, sinusitis, bronchitis, or unspecific dyspnea	8	9	10
Asthma/COPD exacerbation	0	1	2
Endocrinologic			
Patients reporting hypoglycemic episodes	6	7	13
Traumatic bone fractures	2	4	0
Reduction ≥ 0.5 T-score in femoral neck	0	1	0
Hypertriglyceridemia	0	0	1
Gynecologic			
Benign breast nodule and/or pain	1	1	0
Infectious Diseases			
Pneumonia	0	0	1
Tonsillar abscess	0	0	1
Endocariditis	0	1	0
Cellulitis	0	1	0
Urologic			
Diagnosis of prostate cancer	0	0	1
Diagnosis of bladder cancer	0	0	0
Kidney stones	0	1	0

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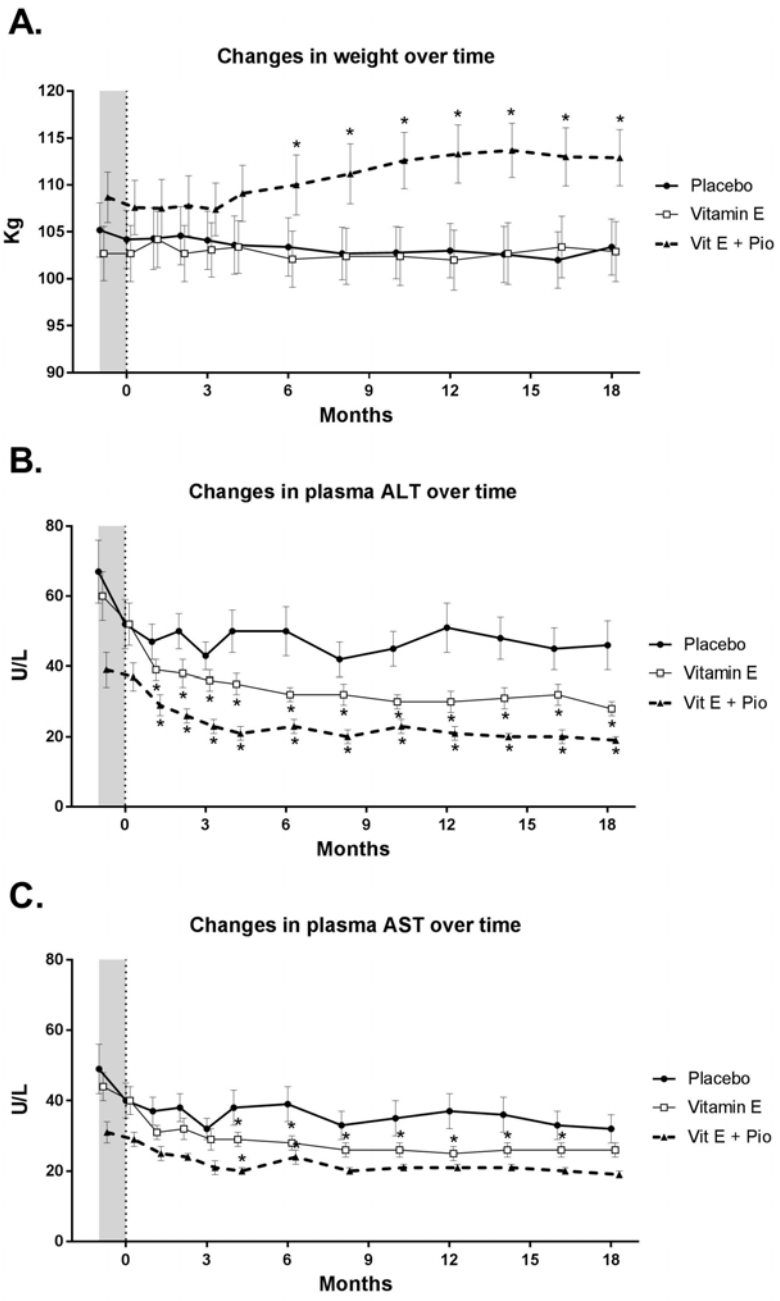
Other			
Subdural hematoma	0	1	0
Biopsy-related complications	2	1	2
Back or joint pain	4	6	9
Back, joint, or hernia repair surgery	1	1	1
Newly developed anemia	0	1	1

* Two of these patients also required treatment with furosemide.

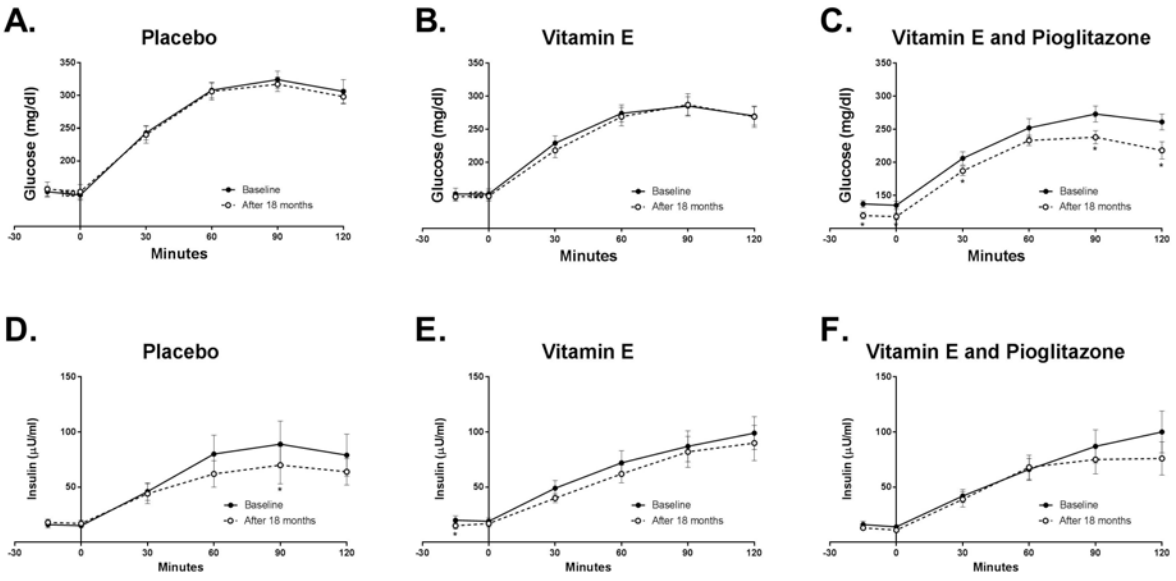
SUPPLEMENTARY DATA

Supplementary Figure S1. Changes in weight (panel A), plasma ALT (panel B), and plasma AST (panel C) over 18 months of follow-up. *p<0.05 compared to placebo group. Data presented as mean ± standard error.



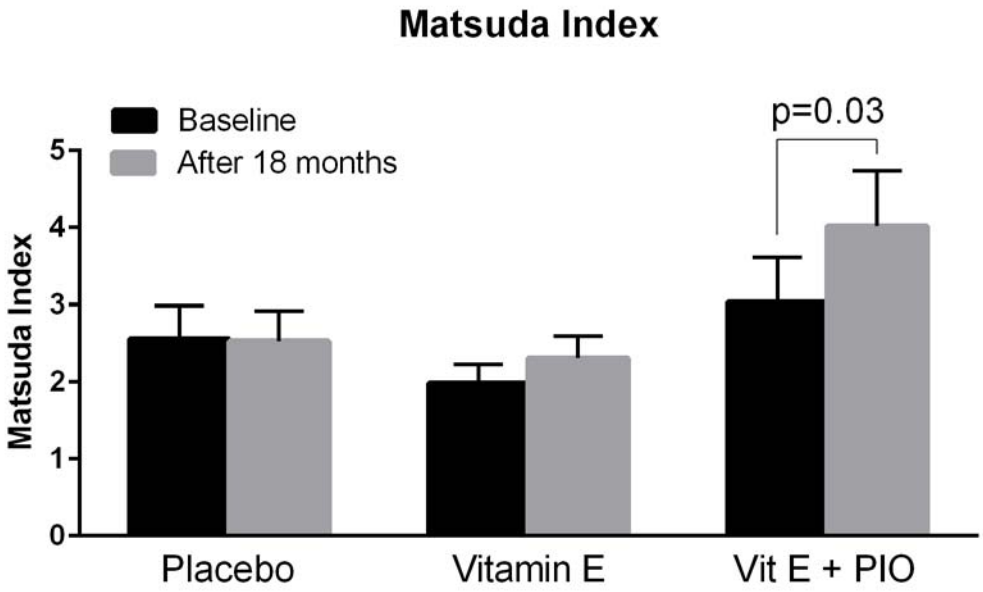
SUPPLEMENTARY DATA

Supplementary Figure S2. Changes in plasma glucose and insulin concentrations during an oral glucose tolerance test in the placebo (panels A and D), vitamin E (panels B and E), and combination therapy (panels C and F) groups. *p<0.05 compared to baseline concentrations. Data presented as mean ± standard error.



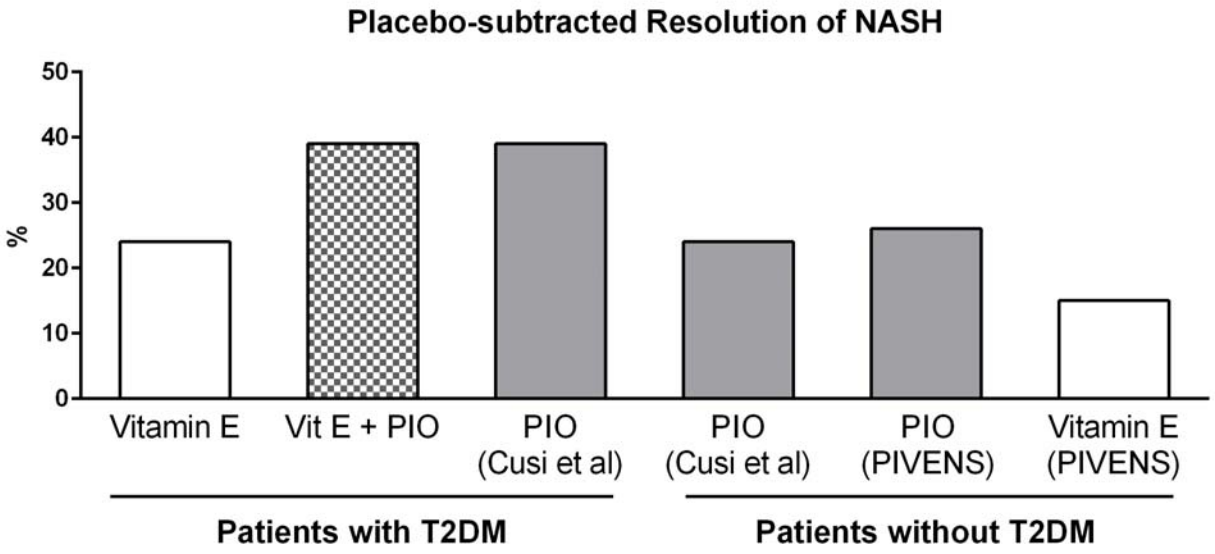
SUPPLEMENTARY DATA

Supplementary Figure S3. Changes in insulin sensitivity expressed as the Matsuda Index during an oral glucose tolerance test. Data presented as mean ± standard error.



SUPPLEMENTARY DATA

Supplementary Figure S4. Placebo-subtracted resolution of NASH compared to prior studies assessing vitamin E and/or pioglitazone, dividing patients depending on the presence or absence of T2DM. Data presented as placebo-subtracted proportion for the multiple imputation analysis.



SUPPLEMENTARY DATA

Supplementary Figure S5. Placebo-subtracted primary outcome compared to our prior study assessing the same outcome with pioglitazone alone, dividing patients depending on the presence or absence of T2DM. Data presented as placebo-subtracted proportion for the multiple imputation analysis.