## **Supplementary Table S1.** Randomized controlled trials *excluded* at the stage of eligibility according to the PRISMA flow diagram.

Investigator, Ref.	Study characteristics	Main findings	Exclusion reasons
Anushiravani et al. (1)	150 patients with NAFLD were randomized to five groups: lifestyle plus placebo, metformin, silymarin, pioglitazone, or vitamin E for 3 months	Silymarin, pioglitazone and vitamin E improved serum aminotransferases in patients with NAFLD	Unsatisfactory study design (low quality)
Handzlil et al. (2)	42 patients with NAFLD randomized to dietary treatment alone (n = 21) or to diet plus metformin (n = 21)	Metformin therapy combined with dietary treatment was effective for the reduction of hepatic steatosis and fibrosis evaluated by liver ultrasonography and elastography, respectively	Unsatisfactory study design (low quality)
Bril et al. (3)	101 NASH patients with type 2 diabetes or pre-diabetes were randomly assigned to pioglitazone or placebo for 18 months	Pioglitazone reduced liver fibrosis in patients with type 2 diabetes rather than in patients with prediabetes	Data already included in another eligible RCT (see ref. #23 of the manuscript)
Joy et al. (4)	12 patients with biopsy- proven NASH were randomized to sitagliptin or placebo for 24 weeks	Sitagliptin did not improve fibrosis score or NAS after 24 weeks when compared to placebo	Unsatisfactory sample size
Gluud et al. (5)	Individual patient data of 12 RCTs on lixisenatide vs. placebo and 3 RCTs with active comparators	Lixisenatide increased the proportion of obese or overweight patients with type 2 diabetes who achieved normalisation of serum ALT	Unsatisfactory study design (systematic review with individual patient data meta- analysis)
Shields et al. (6)	19 patients with NASH were randomized to dietary or metformin for 12 months	Metformin had a small beneficial effect on serum liver enzymes or liver histology in patients with NASH	Unsatisfactory sample size
Uygun et al. (7)	36 patients NASH were randomized to dietary treatment alone or to diet plus metformin therapy for 6 months	Metformin decreased serum aminotransferase levels compared to dietary alone. No significant differences in necro-inflammatory activity or fibrosis were observed between the groups	Unsatisfactory sample size
Armstrong et al. (8)	LEAD & LEAD-2 programs: 3258 patients with type 2 diabetes who were unable to maintain good glycemic control with diet and exercise alone, or with oral hypoglycemic treatment	Liraglutide 1.8 mg/day reduced serum ALT levels compared to placebo (and was dose responsive); lower doses of liraglutide (0.6 and 1.2 mg/day) had similar effects as placebo. In LEAD-2, liraglutide improved liver fat content in a dose dependent way; however, there was no significant difference between liraglutide and placebo after adjusting for weight loss or HbA1c	Unsatisfactory inclusion criteria (no information on alcohol intake or diagnosis of NAFLD by imaging or biopsy)
Leiter et al. (9)	Patients with type 2 diabetes pooled from four placebo-controlled trials with canaglifozin 100 and 300 mg/day (n=2313), and two active-controlled trials of canagliflozin 300 mg/day vs.	Canagliflozin provided significant improvements in ALT, AST and GGT levels vs. either placebo or 100-mg sitagliptin treatment	Unsatisfactory inclusion criteria (no information on alcohol intake or diagnosis of NAFLD by imaging or biopsy)

	sitagliptin 100 mg/day (n=1488)		
Sattar et al. (10)	Patients with type 2 diabetes included in the EMPA-REG OUTCOME trial (n=7020), pooled data from four 24-week placebo-controlled trials (n=2477) and a trial of empagliflozin vs. glimepiride over 104 weeks (n=1545)	Empaglifozin 10-25 mg/day provided significant improvements in serum ALT, levels vs. either placebo or glimepiride treatment. ALT reductions were largely independent of concomitant changes in body weight or HbA1	Unsatisfactory inclusion criteria (no information on alcohol intake or diagnosis of NAFLD by imaging or biopsy)
Bril et al. (11)	Patients with type 2 diabetes and biopsy-proven NASH (n=105) were randomized to vitamin E 400 IU b.i.d., vitamin E 400 IU b.i.d. plus pioglitazone 45 mg/day, or placebo. Eighty-six patients completed the 18-month study	More patients on combination therapy (pioglitazone <i>plus</i> vitamin E) improved liver histology versus placebo, but not with vitamin E alone	Data already included in another eligible RCT (see ref. #23 of the manuscript)

## **REFERENCES** for the table

- 1. Anushiravani A, Haddadi N, Pourfarmanbar M, Mohammadkarimi V. Treatment options for nonalcoholic fatty liver disease: a double-blinded randomized placebo-controlled trial. Eur J Gastroenterol Hepatol. 2019;31:613-617.
- Handzlik G, Holecki M, Kozaczka J, Kukla M, Wyskida K, Kędzierski L, et al. Evaluation of metformin therapy using controlled attenuation parameter and transient elastography in patients with non-alcoholic fatty liver disease. Pharmacol Rep. 2019;71:183-188.
- 3. Bril F, Kalavalapalli S, Clark VC, Lomonaco R, Soldevila-Pico C, Liu IC, et al. Response to pioglitazone in patients with nonalcoholic steatohepatitis with vs without type 2 diabetes. Clin Gastroenterol Hepatol. 2018;16:558-566.
- 4. Joy TR, McKenzie CA, Tirona RG, Summers K, Seney S, Chakrabarti S, et al. Sitagliptin in patients with non-alcoholic steatohepatitis: A randomized, placebo-controlled trial. World J Gastroenterol. 2017;23:141-150.
- 5. Gluud LL, Knop FK, Vilsbøll T. Effects of lixisenatide on elevated liver transaminases: systematic review with individual patient data meta-analysis of randomised controlled trials on patients with type 2 diabetes. BMJ Open. 2014;4:e005325.
- 6. Shields WW, Thompson KE, Grice GA, Harrison SA, Coyle WJ. The effect of metformin and standard therapy versus standard therapy alone in nondiabetic patients with insulin resistance and nonalcoholic steatohepatitis (NASH): a pilot trial. Therap Adv Gastroenterol. 2009;2:157-163.
- 7. Uygun A, Kadayifci A, Isik AT, Ozgurtas T, Deveci S, Tuzun A, et al. Metformin in the treatment of patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2004;19:537-544.
- 8. Amstrong MJ, Houlihan DD, Rowe IA, Clausen WH, Elbrond B, Gough SC, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther. 2013;37:234-242.
- 9. Leiter LA, Forst T, Polidori D, Balis DA, Xie J, Sha S. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. Diabetes Metab. 2016;42:25-32.
- 10. Sattar N, Fitchett D, Hantel S, George JT, Zinman B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial. Diabetologia. 2018;61:2155-2163.
- 11. Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. Diabetes Care. 2019;42:1481-1488.