Table 1. Effects of different drug treatments for nonalcoholic steatohepatitis (NASH) on liver histology in main randomized clinical trials (ordered by publication year) that included adult patients with type 2 diabetes mellitus or prediabetes.

Authors, year [ref.]	Active treatment (study sample); % of patients with T2DM or prediabetes	Duration of treatment	Main effects on liver histology
Bugianesi *et al*. 2005 [171]	MET 2 g/day (n=55) vs. Vit. E 800IU/day (n=28) vs. Diet (n=27). 9% with T2DM	12 months	Vitamin E and diet did not produce any beneficial histological effects. MET significantly improved hepatic steatosis, necroinflammation and fibrosis
Belfort *et al*. 2006 [172]	PIO 45 mg/day (n=29) vs. counselling (n=25). 100% with prediabetes or T2DM	6 months	PIO significantly improved hepatic steatosis, necroinflammation, ballooning and fibrosis *vs.* counselling
Ratziu *et al*. 2008 (FLIRT trial) [173]	RSG 8 mg/day (n=32); PL (n=31). 25% with T2DM	12 months	RSG significantly improved hepatic steatosis, without any changes in necro-inflammation and fibrosis
Haukeland *et al*. 2009 [174]	MET 2.5-3.0 g/day (n=24 cases) vs. PL (n=24). 100% with pre-diabetes or T2DM	6 months	No significant differences in hepatic steatosis, necroinflammation or fibrosis were observed between MET and the PL-group
Ratziu *et al*. 2010 (FLIRT-2 trial) [175]	RSG 8 mg/day (RSG-RSG, n=25; PL-RSG, n=28). Open-label extension of the FLIRT trial. 25% with T2DM	24 months	RSG conducted beyond 1 year did not yield any additional improvement on liver histology
Neuschwander-Tetri *al*. 2014 (FLINT trial) [131]	OCA 25 mg/day (n=141) vs. PL (n=142). OCA, n=102; PL, n=98. 52% with T2DM	72 weeks	The study was interrupted for superiority: 45% OCA *vs*. 21% PL had significantly improved hepatic steatosis, lobular inflammation, ballooning, and fibrosis. A marginally greater resolution of NASH was observed after OCA treatment (22% vs. 13%)
Argo *et al*. 2015 [176]	N-3 PUFA 3 g/day (n=17) or PL (n=17). 32% with T2DM	12 months	N-3 PUFA did not lead to improvement in the primary outcome of histological activity in NASH patients (≥2 point NAS reduction). N-3 PUFA led to reduced liver fat by multiple measures

Armstrong *et al*. 2016 (LEAN program) [177]	LIRA 1.8 mg/day (n=26) vs. PL (n=26). 33% with T2DM	48 weeks (extended to 72 weeks)	LIRA significantly improved hepatic steatosis, ballooning and fibrosis. NASH resolution was significantly greater cases after LIRA (39% in LIRA *vs*. 9% in PL, respectively)
Ratziu V *et al* 2016 (GOLDEN-505) [178]	ELA 80 mg/day (n=93) vs. ELA 120 mg/day (n=91), vs. PL (n=92). 40% with T2DM	52 weeks	NASH resolved without fibrosis worsening in more patients in the 120-mg ELA group vs. the PL group (19% vs. 12%). In post-hoc analyses of patients with NAS ≥4 (n=234), ELA120 mg resolved NASH more significantly than placebo (20% vs. 11%). Patients with NASH resolution after receiving ELA 120 mg had reduced hepatic fibrosis compared with those without NASH resolution
Cusi K *et al.* 2016 [179]	A total of 101 patients with prediabetes or T2DM with biopsy-proven NASH were randomized to receive either PIO (45 mg/day), or PL in combination with a low-calorie diet	18 months, followed by an 18-month open-label extension with PIO	Among patients randomly assigned to PIO, 58% achieved the primary histologic outcome and 51% had NASH resolution. PIO treatment was also associated with reduced intrahepatic fat content and improved adipose tissue, hepatic, and muscle insulin sensitivity. All 18-month metabolic and histologic improvements persisted over 36 months of therapy
Joy TR *et al*. 2017 [180]	SITA 100 mg/day (n=6) or PL (n=6). 100% with T2DM	24 weeks	SITA was not significantly better than PL at reducing hepatic fibrosis score or NAS score and its individual histological components
Bril F *et al*. 2017 [181]	Post-hoc analysis of statin use in a randomized trial assessing PIO vs. PL in 101 patients (86 on statins) with T2DM or prediabetes and biopsy-proven NASH	Up to 36 months	No significant changes in liver histology or hepatic insulin resistance were observed in patients who newly started statins or receiving PL during the trial

Abbreviations: ELA = elafibranor; LC = lifestyle changes; LIRA = liraglutide; MET = metformin; NAS = NAFLD activity score; N-3 PUFA = polyunsaturated fatty acids; OCA = obeticholic acid; PIO = pioglitazone; PL = placebo; RSG = rosiglitazone; SITA = sitagliptin; T2DM = type 2 diabetes mellitus; Vit. E = Vitamin E