

Supplementary Table 1 Summary of major clinical trials of antihyperglycemic medications in patients with chronic liver diseases

Dose	Duration	Population	DM	Cirrhosis	Conclusions	Ref.
<u>Metformin</u>						
2 g/d	12 mo	Biopsy-proven NAFLD	DM and non-DM	Non-cirrhotic	Transient improvement in liver chemistries compared to baseline	Nair <i>et al</i> , 2004
1700 mg/d	6 mo	Clinical NASH	Non-DM	-	No differences in necro-inflammatory activity or fibrosis	Uygun <i>et al</i> , 2004
2 g/d	12 mo	Biopsy-proven NAFLD	Non-DM	-	Higher rates of aminotransferase normalization compared to placebo	Buginanesi <i>et al</i> , 2005
2500-3000 mg/d	6 mo	Biopsy-proven NAFLD	DM and non-DM	Non-cirrhotic	No improvement in liver histology	Haukela <i>et al</i> , 2009
2 g/d	48 wk	Biopsy-proven NASH	DM and non-DM	25/26 were non-cirrhotic	Improvement in liver histology and ALT levels compared to baseline	Loomba <i>et al</i> , 2009
500-1000 mg/d	12 mo	Biopsy-proven NASH	Non-DM	-	No improvement in liver function tests or liver histology	Shields <i>et al</i> , 2009
1700 mg/d	12 mo	Biopsy-proven NAFLD	DM or IGT	-	No improvement in liver function tests or liver histology	Omer <i>et al</i> , 2010
<u>Pioglitazone</u>						
30 mg/d	48 wk	Biopsy-proven NASH	Non-DM	Non-cirrhotic	Improvement in biochemical and histological features of NASH compared to baseline	Promrat <i>et al</i> , 2004
45 mg/d	6 mo	Biopsy-proven	DM or IGT	Non-cirrhotic	Greater reduction in	Belfort <i>et al</i> ,

		NASH			aminotransferase levels, steatosis, balloon necrosis, and inflammation compared to placebo	2006
30 mg/d	96 wk	Biopsy-proven NASH	Non-DM	Non-cirrhotic	Greater reduction in aminotransferase levels, steatosis, and inflammation compared to placebo	Sanyal <i>et al</i> , 2010
30 mg/d	12 mo	Biopsy-proven NASH	Non-DM	30/31 were non-cirrhotic	Greater reduction in aminotransferase levels, histological features of liver injury, fibrosis compared to placebo	Aithal <i>et al</i> , 2008
45 mg/d	36 mo	Biopsy-proven NASH	DM or IGT	43/50 were non-cirrhotic	Persistent metabolic and histologic improvement compared to placebo	Cusi <i>et al</i> , 2016
45 mg/d	18 mo	Biopsy-proven NASH	DM or IGT	-	Greater reduction in liver fibrosis and insulin sensitivity in DM group compared to IGT group	Bril <i>et al</i> , 2018
45 mg/d	48 wk	Biopsy-proven hepatic steatosis with HIV/HCV - coinfection	Non-DM	Non-cirrhotic	Reduction in hepatic steatosis compared to baseline	Matthews <i>et al</i> , 2015
<u>Acarbose</u>						
300 mg/d	28 wk	Biopsy-proven	DM	Compensated	Reduction in fasting,	Gentile <i>et al</i> ,

		cirrhosis		Cirrhotic	postprandial, and mean glycemia compared to baseline	2001
300 mg/d	8 wk	Biopsy-proven cirrhosis	DM	Cirrhotic with low-grade encephalopathy	Greater reduction in ammonia level and improvement in intellectual function compared to placebo	Gentile <i>et al</i> , 2005
<i>Miglitol</i>						
150 mg/d	48 wk	Biopsy-proven NASH	DM or IGT	Non-cirrhotic	Improvement in steatosis and lobular inflammation	Komatsu <i>et al</i> , 2018
<i>Liraglutide</i>						
0.9 mg/d	96 wk	Biopsy-proven NASH	DM	9/10 were non-cirrhotic	Improvement in liver function and histological features compared to baseline	Eguchi <i>et al</i> , 2015
1.8 mg/d	48 wk	Biopsy-proven NASH	DM and non-DM	24/26 were non-cirrhotic	Higher rate of histological resolution of NASH with no worsening in fibrosis compared to placebo	Armstrong <i>et al</i> , 2016
1.8 mg/d	24 wk	Hepatic steatosis on imaging	DM	-	Improved liver function and reduced intrahepatic fat compared to baseline	Feng <i>et al</i> , 2017
1.8 mg/d	26 wk	Hepatic steatosis on imaging	DM	-	Reduction in intrahepatic lipid content compared to baseline	Yan <i>et al</i> , 2019
<i>Exenatide</i>						
20 mcg/d	26 wk	Hepatic steatosis on imaging	DM	-	Greater reduction in hepatic triglyceride	Dutour <i>et al</i> , 2016

						content compared to placebo	
<u>Vildagliptin</u>							
100 mg/d	6 mo	-	DM	-		Greater reduction in hepatic triglyceride levels compared to placebo	Macauley <i>et al</i> , 2015
<u>Sitagliptin</u>							
100 mg/d	24 wk	Hepatic steatosis on imaging	DM or IGT	-		No better than placebo in reducing liver fat	Cui <i>et al</i> , 2016
50-100 mg/d	52 wk	Hepatic steatosis on imaging	DM	-		No changes in aminotransferase levels	Deng <i>et al</i> , 2017
100 mg/d	52 wk	Biopsy-proven NASH	DM and non-DM	Non-cirrhotic		Reduction in hepatic steatosis and ballooning compared to baseline	Alam <i>et al</i> , 2018
100 mg/d	26 wk	Hepatic steatosis on imaging	DM	-		Reduction in intrahepatic lipid content compared to baseline	Yan <i>et al</i> , 2019
<u>Canagliflozin</u>							
300 mg/d	24 wk	Most have clinical NAFLD	DM	-		Greater reduction in intrahepatic triglyceride compared to placebo	Cusi <i>et al</i> , 2018
<u>Dapagliflozin</u>							
10 mg/d	24 wk	Hepatic steatosis on imaging	DM	-		Reduction in placebo-corrected total body weight and total body fat mass compared to baseline	Bolinder <i>et al</i> , 2012
10 mg/d	12 wk	Hepatic steatosis on imaging	DM	-		Reduction in liver fat content and biomarkers of hepatocyte injury compared to baseline	Eriksson <i>et al</i> , 2018

5 mg/d	24 wk	Clinical NAFLD	DM	19/33 had no significant fibrosis	Reduction in hepatic steatosis, liver stiffness, and aminotransferase levels compared to baseline	Shimizu <i>et al</i> , 2018
<u>Empagliflozin</u>						
10 mg/d	20 wk	Hepatic steatosis on imaging	DM	Non-cirrhotic	Greater reduction in liver fat content and ALT level compared to placebo	Kuchay <i>et al</i> , 2018
25 mg/d	24 wk	33/42 had hepatic steatosis on imaging	DM	-	Greater reduction in liver fat content compared to placebo	Kahl <i>et al</i> , 2020
<u>Ipragliflozin</u>						
50 mg/d	24 wk	Clinical NAFLD	DM	-	Reduction in hepatic steatosis, aminotransferase levels, and body weight compared to baseline	Ito <i>et al</i> , 2017