Obesity: Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

May 2020

Defining NAFLD

NAFLD is the presence of hepatic steatosis on either imaging or liver histology, or increased echogenicity and coarsened echotexture on liver ultrasound.[1-3]

- >5% of hepatocytes showing steatosis[1,2]
- In individuals who consume little/no alcohol[1,2]
- With no other secondary cause for hepatic steatosis (eg, alcohol, steatogenic drugs, autoimmune causes, viral hepatitis)[1,2]
- USFLI >30 (in the absence of heavy alcohol use and other known liver disease)[3]

1.Loomba R. *J Hepatol*. 2017 Feb;68(2):296-304. 2. Marcuccilli G, et al. *Int J Mol Sci*. 2016;17:562. 3. Tolman KG, et al. Ther Clin Risk Manag. 2007 Dec;3(6):1153-1163. 4. Le MH, et al. *PLoS One*. 2017 March 27;12(3):e0173499.

Defining NAFLD: NAFL and NASH

NAFLD can be broadly subdivided into NAFL and NASH[1,2]

- NAFL is a nonprogressive form of NAFLD[3]
  - Hepatic steatosis without hepatocellular injury (hepatocyte ballooning)
  - Minimal risk of progression to cirrhosis and liver failure
- NASH is a progressive form of NAFLD[3]
  - Hepatic steatosis and inflammation with hepatocyte ballooning, with or without fibrosis
  - Substantial risk of progression to liver fibrosis, cirrhosis, and/or mortality from liver dysfunction

1. Loomba R. *J Hepatol*. 2017 Feb;68(2):296-304. 2. Marcuccilli G, et al. *Int J Mol Sci*. 2016;17:562. 3. Rausch JC, Lavine JE, Chalasani N, et al. Genetic Variants Associated With Obesity and Insulin Resistance in Hispanic Boys With Nonalcoholic Fatty Liver Disease. J Pediatr Gastroenterol Nutr. 2018;66(5):789-796.

Prevalence of NAFLD

- NAFLD is the most common liver disease worldwide[1,2]
  - 2nd leading indication for liver transplantation[2]
  - 3rd leading cause of HCC in US[2]
- In Western countries, affects up to 30% of general population[3-6]
  - 3% to 5% of global population[7]
  - >10% of patients with NAFLD have advanced fibrosis[4]
  - 2% to 5% have substantial liver injury[5]
  - 1% to 2% will progress to NASH cirrhosis[5]
- In 2013, NASH was the second leading indication for liver transplantation in the US, accounting for 15.8% of waitlist registrants (170% increase from 2004).[8,9]
- Increased risk in patients with metabolic syndrome, obesity, T2D[3,10]

1. Marcuccilli G, et al. *Int J Mol Sci*. 2016;17:562. 2. Wong VW. *Adv Exp Med Biol*. 2018;1061:149-157. 3. Loomba R, et al. *Nat Rev Gastroenterol Hepatol*. 2013; 10:686–690. 4. Le MH, et al. *PLoS One*. 2017 March 27;12(3):e0173499. 5. Neuschwander-Tetri BA. *BMC Medicine*. 2017;15:45. 6. Sumida Y, et al. *J Gastroenterol*. 2018;53(3):362-376. 7. Povsic M, et al. *Adv Ther*. 2019 Jul;36(7):1574-1594. 8. Wong RJ, et al. *Gastroenterology*. 2015 Mar;148(3):547-55. 9. Mikolasevic I, et al. *World J Gastroenterol*. 2018 April 14;24(14):1491-1506. 10. Targher G, et al. *Nat Rev Nephrol*. 2017 May;13(5):297-310. 11. Vreman, Rick A et al. BMJ open vol. 7,8 e013543.

Symptoms of NAFLD

- Early stage NAFLD usually is asymptomatic or “silent.”[1]
- Patients with more advanced disease (NASH) may experience:[1]
  - Fatigue, malaise
  - Pain in the upper right abdomen
- Symptoms of cirrhosis due to NASH progression:[2-3]
  - Worsening fatigue
  - Ascites (swelling in the belly)
  - Jaundice
  - Enlarged liver and/or spleen, or breasts (men)
  - Red palms
  - Internal bleeding (patients may notice bruising or bleeding)

1. Bakhutashvili V, et al. Nonalcoholic fatty liver disease. In: Conn's Current Therapy 2020. Elsevier; 2020. 2. Carrion AF, et al. Cirrhosis. In: Conn’s Current Therapy 2020. Elsevier; 2020. 3. NIDDK. Symptoms & causes of cirrhosis. 2018. https://www.niddk.nih.gov/health-information/liver-disease/cirrhosis/symptoms-causes. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Clinical Burden of NAFLD

- NAFLD is a multisystem disease[1]
  - Affects extra-hepatic organs and regulatory pathways
- Burden is not confined to liver-related morbidity/mortality[1]
  - Increased risk of T2D, CVD, metabolic syndrome, liver fibrosis, and CKD[2]
- NAFLD increases mortality risk[3]
  - Majority of deaths among patients with NAFLD are attributable to CVD[1,3,4]
  - Significantly greater overall mortality in patients with advanced fibrosis[3]

1. Byrne CD, et al. *J Hepatol*. 2015 Apr;62(1 Suppl):S47-S64. 2. Targher G, et al. *Nat Rev Nephrol*. 2017 May;3(5):297-310. 3. Le MH, et al. *PLoS One*. 2017 March 27;12(3):e0173499. 4. Diordjevic DB, et al. *Curr Vasc Pharmacol*. 2018;16(3):228-238. CKD, chronic kidney disease; CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; T2D, type 2 diabetes.

Pathophysiology of NAFLD

- NAFLD pathophysiology is complex and not well understood.[1]
- NAFLD is considered a hepatic manifestation of the metabolic syndrome.[1]
- Adiposity-based chronic disease/obesity predisposes patients to NAFLD.[1-4]
- Insulin resistance is the major mechanism in NAFLD/NASH development and progression.[5]
- Also involved: adipokines, inflammation, lipid metabolism dysfunction, oxidative stress, pro-coagulant status, proinflammatory cytokines.[6]
- Increasing evidence links NAFLD and CKD.[7]

1. Doulberis M, et al. *Metabolism*. 2017;71:182-197. 2. Toshikuni N, et al. *World J Gastroenterol*. 2014;20:8393-8406. 3. Berzigotti A, et al. *Hepatology*. 2011 Aug;54(2):555-61. 4. Mechanick JI, et al. *Endocr Pract*. 2017 Mar;23(3):372-378. 5. Engin A. *Adv Exp Med Biol*. 2017;960:443-467. 6. Diordjevic DB, et al. *Curr Vasc Pharmacol*. 2018;16(3):228-238. 7. Targher G, et al. *Nat Rev Nephrol*. 2017 May;13(5):297-310. CKD, chronic kidney disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Screening for NAFLD

- Screening for NAFLD is recommended for patients with:[1-2]
  - Insulin resistance, metabolic syndrome, and/or obesity
  - Abnormal liver enzymes (ie, increased ALT, AST, or γGT)
  - Incidental discovery of steatosis
  - Persistently high serum ferritin/increased iron saturation
- Exclude competing etiologies (eg, chronic viral hepatitis, hemochromatosis, autoimmune liver disease)[1,2]
- Rule out significant fibrosis (≥F2) using surrogate markers (NFS, FIB-4, ELF, or FibroTest®)[1,2]
  - Refer patients for transient elastography if ≥F2 cannot be ruled out.[1]
- If ≥F2 is confirmed, final diagnosis of disease severity by liver biopsy (gold standard).[1-2]

1. EASL, et al. *J Hepatol.* 2016 Jun;64(6):1388-4022. 2. Chalasani N, et al. *Hepatology* (67);1:2018. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, Enhanced Liver Fibrosis; FIB-4, fibrosis 4 calculator; FLI, fatty liver index; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; US, ultrasound; γGT, γ-glutamyl-trans-peptidase.

Diagnosis of NAFLD via Conventional Imaging: Ultrasonography

Ultrasound is the recommended first-line imaging modality to diagnose hepatic lipid accumulation in clinical practice.[1]

Benefits[2]

- Most commonly used modality, due to limitations of other noninvasive tests
- Widely available
- Safe and well tolerated
- Can be performed on all scanners

Limitations[1,2]

- Lacks sensitivity to detect liver fat content at 5%
- Limited sensitivity if <30% of hepatocytes are steatotic
- Qualitatively interpreted; findings may be influenced by factors other than presence/degree of hepatic steatosis
- Limited accuracy, repeatability, reproducibility, especially in individuals with obesity

To detect hepatic steatosis, quantitative ultrasound may be superior to conventional ultrasound.[2]

1. Marcuccilli G, et al. *Int J Mol Sci*. 2016;17:562. 2. Loomba R. *J Hepatol.* 2018 Feb;68(2):296-304. NAFLD, nonalcoholic fatty liver disease.

Diagnosis of NAFLD via Liver Biopsy

Ultrasound is the recommended first-line imaging modality to diagnose hepatic lipid accumulation in clinical practice.[1]

Benefits

- Confirms/excludes NAFLD diagnosis, especially in setting of competing etiologies or in patients with atypical clinical features[2,3]
- Distinguishes between NAFL, NAFL with inflammation, and NASH[2]
- Provides information on disease severity, inflammatory activity, and fibrosis stage[2]

Limitations

- Invasive and expensive[1]
- Sampling error[4]
- Intraobserver and interobserver variability in interpretation[4]
- Adverse effects include pain, infection, bleeding/hemorrhage, and death (rare)[1,4]

To facilitate risk stratification, there is a compelling need for non-invasive assessments that detect the presence of hepatic steatosis and NASH and identify fibrosis stage.[1]

1. Loomba R. *J Hepatol.* 2018 Feb;68(2):296-304. 2. Chalasani N, et al. *Hepatology* (67);1:2018. 3. Rockey DC, et al. *Hepatology*. 2009 Mar;49(3):1017-44. 4. Bakhutashvili V, et al. Nonalcoholic fatty liver disease. In: Conn's Current Therapy 2020. Elsevier; 2020. NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Diagnosis of NAFLD via Conventional Imaging: CT and CAP

- Computed Tomography
  - Rarely used to diagnose NAFLD[1]
  - Typically an incidental finding on abdominal CT performed for another indication[1]
  - Density of liver to spleen ratio is typically used to detect hepatic steatosis[1]
  - Due to ionizing radiation exposure, not recommended to assess hepatic steatosis[1]
- Controlled Attenuation Parameter
  - Available on newer FibroScan machines as an adjunct to liver stiffness measurement by VCTE[1]
  - May be used to detect hepatic steatosis and fibrosis; does not provide reliable quantitative estimate of liver fat content[1,2]

1. Loomba R. *J Hepatol*. 2018 Feb;68(2):296-304. 2. Eddowes PJ, et al. *Gastroenterology*. 2019 May;156(6):1717-1730. CAP, controlled attenuation parameter; CT, computed tomography; NAFLD, nonalcoholic fatty liver disease; VCTE, vibration controlled transient elastography.

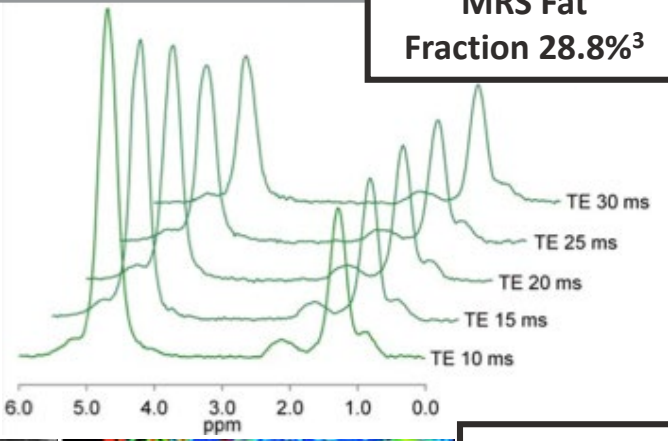
Quantifying NAFLD Liver Fat and Fibrosis with Novel Imaging Modalities

Liver stiffness/elasticity can be used as a surrogate for fibrosis; ideally, imaging methods would evaluate the entire liver.[1]

MRS (gold standard to quantify hepatic TG content)[1]

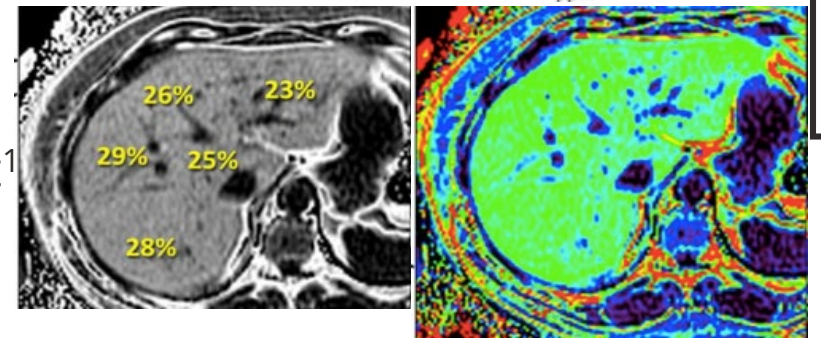
- Can yield an accurate NAFLD diagnosis if liver fat content is ≥5%[1]
- Can quantify liver fat content beyond the presence of HS[1]
- Time-consuming; requires special expertise[1]
- Affords only minimal spatial coverage; high sampling error risk[1]
- Equipment is not universally available[1]

MRS Fat Fraction 28.8%[3]



MRI-PDFF (MRI without spectroscopy):

- Provides image of liver to identify exact region of interest, and accurate estimate of liver fat content[1]
- Preferred vs CAP to grade steatosis[2]



MRS-PDFF Fat Fraction 28.8%[3]

1. Loomba R. *J Hepatol.* 2018 Feb;68(2):296-304. 2. Marcuccilli G, et al. *Int J Mol Sci*. 2016;17:562. 3. Loomba R, et al. Hepatology. 2015 Apr;61(4):1239-50. CAP, controlled attenuation parameter; HS, hepatic steatosis; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; PDFF, proton density fat fraction; TG, triglycerides.

NASH Progression and Presentation

- An estimated one-third of patients with NAFLD will progress to NASH; prevalence may be higher because liver biopsy is needed to confirm diagnosis.[1,2]
- NASH is asymptomatic[3]
  - Linked to key features of the metabolic syndrome: obesity, dyslipidemia, and glucose intolerance
  - Histologically indistinguishable from alcoholic hepatitis
- Whereas NAFLD can be diagnosed with imaging, NASH requires liver biopsy to identify the presence and location of inflammation, hepatocyte ballooning, Mallory-Denk bodies, and early fibrosis.[4]

1. Povsic M, et al. *Adv Ther*. 2019 Jul;36(7):1574-1594. 2. Polanco-Briceno S, et al. *BMC Res Notes*. 2016;9:157. 3. Kowdley KV. *Gastroenterol Hepatol (N Y)*. 2014;10(3):184-186. 4. Neuschwander-Tetri BA. *BMC Medicine*. 2017;15:45. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; US, United States.

NASH Disease Progression: Hepatocellular Carcinoma

- NASH-related HCC is the fastest growing indication for liver transplant in HCC candidates.
  - As hepatitis C prevalence declines, there is likely to be an increase in HCC owing to NASH, due to obesity and T2D epidemics.
- Annual HCC incidence in patients with NASH-related cirrhosis ranges from 2.6%-12.8%.
  - Patients may progress to HCC in the absence of cirrhosis.
- Segmental liver resection or transplantation are the only curative therapeutic options for NASH-related HCC.

Cholankeril G, et al. *World J Gastroenterol*. 2017 April 18; 9(11): 533-543. HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2D, type 2 diabetes.

Risk Factors for Progression from NAFLD to NASH

- T2D[1,2]
- Obesity[1,2]
- Older age[1,2]
- Liver fibrosis[2]
  - Can occur with NAFLD, but progression is slower than with NASH
  - Reduced survival if fibrosis occurs with hepatocyte ballooning, portal inflammation

Identification of patients at risk for progression may prompt the use of proven therapies.[2]

1. Radaelli MG, et al. *J Endocrinol Invest*. 2018 May;41(5):509-521 2. Neuschwander-Tetri BA. *BMC Medicine*. 2017;15:45. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2D, type 2 diabetes.

NAFLD Prevention and Treatment: Lifestyle Modifications

- Lifestyle intervention and modification—exercise, diet, and weight loss—is the cornerstone of NAFLD prevention and treatment.[1-3]
- Maintaining physical activity >150 min/week, or otherwise increasing activity level by >60 min/week, has been shown to reduce serum aminotransferases.[1]
- Optimal diets: Low-carbohydrate, low-fat, low-glycemic-index, Mediterranean[2,4]
  - Mediterranean has shown significant improvement in steatosis vs high-fat, low-carbohydrate diet, despite similar weight loss[1]
  - Long-term calorie-restricted diet is associated hepatic fat mobilization and CV risk improvement[1]
- Weight loss can reduce liver fat, inflammation, fibrosis, and scarring.[1,5]
  - To improve steatosis: Weight loss ≥3%-5% of baseline body weight[1]
  - To improve histopathologic features of NASH, including fibrosis: Weight loss 7%-10% of baseline body weight [1]
  - Rapid weight loss via fasting can worsen NAFLD[5]
  - Patients with BMI≥35 kg/m^2 and NAFLD should be considered for bariatric surgery[6]

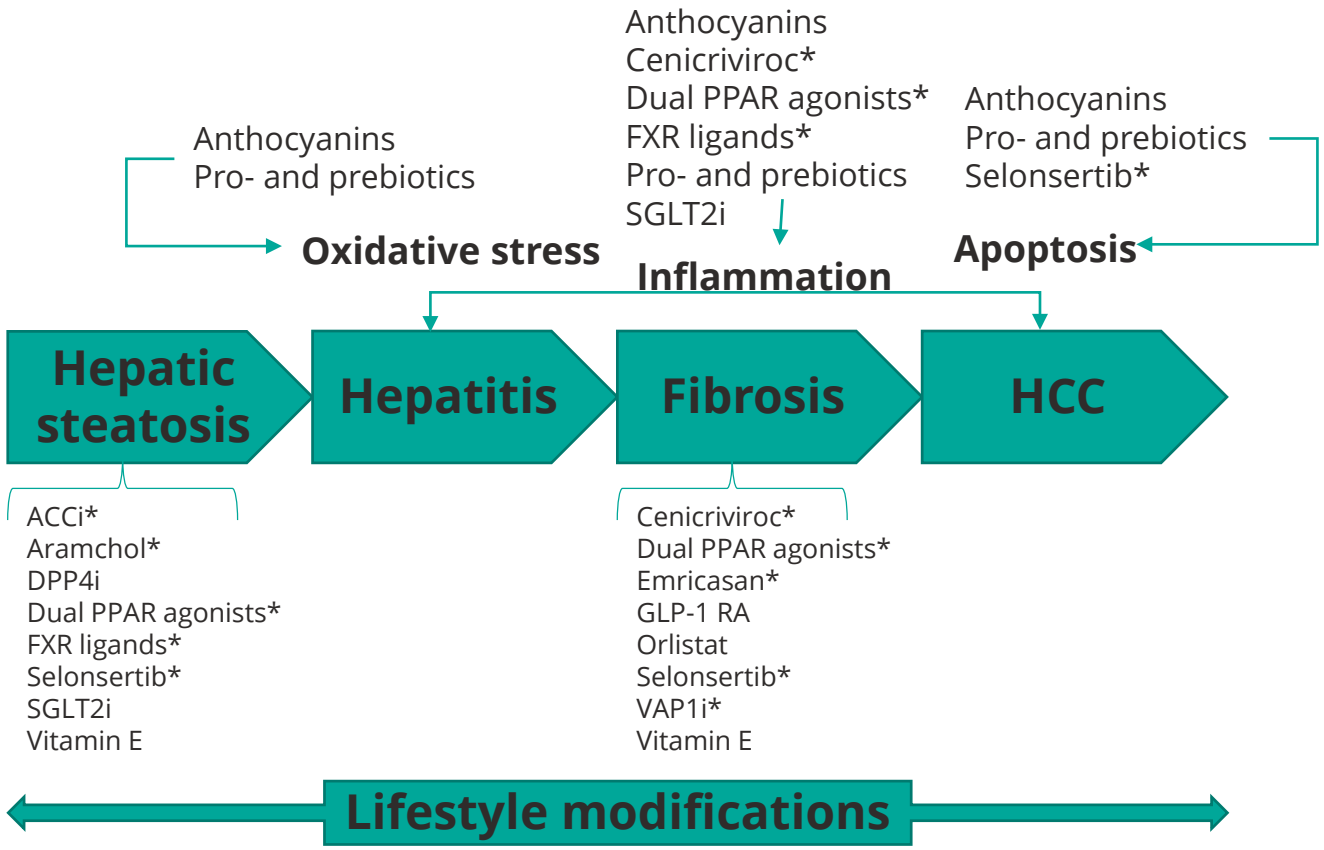
1. Chalasani N, et al. *Hepatology* (67);1:2018. 2. Wong VW. *Adv Exp Med Biol*. 2018;1061:149-157. 3. Radaelli MG, et al. *J Endocrinol Invest*. 2018 May;41(5):509-521. 4. Neuschwander-Tetri BA. *BMC Medicine*. 2017;15:45. 5. NIDDK. https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/treatment. 6. Mechanick JI, et al. *Endocr Pract*. 2019 Dec;25(12):1346-1359. BMI, body mass index; CV, cardiovascular; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2D, type 2 diabetes.

Treating NAFLD

- There are currently no FDA-approved pharmaceutical interventions for NAFLD or NASH.[1]
- Treatment is focused on addressing associated/coexisting conditions (dyslipidemia, obesity, T2D) to control glycemia, lipids, and liver function.[1,2]
- Pharmaceuticals to treat liver disease should generally be limited to patients with confirmed NASH.[3]
  - Treatment options: TZDs (pioglitazone), GLP-1 RA (liraglutide), antioxidants (vitamin E)[3-5]
  - In a phase 4 clinical trial, the SGLT2i empagliflozin reduced hepatic fat in patients with T2D.[6]
- Statins are safe but underutilized for patients with NAFLD or NASH.[2,7]
  - May reduce liver enzymes and substantially reduces CVD morbidity/mortality in patients with NAFLD/NASH[7]
  - Provide a protective effect on steatosis, steatohepatitis, and fibrosis[7]

1. Jeznach-Steinhagen A, et al. *Medicina (Kaunas)*. 2019;55(5):166. 2. Diordjevic DB, et al. *Curr Vasc Pharmacol*. 2018;16(3):228-238. 3. Chalasani N, et al. *Hepatology* (67);1:2018. 4. Wong VW. *Adv Exp Med Biol*. 2018;1061:149-157. 5. Garvey WT, et al. *Endocr Pract*. 2016 Jul;22 Suppl 3:1-203. 6. Kahl S, et al. *Diabetes Care* 2020 Feb; 43(2):298-305. 7. Athyros VG, et al. *Curr Vasc Pharmacol*. 2018;16(3):246-253. CVD, cardiovascular disease; FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinediones.

Available and Potential Future Therapies for Various Stages of NAFLD



* Therapy in development

1. Jeznach-Steinhagen A, et al. Medicina (Kaunas). 2019;55(5):166. ACCi, acetyl-CoA carboxylase inhibitors; DPP4i, dipeptidyl peptidase 4 inhibitor; FXR, farnesoid X receptor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular cancer; NAFLD, nonalcoholic fatty liver disease; PPAR, peroxisome proliferator-activated receptors; SGLT2i, sodium-glucose cotransporter 2 inhibitor; VAP1i, vascular adhesion protein-1 inhibitors.

Pharmacologic Treatments Used for NAFLD and/or NASH in Patients With T2D

Medication	Impact				Side effects	Notes
	Body weight	ALT	Hepatic steatosis	Liver histology		
Metformin	↓	↓	No affect	No affect	GI problems; lactate acidosis	Suitable for patients with NAFLD/NASH (except in the setting of advanced cirrhosis); no specific influence on liver histology; beneficial pleiotropic effects
Pioglitazone	↑	↓	↓	Improved	Swelling; weight gain	Improves hepatic ballooning degeneration, lobular inflammation, and fibrosis; modifies natural course of NASH
GLP-1 RA	↓	↓	↓	Improved	Headache; GI problems; URTI	Liraglutide has led to clinically significant NASH resolution; liraglutide and exenatide have stopped liver fibrosis progression
DPP4i	No affect	↓	↓	No data	Headache; GI problems; URTI	Sitagliptin reduces aminotransferase activity
SGLT2i	↓	↓	No effect	Improved	Urogenital infections	Canagliflozin suppresses hepatic TG accumulation; empagliflozin lowers inflammatory marker levels, aminotransferase activity, and hepatic fat

1. Jeznach-Steinhagen A, et al. *Medicina (Kaunas)*. 2019;55(5):166. 2. Kahl S, et al. *Diabetes Care* 2020 Feb; 43(2):298-305. ALT, alanine aminotransferase; DPP4i, dipeptidyl peptidase 4 inhibitor; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TG, triglycerides; URTI, upper respiratory tract infection.

Thank You

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