Time to Include Nonalcoholic Steatohepatitis in the Management of Patients With Type 2 Diabetes

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Nonalcoholic fatty liver disease (NAFLD) is today the most common cause of chronic liver disease and second only to viral hepatitis as a cause of liver transplantation in the U.S. (1,2). It encompasses conditions from simple steatosis (NAFL), believed to be associated with slow disease progression, to the more severe and progressive form known as nonalcoholic steatohepatitis (NASH). NASH is characterized by hepatocellular injury in the form of hepatocyte ballooning (necrosis) and predominantly lobular inflammation. The severity of hepatic fibrosis is defined in stages. They range from stage F0, or no fibrosis, to mild (stage F1), moderate (stage F2, with zone 3 sinusoidal fibrosis plus periportal fibrosis), or advanced fibrosis, with bridging fibrosis (stage F3) or cirrhosis (stage F4). NASH may lead to cirrhosis and to the development of hepatocellular carcinoma, but even moderate-to-severe fibrosis (F2-F3) is associated with higher mortality (1,2). Advanced liver fibrosis and cirrhosis occur more often in obesity but, in particular, in patients with type 2 diabetes (T2D) (3). Endocrinologists should be aware that patients with NAFLD are also at a two- to threefold increased risk of both progression from prediabetes to diabetes and development of cardiovascular disease (4,5). Taken together, there is a consensus that patients with T2D and NASH are at a much higher risk of hepatic and extrahepatic morbidity and premature death than in the absence of liver disease.

Within this context, Younossi et al. (6) report in the current issue of *Diabetes Care* an important study on the clinical and economic burden of NASH in patients with T2D in the U.S. This is so far the most comprehensive effort to systematically outline the magnitude of the problem in patients with diabetes. The authors used 2017 annual direct medical costs attributed to diagnosed diabetes reported by the American Diabetes Association (7) and applied prevalence rates and well-validated statistical models from prior work in populations with NASH (3,8–10). The results were staggering for anyone involved in the care of patients with diabetes. The overall prevalence of NAFLD was >70% (47% with NAFL plus 26% with NASH), for a total of >18 million patients with T2D having NAFLD (not including patients in the U.S. with undiagnosed T2D). The economic burden was, as expected, driven by diabetes care, as about two-thirds had simple steatosis (NAFL), which infrequently will develop into advanced liver disease. However, health care expenses were substantially higher in those with NASH. The total liver-related cost of NASH versus NAFL was about 24 times higher at $2,275 versus $95 per person-year, respectively. The economic burden for the group with prevalent NASH and T2D was $642 billion, with $482.2 billion (75%) attributable to diabetes care and $160.3 billion (25%) to NASH-related liver care. Over the next 20 years, NASH and T2D would be potentially responsible for 64,900 liver transplants (29% of the total estimated liver transplants performed), 812,000 liver-related deaths, 1.37 million cardiovascular deaths, 1.27 million cases of decompensated cirrhosis person-years, and 479,000 hepatocellular carcinoma person-years. Weaknesses of the study include those intrinsic to the assumptions of any disease model. The true prevalence of NASH will not be exactly known in the foreseeable future until a fully reliable noninvasive test is available. Systematic liver biopsies for all potential patients with NASH (i.e., anyone with NAFL) would expose many patients to an unnecessary risk and would be clearly unethical. Still, for this study the authors used data from the best sources available on both T2D and NASH. The model was conservative as it did not include potentially higher diabetes care costs from worse diabetes micro- and macrovascular complications from having NAFLD/

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NASH (5,11,12). A second limitation is that the natural history of steatohepatitis and liver fibrosis is still unclear, in large part because of the same diagnostic/monitoring limitations as exist for estimating the prevalence of NASH (i.e., doing repeated liver biopsies over time). However, recent prospective long-term follow-up studies from the multicenter NASH Clinical Research Network (CRN) consortium (13,14) appear to confirm the assumptions included in the model by Younossi et al. (6).

The above results call on endocrinologists to view NASH as a frequent and serious complication of T2D and to be proactive in the early identification of patients at risk for liver fibrosis. However, the challenge remains how to separate patients with diabetes with the more benign form of the disease (NAFL) from those who have steatohepatitis (NASH), as well as those with or without moderate-to-severe fibrosis (≥F2) that would benefit from aggressive lifestyle intervention and therapies such as pioglitazone or glucagon-like peptide 1 receptor agonists (GLP-1RAs). There are several diagnostic algorithms with the goal to identify patients with NASH fibrosis, as reviewed elsewhere, some more focused on patients from hepatology clinics (15,16) or for primary care physicians and endocrinologists (17). They are based on a combination of blood testing and imaging (usually elastography either at point-of-care [Fibroscan] or by magnetic resonance). Blood diagnostic panels combine clinical demographics (BMI, T2D) with routine chemistries, while there are also specific commercially available plasma biomarkers to diagnose NASH or fibrosis. To summarize a large body of data, noninvasive plasma tests have had limited accuracy to diagnose NASH or early stages of fibrosis but have been useful for the diagnosis of advanced disease (≥F3). In other words, they are used best to rule out severe disease (good specificity and negative predictive value) than to establish an early diagnosis (they usually have modest sensitivity and positive predictive value) or monitor the disease (1,2,18). Another caveat is that they usually perform better in hepatology clinics, where there are more patients with advanced liver fibrosis and cirrhosis, than in nonhepatology settings, where cirrhosis is less common (19–22). Finally, few studies have focused only on patients with T2D.

Acknowledging the above gaps, the study by Bril et al. (23) in this issue of *Diabetes Care* did a head-to-head comparison of the most commonly used plasma biomarkers and diagnostic panels to establish their true value in 213 patients with T2D not being followed in a hepatology setting. Their key findings were that for the diagnosis of NASH none of the currently available panels or biomarkers (cytokeratin 18 [CK-18], NashTest 2, HAIR, BARD, or OWLiver) was able to outperform plasma ALT (area under the curve [AUC] 0.78 [0.71–0.84]), while for advanced fibrosis (≥F3) none of the plasma tests (fragments of propeptide of type III procollagen [PRO-C3], APRI, FIB-4, Fibrotest, or NAFLD fibrosis score) was significantly better than plasma AST (AUC 0.85 [0.80–0.91]). These results suggest that plasma ALT and AST as stand-alone tests can be helpful, although they often fall short of clearly guiding management on an individual basis. On the more positive side, plasma PRO-C3 showed a trend to be better than plasma AST (AUC 0.90 [0.85–0.95] vs. 0.85 [0.80–0.91]) and held hope that sequential use of plasma AST (≥26 IU/L) followed by PRO-C3 or future biomarkers may help limit the number of liver biopsies. Still, a high number of patients (about one-third) would have needed a liver biopsy. Of note, noncommercial diagnostic panels such as FIB-4, NAFLD fibrosis score, and APRI also performed relatively well compared with PRO-C3. The limitations of the study were the relatively small sample size and its cross-sectional nature that did not allow conclusions to be drawn regarding the value of screening relative to disease progression or clinical outcomes. However, it contributes to the field about the value of AST/ALT in a population with diabetes and by calling for more reliable tests for the diagnosis of NASH and advanced fibrosis in T2D. The overall poor results speak to the complex biology of liver fibrosis, where both fibrogenesis and fibrinolysis determine fibrosis progression over time with fluctuations depending on profibrotic stimulus (24,25). Significant work is being done in the field to validate novel and more sophisticated fibrosis biomarkers (26). Future studies will help us enter a new era of precision medicine where biomarkers will identify and target therapy to those with more active disease at risk for cirrhosis.

The above sets the stage for discussing what treatment options we currently have for patients with T2D and NASH. Vitamin E is effective in patients with biopsy-proven NASH without diabetes (1,4) but has had more mixed results in a recent proof-of-concept randomized controlled trial (RCT) in patients with T2D (27). A larger, long-term study may be needed to clarify its role in this setting and dispel lingering safety concerns. Given that diabetes and NASH often overlap, an approach that treats both would be logical and cost-effective. Among pharmacological agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of T2D, the insulin sensitizer metformin has not shown clinical efficacy (1,4). In contrast, there are now five RCTs where pioglitazone has consistently improved steatohepatitis, with a treatment difference of about 30 to 40 percentage points compared with placebo (27–31). A modest effect on fibrosis has been reported in some of these trials (28,30). The thiazolidinedione has been incorporated as an option into current liver (1,2) and diabetes (32) treatment guidelines. In RCTs, dipeptidyl peptidase 4 inhibitors have been largely negative for the treatment of NASH (33,34; reviewed in 4,35,36). However, in several small proof-of-concept RCTs, GLP-1RAs have been reported to normalize plasma aminotransaminases and decrease hepatic steatosis (35,36) and even improve liver histology (37,38). Most studies have used liraglutide and the benefit has usually been proportional to the degree of weight loss, although other mechanisms may be at play. Results from the semaglutide NASH trial in the second half of 2020 are awaited with significant expectation (ClinicalTrials.gov reg. no. NCT02970942).

Studies in animal models of NAFLD (39–41) and uncontrolled clinical trials (42–47) support the notion that sodium–glucose cotransporter 2 inhibitors (SGLT2i) could play a valuable role in NAFLD. However, only recently more carefully designed RCTs have assessed their safety and efficacy in patients with T2D (Table 1) (48–52). In this issue of *Diabetes Care*, Kahl et al. (52) report on the first RCT with empagliflozin, where 84 well-controlled patients with T2D (baseline HbA_{1c} 6.6% ± 0.5%) were randomized to empagliflozin or placebo for 24 weeks. The study included state-of-the-art liver fat (^{1}H-MRS) and metabolic measurements. The main findings were a 22% reduction in liver fat ($P = 0.009$ vs. placebo) associated with a 2.5-kg placebo-corrected weight loss (~2.4%). Treatment did not

Table 1—Effect of SGLT2i in NAFLD

Author, year	Agent	*n*	Duration (weeks)	Comparator	Main study results		
					Body weight*	ALT	Liver fat*
Prospective open-label studies							
Ito et al., 2017 (42)	Ipragliflozin	66	24	Pioglitazone	↓ 3.7%	↓	↓¶
Ohta et al., 2017 (43)	Ipragliflozin	20	24	Standard care	↓ 2.5%	↓	↓ 39%
Shibuya et al., 2018 (44)	Luseogliflozin	32	24	Standard care	↓ 3.2%	Unchanged	↓¶
Kuchay et al., 2018 (45)	Empagliflozin	50	20	Standard care	↓ 1.1%	↓	↓ 26%
Shimizu et al., 2019 (46)	Dapagliflozin	57	24	Standard care	↓ 3.1%	↓	↓†
Inoue et al., 2019 (47)	Canagliflozin	20	52	Standard care	↓ 3.4%	↓	↓ 31%
Randomized controlled trials							
Bolinder et al., 2012 (48)	Dapagliflozin	67	24	Placebo	↓ 2.2%	—	Unchanged
Eriksson et al., 2018 (49)	Dapagliflozin	84	12	Placebo	↓ 2.2%	↓	↓ 10%§
Cusi et al., 2019 (50)	Canagliflozin	56	24	Placebo	↓ 3.4%	Unchanged	↓ 18%§
Latva-Rasku et al., 2019 (51)	Dapagliflozin	32	8	Placebo	↓ 2.1%	Unchanged	↓ 13%
Kahl et al., 2019 (52)	Empagliflozin	84	24	Placebo	↓ 2.4%	Unchanged	↓ 22%

Arrows indicate statistically significant changes vs. comparator. *Comparison-corrected (open-label) or placebo-corrected relative treatment difference in weight and liver fat measured with MRI-based imaging techniques. ¶Liver fat measured as liver-to-spleen attenuation ratio on computed tomography. In Ito et al. (42) the decrease in liver fat was similar to pioglitazone (comparator). †Significant improvement in liver fat by controlled attenuation parameter (CAP; Fibroscan). §Not significant compared with placebo.

improve hepatic, muscle, or adipose tissue insulin sensitivity, although there was modest increase in plasma high-molecular-weight plasma adiponectin, suggesting an improvement in adipose tissue biology and function. Still, adiponectin remained significantly low and less than ~50% of normal. There were no significant placebo-corrected changes in several adipokines (interleukin [IL]-1Ra, tumor necrosis factor α, IL-6, and fibroblast growth factor 21) and in biomarkers of liver fibrosis (CK18-M30 and -M65), in contrast to an earlier study with dapagliflozin (49). The relative liver fat reduction was in the range observed in earlier RCTs with canagliflozin (50) but somewhat greater than with dapagliflozin (48,49,51) in patients with T2D and NAFLD. An improvement in hepatic insulin sensitivity and insulin secretion was observed in an earlier study with canagliflozin, along with a 38% reduction in liver fat compared with a 20% decrease with placebo (placebo-corrected difference of 18%; $P = 0.09$). Of note, in this RCT all patients received dietary advice, which likely accounted for the significant change in liver fat with placebo and highlighted the need for placebo-controlled studies in the field. Nevertheless, more patients on canagliflozin versus placebo lost ≥5% of body weight and had a ≥30% reduction in liver fat (38% vs. 7%, $P = 0.009$).

Where do we go from here with SGLT2i in NASH? In the RCTs summarized in Table 1, patients' HbA_{1c} was rather well controlled (6.5–7.6%), so one may speculate a greater effect in NAFLD in a "real-world" cohort of patients with uncontrolled T2D. We also do not have information from controlled trials on how changes in ALT and steatosis with SGLT2i treatment translate to liver histology, but benefit has been reported in small uncontrolled clinical studies (53–55). A recent meta-analysis of 11 studies in 6,745 patients with T2D treated with canagliflozin reported a significant reduction in AST (56), ALT, and γ-glutamyl transferase, although results from smaller RCTs have been less consistent and depended on the baseline AST/ALT. Given the clinical cardiovascular and renal benefits of SGLT2i by mechanisms not initially anticipated, some on inflammation and profibrotic pathways (39–41), this class deserves further study in patients with steatohepatitis. In many studies (Table 1), SGLT2i reduced hepatic steatosis more than expected for the rather modest weight loss, suggesting additional weight-independent mechanisms. Furthermore, a reduction of liver fat may not necessarily be proportional to the improvement in necroinflammation or fibrosis, as recently suggested with pioglitazone (57).

In summary, it is time to include NASH in the management plan of patients with T2D in the same way as today it includes diabetic retinopathy or nephropathy. The American Diabetes Association in the 2019 Standards of Care guidelines recommends that "patients with type 2 diabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for the presence of nonalcoholic steatohepatitis and liver fibrosis" (recommendation 4.14) (58). Given the potential cardiometabolic and liver-specific complications associated with NASH, endocrinologists and the diabetes team must be at the forefront of disease prevention. Future studies should aim to better understand the natural history of liver disease in patients with diabetes, the biology of liver fibrosis to find novel plasma biomarkers that will identify "rapid disease progressors," and the impact of NAFLD on micro- (11) and macrovascular (5,12) diabetes complications. This knowledge will be essential to develop cost-effective screening and long-term monitoring algorithms. We are also still at the dawn of treatment for NASH. While weight loss and exercise remain the cornerstone of NAFLD management, only a few short-term (≤12 months) controlled studies have been performed. Large, long-term multicenter lifestyle intervention studies are needed. Within this context, the role of SGLT2i will need to be better established, in particular, their efficacy as add-on

therapy to new or already available FDA-approved medications for T2D with proven efficacy in NASH (i.e., add-on to pioglitazone, GLP-1RAs?). Finally, many novel pharmacological agents are being tested and will likely soon expand our treatment options. All health care providers taking care of patients with diabetes need to embrace today the evolving clinical challenge posed by NASH, educate their patients, and be proactive in the diagnosis and monitoring of patients with this "new complication" of T2D.

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References

1. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357
2. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia 2016;59:1121–1140
3. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 2019;71:793–801
4. Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2019;7:313–324
5. Akshintala D, Chugh R, Amer F, Cusi K. Nonalcoholic fatty liver disease: the overlooked complication of type 2 diabetes. In *Endotext* [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK544043/. Accessed 5 December 2019
6. Younossi ZM, Tampi RP, Racila A, et al. Economic and clinical burden of nonalcoholic steatohepatitis in patients with type 2 diabetes in the United States. Diabetes Care 2020;43:283–289
7. Yang W, Dall TM, Beronjia K, et al.; American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917–928
8. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018;67:123–133
9. Younossi ZM, Stepanova M, Younossi Y, et al. Epidemiology of chronic liver diseases in the USA in the past three decades. Gut. 31 July 2019 - [Epub ahead of print]. DOI: 10.1136/gutjnl-2019-318813
10. Kim D, Kim W, Adejumo AC, et al. Race/ethnicity-based temporal changes in prevalence of NAFLD-related advanced fibrosis in the United States, 2005-2016. Hepatol Int 2019;13:205–213
11. Musso G, Gambino R, Tabibian JH, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. PLoS Med 2014;11:e1001680
12. Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. Nat Rev Endocrinol 2018;14:99–114
13. Kleiner DE, Brunt EM, Wilson LA, et al.; Nonalcoholic Steatohepatitis Clinical Research Network. Association of histologic disease activity with progression of nonalcoholic fatty liver disease. JAMA Netw Open 2019;2:e1912565
14. Sanyal AJ, Van Natta ML, Lazo M, et al. A prospective longitudinal study of clinical outcomes in adults with nonalcoholic fatty liver disease. Presented at The Liver Meeting 2019—the 70th Annual Meeting of the American Association for the Study of Liver Diseasesa (AASLD), 8–12 November 2019, Boston, MA [Abstract #1190]
15. Rinella ME, Sanyal AJ. Management of NAFLD: a stage-based approach. Nat Rev Gastroenterol Hepatol 2016;13:196–205
16. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 2019;156:1264–1281.e4
17. Bril F, Cusi K. Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action. Diabetes Care 2017;40:419–430
18. Siddiqui MS, Yamada G, Vuppalanchi R, et al.; NASH Clinical Research Network. Diagnostic accuracy of noninvasive fibrosis models to detect change in fibrosis stage. Clin Gastroenterol Hepatol 2019;17:1877–1885.e5
19. Bazick J, Donithan M, Neuschwander-Tetri BA, et al. Clinical model for NASH and advanced fibrosis in adult patients with diabetes and NAFLD: guidelines for referral in NAFLD. Diabetes Care 2015;38:1347–1355
20. Bril F, Millán L, Kalavalapalli S, et al. Use of a metabolomic approach to non-invasively diagnose non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2018;20:1702–1709
21. Bril F, Leeming DJ, Karsdal MA, et al. Use of plasma fragments of propeptides of type III, V, and VI procollagen for the detection of liver fibrosis in type 2 diabetes. Diabetes Care 2019;42:1348–1351
22. Bril F, McPhaul MJ, Caulfield MP, et al. Performance of the SteatoTest, ActiTest, NashTest and FibroTest in a multiethnic cohort of patients with type 2 diabetes mellitus. J Investig Med 2019;67:303–311
23. Bril F, McPhaul MJ, Caulfield MP, et al. Performance of plasma biomarkers and diagnostic panels for nonalcoholic steatohepatitis and advanced fibrosis in patients with type 2 diabetes. Diabetes Care 2020;43:290–297
24. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24:908–922
25. Schuppan D, Surabattula R, Wang XY. Determinants of fibrosis progression and regression in NASH. J Hepatol 2018;68:238–250
26. Karsdal MA, Detlefsen S, Daniels SJ, Nielsen MJ, Krag A, Schuppan D. Is the total amount as important as localization and type of collagen in liver fibrosis due to steatohepatitis? Hepatology. 25 September 2019 [Epub ahead of print]. DOI: 10.1002/hep.30969
27. Bril F, Biernacki DM, Kalavalapalli S, 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
28. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–2307
29. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135:1176–1184
30. Sanyal AJ, Chalasani N, Kowdley KV, et al.; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675–1685
31. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016;165:305–315
32. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S90–S102
33. Cui J, Philo L, Nguyen P, et al. Sitagliptin vs. placebo for non-alcoholic fatty liver disease: a randomized controlled trial. J Hepatol 2016;65:369–376
34. Joy TR, McKenzie CA, Tirona RG, et al. Sitagliptin in patients with non-alcoholic steatohepatitis: a randomized, placebo-controlled trial. World J Gastroenterol 2017;23:141–150
35. Khan R, Bril F, Cusi K, Newsome PN. Modulation of insulin resistance in nonalcoholic fatty liver disease. Hepatology 2019;70:711–724
36. Cusi K. Incretin-based therapies for the management of nonalcoholic fatty liver diesease in patients with type 2 diabetes. Hepatology 2019;69:2318–2322
37. Eguchi Y, Kitajima Y, Hyogo H, et al.; Japan Study Group for NAFLD (JSG-NAFLD). Pilot study of liraglutide effects in non-alcoholic steatohepatitis and non-alcoholic fatty liver disease with glucose intolerance in Japanese patients (LEAN-J). Hepatol Res 2015;45:269–278
38. Armstrong MJ, Gaunt P, Aithal GP, et al.; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–690
39. Qiang S, Nakatsu Y, Seno Y, et al. Treatment with the SGLT2 inhibitor luseogliflozin improves nonalcoholic steatohepatitis in a rodent model with diabetes mellitus. Diabetol Metab Syndr 2015;7:104
40. Jojima T, Tomotsune T, Iijima T, Akimoto K, Suzuki K, Aso Y. Empagliflozin (an SGLT2

inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes. Diabetol Metab Syndr 2016;8:45
41. Nishimura N, Kitade M, Noguchi R, et al. Ipragliflozin, a sodium-glucose cotransporter 2 inhibitor, ameliorates the development of liver fibrosis in diabetic Otsuka Long-Evans Tokushima fatty rats. J Gastroenterol 2016;51:1141–1149
42. Ito D, Shimizu S, Inoue K, et al. Comparison of ipragliflozin and pioglitazone effects on nonalcoholic fatty liver disease in patients with type 2 diabetes: a randomized, 24-week, open-label, active-controlled trial. Diabetes Care 2017;40:1364–1372
43. Ohta A, Kato H, Ishii S, et al. Ipragliflozin, a sodium glucose co-transporter 2 inhibitor, reduces intrahepatic lipid content and abdominal visceral fat volume in patients with type 2 diabetes. Expert Opin Pharmacother 2017;18:1433–1438
44. Shibuya T, Fushimi N, Kawai M, et al. Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: a prospective randomized controlled pilot study. Diabetes Obes Metab 2018;20:438–442
45. Kuchay MS, Krishan S, Mishra SK, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT trial). Diabetes Care 2018;41:1801–1808
46. Shimizu M, Suzuki K, Kato K, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. Diabetes Obes Metab 2019; 21:285–292
47. Inoue M, Hayashi A, Taguchi T, et al. Effects of canagliflozin on body composition and hepatic fat content in type 2 diabetes patients with non-alcoholic fatty liver disease. J Diabetes Investig 2019;10:1004–1011
48. Bolinder J, Ljunggren Ö, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab 2012;97:1020–1031
49. Eriksson JW, Lundkvist P, Jansson PA, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. Diabetologia 2018;61:1923–1934
50. Cusi K, Bril F, Barb D, et al. Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. Diabetes Obes Metab 2018;21:812–821
51. Latva-Rasku A, Honka MJ, Kullberg J, et al. The SGLT2 inhibitor dapagliflozin reduces liver fat but does not affect tissue insulin sensitivity: a randomized, double-blind, placebo-controlled study with 8-week treatment in type 2 diabetes patients. Diabetes Care 2019;42:931–937
52. Kahl S, Gancheva S, Straßburger K, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: a randomized, double-blind, phase 4, placebo-controlled trial. Diabetes Care 2020;43:298–305
53. Akuta N, Kawamura Y, Watanabe C, et al. Impact of sodium glucose cotransporter 2 inhibitor on histological features and glucose metabolism of non-alcoholic fatty liver disease complicated by diabetes mellitus. Hepatol Res 2019;49:531–539
54. Seko Y, Nishikawa T, Umemura A, et al. Efficacy and safety of canagliflozin in type 2 diabetes mellitus patients with biopsy-proven nonalcoholic steatohepatitis classified as stage 1-3 fibrosis. Diabetes Metab Syndr Obes 2018; 11:835–843
55. Lai LL, Vethakkan SR, Nik Mustapha NR, Mahadeva S, Chan WK. Empagliflozin for the treatment of nonalcoholic steatohepatitis in patients with type 2 diabetes mellitus. Dig Dis Sci. 25 January 2019 [Epub ahead of print]. DOI: 10.1007/s10620-019-5477-1
56. Li B, Wang Y, Ye Z, et al. Effects of canagliflozin on fatty liver indexes in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. J Pharm Pharm Sci 2018;21:222–235
57. Bril F, Barb D, Lomonaco R, Lai J, Cusi K. Change in hepatic fat content measured by MRI does not predict treatment-induced histological improvement of steatohepatitis. J Hepatol. 4 October 2019 [Epub ahead of print]. DOI: 10.1016/j.jhep.2019.09.018
58. American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S34–S45