References

1. El-Salhy M, Winkel R, Casen C, et al. Efficacy of fecal microbiota transplantation for patients with irritable bowel syndrome at 3 years after transplantation. Gastroenterology 2022;163:982–994.
2. El-Salhy M, Hatlebakk JG, Gilja OH, et al. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. Gut 2020;69:859–867.
3. El-Salhy M, Kristoffersen AB, Valeur J, et al. Long-term effects of fecal microbiota transplantation (FMT) in patients with irritable bowel syndrome. Neurogastroenterol Motil 2022;34:e14200.
4. Aroniadis OC, Brandt LJ, Oneto C, et al. Faecal microbiota transplantation for diarrhoea-predominant irritable bowel syndrome: a double-blind, randomised, placebo-controlled trial. Lancet Gastroenterol Hepatol 2019;4:675–685.
5. Pittayanon R, Lau JT, Yuan Y, et al. Gut microbiota in patients with irritable bowel syndrome—a systematic review. Gastroenterology 2019;157:97–108.
6. Levy M, Kolodziejczyk AA, Thaiss CA, et al. Dysbiosis and the immune system. Nat Rev Immunol 2017;17:219–232.
7. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997;11:395–402.
8. Roalfe AK, Roberts LM, Wilson S. Evaluation of the Birmingham IBS symptom questionnaire. BMC Gastroenterol 2008;8:30.
9. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. Am J Gastroenterol 2000;95:999–1007.
10. Dove LS, Lembo A, Randall CW, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. Gastroenterology 2013;145:329–338.e1.
11. Yiannakou Y, Agrawal A, Allen PB, et al. UK clinical experience up to 52 weeks with linaclotide for irritable bowel syndrome with constipation. Therap Adv Gastroenterol 2018;11:1756284818798791.
12. Vancak V, Goldberg Y, Levine SZ. Guidelines to understand and compute the number needed to treat. Evid Based Ment Health 2021;24:131–136.
13. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27(Suppl):S178–S189.
14. Spiegel B, Bolus R, Harris LA, et al. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. Aliment Pharmacol Ther 2009;30:1159–1170.
15. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158.
16. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407–415.
17. Camilleri M. Diagnosis and treatment of the irritable bowel syndrome: a review. JAMA 2021;325:865–877.
18. Camilleri M, Chedid V. Actionable biomarkers: the key to resolving disorders of gastrointestinal function. Gut 2020;69:1730–1737.

Correspondence
Address correspondence to: Michael Camilleri, MD, Mayo Clinic, 200 First Street SW, Charlton Building, Room 8-110, Rochester, Minnesota 55905. e-mail: camilleri.michael@mayo.edu.

Conflicts of Interest
This author discloses the following: Michael Camilleri: consulting for Ironwood, Novome, Cosmo Pharmaceuticals, Protagonist Therapeutics, and Invea Therapeutics. The remaining author discloses no conflicts.

Funding
Michael Camilleri is supported by grant R01-DK115950 from National Institutes of Health.

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2022.06.087

Aldehyde "Adduction" Explains Synergy of Smoking and Alcohol in Promoting Pancreatitis

See "Malondialdehyde-acetaldehyde extracellular matrix protein adducts attenuate unfolded protein response during alcohol and smoking-induced pancreatitis" by Bhatia R, Thompson CM, Clement EJ, et al, on page 1064.

Pancreatitis is the inflammatory disorder of the pancreas, which often forms a disease continuum starting with a so-called sentinel attack of acute pancreatitis (AP), followed by recurrent AP (RAP) episodes, and eventual progression to chronic pancreatitis (CP).[1] The risk of recurrence after the first AP attack is ~10% to 30%, and the risk of progression from RAP to CP is ~25% to 35%.[2–4] Progression after the sentinel episode of AP to RAP and ultimately to CP is often associated with environmental or genetic risk factors, or both.[3,5,6]

The most common environmental risk factor is alcohol, which is responsible for 43% to 76% of pancreatitis etiology.[3,7] Smoking has been identified as an independent risk factor responsible for 61% of pancreatitis cases, and it can also amplify the hazardous effects of alcohol.[3,7–10] The mechanisms by which these risk factors synergize are currently being explored.[11] In a 2017 study, Lugea et al[12] demonstrated that cigarette smoke together with alcohol

contribute to CP pathogenesis through endoplasmic reticulum (ER) stress in pancreatic acinar cells. In this issue of *Gastroenterology*, findings of Bhatia et al[13] provide an even closer mechanistic link between chronic ethanol and smoke exposure and ER stress–induced pancreatitis.

Activation of ER stress mechanisms has been recognized as a key pathologic event in both the development of AP and progression to CP.[14,15] During ER stress, cells initiate the unfolded protein response to cope with accumulating unfolded or misfolded proteins, or both, in the ER. Main modules of the unfolded protein response include the (1) protein kinase RNA-like ER kinase (PERK), the (2) activating transcription factor 6 (ATF6), and the (3) inositol-required enzyme 1 (IRE1), which are localized to the ER membrane and become activated during ER stress. Among these 3 distinct branches, alcohol activates the IRE1 arm, leading to higher levels of the spliced form of the transcription factor X-box binding protein 1 (XBP1) in the cytoplasm. Spliced XBP1 then translocates to the nucleus and increases the expression of chaperone proteins as part of the adaptive response. Continued ER stress and a defective XBP1 response activate the PERK branch, which leads to the upregulation of the proapoptotic transcription factor cytidine-cytidine-adenosine-adenosine-thymidine (CCAAT)-enhancer-binding protein homologous protein (CHOP, also known as DNA damage-inducible transcript 3 [DDIT3]) and results in cell death. Toxic chemicals in the cigarette smoke extract were shown to promote cell death via dysregulation of the unfolded protein response.[16,17] Lugea et al[12] discovered that cigarette smoke reduced spliced XBP1 protein expression levels, thereby suppressing the adaptive response to alcohol, which resulted in sustained PERK activation and increased CHOP expression, followed by acinar cell death and pancreatitis. Nevertheless, the exact molecular mechanism leading to the downregulation of spliced XBP1 remained unclear.

To tackle this knowledge gap, in the present study, Bhatia et al[13] performed proteomic analysis on a mouse model of secretagogue-induced RAP/CP with chronic alcohol and cigarette smoke extract exposure. They identified stable malondialdehyde-acetaldehyde adducts on the deposited extracellular matrix proteins in the pancreas of mice with RAP/CP and in pancreatic samples from patients with CP. Curiously, they found that the stable malondialdehyde-acetaldehyde adducts generated by alcohol and smoking significantly inhibited XBP1 expression, leading to unresolved ER stress and acinar cell death. In addition, they observed that stable malondialdehyde-acetaldehyde adducts lingered after the cessation of alcohol and smoking and delayed pancreatic recovery by suppressing the expression of cyclin-dependent kinases, cell cycle–associated proteins, and regeneration markers.

Cigarette smoking and alcohol consumption are the main sources of acetaldehyde and malondialdehyde exposures. With respect to smoking, acetaldehyde is formed from the pyrolysis of tobacco, and malondialdehyde is the by-product of interaction of cellular lipids with cigarette smoke.[18] Similarly, alcohol metabolism yields acetaldehyde via the action of alcohol dehydrogenase and produces malondialdehyde through lipid peroxidation.[18] High concentrations of acetaldehyde and malondialdehyde react with proteins and form hybrid adducts. Stable malondialdehyde-acetaldehyde adducts were previously shown to stimulate proinflammatory responses in liver[19] and lung[18] diseases; however, this is the first report on their role in the context of pancreatitis. Although not studied directly, the authors speculate that malondialdehyde-acetaldehyde adducts on extracellular matrix proteins activate scavenger receptors, thereby leading to acinar cell death and fibroinflammatory responses.

Alcohol abuse often concurs with cigarette smoking, and >80% of patients with alcohol-induced CP have been identified as smokers.[20] Because the organ damage caused by these substances is reversible to a certain extent, participating in cessation programs ought to be a straightforward and immediate response in disease management. On the other hand, the present study indicates that pancreatic regeneration is significantly delayed long after the cessation of exposure to cigarette smoke extract and alcohol. Thus, therapeutic interventions should aim at the prevention of pancreatic damage and specifically inhibit pathways activated by the pancreatitis-causing toxic substances. In this regard, the discovery of Bhatia et al[13] identifies malondialdehyde-acetaldehyde adducts as novel therapeutic targets in the prevention and treatment of pancreatitis associated with alcohol abuse and smoking.

ANDREA GEISZ
Department of Molecular and Cell Biology
Boston University Henry M. Goldman School of Dental Medicine
Boston, Massachusetts

References

1. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252–1261.
2. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol 2012;107:1096–1103.
3. Sankaran SJ, Xiao AY, Wu LM, et al. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015;149:1490–1500.
4. Guda NM, Muddana V, Whitcomb DC, et al. Recurrent acute pancreatitis: international state-of-the-science conference with recommendations. Pancreas 2018;47:653–666.
5. Liu QY, Abu-El-Haija M, Husain SZ, et al. Risk factors for rapid progression from acute recurrent to chronic pancreatitis in children: Report from INSPPIRE. J Pediatr Gastroenterol Nutr 2019;69:206–211.
6. Ahmed Ali U, Issa Y, Hagenaars JC, et al. Dutch Pancreatitis Study Group. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016;14:738–746.

7. Singhvi A, Yadav D. Myths and realities about alcohol and smoking in chronic pancreatitis. Curr Opin Gastroenterol 2018;34:355–361.
8. Hegyi P, Parniczky A, Lerch MM, et al; International Consensus Guidelines for Risk Factors in Chronic Pancreatitis. Recommendations from the Working Group for the International Consensus Guidelines for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. Pancreatology 2020;20:579–585.
9. Tolstrup JS, Kristiansen L, Becker U, et al. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. Arch Intern Med 2009;169:603–609.
10. Szentesi A, Farkas N, Sipos Z, et al. Alcohol consumption and smoking dose-dependently and synergistically worsen local pancreas damage [published online ahead of print January 19, 2022]. Gut https://doi.org/10.1136/gutjnl-2021-326853.
11. Sahin-Tóth M, Hegyi P. Smoking and drinking synergize in pancreatitis: multiple hits on multiple targets. Gastroenterology 2017;153:1479–1481.
12. Lugea A, Gerloff A, Su HY, et al. The combination of alcohol and cigarette smoke induces endoplasmic reticulum stress and cell death in pancreatic acinar cells. Gastroenterology 2017;153:1674–1686.
13. Bhatia R, Thompson CM, Clement EJ, et al. Malondialdehyde-acetaldehyde extracellular matrix protein adducts attenuate unfolded protein response during alcohol and smoking-induced pancreatitis. Gastroenterology 2022;163:1064–1078.
14. Kubisch CH, Logsdon CD. Secretagogues differentially activate endoplasmic reticulum stress responses in pancreatic acinar cells. Am J Physiol Gastrointest Liver Physiol 2007;292:G1804–G1812.
15. Sah RP, Garg SK, Dixit AK, et al. Endoplasmic reticulum stress is chronically activated in chronic pancreatitis. J Biol Chem 2014;289:27551–27561.
16. Geraghty P, Wallace A, D'Armiento JM. Induction of the unfolded protein response by cigarette smoke is primarily an activating transcription factor 4-C/EBP homologous protein mediated process. Int J Chron Obstruct Pulmon Dis 2011;6:309–319.
17. Kassay N, Toldi V, Tőzsér J, et al. Cigarette smoke toxin hydroquinone and misfolding pancreatic lipase variant cooperatively promote endoplasmic reticulum stress and cell death. PLoS One 2022;17:e0269936.
18. McCaskill ML, Kharbanda KK, Tuma DJ, et al. Hybrid malondialdehyde and acetaldehyde protein adducts form in the lungs of mice exposed to alcohol and cigarette smoke. Alcohol Clin Exp Res 2011;35:1106–1113.
19. Tuma DJ. Role of malondialdehyde-acetaldehyde adducts in liver injury. Free Radic Biol Med 2002;32:303–308.
20. Shiffman S, Balabanis M. Do drinking and smoking go together? Alcohol Health Res World 1996;20:107–110.

Correspondence
Address correspondence to: Andrea Geisz, PhD, Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, 72 East Concord Street, Boston, Massachusetts 02118. e-mail: geisz@bu.edu.

Conflicts of interest
The author discloses no conflicts.

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2022.07.067

Needle-free Nonalcoholic Fatty Liver Disease Prognostication: Moving One Step Closer

See "Liver stiffness on magnetic resonance elastography and the MEFIB index and liver-related outcomes in nonalcoholic fatty liver disease: a systematic review and meta-analysis of individual participants," by Ajmera V, Kim BK, Yang K, et al, on page 1079.

The high prevalence, phenotypic diversity in the patient population, variability in disease progression rates, and increased risk of cardiovascular disease makes risk stratification of nonalcoholic fatty liver disease (NAFLD) challenging.[1] Liver fibrosis is the key histological feature predictive of liver-related outcomes in NAFLD.[2] However, the limitations of liver biopsy, the current gold standard for staging hepatic fibrosis, are well-known.[3] Thus, developing effective noninvasive tests (NITs) for disease staging and determination of progression risk has long been a holy grail of the NAFLD field.

Several NITs initially developed for staging chronic hepatitis C infection, such as the Fibrosis-4 index (FIB-4) and vibration controlled transient elastography (VCTE), have been adapted, with different cutoff values, for noninvasive fibrosis assessment in NAFLD.[4,5] Other metrics, such as the NAFLD Fibrosis Score and BARD score, have been developed specifically for NAFLD and incorporate metabolic risk factors such as diabetes and obesity.[6,7] However, these NITs of liver fibrosis in NAFLD have several limitations of their own. First, NITs have a high negative predictive value (scores below the low cutoff value), but low positive predictive value (scores above the high cutoff value) for advanced fibrosis. Second, some patients may be classified in the intermediate risk category between the low- and high-cutoff values.[8] This situation necessitates the use of additional NITs or liver biopsy for disease staging. Thus, there remains a strong clinical need for developing additional tools and risk stratification pathways for determining disease stage and prognosis in NAFLD.