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More reflux after sleeve gastrectomy than gastric bypass at 10 years

BY MARLENE BUSKO

Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) each led to good and sustainable weight loss 10 years later, although reflux was more prevalent after SG, according to the Sleeve vs. Bypass (SLEEVEPASS) randomized clinical trial.

At 10 years, there were no statistically significant between-procedure differences in type 2 diabetes remission, dyslipidemia, or obstructive sleep apnea, but hypertension remission was greater with RYGB.

However, importantly, the cumulative incidence of Barrett's esophagus was similar after both procedures (4%) and markedly lower than reported in previous trials (14%-17%).

To their knowledge, this is the largest randomized controlled trial with the longest follow-up comparing these two laparoscopic bariatric surgeries, Paulina Salminen, MD, PhD, and colleagues write in their study published online in JAMA Surgery

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Low-carb, high-fat diet reduces liver fat, improves A1c

BY BECKY MCCALL

LONDON – A low-carbohydrate, high-fat (LCHF) diet reduced the progression of nonalcoholic fatty liver disease (NAFLD), and despite no calorie restriction, participants with both NAFLD and type 2 diabetes lost 5.8% of their body weight, according to a randomized controlled study.

"Based on these results, the LCHF diet may be recommended to people with NAFLD and type 2 diabetes," said Camilla Dalby Hansen, MD, department of gastroenterology and hepatology, Odense University Hospital (Denmark), who presented the data at the International Liver Congress 2022.

"Basically, if you have fat in your liver, you will benefit from eating fat," she said.

The LCHF diet was compared with a low-fat, high-carbohydrate diet more typically followed for these conditions. The low-fat diet was also found to reduce the progression of NAFLD, but to a lesser extent than the LCHF diet.

Dr. Dalby Hansen called their study one of the most extensive investigations of the LCHF diet in patients with type 2 diabetes and fatty liver disease.

"Combining this [reduction in NAFLD score] with the huge weight loss, the lower HbA1c [blood sugar], the lowering of

See **Diet** · *page 6*

INSIDE

IBD study looks at postacute COVID

BY JIM KLING

MDedge News

A new study among patients with inflammatory bowel disease (IBD) suggests that viral antigen persistence in the gut may contribute to post–acute COVID-19 syndrome.

Post–acute COVID-19 syndrome is now understood to be a multiorgan condition with symptoms that may include fatigue, cognitive dysfunction, and pain. Poor baseline health and severe acute infection are risk factors for the condition, but nonhospitalized illness can also lead to persistent symptoms.

Researchers found that nearly two-thirds of IBD patients had persistence of the antigen in infected tissues up to 8 months after a mild

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LOOK BACK

A valuable learning experience

BY COLIN W. HOWDEN, MD, AGAF

It was a pleasure to serve as editor in chief (EIC) of GI & Hepatology News from 2011 to 2016. As the second EIC of the newspaper, I was preceded by Dr. Charles J. Lightdale – big shoes to fill! I was fortunate to attract a strong group of associate editors who covered many key areas of interest for the paper's readership. With the enthusiastic support of American Gastroenterological Association staff members, we published once-monthly and received generally positive feedback from readers – predominantly U.S.-based AGA members.

Serving as EIC was also a learning opportunity for me. A number of potentially newsworthy items were brought to my attention – some of which I would not otherwise have seen. Although not all were of direct relevance to the readership, I believe that most of those we published were of value.


Dr. Howden

One rewarding aspect of the editorship was the opportunity to liaise with those experts from whom I solicited commentaries on some of our featured items. These busy individuals were consistently generous with their time and expertise, and I believe that their contributions added to the paper's overall appeal.

I initiated the inclusion of two DDSEP questions per edition, and am pleased that this feature continues. One less successful venture was the attempt at a Correspondence section, which ultimately proved too cumbersome to maintain.

I congratulate the AGA on the 15th anniversary of GIHN and I wish the current EIC, Dr. Megan A. Adams, and her editorial colleagues continued success in providing this benefit to AGA members. ■

Colin W. Howden, MD, AGAF, is professor emeritus in the division of gastroenterology, department of medicine, at the University of Tennessee, Memphis. He is a consultant for Allakos, Ironwood, Phathom, and RedHill Biopharma. He is a member of speakers' bureaus for Alnylam, RedHill Biopharma, and Sanofi/Genzyme. He owns stock in Antibe Therapeutics.

THEN AND NOW

Inflammatory bowel diseases

BY BHARATI KOCHAR, MD, MS

In the 15 years between 2007 and 2022, demographics, treatment options, management and monitoring strategies, and even outcomes have dramatically changed in inflammatory bowel diseases (IBD) creating a whole new landscape for the disease.

In 2007, IBD seemed to be primarily a disease of White and Jewish ancestry. While prevalence of IBD is still highest in the Western world, there is now increasing incidence, even accounting for detection bias, in people of all other ancestries globally. Incidence of IBD in children under the age of 18 years is also rising. Patients with IBD are living longer and, despite the notion that IBD is a disease primarily of younger adults, nearly one-third of Americans with IBD are 60 years and older.

"Adalimumab aids in Crohn's disease" read the front page of the inaugural issue of GI & Hepatology News in January 2007. The article highlighted the GAIN study, which demonstrated that patients who lost response to infliximab responded to adalimumab, the second anti–tumor necrosis factor (TNF) agent approved for the treatment of Crohn's disease and subsequently

Continued on following page

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ulcerative colitis. Over the subsequent 15 years, the armamentarium of treatment options for Crohn's disease and ulcerative colitis have rapidly proliferated: there are now four anti–TNF agents, two anti-integrin agents, two anti-interleukin agents, two Janus kinase inhibitors and a sphingosine-1 receptor modulator approved for the treatment of IBD. Many more promising treatment options are in trials. Other mechanisms are under investigation as well, including antimicrobial therapies for ulcerative colitis and stem cell therapeutics for the treatment of refractory perianal fistulizing Crohn's disease. Perhaps even more novel – dietary therapies are more rigorously under investigation.

Dr. Kochar

"Ulcerative colitis guidelines endorse combined therapy" reads another headline from the inaugural GI & Hepatology News issue. The article discusses the European Crohn's and Colitis Organisation's consensus guideline that topical and systemic agents used together are superior to either used alone, referring specifically to mesalamine, both systemic and topical as well as the additional of topical corticosteroid to systemic mesalamine. Combination therapy has a completely new meaning in modern times.

The combination of increased treatment options, decreased reliance on corticosteroids, and stringent treatment strategies has resulted in improved outcomes.

With the publication of the SONIC trial in 2010, combination therapy referred to an anti-TNF in combination with an immunomodulator for the ensuing decade. However, in this new era of IBD treatment, combination therapy could also mean a biologic with a small molecule or even combination biologics, for which there is an ongoing randomized controlled trial. On the topic of treatment strategies, one of the biggest shifts in the IBD treatment paradigm is the bottom-up versus top-down approach of treatment, with increasing evidence to suggest that early biologic initiation is more effective, especially in patients with Crohn's disease. Therapeutic drug monitoring is mainstream. Treat-to-target strategies to achieve more stringent outcomes, such as biomarker, endoscopic, and histologic normalization, especially in ulcerative colitis, have evolved to become the norm in 2022.

The combination of increased treatment options, decreased reliance on corticosteroids, and stringent treatment strategies has resulted in improved outcomes: IBD-related hospitalizations, surgeries, and even mortality have declined since 2007. The growing recognition and focus on extra-intestinal manifestations, including fatigue, and the gut-brain axis are important steps to improving the overall quality of life of patients with IBD. Beyond treating the disease, we are now learning how to treat the patient. We will be developing personalized strategies to identify the right patient for the right treatment, including patient-level clinical and biologic markers. We need to identify those who are at risk for IBD to prevent the disease at a preclinical phase. Concomitantly, we must continue the quest to cure the disease! ■

➤ UPPER GI TRACT

Baclofen shows limited role in GERD

NEBARI/THINKSTOCK

BY JIM KLING
MDedge News

A randomized clinical trial indicated that add-on baclofen may be of benefit to patients on adequate doses of proton-pump inhibitors (PPI) with refractory gastroesophageal reflux disease (GERD). However, the benefit was limited to a subset of patients with positive symptom association probability (SAP), which was calculated using 24-hour combined multichannel intraluminal impedance and pH monitoring (24h pH-MII).

"Empirical add-on therapy with baclofen in GERD patients with persisting typical symptoms in spite of double-dose PPI therapy does not seem justified. The use of baclofen should be limited to patients who display a positive SAP for typical reflux symptoms (heartburn and/or regurgitation) during PPI therapy," researchers led by Ans Pauwels, PhD, MPharmSc, of Catholic University Leuven (Belgium) concluded in Alimentary Pharmacology & Therapeutics (2022 Jun 3. doi: 10.1111/apt.17068).

Asked to comment, Philip Katz, MD, AGAF, professor of medicine and director of GI Function Laboratories at Weill Cornell Medicine, New York, and a coauthor of some recent GERD guidelines said, "What it tells me is that baclofen may be useful to a patient population that has an accurate diagnosis of reflux hypersensitivity. The difficulty with this study is that the patients you would expect to be helped by baclofen, which were patients who satisfied the criteria for true GERD, didn't have any improvement."

PPIs are effective at reducing acid reflux and promoting esophageal healing in GERD patients, but they have little effect on non–acid reflux. Heartburn is most often tied to acid reflux, but regurgitation occurs with similar frequency during both acid and non–acid episodes.

Up to 50% of patients still have reflux despite PPI treatment, and many of these patients will respond to higher PPI doses. However, those who don't respond are left with few treatment choices.

Reflux events generally occur during transient lower esophageal sphincter relaxations (TLOSRs), and this mechanism is predominant in mild and moderate GERD. A gamma-aminobutyric acid type B receptor agonist, baclofen reduces TLOSRs and associated reflux episodes following meals. Few studies have examined the clinical potential of baclofen in refractory GERD, and it generally is used only after determining that ongoing weakly acidic reflux is responsible for symptoms, using 24h pH-MII.

The study included about 60 patients who underwent 24-hour monitoring while taking a PPI twice daily. Over a 2-week run-in period, participants filled out daily diaries and were randomized to placebo or baclofen 3 times daily over 4 weeks. The baclofen dose was 5 mg for the first week, then 10 mg for the next 3 weeks.

At the end of treatment, 24h pH-MII was repeated. The researchers found no significant decreases in non–acid reflux events after placebo treatment (corrected $P = .74$) and a trend toward a reduction following baclofen treatment (corrected $P = .12$).

Although the results won't change his practice significantly, Dr. Katz congratulated the authors on the thoroughness of the study. However, he noted that well-being is a difficult endpoint to study: "The importance of this study to me is that it confirms that baclofen shouldn't be used empirically since there was no improvement in patients who were functional, and it was hard to find improvement in any group. This reinforces the need for a thorough workup of the patient with GERD."

The drug also had some tolerability issues: 16% of patients on baclofen discontinued its use because of adverse events such as drowsiness, dizziness, headache, and nausea.

An important limitation of the study is that the researchers recruited patients with persistent GERD symptoms despite use of PPIs. "Calling it refractory GERD is tricky because they didn't prove they had GERD before they were enrolled in the study. That being said, the researchers did a very rigorous, very careful study to try and find potentially some place that baclofen might benefit patients," said Dr. Katz.

The authors of the study and Dr. Katz have no relevant financial disclosures. ■

Exploring long-term results

Reflux *from page 1*

(2022 Jun 22. doi: 10.1001/jamasurg.2022.2229).

They aimed to clarify the "controversial issues" of long-term gastroesophageal reflux disease (GERD) symptoms, endoscopic esophagitis, and Barrett's esophagus after SG vs. RYGB.

The findings showed that "there was no difference in the prevalence of Barrett's esophagus, contrary to previous reports of alarming rates of Barrett's [esophagus] after sleeve gastrectomy," Dr. Salminen from Turku (Finland) University Hospital, told this news organization in an email.

"However, our results also show that esophagitis and GERD symptoms are significantly more prevalent after sleeve [gastrectomy], and GERD is an important factor to be considered in the preoperative assessment of bariatric surgery and procedure choice," she said.

"We have two good procedures providing good and sustainable 10-year results for both weight loss and remission of comorbidities" for severe obesity.

The takeaway is that "we have two good procedures providing good and sustainable 10-year results for both weight loss and remission of comorbidities" for severe obesity, a major health risk, Dr. Salminen summarized.

10-year data analysis

Long-term outcomes from randomized clinical trials of laparoscopic SG vs. RYGB are limited, and recent studies have shown a high incidence of worsening of de novo GERD, esophagitis, and Barrett's esophagus, after laparoscopic SG, Dr. Salminen and colleagues write.

To investigate this hypothesis, they analyzed 10-year data from SLEEVEPASS, which had randomized 240 adult patients with severe obesity to either SG or RYGB at three hospitals in Finland during 2008-2010.

At baseline, 121 patients were randomized to SG and 119 to RYGB. They had a mean age of 48 years and a mean body mass index of 45.9 kg/m^2, and 70% were women.

Two patients never had the surgery, and at 10 years, 10 patients had died of causes unrelated to bariatric surgery.

At 10 years, 193 of the 288 remaining patients (85%) completed the follow-up for weight loss and other comorbidity outcomes, and 176 of 228 (77%) underwent gastroscopy.

The primary study endpoint of the trial was percent excess weight loss (%EWL). At 10 years, the median %EWL was 43.5% after SG vs. 50.7% after RYGB, with a wide range for both procedures (roughly 2%-110% excess weight loss). Mean estimate %EWL was not equivalent, with its being 8.4% in favor of RYGB.

After SG and RYGB, there were no statistically significant differences in type 2 diabetes remission (26% and 33%, respectively), dyslipidemia (19% and 35%, respectively), or obstructive sleep apnea (16% and 31%, respectively).

Hypertension remission was superior after RYGB (8% vs. 24%; $P = .04$).

Esophagitis was more prevalent after SG (31% vs. 7%; $P < .001$).

'Very important study'

"This is a very important study, the first to report 10-year results of a randomized controlled trial comparing the two most frequently used bariatric operations, SG and RYGB," Beat Peter Müller, MD, MBA, and Adrian Billeter, MD, PhD, who were not involved with this research, told this news organization in an email.

"The results will have a major impact on the future of bariatric surgery," according to Dr. Müller and Dr. Billeter, from Heidelberg (Germany) University.

The most relevant findings are the GERD outcomes, they said. Because of the high rate of upper endoscopies at 10 years (73%), the study allowed a good assessment of this condition.

"While this study confirms that SG is a GERD-prone procedure, it clearly demonstrates that GERD after SG does not induce severe esophagitis and Barrett's esophagus," they said.

Most importantly, the rate of Barrett's esophagus, the precursor lesion of adenocarcinomas of the esophagogastric junction is similar (4%) after both operations and there was no dysplasia in either group, they stressed.

"The main problem after SG remains new-onset GERD, for which still no predictive parameter exists," according to Dr. Müller and Dr. Billeter.

"The take-home message … is that GERD after SG is generally mild and the risk of Barrett's esophagus is equally higher after SG and RYGB," they said. "Therefore, all patients after any bariatric operations should undergo regular upper endoscopies."

However, "RYGB still leads to an increase in proton-pump inhibitor use, despite RYGB being one of the most effective antireflux procedures," they said. "This finding needs further investigation."

Furthermore, "a 4% Barrett esophagus rate 10 years after RYGB is troublesome, and the reasons should be investigated," they added.

"Another relevant finding is that, after 10 years, RYGB has a statistically better weight loss, which reaches the primary endpoint of the SLEEVEPASS trial for the first time," they noted; yet the clinical relevance of this is not clear, since there was no difference in resolution of comorbidities, except for hypertension.

Gyanprakash A. Ketwaroo, MD, MSc, of Baylor College of Medicine, Houston, who was not involved with this research, agreed that "the study shows durable and good weight loss for either type of laparoscopic surgery with important metabolic effects and confirms the long-term benefits of weight-loss surgery."

"What is somewhat new is the lower levels of Barrett's esophagus after sleeve gastrectomy compared with several earlier studies," he told this news organization in an email.

"This is somewhat incongruent with the relatively high incidence of postsleeve esophagitis noted in the study, which is an accepted risk factor for Barrett's esophagus," he continued. "Thus, I believe concern will still remain about GERD-related complications, including Barrett's [esophagus], after sleeve gastrectomy."

"This paper highlights the need for larger prospective studies, especially those that include diverse, older populations with multiple risk factors for Barrett's esophagus," Dr. Ketwaroo said.

Looking ahead

Using a large data set, such as that from SLEEVEPASS and possibly with data from the SM-BOSS trial and the BariSurg trial, with machine learning and other sophisticated analyses might identify parameters that could be used to choose the best operation for an individual patient, Dr. Salminen speculated.

"I think what we have learned from these long-term follow-up results is that GERD assessment should be a part of the preoperative assessment."

"I think what we have learned from these long-term follow-up results is that GERD assessment should be a part of the preoperative assessment, and for patients who have preoperative GERD symptoms and GERD-related endoscopic findings (e.g., hiatal hernia), gastric bypass would be a more optimal procedure choice, if there are no contraindications for it," she said.

Patient discussions should also cover "long-term symptoms, for example, abdominal pain after RYGB," she added.

"I am looking forward to our future 20-year follow-up results," Dr. Salminen said, "which will shed more light on this topic of postoperative [endoscopic] surveillance.

She added that, in the meantime, "preoperative gastroscopy is necessary and beneficial, at least when considering sleeve gastrectomy."

The SLEEVEPASS trial was supported by the Mary and Georg C. Ehrnrooth Foundation, the Government Research Foundation (in a grant awarded to Turku University Hospital), the Orion Research Foundation, the Paulo Foundation, and the Gastroenterological Research Foundation. Dr. Salminen reported receiving grants from the Government Research Foundation awarded to Turku University Hospital and the Mary and Georg C. Ehrnrooth Foundation. Another coauthor received grants from the Orion Research Foundation, the Paulo Foundation, and the Gastroenterological Research Foundation during the study. No other disclosures were reported. ■

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Bread out, unsaturated fats in

Diet *from page 1*

blood pressure in women, the rise in HDL levels, and reduction in triglycerides – all in all, this diet is very promising," she said.

Stephen Harrison, MD, visiting professor, University of Oxford (England), medical director of Pinnacle Clinical Research and president of Summit Clinical Research, San Antonio, commended Dr. Dalby Hansen on her methodology, which included before-and-after liver biopsies. "It's a heinous effort to do paired liver biopsies in a lifestyle modification trial. That's huge."

"This study tells me that the way we manage patients doesn't change – it is still lifestyle modification," said Dr. Harrison, who was not involved with the study. "It's eat less [rather] than more. It's exercise and try to lose weight. In the long term, we give patients benefit, and we show that the disease has improved, and we offer something that means they can maintain a healthy life."

He added that the relatively small and short trial was informative.

"They improved the NAFLD activity score [NAS]," he said. "I don't know by how much. There was no change in fibrosis, but we wouldn't expect this at 6 months."

"It's provocative work, and it gives us healthy information about how we can help manage our patients from a lifestyle perspective," he concluded.

Do not lose weight – 'eat until you are full'

In the study, 110 participants with type 2 diabetes and NAFLD, aged 18-78 years, were allocated to the LCHF diet, and 55 were allocated to the low-fat diet for 6 months.

The researchers performed liver biopsies at baseline and 6 months, which were blinded for scoring.

Participants had ongoing dietitian consultations, with follow-up visits at 3 and 6 months. Compliance was reported continuously through an online food diary platform.

The primary endpoint was change in glycemic control as measured by A1c level over 6 months. The secondary endpoints composed the proportion of participants with changes in the NAS of at least 2 points over 6 months. Both these measures were compared between the two dietary groups.

The two groups were matched at baseline, with a mean age of 55-57 years, 58% women, 89% with metabolic syndrome, and a mean body mass index of 34 kg/m^2.

In baseline liver disease, F1-level fibrosis was the most common (58%), followed by hepatic steatosis (S1, 47%; S2, 32%), with a median NAS of 3, and 19% had nonalcoholic steatohepatitis.

The special thing about these diets was that participants were told to "not lose weight, but eat until you are full," remarked Dr. Dalby Hansen.

Those on the LCHF diet consumed an average of 61% energy from fat, 13% from carbohydrates, and 23% from protein, compared with the low-fat diet, which comprised an average of 29% energy from fat, 46% from carbohydrates, and 21% from protein.

"It's a lot of fat and corresponds to a quarter of a liter of olive oil per day," said Dr. Dalby Hansen. "They really had to change their mindset a lot, because it was difficult for them to start eating all these fats, especially since we've all been told for decades that it isn't good. But we supported them, and they got into it."

The LCHF diet primarily comprised unsaturated fats – for example, avocado, oil, nuts, and seeds – but also included saturated fats, such as cheese, cream, and high-fat dairy products. Participants were free to eat unsaturated and saturated fats, but Dr. Dalby Hansen and her team advised participants that "good" unsaturated fats were preferable.

"Also, this diet contained vegetables but no bread, no potatoes, no rice, and no pasta. It was low in carbohydrates, below 20%," she added.

Improved glycemic control, reduced liver fat

"We found that the LCHF diet improved diabetes control, it reduced the fat in the liver, and, even though they're eating as many calories as they were used to until they were full, they lost 5.8% of body weight," said Dr. Dalby Hansen in reporting the results. Participants in the low-fat group lost only 1.8% of body weight.

However, mean calorie intake dropped in both groups, by –2.2% in the LCHF group and –8.7% in the low-fat group.

CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

BY OVANES ABRAMYAN; NICHOLAS F. LARUSSO, MD; AND JAMES H. TABIBIAN, MD, PHD

Previously published in Gastroenterology (2019 Mar 1;156[4]:876-8).

A 69-year-old Filipino American woman presented with increasing epigastralgia, worsening appetite, jaundice, and oily diarrhea over the course of 3 months. Her medical history consisted of diabetes, hypertension, hyperlipidemia, and osteopenia being managed with metformin, losartan, and atorvastatin, respectively.

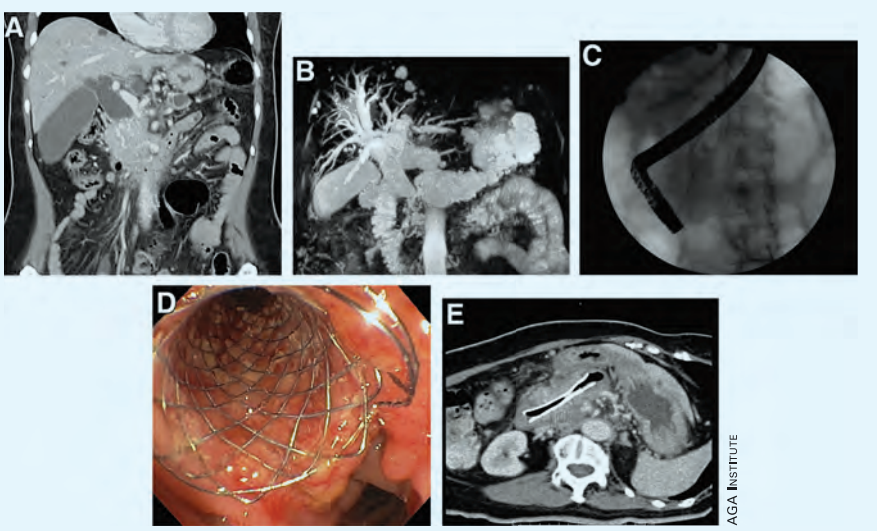
Physical examination revealed she was thin (body mass index, 22 kg/m^2) and jaundiced with moderate tenderness to epigastric palpation and 1+ peripheral pitting edema. Laboratory tests were significant for normal complete blood count and elevated alanine aminotransferase (113 U/L), alkaline phosphatase (235 U/L), bilirubin (7.3 mg/dL), international normalized ratio (1.3), and carbohydrate antigen 19-9 (7,886 U/L). A CT scan of the abdomen revealed severe extrahepatic and intrahepatic ductal dilation, with a common bile duct (CBD) and main pancreatic duct (MPD) diameter of 2.5 and 1.7 cm, respectively, as well an infiltrating, malignant-appearing, 4.5-cm spheroid mass in the head of the pancreas (Figure A). The mass involved the superior mesenteric vein at the portal confluence and encased >50% of the superior mesenteric artery.

To further characterize these findings, magnetic resonance cholangiopancreatography was performed, which additionally revealed multifocal cysts throughout the liver ranging from 0.5 to 5.0 cm in greatest diameter, as seen on maximal intensity projection algorithm (Figure B).

The patient was referred for same-session endoscopic ultrasound examination with fine-needle aspiration (FNA) and endoscopic retrograde cholangiopancreatography (ERCP) for further diagnosis and treatment. Endoscopic ultrasound demonstrated a large, hypoechoic mass in the pancreatic head with severe CBD and MPD dilation proximally, corresponding with the cross-sectional imaging findings; FNA was performed. ERCP demonstrated a long, distal CBD stricture and what appeared to be nonopacification of the right hepatic ductal system; a 10 × 60–mm fully covered self-expanding metallic stent (fcSEMS) was placed across the stricture (Figure C, D). Over the subsequent 3 days, the patient's diarrhea resolved and epigastralgia improved; however, serum liver tests did not downtrend, thus prompting repeat imaging (Figure E).

Based on the patient's clinical history, cross-sectional imaging findings, and only partial response to therapeutic ERCP, what are the patient's likely diagnoses?

The answer is on page 17.



The low-fat group reduced A1c by 3.4 mmol/mol, resulting in a between-group difference of 6.1 mmol/mol.

Both diets also improved the NAS. The proportion of participants who improved their NAS score by 2 or more points was 22% in the LCHF group versus 17% in the low-fat group (P = .58). Additionally, in the LCHF group, 70% of participants improved their score by 1 or more points, compared with 49% in the low-fat group and fewer in the LCHF group experienced a worsening of their score (1% vs. 23%, respectively).

One participant on LCHF had high triglycerides of 12 mmol/L after 3 months. Overall, the low-density lipoprotein increased marginally by 0.2 mmol per liter in the high-fat group, said Dr. Dalby Hansen.

Dr. Dalby Hansen noted some limitations. The findings might not be applicable in more severe NAFLD, dietary assessment relied on self-reporting, no food was provided, and participants had to cook themselves. It was also an open-label study because of the nature of the intervention.

Some hope for more sustainable dieting

Many diets are difficult to adhere to, remarked Dr. Dalby Hansen. "We thought this [diet] might be easier to comply with in the longer term, and we hope that these results might provide patients with more options."

She added that most people who started the diet adapted and complied with it. "However, it might not be for everyone, but I think we can say that, if people try and it fits into their lives, then they go for it."

However, "it is not about going out and eating whatever fat and how much of it you want. It's important that you cut the carbohydrates too," she said. "With this approach, we really saw amazing results."

Dr. Dalby Hansen added that having various diets available, including the LCHF one, meant that as clinicians they could empower patients to take control of their metabolic health.

"We can ask them directly, 'What would fit into their life?' " she said. "We know that one size does not fit all, and I believe that, if we could engage patients more, then they can take control of their own situation."

Asked whether these findings were enough to change guidelines, Zobair Younossi, MD, professor and chairman, department of medicine, Inova Fairfax Medical Campus, Falls Church, Va., remarked that it was the sugar at work here.

"Dietary fat – it's not the same as fat in the liver, and this diet has more to do with the sugar levels," he said.

"I'm always reluctant to take results from a short-term study without long-term follow-up," Dr. Younossi said. "I want to know will patients live longer, and long-term data are needed for this. Until I have that strong evidence that outcomes are going to change, or at least some sign that the outcome is going to change, it is too early to change any guidelines."

Dr. Dalby Hansen reports no relevant financial relationships.

Dr. Harrison reported financial relationships with numerous pharmaceutical companies. Dr. Younossi reports the following financial relationships: research funds and/or consultant to Abbott, Allergan, Bristol Myers Squibb, Echosens, Genfit, Gilead Sciences, Intercept, Madrigal, Merck, and Novo Nordisk. ■

Therapeutic management of NAFLD

In Focus
Brought To You By The New Gastroenterologist

BY EDUARDO VILAR-GOMEZ, MD, AND NAGA CHALASANI, MD, AGAF

Nonalcoholic fatty liver disease (NAFLD) is defined by the presence of hepatic steatosis detected on either imaging or histology in the absence of secondary causes of fatty liver (e.g., excessive alcohol consumption) or other chronic liver diseases.[1] For practical NAFLD diagnosis purposes, excessive alcohol intake can be defined as an active or recent history of more than 21 standard drinks per week in men and more than 14 standard drinks per week in women. For the sake of terminology, NAFLD is characterized by fatty liver infiltration, affecting at least 5% of hepatocytes, with no evidence of hepatocyte injury, whereas nonalcoholic steatohepatitis (NASH) is defined as the presence of necroinflammation with or without fibrosis in a background of fatty liver.[1]

Natural history

NASH and the degree of fibrosis are the two most important determinants of the natural history of NAFLD. NASH can evolve into fibrosis and cirrhosis, whereas advanced fibrosis and cirrhosis (stages 3 or 4 of fibrosis) significantly increase the risk of liver-related decompensation and mortality. NAFLD, per se, has been associated with an increased risk of overall mortality, compared with that of the general population.[2] The three most common causes of mortality for patients with NAFLD are cardiovascular diseases (CVD), extrahepatic malignancies, and liver-related deaths. Mortality and liver-related events, including hepatic decompensation and hepatocellular carcinoma (HCC), may significantly increase in a dose-dependent manner with increasing fibrosis stages, and stages 3 or 4 of fibrosis may display the highest rates of all-cause mortality and liver-related events.[3,4] It is important to note, however, that almost 15% of HCCs occur in patients with NAFLD who do not have cirrhosis.[5] The presence of commonly associated comorbidities such as obesity, insulin resistance or diabetes, dyslipidemia, hypothyroidism, polycystic ovary syndrome, and sleep apnea may contribute to an increased risk of NASH and advanced fibrosis and, therefore, an accelerated clinical course of NAFLD.

Nonpharmacological interventions

Lifestyle modification

Lifestyle modification to achieve weight loss remains a first-line intervention in patients with NAFLD. Weight loss achieved either by hypocaloric diet alone or in conjunction with increased physical activity can be beneficial for all patients with NAFLD. The benefits extend not only to those who are overweight and obese but also to those within normal body weight (lean NAFLD).[1,6,7] Weight loss of approximately 3%-5% is necessary to improve hepatic steatosis, but a greater weight loss (7%-10%) is required to improve other histopathological features like necroinflammatory lesions and fibrosis.[8-10] Individuals with higher body mass index and/or type 2 diabetes (T2D) will require a larger weight reduction to achieve a similar benefit on NAFLD-related features.[7,8] Weight loss via lifestyle changes can also decrease hepatic venous pressure gradient (HVPG), with greater declines reported among those with more than 10% weight loss.[11]

Weight loss can be achieved through a variety of modalities, but long-term maintenance of lost weight is much more challenging. A combination of a hypocaloric diet with a caloric deficit of 500-1,000 kcal/d, alongside moderate-intensity exercise and intensive on-site behavioral treatment, will likely increase the possibility of a sustained weight loss over time.[1,12] A growing body of scientific evidence indicates that a healthy diet that includes a reduction of high–glycemic index foods and refined carbohydrates; increased consumption of monounsaturated fatty acids, omega-3 fatty acids, and fibers; and high intakes of olive oil, nuts, vegetables, fruits, legumes, whole grains, and fish can have beneficial effects on NAFLD and its severity.[13-16] Adherence to these healthy dietary patterns has been associated with a marked reduction in CVD morbidity and mortality and is, thus, a strategic lifestyle recommendation for patients with NAFLD in whom the leading cause of morbidity and death is CVD.[1,3]

Exercise alone in adults with NAFLD may reduce hepatic steatosis, but its ability to improve inflammation and fibrosis has not been proven in well-designed RCTs.[17,18] Physical activity and exercise have been shown to curb both the development and the progression of NAFLD, and beneficial effects could be achieved independent of weight loss.[17,19,20] Most importantly, moderate to vigorous physical activity is likely associated with lower all-cause and cardiovascular mortality in patients with NAFLD.[21]

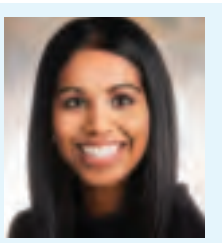
Heavy alcohol intake should be avoided by patients with NAFLD or NASH, and those with cirrhotic NASH should avoid any alcohol consumption given the risk of HCC and hepatic decompensation.[1,4,22] Limiting light to moderate alcohol intake among patients without cirrhosis is still under debate.[1] People with NAFLD may be advised to drink an equivalent of two to three 8-oz cups of regular brewed coffee daily as it has shown certain antifibrotic effects in NAFLD patients.[23]

Dr. Vilar-Gomez is assistant professor in the division of gastroenterology and hepatology at Indiana University, Indianapolis. **Dr. Chalasani** is vice president for academic affairs at Indiana University Health, Indianapolis, and the David W. Crabb Professor of Gastroenterology and Hepatology and an adjunct professor of anatomy, cell biology, and physiology in the division of gastroenterology and hepatology at Indiana University. Dr. Vilar-Gomez reports no financial conflicts of interest. Dr. Chalasani serves as a paid consultant to AbbVie, Boehringer-Ingelheim, Altimmune, Madrigal, Lilly, Zydus, and Galectin. He receives research support from Galectin and DSM.

Nonalcoholic fatty liver disease (NAFLD) is defined by the presence of hepatic steatosis in the absence of secondary causes of liver disease. The prevalence of NAFLD has been precipitously rising in recent decades and, now, is the most common liver disorder in Western industrialized countries.

The In Focus article for August, which is brought to you by The New Gastroenterologist, provides an excellent, comprehensive review of the diagnosis and treatment of NAFLD. Experts Dr. Naga Chalasani and Dr. Eduardo Vilar-Gomez (Indiana University) review the natural history of NAFLD, as well as a multifaceted management approach that includes dietary and lifestyle modifications, pharmacotherapy, and surgical options. Longitudinal follow-up and treatment of comorbidities are also essential.

Vijaya L. Rao, MD
Editor in Chief
The New Gastroenterologist



Dr. Rao

Bariatric surgery

Bariatric surgery is an attractive therapeutic option for eligible obese patients with NAFLD. Bariatric surgery has the potential for inducing great weight loss and, therefore, reverses not only the steatosis, inflammation, and fibrosis among NAFLD individuals but also important comorbid conditions like T2D. A recent systematic review and meta-analysis examining data on the effects of bariatric surgery on histologic features of NAFLD from 32 cohort studies (no randomized clinical trials included) showed that bariatric surgery was associated with significant improvements in steatosis (66%), lobular inflammation (50%), ballooning degeneration (76%), and fibrosis (40%), and the benefits were significantly higher in those who underwent Roux-en-Y gastric bypass (RYGB). Of note, worsening of liver histology, including fibrosis, could be seen in up to 12% of patients who underwent bariatric surgery.[24] The postsurgical weight regained after RYGB could explain partly the lack of fibrosis improvement or even worsening of fibrosis, although further research is needed to clarify these controversial findings.

RYGB and sleeve gastrectomy (SG) are the most commonly performed bariatric surgeries worldwide. Patients who undergo RYGB achieve higher weight loss when compared with those treated with SG.[25] Among all bariatric procedures, RYGB could result in a higher proportion of complete resolution of NAFLD than SG, although evidence is inconclusive on fibrosis improvement rates.[24,26] Most recently, a single-center RCT has compared the effects of RYGB vs. SG on liver fat content and fibrosis in patients with severe obesity and T2D.[27] Data showed that both surgical procedures were highly and equally effective in reducing fatty liver content (quantified by magnetic resonance imaging), with an almost complete resolution of the fatty liver at 1 year of both surgical interventions. The beneficial effects of both GB and SG on fibrosis (assessed by enhanced liver test [ELF]) were less evident with no substantial difference between the two groups. Importantly, 69% of participants had an increase in their ELF scores during the study, despite the majority of participants achieving significant reductions in their body weights and better glycemic control at the end of the study. These findings might be considered with caution as several factors, such as the duration of the study (only 1 year) and lack of a liver biopsy to confirm fibrosis changes over time, could be influencing the study results.

Among all NAFLD phenotypes, those with cirrhosis and, most importantly, hepatic decompensation appear to be at increased risk of perioperative mortality and inpatient hospital stays than those without cirrhosis.[28,29] Bariatric surgery is an absolute contraindication in patients with decompensated cirrhosis (Child B and Child C). Among compensated–Child A–cirrhotics, those with portal hypertension are at increased risk of morbidity and perioperative mortality.[30] A recent analysis of National Inpatient Sample data suggested that the rates of complications in those with cirrhosis have decreased with time, which could be due to a better selection process and the use of more restrictive bariatric surgery in those with cirrhosis. Low-volume centers (defined as less than 50 procedures per year) and nonrestrictive bariatric surgery were associated with a higher mortality rate. These data may suggest that patients with cirrhosis should undergo bariatric surgery only in high-volume centers after a multidisciplinary evaluation.[31] Bariatric endoscopy is emerging as a new treatment for obesity, but the long-term durability of its effects remains to be determined.

A recent retrospective cohort study, including 1,158 adult patients who had biopsy-proven NASH, has investigated the benefits of bariatric surgery on the occurrence of major adverse liver and cardiovascular outcomes in 650 patients who underwent bariatric surgery, compared with 508 patients who received nonsurgical usual care. This study showed that bariatric surgery was associated with 88% lower risk of progression of fatty liver to cirrhosis, liver cancer, or liver-related death, and 70% lower risk of serious CVD events during a follow-up period of 10 years.[32] Within 1 year after surgery, 0.6% of patients died from surgical complications. The potential benefits of bariatric surgery in patients with NAFLD must be balanced against surgical risk, especially in eligible obese individuals with established cirrhosis. Data from a retrospective cohort study have shown that bariatric surgery in obese cirrhotic patients does not seem to associate with excessive mortality, compared with noncirrhotic obese patients.[33] More data on immediate complication rates and long-term outcomes in patients with NAFLD by type of bariatric surgery are also required.

NAFLD as a standalone is not an indication for bariatric surgery. However, it could be considered in NAFLD patients who have a BMI of 40 kg/m^2 or more without coexisting comorbidities or with a BMI of 35 kg/m^2 or more and one or more severe obesity-related comorbidities, including T2D, hypertension, hyperlipidemia, or obstructive sleep apnea. Bariatric surgery must always be offered in centers with an experienced bariatric surgery program.[1]

Management of comorbidities

Given the multiple comorbidities associated with NAFLD and the potential to influence its severity, a comprehensive and multidisciplinary approach is needed to ameliorate not only the progression of liver disease but also those complications related to metabolic syndrome, hyperlipidemia, hypertension, diabetes, and other related conditions. Of note, all patients with NAFLD should receive aggressive management of comorbidities regardless of the severity of NAFLD. Ideally, a multidisciplinary team – including a primary care provider, an endocrinologist for patients with T2D, and a gastroenterologist/hepatologist – is needed to successfully manage patients with NAFLD.

It is well recognized that individuals with biopsy-proven NAFLD are at a higher risk of coronary heart disease, stroke, congestive heart failure, and death resulting from CVD when compared with the non-NAFLD population, and excess in CVD morbidity and mortality is evident across all stages of NAFLD and increases with worsening disease severity.[34] The strong association between CVD and NAFLD has important clinical implications that may influence the decision to initiate treatment for primary prevention, including lipid-lowering, antihypertensive, or antiplatelet therapies.[35] Statins are widely used to reduce LDL cholesterol and have been proven to be safe in NAFLD, including for those with elevated liver enzymes and even in compensated cirrhosis, in several studies conducted during the last 15 years.[36] Statins are characterized by anti-inflammatory, anti-oxidative, antifibrotic, and plaque-stabilizing effects, whereby they may improve vascular and hepatic function among patients with NAFLD and reduce cardiovascular risk.[37] Statin use for the treatment of NAFLD is still controversial and off-label and is not specifically recommended to treat NASH, but positive results have been shown for reductions in liver enzymes.[1] A recent meta-analysis of 13 studies showed that continued use of statin in cirrhosis was associated with a 46% and 44% risk reduction in hepatic decompensation and mortality, respectively.[38]

The Food and Drug Administration has approved omega-3 (n-3) fatty acid agents and fibrates for the treatment of very high triglycerides (500 mg/dL or higher); however, no specific indications exist to treat NAFLD.[1] Fenofibrate is related to mild aminotransferase elevations and, in some cases, severe liver injury, so caution must be paid, especially within 2 days of taking the drug.[39,40]

Table 1. Indications of liver-directed pharmacotherapy and management of comorbidities based on NAFLD phenotypes

	Liver directed pharmacotherapy	Management of comorbidities
NAFL	No	Yes
NASH with fibrosis stages 0 or 1	Probably not	Yes
NASH with fibrosis stages 2 or 3	Yes	Yes
NASH with cirrhosis	Yes	Yes

NAFLD phenotypes that need liver pharmacotherapy

There are still no FDA-approved drugs or biological treatments for NASH. Pharmacological interventions aiming primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and clinically significant fibrosis (fibrosis stages of 2 or greater).[1,4] For FDA approval, medications used for treating NAFLD with fibrosis need to meet one of the following endpoint criteria: resolution of NASH without worsening of fibrosis, improvement in fibrosis without worsening of NASH, or both. In addition to those criteria, a new medication might improve the metabolic profile and have a tolerable

Continued on following page

Dr. Eduardo Vilar-Gomez and Dr. Naga Chalasani

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safety profile. Table 1 displays those NAFLD phenotypes that will likely benefit from liver-directed therapy.

Obeticholic acid as an experimental therapy for NASH

A planned month-18 interim analysis of a multicenter, phase 3 RCT examined the efficacy and safety of obeticholic acid (OCA), a farnesoid X receptor agonist, in patients with NASH and stages 1-3 of fibrosis. The primary endpoint (fibrosis reduction 1 stage or more with no worsening of NASH) was met by 12% of patients in the placebo group, 18% of patients receiving OCA 10 mg (P = .045), and 23% of those receiving OCA 25 mg (P = .0002). An alternative primary endpoint of NASH resolution with no worsening of fibrosis was not met. OCA 25 mg led to the highest rates of pruritus and hyperlipidemia, compared with OCA 10 mg.[42] These side effects seem to be related to the activation of the farnesoid X receptor.[43]

Table 2. Liver-directed pharmacotherapy options

Medications	Histology efficacy
Pioglitazone	Yes
Vitamin E	Yes
Semaglutide	Yes
Liraglutide	Possibly
Metformin	No
Ursodeoxycholic acid	No
Omega-3 polyunsaturated fatty acid	No
Milk thistle	Probably not
Angiotensin-converting enzyme inhibitors	Probably not

Dr. Eduardo Vilar-Gomez and Dr. Naga Chalasani

Note: All options are off label in the United States.

Currently available but off-label medications

Vitamin E, an antioxidant, administered at a daily dose of 800 IU/day improves steatosis, inflammation, and ballooning, but not fibrosis in nondiabetic adults with biopsy-proven NASH.[44] Vitamin E for 96 weeks was associated with a significantly higher rate of improvement in NASH (43% vs. 19%, P less than .01), compared with placebo.[44] In the Treatment of Nonalcoholic Fatty Liver Disease in Children trial (TONIC), which examined vitamin E (800 IU/day) or metformin (500 mg twice daily) against placebo in children with biopsy-proven NAFLD, resolution of NASH was significantly greater in children treated with vitamin E than in children treated with placebo (58% vs. 28%, P less than .01). Metformin did not significantly improve the NASH resolution rates, compared with placebo (41% vs. 28%, P = .23). Vitamin E could be recommended for nondiabetic adults or children if lifestyle modifications do not produce the expected results as a result of noncompliance or ineffectiveness. Since continued use of vitamin E has been suggested to be associated with a very small increase in the risk for prostate cancer (an absolute increase of 1.6 per 1,000 person-years of vitamin E use) in men, risks and benefits should be discussed with each patient before starting therapy. A meta-analysis of nine placebo-controlled trials including roughly 119,000 patients reported that vitamin E supplementation increases the risk of hemorrhagic stroke by 20% while reducing ischemic stroke by 10%. It was estimated that vitamin E supplementation would prevent one ischemic stroke per 476 treated patients while inducing one hemorrhagic stroke for every 1,250 patients. It is noteworthy that the combination of vitamin E with anticoagulant and/or antiplatelet therapy was not examined in this trial, so we could not determine how combination therapy might affect the risk of ischemic or hemorrhagic stroke.[45]

Thiazolidinediones drugs have been reported to be effective in improving NAFLD in many human studies. Evidence from RCTs suggests that pioglitazone could significantly improve glucose metabolism, alanine aminotransferase, and liver histology – such as hepatic steatosis, lobular inflammation, and ballooning degeneration – among patients with or without T2D. However, the beneficial effects on improving fibrosis remain to be verified.[1,46] Because of safety concerns, the risk/benefit balance of using pioglitazone to treat NASH should be discussed with each patient.[47,48] Pioglitazone has been associated with long-term risk of bladder cancer,[49] congestive heart failure,[50] and bone fractures.[51] Data from the Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis (PIVENS) trial showed that pioglitazone was significantly associated with weight gain but with no other serious adverse events. However, this study was not powered to test any safety-related hypotheses.[44]

Glucagon-like peptide 1 analogs have been reported to induce weight loss and reduce insulin resistance, which may lead to improvements in NAFLD. Phase 2 RCTs of glucagon-like peptide 1 receptor agonists (liraglutide and semaglutide) for the treatment of biopsy-proven NASH showed significant improvements in serum liver enzymes, steatosis, and inflammation, as well as NASH resolution without worsening liver fibrosis, although no direct benefit was observed in reversing fibrosis.[52,53] One of these studies explores the efficacy and safety of different doses of daily subcutaneous semaglutide vs. placebo on the rates of resolution of NASH with no worsening of fibrosis. The highest dose (0.4 mg) showed the greatest difference (59% vs. 17%, P less than .01), compared with the placebo arm. However, there was no difference in improvement in fibrosis stage between the two groups (43% in the 0.4-mg group vs. 33% in the placebo group, ^{P} = .48).[53] Gastrointestinal adverse events were common in the semaglutide arm.

"Spontaneous" NASH resolution and fibrosis improvement are commonly seen in participants assigned to placebo arms in clinical trials. A recent meta-analysis of 43 RCTs including 2,649 placebo-treated patients showed a pooled estimate of NASH resolution without worsening of fibrosis and 1-stage reduction or more in fibrosis of 12% and 19%, respectively. Relevant factors involved in "spontaneous" NASH improvement are unknown but could be related to changes in BMI resulting from lifestyle changes, race and ethnicity, age, and, likely, NAFLD-related genetic variations, although more data are needed to better understand the histologic response in placebo-treated patients.[54]

Semaglutide injections (2.4 mg once weekly) or (2.0 mg once weekly) have been recently approved by the FDA for chronic weight management in adults with obesity or overweight with at least one weight-related condition or glucose control of T2D, respectively. Of note, the semaglutide dose used in the NASH trial is not currently available for the treatment of patients who are overweight/obese or have T2D, but the beneficial effects on body weight reductions and glucose control are similar overall to the effects seen with currently available doses for management of obesity or diabetes. One may consider using semaglutide in patients who are overweight/obese or have T2D with NASH, but in the senior author's experience, it has been quite challenging to receive the payer's approval, as its use is not specifically approved to treat liver disease.[1]

How to follow patients with NAFLD in the clinic

Once a diagnosis of NAFLD is made, the use of noninvasive testing may aid to identify which patients are at high risk of fibrosis. Easy-to-use clinical tools, such as the NAFLD Fibrosis Score and the Fib-4 index, and liver stiffness measurements (LSM) using vibration-controlled transient elastography (FibroScan) or magnetic resonance elastography (MRE) are clinically useful noninvasive tools for identifying patients with NAFLD who have a higher likelihood of progressing to advanced fibrosis.[1,55] The use of either NAFLD Fibrosis Score (less than -1.455) or Fib-4 index (less than 1.30) low cutoffs may be particularly useful to rule out advanced fibrosis. People with a NAFLD Fibrosis Score (greater than –1.455) or Fib-4 index (greater than 1.30) should undergo LSM via FibroScan. Those with an LSM of 8 kPa or higher should be referred to specialized care, where a decision to perform a liver biopsy and initiate monitoring and therapy will be taken. MRE is the most accurate noninvasive method for the estimation of liver fibrosis. When MRE is available, it can be a diagnostic alternative to accurately rule in and rule out patients with advanced fibrosis. This technique can be preferred in clinical trials, but it is rarely used in clinical practice because it is expensive and not easily available. Reassessment by noninvasive scores at 1-3 years' follow-up will be considered for those with an LSM less than 8 kPa. Patients with NASH cirrhosis should be screened for both gastroesophageal varix and HCC according to the American Association for the Study of Liver Diseases guidelines.[56,57]

See references at MDedge.com/gihepnews/new-gastroenterologist.

AGA Clinical Practice Guideline

Exploring pharmacologic treatment options for irritable bowel syndrome

BY WILL PASS
MDedge News

The American Gastroenterological Association has issued new guidelines for the medical treatment of irritable bowel syndrome (IBS).

The guidelines, which are separated into one publication for IBS with constipation (IBS-C) and another for IBS with diarrhea (IBS-D), are the first to advise clinicians in the usage of new, old, and over-the-counter drugs for IBS, according to a press release from the AGA.

"With more treatments available, physicians can tailor a personalized approach based on the symptoms a patient with IBS is experiencing," AGA said.

Published simultaneously in Gastroenterology, the two guidelines describe a shared rationale for their creation, noting how the treatment landscape has changed since the AGA last issued IBS guidelines in 2014.

"New pharmacological treatments have become available and new evidence has accumulated about established treatments," both guidelines stated. "The purpose of these guidelines is to provide evidence-based recommendations for the pharmacologic management" of individuals with IBS "based on a systematic and comprehensive synthesis of the literature."

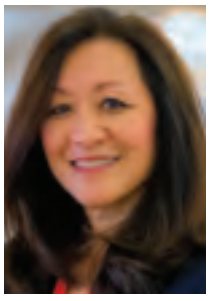
IBS-C

In the IBS-C guidelines (Gastroenterology. 2022 Jul 1;163[1]:118-36), co–first authors Lin Chang, MD, AGAF, of the University of Los Angeles, and Shahnaz Sultan, MD, MHSc, AGAF, of the Minneapolis Veterans Affairs Healthcare System, noted that IBS-C accounts for "more than a third of IBS cases," with patients frequently reporting "feeling self-conscious, avoiding sex, difficulty concentrating, [and] not feeling able to reach one's full potential."


Dr. Sultan

They offered nine pharmacologic recommendations, eight of which are conditional in nature, with certainty in evidence ranging from low to high.

The only strong recommendation with a high certainty in evidence is for linaclotide.


Dr. Chang

"Across four RCTs [randomized controlled trials], linaclotide improved global assessment of IBS-C symptoms (FDA responder), abdominal pain, complete spontaneous bowel movement response, as well as adequate global response," Dr. Chang and colleagues wrote.

Conditional recommendations with moderate certainty in evidence are provided for tenapanor, plecanatide, tegaserod, and lubiprostone. Recommendations for polyethylene glycol laxatives, tricyclic antidepressants, and antispasmodics are conditional and based on low-certainty evidence, as well as a conditional recommendation against selective serotonin reuptake inhibitors, also based on low-certainty evidence.

IBS-D

The IBS-D guidelines (Gastroenterology. 2022 Jul 1;163[1]:137-51), led by co–first authors Anthony Lembo, MD, AGAF, of Beth Israel Deaconess Medical Center, Boston, and Dr. Sultan, includes eight conditional recommendations with certainty in evidence ranging from very low to moderate.


Dr. Lembo

Drugs recommended based on moderate-certainty evidence include eluxadoline, alosetron, and rifaximin, with the added note that patients who respond to rifaximin but have recurrence should be treated again with rifaximin. Low-certainty evidence supported recommendations for tricyclic antidepressants, and antispasmodics. Very low–certainty evidence stands behind a recommendation for loperamide.

Again, the panel made a conditional recommendation against SSRIs, also based on low-certainty evidence.

Shared decision-making

Both publications concluded with similar statements about the importance of shared decision-making, plus a practical mindset, in management of IBS.

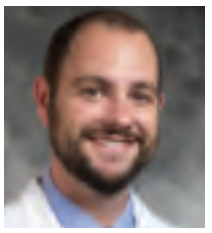
"Acknowledging that multimodal treatments that include dietary and behavioral approaches in conjunction with drug therapy may provide maximal benefits and that treatment choices may be influenced by patient preferences, practitioners should engage in shared decision-making with patients when choosing the best therapy," Dr. Lembo and colleagues wrote. "The importance of the patient-physician relationship is paramount in caring for individuals with IBS, and understanding patient preferences (for side-effect tolerability as well as cost) is valuable in choosing the right therapy."

Both guidelines noted that some newer drugs for IBS have no generic alternative, and preauthorization may be required. Payer approval may depend on previous treatment failure with generic alternatives, they added.

The guidelines were commissioned and funded by the AGA Institute. The authors disclosed relationships with Ardelyx, Immunic, Protagonist, and others.

You can make a difference


Dr. Camilleri


Dr. Sullivan

The American Gastroenterological Association Research Foundation is the charitable arm of the AGA and plays an important role in medical research by providing grants to young scientists at a critical time in their career.

"I am beyond excited to be able to continue my journey as a young physician-scientist with the funding support. I truly understand that my career would not be possible without those who generously support scientific research. I am humbled at the opportunity to contribute to something larger than myself. As such, I am extremely grateful to the AGA Research Foundation and its donors who continue to support this vision of a future where suffering related to digestive diseases has been eliminated," said Brian A. Sullivan, MD, a 2021 AGA Research Scholar Award recipient, who is a physician-scientist aspiring to lead a collaborative research program and develop more effective strategies for colorectal cancer prevention.

In the past decade alone, we've witnessed seminal work in colorectal cancer genetics and a renaissance in the understanding of inflammatory bowel syndrome and the gut microbiome. However, continued progress in advancing the treatment and cure of digestive diseases is at risk because of cuts in government spending. Without help from other funding sources, young investigators are struggling to continue their research, build their research portfolio, and obtain federal funding.

Your contribution makes a difference

With donations from AGA members, we can provide young researchers with a secure, ongoing stable source of funding that drives advancement in the diagnosis, treatment and cure of digestive diseases. Everyone benefits from GI research developed by dedicated investigators.

"I donated to the AGA Research Foundation to ensure the vitality of our specialty, and to fund the research of future generations of gastroenterologists. Funding from organizations like the AGA Research Foundation is crucial for young scientists and gastroenterologists to launch their careers. At the start of my career, I received two AGA research awards. As a grateful recipient of such funding, I felt it was my turn to support the mission of the organization that I regard as my academic home away from home institution," said Michael Camilleri, MD, AGAF, chair of the AGA Research Foundation and AGA past president.

Many breakthroughs have been achieved through gastroenterological and hepatological research over the past century, forming the basis of the modern medical practice. Join fellow AGA members by contributing to this tradition of discovery.

Make a tax-deductible donation to the AGA Research Foundation at www.gastro.org/donate or by mail to 4930 Del Ray Avenue, Bethesda, MD 20814.

Learn more about the AGA Research Foundation at https://foundation.gastro.org. ■

Understanding proposed changes to Medicare payment policies

On July 7, the Centers for Medicare & Medicaid Services released the calendar year (CY) 2023 Medicare Physician Fee Schedule Proposed Rule and can now be found in the Federal Register.

Good news!

In a win for patients, and thanks to collective advocacy efforts from AGA and partner societies, CMS is proposing to expand the regulatory definition of "colorectal cancer screening tests" and waive cost sharing for a necessary follow-up colonoscopy after a positive stool-based screening test.

Looming cuts

The rule proposes 4% cuts to Medicare physician reimbursement through required decreases in the conversion factor and expiration of temporary fixes passed by Congress. AGA will continue to work with a coalition of national and state medical societies in urging Congress to prevent these cuts before Jan. 1, 2023.

What to know

- CMS expands colorectal cancer screening in a proposal to waive cost sharing for a follow-up colonoscopy to a positive stool-based colorectal cancer screening test and to cover the service for individuals 45 years of age and above.
- Medicare payment cuts are looming with cuts to the proposed CY 2023 conversion factor.
- Split/shared visits policy delayed until CY 2024.
- Payment rates for new bariatric device codes proposed. ■

Don't let insurance policies burden GI practices

Join us at AGA Advocacy Day on Thursday, Sept. 22, 2022, to virtually meet with your members of Congress to urge them to rein in insurance policies like prior authorization and step therapy.

If GI providers don't have a seat at the table and engage with lawmakers, these decisions will be influenced by payers and other parties that do not have your or your patients' best interests at heart.

AGA Advocacy Day is held shortly before the end of the fiscal year – prime time to educate policymakers and their staff about your everyday challenges and the reality of GI patient care in your state. We will also discuss the need for robust federal funding for GI research and the devastating impact that Medicare cuts could have on your practice.

Register today and AGA will take care of the rest, including scheduling your meetings and providing comprehensive advocacy training. Now more than ever, your voice needs to be heard on Capitol Hill. ■

CRC screening coverage continuum is complete

In a huge win for patients, Medicare will begin covering colonoscopies after a positive noninvasive stool test starting in 2023. Medicare was previously the only insurer who did not cover this critical prevention procedure.

This change comes after a year of advocacy led by AGA – including multiple meetings with senior officials at HHS and legislative pressure by members across the country.

"Cost-sharing is a well-recognized barrier to screening and has resulted in disparities. Patients can now engage in CRC screening program and be confident that they will not face unexpected cost-sharing for colonoscopy after a positive noninvasive screening test," said David Lieberman, MD, AGAF, who met with Centers for Medicare & Medicaid Services officials multiple times to push this policy forward. "AGA knows that increased participation in screening will further reduce the burden of colorectal cancer."

"This is a win for all patients and should elevate our nation's screening rates while lowering the overall cancer burden, saving lives. Importantly, the CMS proposed rule changes will lessen colorectal cancer disparities eliminating a financial burden for many patients," said AGA president John Carethers, MD, AGAF, who met with CMS in early July to advocate for this change.

Thank you to everyone in the GI community who advocated for this important change!

CMS announced the coverage change as part of the 2023 Medicare proposed rule, which was released July 7. The rule must be finalized this fall before taking effect Jan. 2, 2023. ■

Two genetic intestinal diseases linked

BY JIM KLING
MDedge News

Two genes that have been linked separately to rare intestinal diseases appear to share a functional relationship. The genes have independently been linked to osteo-oto-hepato-enteric (O2HE) syndrome and microvillus inclusion disease (MVID), which are characterized by congenital diarrhea and, in some patients, intrahepatic cholestasis.

It appears that one gene, UNC45A, is directly responsible for the proper function of the protein encoded by the other gene, called MYO5B, according to investigators, who published their findings in Cellular and Molecular Gastroenterology and Hepatology (2022 Apr 11. doi: 10.1016/j.jcmgh.2022.04.006). UNC45A is a chaperone protein that helps proteins fold properly. It has been linked to O2HE patients experiencing congenital diarrhea and intrahepatic cholestasis. The mutation has been identified in four patients from three different families with O2HE, which can also present with sensorineural hearing loss and bone fragility. Cellular analyses have shown that the mutation leads to reduction in protein expression by 70%-90%.

Intestinal symptoms similar to those in O2HE have also been described in diseases caused by mutations in genes that encode the myosin motor proteins that are involved in cellular protein trafficking. This group of disorders includes MVID. The researchers hypothesized that the UNC45A mutation in O2HE might lead to

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Congenital diarrheas and enteropathies (CoDEs) are rare monogenic disorders caused by genes important for intestinal epithelial function. The increasing availability of exome sequencing in clinical practice has accelerated the discovery of new genes associated with these disorders over the past few years. Several CoDE disorders revolve around defects in trafficking of vesicles in epithelial cells. One of these is microvillus inclusion disease which is caused by loss-of-function variants in the gene MYO5B, which encodes an important epithelial motor protein. This study by Li and colleagues reveals that a recently discovered novel CoDE gene and protein, UNC45A, is functionally linked to MYO5B and that loss of UNC45A in cells causes a very similar cellular phenotype to MYO5B-deficient cells.

These studies together highlight the importance of a functional epithelial vesicular trafficking system for normal intestinal fluid and electrolyte transport and add to a growing list of CoDE disease genes that affect this pathway. Further studies are needed to understand the exact mechanisms involved in the UNC45A-MYO5B interaction and how this might be leveraged for therapies. Both UNC45A and MYO5B disease result in a devastating loss of nutrient absorption in patients often requiring lifelong parenteral nutrition and intensive medical management. Understanding the cell biology of these rare intestinal diseases is a critical first step in developing potential disease-modifying therapies that may transform the lives of these patients.


Dr. Thiagarajah

Jay Thiagarajah, MD, PhD, attending in the division of gastroenterology, hepatology, and nutrition and codirector of the congenital enteropathy program at Boston Children's Hospital, as well as assistant professor in pediatrics at Harvard Medical School, also in Boston. Dr. Thiagarajah stated he had no relevant conflicts to disclose.

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" on page 6: Pancreatic adenocarcinoma arising from main duct intraductal papillary mucinous neoplasm with inadvertent main pancreatic duct stenting.

The fine-needle aspiration (FNA) was positive for carcinoma with abundant mucin, which, taken together with the imaging findings, was indicative of pancreatic adenocarcinoma arising from main duct intraductal papillary mucinous neoplasm (M-IPMN).

The post–endoscopic retrograde cholangiopancreatography (ERCP) CT revealed inadvertent placement of the fully covered self-expanding metallic stent (fcSEMS) within the main pancreatic duct (MPD) stricture and persistent common bile duct (CBD) obstruction. On post hoc review of the fluoroscopic and cross-sectional imaging, it became evident that the massively dilated MPD was mistaken during ERCP for the CBD and left hepatic duct (Figure F). In addition, the patient also had several cysts within the liver (compatible with incidental polycystic liver disease), which further complicated real-time image interpretation.

Based on multidisciplinary discussion, the precedent of a prior series of successful palliative MPD stenting in the setting of adenocarcinoma,[1] and the notable improvement in the patient's steatorrhea and abdominal pain, the initially placed fcSEMS was left in situ across the MPD stricture, and a second fcSEMS was successfully deployed across the CBD stricture (Figure G), resulting in prompt improvement in serum liver tests. The patient was thereafter initiated on palliative chemotherapy with gemcitabine and abraxane and has maintained clinically stable disease for the last 9 months.

M-IPMN is a premalignant condition in which endoscopy plays an important role. In our patient, because of anatomic and morphologic abnormalities, including the massive dilation of the MPD and severe distal biliary compression in the context of an obstructing pancreatic head mass arising from M-IPMN, initial deployment of the fcSEMS occurred unwittingly into the MPD. Little is known about the impact of fcSEMS in the MPD in patients with pancreatic adenocarcinoma, although in select cases, alleviation of pain caused by MPD obstruction and improvement in quality of life have been reported.[2,3] In the case of our patient, fcSEMS placement in the MPD indeed led to symptomatic relief as manifested by a decrease in both diarrhea and pain and an increase in appetite; the addition of a fcSEMS in the CBD led to serum liver test normalization and permitted the initiation of chemotherapy. Further studies are needed to examine the outcomes of palliative MPD stenting in patients with obstructing pancreatic malignancies as well as the epidemiology and biology of M-IPMN and associated pancreatic adenocarcinoma in minority populations.

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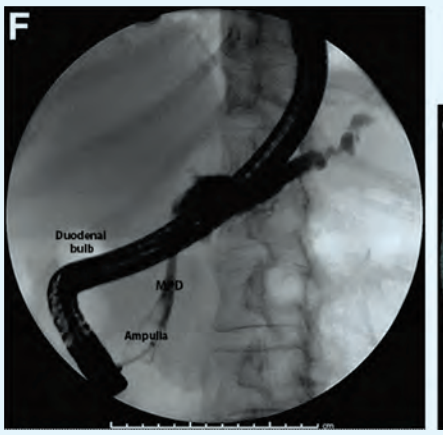

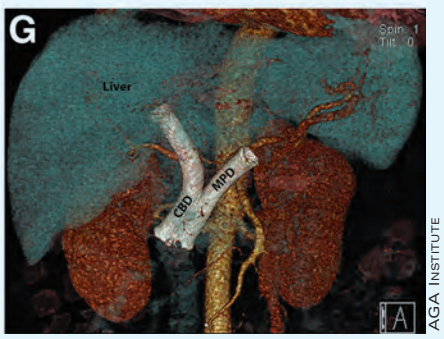

AGA Institute

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similar symptoms as MVID and others through the altered protein's failure to assist in the folding of myosin proteins, although to date only the myosin IIa protein has been shown to be a target of UNC45A.

To investigate the possibility, they examined in more detail the relationship between UNC45A and intestinal symptoms. There are various known mutations in myosin proteins. Some have been linked to deafness, but these do not appear to contribute to intestinal symptoms since patients with myelin-related inherited deafness don't typically have diarrhea. Bone fragility, also sometimes caused by myosin mutations, also appears to be unrelated to intestinal symptoms.

Previous experiments in yeast suggest that the related gene UNC45 may serve as a chaperone for type V myosin: Loss of a yeast version of UNC45 caused a type V myosin called MYO4P to be mislocalized in yeast. In zebrafish, reduction in intestinal levels of the UNC45A gene or the fish's version of MYO5B interfered with development of intestinal folds.

The researchers used CRISPR-Cas9 gene editing and site-directed mutagenesis in intestinal epithelial and liver cell lines to investigate the relationship between UNC45A and MYO5B mutants. UNC45A depletion or introduction of the UNC45A mutation found in patients led to lower MYO5B expression. In epithelial cells, loss of UNC45A led to changes in MYO5B–linked processes that are known to play a role in MVID pathogenesis. These included alteration of microvilli development and interference with the location of rat sarcoma–associated binding protein (RAB) 11A–positive recycling endosomes. When normal UNC45A was reintroduced to these cells, MYO5B expression returned. Reintroduction of either UNC45A or MYO5B repaired the alterations to recycling endosome position and microvilli development.

Loss of UNC45A did not appear to affect transcription of the MYO5B gen, which suggests a functional interaction between the two at a protein level.

UNC45A has been shown to destabilize microtubules. Exposure of a kidney epithelial cell line to the microtubule-stabilizing drug taxol also led to displacement of RAB11A-positve recycling endosomes, though the specific changes were different than what is seen in MYO5B mutants.

The researchers were unable to validate the findings in tissue derived from O2HE patients because of insufficient material, but they maintain that the cell lines used have proven to be highly predictive for the cellular characteristics of MVID.

Overall, the study suggests that reductions in MYO5B and subsequent changes to the cellular processes that depend on it may underlie the intestinal symptoms caused by UNC45A mutations.

The researchers noted that O2HE patients have different phenotypes. Of the four patients they studied, three had severe chronic diarrhea and required parenteral nutrition. One patient later had the diarrhea resolve and her sister did not have diarrhea at all. This heterogeneity in severity and duration of clinical symptoms may be driven by differences in the molecular effects of patient-specific mutations. The two siblings had mutations in a different region of the UNC45A gene than the other two participants.

"Taken together, this study revealed a functional relationship between UNC45A and MYO5B protein expression, thereby connecting two rare congenital diseases with overlapping intestinal symptoms at the molecular level," the authors wrote.

The authors reported that they had no conflicts of interest. ■

New insights into worldwide BTC incidence

BY JIM KLING
MDedge News

Incidence and mortality for biliary tract cancer (BTC) are both on the rise worldwide, according to a new analysis of data from the International Agency for Research on Cancer and the World Health Organization.

This diverse group of hepatic and perihepatic cancers include gallbladder cancer (GBC), intrahepatic and extrahepatic cholangiocarcinoma (ICC and ECC), and ampulla of Vater cancer. Although BTC is considered rare, incidence of its subtypes can vary significantly by geographic region. Because BTC is typically asymptomatic in its early stage, diagnosis is often made after tumors have spread, when there are few therapeutic options available. In the United States and Europe, 5-year survival is less than 20%.

Although previous studies have examined worldwide BTC incidence, few looked at multiple global regions or at all subtypes.

Although previous studies have examined worldwide BTC incidence, few looked at multiple global regions or at all subtypes. Instead, subtypes may be grouped together and reported as composites, or BTC is lumped together with primary liver cancer. "To our knowledge, this is the first report combining data on worldwide incidence and mortality of all BTC subtypes per the International Classification of Diseases, Tenth Revision," the authors wrote in the study, published online in Gastro Hep Advances (2022 Apr 15. doi: 10.1016/j.gastha.2022.04.007).

The researchers pointed out that classification coding systems have improved at defining BTC subtypes, so that studies using older coding subtypes could cause misinterpretation of incidence rates.

BTC subtypes also have unique sets of risk factors and different prognoses and treatment outcomes. "Thus, there is a need to define accurate epidemiologic trends that will allow specific risk factors to be identified, guiding experts in implementing policies to improve diagnosis and survival," the authors wrote.

The study included data from 22 countries. BTC incidence ranged from 1.12 cases per 100,000 person-years in Vietnam to 12.42 in Chile. As expected, incidence rates were higher in the Asia-Pacific region (1.12-9.00) and South America (2.73-12.42), compared with Europe (2.00-3.59) and North America (2.33-2.35). Within the United States, Asian Americans had a higher BTC incidence than the general population (2.99 vs. 2.33).

In most countries, new cases were dominated by GBC, while ICC was the most common cause of death.

In each country, older patients were 5-10 times more likely to die than BTC patients generally. The sixth and seventh decades of life are the most common time of diagnosis, and treatment options may be limited in older patients.

Risk factors for BTC may include common comorbidities like obesity, nonalcoholic fatty liver disease, and diabetes. Each is increasing

Continued on following page

Lingering symptoms

COVID *from page 1*

(nonhospitalized) acute COVID-19 infection. The study is the first to tie gut antigen persistence to post–acute COVID symptoms, and the results imply that the antigen may lead to immune perturbation and ongoing symptoms.

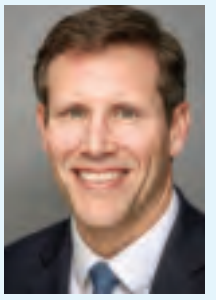
The study was published online in Gastroenterology (2022 May 1. doi: 10.1053/j.gastro.2022.04.037).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses the membrane-bound angiotensin-converting enzyme 2 to gain entry into cells, which is expressed in the brush border enterocytes, as well as elsewhere in the body.

Previous research using intestinal epithelial organoids confirmed that SARS-CoV-2 is capable of infecting the human epithelium and that the virus can be detected in anal swabs long after it is cleared from nasal passages (Science. 2020 Jul 3;369[6499]:50-4).

One potential explanation is viral immune perturbation or inflammatory tissue injury. Supporting evidence includes neural accumulation of memory T cells in patients with neuropsychiatric symptoms such as malaise and depression, and similar changes are seen with age-related immune senescence and tissue injury. Hyperactivated B and T cells, as well as other innate immune cells, have also been linked to postacute COVID-19, as has heightened expression of proinflammatory cytokines.

Understanding the cause and risk factors for the post–acute COVID-19 condition is an urgent research priority. The study by Zollner et al. found new clues about the cause of the post–COVID-19 condition in intestinal tissues of patients with IBD. The first important finding was that most adult patients with IBD have persistent viral antigen in their intestine months after even mild acute COVID-19. Importantly, researchers could not recover replicating virus from these tissues, indicating there was unlikely persistent active infection or viral transmissibility. The second major finding was that the presence of persistent viral antigen in intestinal tissue was strongly associated with postacute COVID-19 symptoms. This suggests that persistence of SARS-CoV-2 antigen after acute infection could perpetuate an ongoing inflammatory response that causes the post–acute COVID-19 condition.



Dr. Rosen

Since the researchers studied only IBD patients, we do not know if the findings are generalizable to healthy patients after mild acute COVID-19. Although they found some impairment of T-cell responses to the virus in patients on anti–tumor necrosis factor therapy, there was no association of immunosuppressive therapy and either viral antigen persistence or post–acute COVID-19 symptoms. Therefore, it is not clear whether IBD or IBD treatment delays viral antigen clearance.

Zollner et al. used the intestine as a window onto how this virus may lead to long-lasting symptoms in IBD patients. However, it does not change our understanding that corticosteroids, poorly controlled IBD, and comorbidities, and not biologic or immunomodulator therapy, increase the risk of severe illness and mortality related to acute COVID-19 in IBD patients.

Michael J. Rosen, MD, MSCI, is Endowed Professor for Pediatric IBD & Celiac Disease and director for the Center for Pediatric IBD & Celiac Disease at Stanford (Calif.) University. Dr. Rosen served on an advisory board for Pfizer.

To explore the potential role of persistent viral antigens, the researchers gathered biopsies during upper- and lower-gastrointestinal endoscopy in 46 patients with IBD whose prior

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individually, which may in turn contribute to rising BTC incidence. Observational analyses suggest that obesity may contribute to risk of ECC and gallbladder cancer (Obesity [Silver Spring]. 2016 Aug;24[8]:1786-802), while diabetes and obesity may raise the risk of ICC (Am J Gastroenterol. 2018 Oct;113[10]:1494-505). Smoking is associated with increased risk of all BTC subtypes except GBC, and alcohol consumption is associated with ICC (J Natl Cancer Inst. 2019 Dec 1;111[12]:1263-78).

"This study highlights how each subtype may be vulnerable to specific risk factors and emphasizes the value of separating epidemiologic data by subtype in order to better understand disease etiology," the researchers wrote.

Risk factors associated with incidence and mortality from BTC aren't limited to clinical characteristics. Genetic susceptibility may also play a role in incidence and mortality of different subtypes. There is also a relationship between gallstones and BTC risk. In Chile, about 50% of women have gallstones versus 17% of women in the United States. The cancer incidence is 27 per 100,000 person-years in Chile and 2 per 100,000 person-years in the United States. BTC is also the leading cause of cancer death among women in Chile.

The authors also highlighted the high rates of gallbladder cancer in India, despite a low prevalence of gallstones. Incidences can vary with geography along the flow of the Ganges River, which might reflect varying risks from contamination caused by agricultural runoff or industrial or human waste.

"This study highlights how each subtype may be vulnerable to specific risk factors and emphasizes the value of separating epidemiologic data."

Worldwide BTC incidence and mortality was generally higher among women than men, with the exception of ampulla of Vater cancer, which was more common in men.

The study is limited by quality of data, which varied significantly between countries. Mortality data were missing from some countries known to have high BTC incidence. The databases had few survival data, which could have provided insights into treatment efficacy.

The study was funded by AstraZeneca. The authors have extensive financial relationships with pharmaceutical companies. ■

Biliary tract cancers are understudied malignancies with poor prognoses. A major impediment to a deeper understanding of BTC epidemiology is that the term BTC encompasses a heterogeneous group of cancers including cholangiocarcinoma (both intrahepatic and extrahepatic), as well as ampullary and gallbladder cancer.

Studies have often lumped all BTC subgroups together despite differences in their geographic distribution, risk factors, and underlying pathogenesis. Furthermore, epidemiological reporting has often grouped "intrahepatic liver and bile duct cancers" which include hepatocellular carcinoma, a biologically different entity requiring a separate management strategy.

Dr. Bhan

This study by Baria et al. takes the important next step of analyzing BTC incidence and mortality at a worldwide level while providing granular data on geographic variations in BTC subtypes. The most notable finding is the increasing incidence and mortality of BTCs in most countries studied, the latter of which is possibly driven by intrahepatic cholangiocarcinoma's particularly poor prognosis. The high rates of BTC incidence and mortality in Asian countries may be driven by cholangiocarcinoma and its known risk factors including chronic hepatitis B and C viruses and liver fluke infection. Future drivers of incidence will likely include metabolic syndrome.

The study highlights the importance of future policy work to address the risk factors for BTCs that vary by region and that will likely evolve over time. It also stresses the urgent need for both early diagnostic strategies and improved biomarker-driven medical therapy, areas of ongoing research requiring accelerated development.

Irun Bhan, MD, is a transplant hepatologist at Massachusetts General Hospital and instructor at Harvard Medical School, Boston. He has no relevant conflicts.

Continued from previous page

COVID-19 infection (mean, 7.3 months previous) had been confirmed by polymerase chain reaction and who were seen at the IBD outpatient unit of the investigators' institution. In all, 43.5% of patients were female, and the average age was 44.67 years. Overall, 67.4% had been diagnosed with Crohn's disease, 28.3% with ulcerative colitis, and 4.3% with unclassified IBD; 23.9% had a history of exposure to anti–tumor necrosis factor therapy. Among patients in the study, 32 of the patients tested positive for mucosal SARS-CoV-2 RNA, and there was no association between the presence of viral RNA and IBD type.

The researchers found that 52%-70% of patients had antigen persistence in any gut segment, as measured by nucleocapsid immunofluorescence or expression of one of four viral transcripts. They detected persistence of the nucleocapsid in epithelial cells and CD8+ T cells. Viral antigens persisted in patients with and without exposure to immunosuppressive therapy, and there was no association with antigen persistence and severity of acute COVID-19 infection or the presence of inflammation at the time of the endoscopy.

The researchers believed that the persistent viral antigen levels reflect incomplete clearance from the original infection rather than a latent or persistent infection because they could not replicate the virus in biopsy samples. Most biopsies within a patient produced some, but not all, of the viral transcripts tested. The authors suggest that immunosuppressive therapy may lead to incomplete viral clearance. Some patients lacked humoral nucleocapsid IgG antibodies, especially among those with gut antigen persistence.

The researchers believed that persistent viral antigen levels reflect incomplete clearance from the original infection rather than a latent or persistent infection because they could not replicate the virus in biopsy samples.

In fact, only patients with gut viral RNA persistence had symptoms of postacute COVID. "This observation strongly argues for a role of viral antigen persistence in postacute COVID-19 and it appears plausible that SARS-CoV-2 antigen persistence, possibly in infected tissues beyond the gut, could impact host immune responses underlying the postacute COVID-19 syndrome," the researchers wrote.

There is precedent for such a phenomenon in influenza. Mouse models have shown that ineffective clearance can influence adaptive immune responses and memory T-cell formation in lymph nodes of the lung (J Exp Med. 2010 Jun 7;207[6]:1161-72). Another report found that COVID-19 pneumonia survivors have persistent changes to pulmonary CD8+ T cells (Sci Immunol. 2021 Nov 12. doi: 10.1126/sciimmunol.abk1741).

The study is limited by its small sample size and a lack of a replication cohort. The study was also conducted in IBD patients because the researchers believed they were at higher risk of COVID-19 infection, although the researchers note that viral antigen persistence has been observed 2 months after recovery from COVID-19 in patients without IBD or exposure to immunosuppressants (Nature. 2021 Mar;591[7851]:639-44).

The researchers call for studies in patients without IBD to determine whether viral antigen persistence is a key mechanism in postacute COVID-19.

The researchers have no relevant financial disclosures. ■

The Best of DDW 2022: Feel the history

BY URI LADABAUM, MD, MS

"The Best of DDW" elicits in the minds of most readers a compilation of the most important clinical and scientific content presented at DDW.

But I am not referring to that.

The "Best of DDW 2022" was the American Gastroenterological Association Presidential Plenary Session thanks to the humanity and vision of outgoing AGA President John Inadomi, MD.[1] I sat in the audience, misty eyed, as each presenter addressed issues that strike deep into our humanity – the social determinants of health that have festered for far too long, leading to intolerable differences in health outcomes and amplified by racism.

As the table on stage slowly filled in, an amazing picture took shape. A majority of the speakers were Black gastroenterologists and hepatologists, and among them many were young women. As I watched the video of a group of young Black gastroenterologists and hepatologists reaching out to the community, I asked myself "Has anything like this ever happened at a major national medical association meeting in the United States? Ever?" And then it occurred to me: "And just imagine, this exactly 2 days before the 2-year anniversary of the death of George Floyd."


Dr. Ladabaum

The plenary session happened on May 23, and I was conscious about the dates because I will never forget that George Floyd was killed on May 25, 2020 – my 55th birthday. The juxtaposition of his death and my birthday 2 years ago shook me profoundly, prompting me to write down my reflections and my hope that, in the national reactions that followed, we were seeing the beginning of true change.[2] Two years later, despite our national divisions and serious challenges, I have reasons for hope.

On May 24, I ran into a colleague who was a Black woman. I have stopped being afraid to bring up previously untouchable subjects. I asked her what she thought about the AGA Plenary. She said she was glad that she is here to see it – that her parents never got the chance.

I admitted to her that I often ask myself what more I could and should be doing. I'm trying to do what I can in recruitment, education, in my personal life. What more? She said that one thing we really need is for people who look like me to amplify the message.

So here it is: Readers, listen to the plenary talks if you were not there. At minimum, behold the following line-up of speakers and topics. Feel the history.

This was the Best of DDW 2022:

- Dr. John Inadomi: Julius Friedenwald Recognition of Timothy Wang.
- Dr. Inadomi: Presidential Address: Don't talk: Act. The relevance of DEI to gastroenterologists and hepatologists and the imperative for action.
- Dr. Byron L. Cryer and Dr. Sandra M. Quezada: AGA Equity Project: Accomplishments and what lies ahead.
- Dr. Sophie M. Balzora: The genesis and goals of the Association of Black Gastroenterologists and Hepatologists.
- Dr. Monica Webb Hooper: Increasing racial and ethnic diversity in clinical trials: What we need to do.
- Dr. Rachel Blankson Issaka: Reducing disparities in colorectal cancer.
- Dr. Lauren Nephew: Reducing disparities in liver disease.
- Dr. Fernando Velayos: Reducing disparities in IBD. ∎

Dr. Uri Ladabaum is with the division of gastroenterology and hepatology in the department of medicine at Stanford (Calif.) University. He reports serving on the advisory board for UniversalDx and Lean Medical and as a consultant for Medtronic, Clinical Genomics, Guardant Health, and Freenome.

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The importance of understanding disparities in IBD

BY FERNANDO VELAYOS, MD, MPH, AGAF

ASSESSING HOW RACE and other characteristics may impact the presentation and outcomes of patients with inflammatory bowel disease (IBD) is a powerful method for understanding the basic underpinnings of IBD (microbiome, environmental, immune, and genetic). Yet, exclusively viewing race with this biologic lens leaves out another critical explanation for potential differences in IBD presentation and outcomes, which is health disparities.

Health disparities are a specific type of health difference, linked with economic, social, or environmental disadvantages and in groups traditionally subjected to discrimination, exclusion, or disadvantages. These social determinants of health can, many times, have an even greater effect on disease presentation and outcomes than biological determinants. In the field of IBD, racial disparities are an underrecognized and understudied area. Yet what we do know is enough to demonstrate that critical disparities in IBD exist and that additional study and action are needed.


Dr. Velayos

For example, surgery is more

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common in African Americans and Hispanics compared to Whites with IBD.[1] Despite these findings, African Americans and Hispanics tend to have low use of biologics early in the disease course. Surgical outcomes are also worse in African Americans and Hispanics, who experience increased morbidity, mortality, and readmission after surgery.[2]

While the above outcomes may be attributable to inherent biologic differences, disparities quite likely have an important role. African Americans for example are less likely to see a GI or IBD specialist, more likely use the emergency room for their IBD care, and more likely to delay health visits because of transportation and financial issues. Non-Whites are more often seen in low–IBD volume hospitals, which can affect surgical outcomes. African Americans and Hispanics more often have reduced health literacy, which could affect their confidence and understanding in starting biologic therapy.

Fortunately, understanding and eliminating disparities in IBD is increasingly recognized as a priority area for research and action by the AGA and funding societies. We can do our part in many ways. We can immediately impact what is in our control right now (asking patients what economic and social barriers they may have to accessing care). We can advocate where we may not have direct control (policies that improve health access and social determinants of health). Finally, we can better understand and study social determinants of health in our research to get a more comprehensive picture of how health disparities affect IBD presentation and outcomes. ■

Dr. Velayos is chief of gastroenterology at San Francisco Medical Center of the Permanente Medical Group, regional lead for inflammatory bowel disease for Northern California Kaiser Permanente, and chair of the immunology, microbiology, and inflammatory bowel disease section for the American Gastroenterological Association. He has no relevant conflicts to declare.

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