Digestive Diseases Interagency Coordinating Committee

Gallstone Disease: Research Challenges

Virtual Meeting
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Welcome and Introductions

Stephen P. James, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)

Dr. Stephen James welcomed members and attendees to the NIDDK Digestive Diseases Interagency Coordinating Committee (DDICC) meeting on current challenges and opportunities in gallstone research. The meeting agenda features three speakers providing expert updates on this topic, followed by interagency reports and ending with a discussion on future opportunities and challenges to gallstone research. Attendees were reminded that the purpose of the DDICC is to facilitate cooperation among federal partners and departments to better understand, manage, treat and prevent digestive diseases. Each meeting examines a specific area of digestive disease research, with invited speakers summarizing current research and Committee members reporting on the status of their organization's research portfolio and initiatives in the topic area.

Chaired by the Director of the NIDDK Division of Digestive Diseases and Nutrition (DDDN), the DDICC includes members from multiple U.S. Department of Health and Human Services agencies (e.g., NIH, Food and Drug Administration [FDA], Agency for Healthcare Research and Quality [AHRQ] and Centers for Disease Control and Prevention [CDC]). The most common federal departments include the U.S. Departments of Agriculture [USDA], Veterans Affairs (VA), and Defense [DoD]. Dr. James noted that attendance is driven by the shared interest in the research topic. The aim is to share information and ideas on important topics, which can inform new research and/or practices.

In terms of digestive diseases funding at the NIH, research is driven by the varying research missions across at least 20 of the 26 NIH Institutes and Centers. The three Institutes that provide the bulk of research funding in digestive diseases are the NIDDK, National Cancer Institute (NCI), and National Institute of Allergy and Infectious Diseases (NIAID). Further details can be accessed from the NIH Research, Condition, and Disease Categorization reports prepared for Congress and the public.

Epidemiology of Gallstone Disease and Its Complications in the United States
W. Ray Kim, M.D.
Stanford University

Dr. W. Ray Kim discussed the prevalence, epidemiological risk factors, spectrum, burden, hospitalization trends, and long-term outcome of gallstone disease. Data sources included the CDC's Third National Health and Nutrition Examination Survey (NHANES III) and the Agency for Healthcare Research and Quality–sponsored Healthcare Cost and Utilization Project (HCUP) databases. Dr. Kim credited most of the epidemiological data on gallstone disease to publications from Dr. James E. Everhart, an epidemiologist and former member of DDDN, NIDDK, and Dr. Constance E. Ruhl, a collaborator and contractor from Social & Scientific Systems, Inc.

Worldwide, these is great variability in the prevalence of gallstone disease, with areas of high prevalence (i.e., "hot spots") within native populations in North and South America (50-70%) and, to a lesser extent, in Northern Europe (20-30%). Conversely, the prevalence is low in Sub-Saharan Africa (<5%) and East Asia countries such as China, Japan and Thailand (4-5%). The variability appears to reflect both environmental and genetic risk factors, although some degree of under-reporting may account for the differences, particularly in less developed settings.

The NHANES III survey conducted in the United States between 1988 to 1994 in civilian, non-institutionalized adults has provided the most accurate information on rates of gallbladder disease among Americans. NHANES III used a stratified probability sample design with an oversampling of Mexican Americans and non-Hispanic African Americans. Gallstones were assessed by ultrasonography, and the diagnosis of gallbladder disease was based on the finding of gallstones or evidence of previous cholecystectomy. A total of 14,297 adults were examined, 76% of the entire cohort of persons enrolled in NHANES III. The overall prevalence of gallbladder disease, across all race and ethnicities, was 7.9% in men and 16.6% in women. The prevalence increased with age, and the highest prevalence was found in Mexican American women, which rose from 10% in 20 to 29-year-olds to 44% in 60 to 74-year-olds. Strikingly, a higher body mass index was associated with increased prevalence of gallstone disease in women across all race and ethnicities, but not in men. Other epidemiological correlates to gallbladder disease included diabetes and alcohol consumption, which was associated with a lower prevalence. Modifiable risk factors included elevated serum cholesterol levels, smoking, lower levels of physical activity and, in women, number of live births.

Other epidemiologic studies have reported the association of gallstones with other potentially modifiable risk factors including rapid weight loss, diet, prolonged total parenteral nutrition, medications (ceftriaxone, thiazide diuretics, estrogens), and liver cirrhosis. In terms of natural history, patients are often asymptomatic and develop symptoms with episodes of cholecystitis, cholangitis, or gallstone pancreatitis at rates of 1 to 2% per year. Between 26 to 33% of men versus 43 to 48% of women with gallstones ultimately undergo cholecystectomy, suggesting that gender plays a role in both the formation of gallstones as well as symptomatic gallstone disease. A long-term complication of gallstone disease is gallbladder cancer, a rare but highly fatal malignancy.

Gallstone disease has a low rate of associated mortality, but a high economic burden on the health care system. Compared to other benign digestive diseases with a similar mortality rate, annual gallstone disease costs were estimated to be $6.2 billion compared to $2.1 billion for inflammatory bowel disease. At the time of these analyses, gallstone disease accounted for 5% of all inpatient care for gastrointestinal diseases. Interesting, both total hospitalizations and estimated yearly costs for gallstone disease has subsequently decreased in the United States. The hospitalizations for gallstone disease totaled

approximately 350,000 in 1998 but only 276,000 in 2014 while estimated costs decreased from $4.2 billion in 2001 to $3.2 billion in 2014. The major reason for these declines appears to be a decrease in admissions for elective cholecystectomy, the result of the introduction and now wide-spread use of laparoscopic cholecystectomy which can be accomplished with a half-day stay in an outpatient surgical facility.

Long-term outcomes of gallstone disease and cholecystectomy were assessed in the NHANES III follow-up study which demonstrated a statistically significant reduction in survival in individuals with gallstone disease in comparison to those without gallstones over a 20-year period, with a 30 percent increase in risk of death. The highest all-cause mortality in gallstone disease and cholecystectomy patients was attributed to cardiovascular disease, followed by cancer.

Thus, an estimated 20% of the adult U.S. population has gallstone disease. Major risk factors are female sex, race (Hispanic, Native American), and age. Important modifiable risk factors include BMI, physical activity and diabetes. The role of the recent rise in rates of obesity, inactive lifestyle, and diabetes on rates of gallstones in the United States is not clear. The major economic burden of gallstone disease is hospital-based but may have declined because of improvements in surgical management. The long-term consequences of gallstone appear to be important but are not well defined. In recent years, there has been no decline in rates of gallstone disease in the United States. Despite its importance, there have been no inroads into means of prevention.

Discussion

- Dr. Bishr Omary called attention to updates on the burden of GI, liver, and pancreatic diseases in the United States using national data sources authored by Dr. Anne Peery and colleagues at the University of North Carolina, Chapel Hill, which might apply to this topic.

- Dr. Hashem El-Serag sought clarity on whether data sources on outpatient cholecystectomies accompanied by imaging data were contained in centralized public databases. Dr. Kim clarified that such data have not been published but noted that hospital-affiliated ambulatory surgery databases might be a source to such information.

Selected Bibliography

- Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999; 117: 632-9. 10464139

- Katsika D, Grjibovski A, Einarsson C, Lammert F, Lichtenstein P, Marschall HU. Genetic and environmental influences on symptomatic gallstone disease: a Swedish study of 43,141 twin pairs. Hepatology 2005; 41: 1138-43. 15747383

- Ruhl CE, Everhart JE. Gallstone disease is associated with increased mortality in the United States. Gastroenterology 2011; 140: 508-16. 21075109

- Ruhl CE, Everhart JE. Relationship of non-alcoholic fatty liver disease with cholecystectomy in the US population. Am J Gastroenterol 2013;108: 952-8. 23545713

- Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver 2012; 6: 172-87. 22570746

- Williams TP, Dimou FM, Adhikari D, Kimbrough TD, Riall TS. Hospital readmission after emergency room visit for cholelithiasis. J Surg Res 2015; 197: 318-23. 25959838
- Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, Jensen ET, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology 2019; 156: 254-272.e11. 30315778

Pathogenesis of Cholesterol Gallstones

David Q. H. Wang, M.D., Ph.D.
Albert Einstein College of Medicine

Dr. David Q. H. Wang provided an update on the pathogenesis of cholesterol gallstone formation. Gallstone disease is an ancient condition, having been found in Egyptian mummies from more than 3,500 years ago. Insights into their pathophysiology, however, are more recent. In 1968, William Admirand and Donald Small proposed the cholesterol saturation index as a unifying theory of cholesterol gallstone formation in humans. The hepatic transporters of the lipids responsible for the cholesterol saturation index were identified in the 1990s and early 2000s, including the ATP-binding cassette (ABC) subfamily B member 4 (ABC B4) for phospholipid secretion, ABC G5/G8 for cholesterol secretion, and ABC B11 for bile acid secretion. These transporters secrete lipids into bile where they form micelles and vesicles that keep cholesterol in solution and allow delivery of bile acids to the intestine where they act to digest fats. Dr. Wang and his colleagues used a model bile system to study the crystallization process of cholesterol and identified five cholesterol crystallization pathways which involve these three components. The importance of these five pathways have been confirmed in studies of both animal and human bile.

Epidemiological studies suggest that genetic factors play a major role in gallstone formation in high-risk populations. In the 1990s, Dr. Wang and colleagues used a gallstone-susceptible mouse model (C57L/J) to investigate the gallstone genes through the combined use of genomic strategies and phenotypic studies. Cholecystectomy was performed on mice at different times during 8 weeks of feeding a lithogenic diet, and the gallbladder bile was analyzed by phase contrast and polarizing light microscopy. The results revealed patterns of cholesterol crystallization and gallstone formation that closely recapitulated aspects of the pathophysiology of gallstone disease in humans. Further studies in 15 strains of inbred mice revealed similar results but with variable rates of stone formation, with the highest gallstone prevalence in C57L mice and the lowest in gallstone-resistant AKR/J mice. Among 135 backcross progeny of the gallstone-susceptible and -resistant mouse strains, 102 mice developed gallstones when fed a lithogenic diet while 33 did not. This 3:1 ratio suggested that more than two gallstone genes were expressed in C57L mice. Further studies showed that heterozygous (C57L × AKR) F1 mice had a similar propensity to form gallstones as the parenteral, gallstone-susceptible mice, regardless of gender. These data suggested that gallstone disease is a dominant trait that is determined by multiple genes.

Quantitative trait locus (QTL) analysis of the backcross ([C57L × AKR] × AKR) mouse genome was used to generate a genetic linkage map and demonstrated the first gallstone gene (*Lith1)* on mouse chromosome 2. Additional QTL mapping in 15 mouse strains subsequently identified 27 *Lith* genes. Moreover, more than 50 known genes have been found to contribute to gallstone formation in mice. Thus, this mouse QTL linkage map enabled (1) identification of the human *LITH* genes, (2) investigation into the pathogenesis and pathophysiology of cholesterol gallstone disease, and (3) identification of targets for preventing or treating gallstone disease.

Based on the mouse gallstone (*Lith*) gene map several human homologues that also appear to be gallstone (*LITH*) genes have been identified. The *ABCG5/G8* transporter is a candidate gene for the *Lith9* gene on chromosome 17 in mice, leading to the identification of the human *LITH9-ABCG5/G8* variants in German, Chinese, Swedish, Indian, Canadian, and Chilean Hispanic populations. These variants were found in 21% of gallstone patients compared to 6.8% of population controls. The importance of human gallstone genes has been reported from analyses of a large Swedish cohort of twins, which indicated that genetic factors account for at least 25% of symptomatic gallstone disease. Clearly, multiple genes contribute to the genetic risk for gallstones in humans and use of the mouse gallstone (*Lith*) gene map has aided in identifying human homologues.

An example of the potential contribution of the mouse gallstone gene map relates to the role of female sex hormones in gallstone disease. Clinical studies strongly suggest that high levels of estrogen in serum contribute to the formation of gallstones in women during and after pregnancy as well as in men receiving estrogen therapy after castration surgery for prostate cancer. Gallstone formation appears to be mediated by the estrogen receptor-alpha (ER-α), but not ER-β, in the liver and gallbladder via different lithogenic pathways. Moreover, G protein-coupled receptor 30 (GPR30), a new estrogen receptor, was found to be a gallstone gene, *Lith18*, in mice. Dr. Wang and his colleagues generated ER-α and GPR30 knock-out mice and revealed that both strains of mice formed gallstones through two different cholesterol crystallization pathways.

While genetic factors play an important role in pathogenesis of gallstones in humans, environmental factors are also influential. These factors include physical inactivity, weight loss (from bariatric surgery, medications or dietary interventions), gastrointestinal factors such as gallbladder motility and diet and probably the gut microbiome.

In terms of prevention, ezetimibe, an intestinal cholesterol absorption inhibitor, has been shown to decrease the risk of cholesterol gallstone formation in mice, and pilot studies in humans have been proposed. Efforts are underway to study the effects of beta-muricholic acid, a more hydrophilic bile acid that is a major component in mouse bile, on the prevention and dissolution of cholesterol gallstones. Finally, farnesoid X receptor agonists (that affect cholesterol and bile acid metabolism) and gene therapy approaches might be used to treat gallstone disease in the future.

Thus, the pathogenesis of gallstone disease seems to involve interactions of multiple factors that lead to the formation of cholesterol gallstones: (1) genetic factors and *LITH* genes, (2) hepatic hypersecretion of biliary cholesterol, (3) gallbladder hypomotility, (4) rapid phase transitions of cholesterol, and (5) intestinal factors. These factors act together to facilitate cholesterol nucleation and crystallization, and ultimately promote the formation of cholesterol gallstones. Future research should focus on the roles of nuclear receptors, intestinal microbiota, dyslipidemia, hyperinsulinemia, nonalcoholic fatty liver disease, obesity, diabetes, aging, and sedentary lifestyle in the mechanisms underlying the formation of cholesterol gallstones.

Selected Bibliography

- Admirand WH, Small DM. The physicochemical basis of cholesterol gallstone formation in man. J Clin Invest 1968; 47: 1043-52. 5645851
- Wang DQ-H, Carey MC. Complete mapping of crystallization pathways during cholesterol precipitation from model bile: Influence of physical-chemical variables of pathophysiologic relevance and identification of a stable liquid crystalline state in cold, dilute and hydrophilic bile salt-containing systems. J Lipid Res 1996; 37: 606-30. 8728323
- Wang DQ-H, Paigen B, Carey MC. Phenotypic characterization of *Lith* genes that determine susceptibility to cholesterol cholelithiasis in inbred mice: physical chemistry of gallbladder bile. J Lipid Res 1997; 38: 1395-1411. 9254065

- Maurer KR, Everhart JE, Ezzati TM, Johannes RS, Knowler WC, Larson DL, Sanders R, et al. Prevalence of gallstone disease in Hispanic populations in the United States. Gastroenterol 1989; 96: 487-92. 2642879
- Moschetta A, Bookout AL, Mangelsdorf DJ. Prevention of cholesterol gallstone disease by FXR agonists in a mouse model. Nat Med 2004; 10: 1352-8. 15558057
- Wang HH, Portincasa P, Mendez-Sanchez N, Uribe M, Wang DQ-H. Effect of ezetimibe on the prevention and dissolution of cholesterol gallstones. Gastroenterol 2008; 134: 2101-10. 18442485
- Wang HH, Portincasa P, Afdhal NH, Wang DQ-H. *Lith* genes and genetic analysis of cholesterol gallstone formation. Gastroenterol Clin N Am 2010; 39: 185-207. 20478482

Current Challenges in Surgery for Gallstone Disease: Can Artificial Intelligence Be Part of the Solution?

Carla M. Pugh, M.D., Ph.D.
Stanford University

Dr. Carla M. Pugh remarked on the progress in surgery for gallstone disease from the once-routine open cholecystectomy—in which postoperative pneumonia, wound complications, and pain management were significant—to the same-day laparoscopic cholecystectomy—in which the wound problems and pain are much less. Studies comparing these two approaches report 50 percent decreases in wound infection between open and laparoscopic procedures. Although the outcomes with laparoscopic cholecystectomy have improved significantly, technical issues remain and require care and attention, including avoiding injury to the common bile duct. Both small- (n = 497) and large-scale (n = 43,000) studies report a reduction in cost with laparoscopic cholecystectomies. A 2013 study reported in *The Lancet* concluded that although laparoscopic cholecystectomy for acute and gangrenous cholecystitis is technically demanding, in experienced hands it is safe and effective, does not increase the mortality rate, and reduces the morbidity rate.

Considered the gold standard, the laparoscopic approach introduced and captured videos of the procedure. In surgery, artificial intelligence (AI) has gained popularity as a tool to analyze surgical videos. Dr. Pugh and her colleagues hypothesized that disease severity would have an effect on AI accuracy in identifying the critical view of safety (CVS) and other intraoperative events (e.g., drain insertion). Her team used data from 1,051 laparoscopic cholecystectomy videos (from a video database of 2,000 videos) collected by 31 practicing surgeons from 2 institutions from 2011 to 2019. This study used two methods: AI annotation and surgeon review. A software company performed AI annotation of the videos. Disease severity was measured using the Parkland scale, the CVS was determined based on Strasberg classification, and intraoperative events were categorized. Eight surgeons, with technical expertise in laparoscopic cholecystectomy, conducted a focused video review of procedures that had one or more intraoperative events and a random selection of videos without events; they assessed 385 of the 1,051 videos.

The results revealed that the software video interface allowed a review rate of 50 per hour, which is a major benefit of AI. In terms of the CVS, the accuracy in agreement between AI and the surgeons was 93 percent. The lowest agreement (56 percent) was observed for low severity cases. Dr. Pugh noted that these differences may serve to advance the science of surgical process research and further enhance the field's utilization of AI as a tool to facilitate systematic investigations into surgical decision-making and technique.

Discussion

- Dr. Adnan Alseidi asked about ways to avoid major complications in bile duct injuries when the CVS is not achievable and whether AI can be used to advise when not to apply a CVS. Dr. Pugh noted that AI is well-suited for these types of circumstances; the technology can detect the amount of time a surgeon spends dissecting a specific area or procedural step and allows an anatomical time-out to evaluate pathways from similar anatomies when a CVS is not achievable. AI provides the surgeon opportunities for decision support and an approach for defining disease severity.
- In response to a question from Dr. Dana Andersen about incorporating an AI program into the livestream laparoscopic cholecystectomy (or lap chole), Dr. Pugh pointed out that this effort is being addressed in academic and industry groups and is a goal of this study. She

noted several steps leading to such an effort that she and her team will need to complete, such as establishing AI accuracy in this approach with the software company, identifying a team of experts in video review, and focusing on refining the algorithm. She also noted that an AI system trained to recognize anatomy will be applicable across procedures and diseases. Dr. Alseidi added that using computer vision to recognize anatomical structures will be helpful; he likened this approach to superimposing a virtual coach in the operating room.

- Dr. Kim commented that the instance of symptomatic gallstones and their complications appear to plateau at the population level and asked about designing an AI tool to predict which individuals are likely to develop problems. Dr. Pugh explained that studies in addition to the anatomy—such as disease complexity, variables to evaluate, and potentially gallbladder motility—would need to be considered for such a tool.

Selected Bibliography

- Korndorffer JR Jr, Hawn MT, Spain DA, Knowlton LM, Azagury DE, Nassar AK, Lau JN, et al. Situating artificial intelligence in surgery: a focus on disease severity. Ann Surg 2020; 272: 523-8. 33759839

- Pugh CM, Hashimoto DA, Korndorffer JR Jr. The what? who? and how? of video-based assessment. Am J Surg 2021; 221: 13-8. 32665080

Interagency Presentations
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NIH—National Institute of Diabetes and Digestive and Kidney Diseases
Averell Sherker, M.D.
NIDDK, NIH

The DDDN Portfolio of Gallstone/Gallbladder Research

Dr. Averell Sherker presented analyses of extramural NIH funding for gallstone research over the 20-year period, from 2002 to 2021. During this time, NIDDK received 107 applications for gallstone research (excluding proposals exclusively on cholesterol and bile acid metabolism) of which 50 were eventually funded. Among 26 other NIH Institutes and Centers, 10 have received at least one application, the majority by NIAID and the NCI, and a total of 8 were funded. Dr. Sherker reported that analysis of the NIDDK portfolio over the last 20 years, revealed a significant decrease in funded gallstone research awards across grant programs, including research projects (R awards), career development awards (K awards), and program project/center grants (P01s). Thus, current NIDDK funding for gallstone research has slowly decreased to approximately 20% of levels in the past.

NIH—National Cancer Institute
Jill Koshiol Ph.D. and Sarah Jackson, Ph.D., M.P.H.
NCI, NIH

NCI Studies on Gallbladder Cancer (GBC)

Dr. Jill Koshiol reminded participants that gallstones remain a major risk factor for gallbladder cancer (GBC) and are present in approximately 90 percent of cases. Thus, gallstones are far and away the major risk factor for GBC. The Republic of Chile (Chile) has a high prevalence of gallstones and has one of the highest rates of GBC worldwide. In 2016, Dr. Koshiol and the Infections and Immunoepidemiology Branch (IIB), Division of Cancer Epidemiology and Genetics, NCI, launched the Chile Biliary Longitudinal Study (Chile BiLS), with the aims to investigate risk factors for high-grade gallbladder dysplasia and cancer and to identify means of identifying patients at highest risk and means of early detection. Chile BiLS has identified and screened 19,000 women, aged 50 to 64 years, for gallstones and enrolled a cohort of 4,726 in a prospective study planned for 6-years of follow-up. Dr. Koshiol estimated that the study will identify between 180 to 200 cases of gallbladder dysplasia and cancer. At present, the 2-year follow-up visits are almost completed, and 4-year visits are in progress. Despite the coronavirus disease 2019 (COVID-19) pandemic, the study has maintained an 85 percent compliance rate. To date, more than 1,600 cholecystectomies have been performed and large amounts of data and biospecimens have been collected. The current biorepository contains 507 fresh-frozen biospecimens, 494 RNAlater samples, 304 bile samples, and 887 pre-surgery blood samples.

Dr. Sarah Jackson explained that gallstones have been linked to inflammation and that a cholecystectomy reduces this effect. The NCI's Infections and Immunoepidemiology Branch (IIB) has initiated studies of the broader consequence of inflammation in the development of cancers at sites in the gallbladder, biliary tract, liver, pancreatic, and small intestine. Recently, Drs. Koshiol in collaboration with Dr. Leticia Nogueira have conducted a nested case-control study using the Surveillance, Epidemiology, and End

Results (SEER)–Medicare linked database evaluating gallstones, cholecystectomy, and cancer cases from 1992 to 2005. The results showed that both gallstones and cholecystectomies were associated with increased risk of several digestive system cancers. Because women are twice as likely to develop gallstones as men and may have longer exposure to inflammation from gallstones and exposure to bile from cholecystectomies, Dr. Jackson will extend Drs. Koshiol and Nogueira's findings to investigate sex differences in gallstones and cholecystectomy and the influence of cancer risk in younger individuals using a time-varying approach. This study will examine sex-specific risk of bladder, colon, kidney, lung, oral cavity, pancreas, rectum, and thyroid cancers using two prospective cohorts: Nurses' Health Study (NHS, female nurses) and Health Professionals Follow-Up Study (HPFS, male health professionals).

Selected References

- Koshiol J, Van de Wyngard V, McGee EE, Cook P, Pfeiffer RM, Mardones N, Medina K, et al, for the Chile BiLS Study Group. The Chile Biliary Longitudinal Study: a gallstone cohort. Am J Epidemiol 2021; 190: 196-206. 33524121

- Nogueira L, Freedman ND, Engels EA, Warren JL, Castro F, Koshiol J. Gallstones, cholecystectomy, and the risk of digestive system cancers. Am J Epidemiol 2014; 179: 731-9. 24470530

NIH—National Institute of Biomedical Imaging and Bioengineering (NIBIB)

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Nuclear Medicine Studies of Gallbladder Emptying and Motility

Dr. Peter Kirchner reviewed the current status of cholecystokinin-cholescintigraphy (CCK-CS) for diagnosing cholecystitis, acalculous cholecystitis and functional biliary dyskinesia. CCK-CS is a widely used test for assessing gallbladder emptying that employs radionuclide imaging techniques. In 2011, an interdisciplinary panel was convened to review data on the reliability and reproducibility of the CCK-CS method in adults. The panel recommended using a single, standardized protocol consisting of a fixed sincalide infusion rate (i.e., 0.02 μg/kg/60 minutes), with a normal gallbladder ejection fraction being defined as 38 percent or higher. This panel recognized the need for a large, multicenter, prospective clinical trial to confirm the utility of CCK-CS in the diagnosis of functional gallbladder disease and as a guide to its therapy.

The panel reached an agreement that the adoption of a standardized protocol would be critical to improve how CCK-CS is used to direct patient care and will represent an improvement over the diverse methods currently in use by eliminating the current lack of uniformity and adding both reliability and credibility to the results. Of particularly importance is the need for further work to place the role of this test in assessing functional gall bladder disease.

Selected Bibliography

- DiBaise JK, Richmond BK, Ziessman HA, Everson GT, Fanelli RD, Maurer AH, Ouyang A, et al. Cholecystokinin-cholescintigraphy in adults: consensus recommendations of an interdisciplinary panel. Clin Nucl Med 2012; 37: 63-70. 22157031

- Ziessman HA. Hepatobiliary scintigraphy in 2014. J Nucl Med 2014; 55; 967-75. 24744445

Centers for Disease Control and Prevention
Craig Hales, M.D., M.P.H.
National Center for Health Statistics, CDC

CDC Research Programs on Gallstones and Gallbladder Disease

Dr. Craig Hales explained that NHANES, a nationally representative survey of the United States, uses examination data and samples 10,000 people over a 2-year cycle. Measured data are obtained either at a mobile examination center (MEC) or by in-home interview. The MECs collect biospecimens for more than 500 laboratory tests and conduct 24-hour dietary recalls. Dr. Hales reported that the NHANES 2019–2020 cycle field operations were suspended in March 2020 because of the COVID-19 pandemic. Data collected pre-pandemic are anticipated to be released in May or June of 2021. NHANES 2021–2022 is tentatively scheduled to start summer 2021.

Regarding gallstone disease in NHANES, Dr. Hales highlighted the most common abnormal findings of NHANES III, such as multiple gallstones, abdominal surgical scars, gallbladder wall thickness, size of largest polyp, and size of largest liver cyst. Although not specifically investigating gallstone disease, the JHU Research Data Center reassessed the NHANES III gallbladder ultrasound video images from 2009 to 2010, which had been digitized to a DVD. The group determined and later reported the degree of hepatic steatosis in this data set. The NHANES content related to gallbladder disease is outlined in the *National Health and Nutrition Examination Survey:1999–2020 Survey Content Brochure* and can be accessed from the CDC website.

The NHANES Biospecimen Program is one way to extend the existing gallbladder ultrasound data from NHANES III. Participants consent to have their samples used for future research, and the program maintains biorepositories of DNA, whole-blood, and urine samples. Proposals from external researchers to access the program's biospecimens are evaluated on rolling basis, and the analysis must not have clinical significance to the individual participants. Another way to extend the existing data collected in NHANES III is by linkage to Medicare claims, which is current available through the Research Data Center (https://www.cdc.gov/nchs/data-linkage/index.htm).

Dr. Hales informed the DDICC that the NHANES' new content proposal process for 2023 is open and highlighted some of the evaluation factors, such as public health significance, power of detection, and feasibility.

Selected Bibliography

- Ruhl CE, Everhart JE. Gallstone disease is associated with increased mortality in the United States. Gastroenterology 2011; 140: 508-16. 21075109
- Lazo M, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, Koteish A, et al. Prevalence of nonalcoholic fatty liver disease in the United States: the third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol 2013; 178: 38-45. 23703888

U.S. Department of Veterans Affairs

Divyanshoo R. Kohli, M.D.
Kansas City VA Medical Center

VA Studies on Gallstone/Gallbladder Disease

Dr. Divyanshoo R. Kohli noted that guidelines based upon high-quality, randomized controlled trials often suggest cholecystectomy should be the primary intervention for most gallbladder diseases (e.g., symptomatic cholelithiasis, cholecystitis, gallstone pancreatitis). However, data from these strictly controlled studies may not always be applicable to routine, community practice, and these discrepancies can impact patient care. The example of management guidelines for gallstone pancreatitis illustrates this point.

Cholecystectomy is typically recommended during index hospitalization for gallstone pancreatitis. However, the hallmark study for gallstone pancreatitis, known as the Pancreatitis of biliary origin: Optimal timiNg of CHOlecystectomy (PONCHO) trial, was conducted largely in primarily healthy women in their 40s or 50s. In contrast, a nationwide study from the VA, spanning 10 years from 2009 to 2018, revealed that most veterans with gallstone pancreatitis are men with multiple systemic morbidities, typically in their 60s and 70s. These patients were poorly represented in most prospective clinical trials. Perhaps for this reason, almost half of the veterans with gallstone pancreatitis in the VA survey did not undergo cholecystectomy, and many had severe adverse clinical outcomes (e.g., jaundice, cholangitis, readmission). Another nationwide study of community-based patients using the HCUP Nationwide Readmissions Database reported similar results: i.e. the lack of representation of the typical patient in clinical trials and the difficulty of applying guidelines based upon those trials to a large number of patients in clinical practice with gallstone pancreatitis.

Regarding future clinical research, Dr. Kohli stressed the need to assess outcomes of surgery in non-optimal patients who may be excluded in clinical trials but who more closely mirror the major challenges in current everyday practice. He also stressed the need to explore alternatives to surgery such as endosonographic gallbladder drainage or trans-papillary gallbladder interventions. Finally, major challenges remain for increasing education and awareness about gallbladder disease and the complexities of its management among surgeons, internists, emergency room physicians, hospitalists, clinical and basic researchers, and patients.

Discussion

- Dr. Koshiol clarified that the Chile BiLS cohort is composed of Chilean women who have a high prevalence of gallstones and gallbladder cancer, a malignancy found predominately in women. In contrast, the Chile Maule Cohort (MAUCO), comprises men and women, representative of the general population.

- In response to a question from Dr. Wang about using genetic markers such the Chile-index for analysis of ethnic and racial background, Dr. Koshiol explained that 25 percent of the Chilean population self-identify as Amerindian (Mapuche), the majority identify as Mestizo, and a much smaller group identifies as European. She mentioned Dr. Jackson's previous study demonstrating good correlation between self-identified ancestry and ancestry informative markers in the Chilean population.

Selected Bibliography

- Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, on behalf of the American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. Gastroenterol 2018; 154: 1096-1101. 29409760

- DaCosta DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, Bakker OJ, et al., for the Dutch Pancreatitis Study Group. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): A multicentre randomized controlled trial. Lancet 2015; 386: 1261-8. 26460661

- Garg SK, Bazerbachi F, Sarvepalli S, Majumder S, Vege SS. Why are we performing fewer cholecystectomies for mild acute biliary pancreatitis? Trends and predictors of cholecystectomy form the National Readmissions Database (2010-2014). Gastroenterol Rep 2019; 7(5): 331-7. 31687152

- Kohli DR, Desai M, Kennedy KF, Parasa S, Sharma P. Cholecystectomy for biliary gallstone pancreatitis is often not performed during index hospitalization and is associated with worse outcomes. Clin Gastroenterol Hepatol 2020; 33307183

- Patel SS, Kohli DR, Savas J, Mutha PR, Zfass A, Shah TU. Surgery reduces risk of complications even in high-risk veterans after endoscopic therapy for biliary stone disease. Dig Dis Sci 2018; 63: 781-6. 29380173

Current Opportunities and Challenges in Gallstones Research
Moderators: Stephen P. James, M.D.; Jay H. Hoofnagle, M.D.; and Dana K. Andersen, M.D.
NIDDK, NIH

Dr. James opened the discussion period by posing three major questions, one each based upon the three presentations by the expert speakers. At issue is how Federal agencies can best address these key questions.

Discussion

I. What clues are provided by the current knowledge of the epidemiology and clinical features of gallstone disease, and how might they guide approaches to prevention

Dr. James asked if preventative drugs might be studied in patients undergoing therapy for obesity such as after bariatric surgery or with recently described the glucagon-like peptide-1 receptor agonists. Dr. Wang commented that ursodeoxycholic acid (UDCA) has been an approved therapy for cholelithiasis for more than 40 years, but a second or third drug for the medical dissolution of gallstones is needed. Dr. Hoofnagle explained that therapy with UDCA is generally unsatisfactory because it requires 6 to 24 months to dissolve gallstones, is successful only in a proportion of patients, and the stones tend to reoccur after stopping treatment.

Dr. Andersen pointed out studies indicating that the cost of UDCA treatment exceeds that of a cholecystectomy after a few years because chronic therapy is required. He asked Dr. Wang whether ezetimibe might be effective for reducing the size and/or dissolving gallstones in high-risk patients. Dr. Wang explained that after bariatric surgery, the risk of developing gallstones is short term (i.e., 1–3 years), and that preventive therapy might be a reasonable approach and cost-effective. Animal studies have shown that during the weight loss, there is increased secretion of cholesterol resulting in supersaturated, lithogenic bile. He anticipated that ezetimibe might reduce the biliary cholesterol absorption after bariatric surgery and lower the risk of symptomatic gallstone disease. To date, UDCA has been used in such patients, but results have not been very promising.

Dr. Andersen observed that the incidence of gallbladder and gallstone disease is increased dramatically in patients after bariatric surgery who do not concomitantly receive a cholecystectomy. Gallstone formation is also frequent in patients during marked weight loss, both from severe calorie restricted diets and from weight loss medications. Recently, impressive weight loss has been reported in trials of glucagon-like peptide-1 (GLP-1) receptor agonists which were accompanied by occasional instances of symptomatic gallstone disease. Dr. Andersen asked whether controlled trials of preventive drugs might be included in cohorts of patients expected to achieve dramatic weight loss after bariatric surgery or with GLP-1 receptor agonists. Dr. Wang explained that ezetimibe has been used primarily for cardiovascular disease (i.e., the primary disease) but analyses of effects on gallbladder disease (i.e., the secondary disease) in these studies might be informative as well.

Dr. Omary asked whether studies of gallstone disease pathogenesis and treatment had been considered in Native American populations, who have a high prevalence of gallstone disease and cholecystectomy. He also mentioned that the Chilean cohort described in the Chile BiLS study might be ideal for basic research investigations into pathogenesis and asked about the availability of biospecimens collected in that study that might be used for ancillary studies. Dr. Koshiol explained that the intent is to broadly share the Chile

BiLS resources, and she encouraged such collaborations. Dr. James noted other potential resources: the NIDDK-operated intramural facility (Phoenix Epidemiology and Clinical Research Branch) in Phoenix, Arizona, studying obesity and diabetes in Pima Indians and the National Heart, Lung, and Blood Institute–sponsored cohort studies on heart disease among Native American cohorts.

Dr. Hoofnagle asked Dr. Wang about the effects observed in gnotobiotic animals on development of gallstones as this might indicate the importance of the microbiome in their pathogenesis. Dr. Wang pointed out that the mice used to study gallstone disease were routinely fed high-fat or high-cholesterol diets with co-administration of cholic acid to increase cholesterol absorption. Mice differ from humans in that they have large amounts of beta-muricholic acid in the bile which prevents the spontaneous formation of gallstones. Adding cholic acid to the lithogenic diet in mice makes the bile acid composition similar to that of humans. Furthermore, administration of beta-muricholic acid to humans can result in decrease in the lithogenicity of bile.

Dr. Hoofnagle also noted that Dr. Everhart's analyses of the NHANES database reported that nonalcoholic steatohepatitis (NASH) was more severe in individuals who had undergone cholecystectomy suggesting that this operation is not without long-term adverse consequences. Dr. Wang also mentioned that the 2011 findings demonstrated an association between cholecystectomy and cardiovascular disease and shortened lifespan as well as an increased incidence of NASH.

II. What are the major questions regarding the pathogenesis of gallstone formation, and how might they best be addressed?

Dr. Andersen asked about the correlation of foregut cancers to cholecystectomy and other risk factors, such as changes in bile acid milieu. Dr. Jackson noted that these factors may be related, and Dr. Koshiol pointed out the challenge to disentangle the long-lasting effects of cholecystectomy from the presence of gallstones. She speculated that cytokine measurements before and after surgery could provide some insight, because small-scale studies suggest that a cholecystectomy reduces inflammatory markers (e.g., bile acids, cytokines). Dr. Omary added that it would be valuable to test this hypothesis (i.e., that cholecystectomy reduces inflammatory markers) in animals genetically predisposed to certain cancers.

Dr. Kim commented on the many hypotheses and confounding evidence regarding the association of cancer with a history of cholecystectomy and asked about data on the links to liver cancers (i.e., hepatobiliary cancers) and the potential influence of imaging procedures involved in gallstone surveillance and subsequent organ removal. Dr. Koshiol noted that analysis of SEER–Medicare data over time showed that the association of cholecystectomy and cancer was lessened after 4 to 5 years but did persist, suggesting that other factors are involved. She pointed out a limitation in SEER–Medicare data: lack of information on confounding factors. In addition, these data are self-reported rather than being ultrasound-based. Data on liver cancer are anticipated to be included the SEER-Medicare database, but likely not information on imaging.

Dr. Andersen underscored changes in the gut microbiome post-cholecystectomy, which have also been shown to shift after bariatric surgery, with the hypothesis that these changes are linked to the dramatic and sustained weight loss. He posed two questions: (1) Do changes in gut microbiome play a role in gallstone pathogenesis? (2) Can treatment or alterations in the gut microbiome provide clues to prevention or therapy for gallstone disease?

Dr. Wang noted that cholic and chenodeoxycholic acid are the major bile acids in humans and that when given in high doses, these hydrophobic acid acids can cause liver damage which may explain the association of worsening of liver diseases (NASH) and increase risk of cancers in patients with gallstone disease despite cholecystectomy. UDCA in contrast is a hydrophilic bile acid and has not been linked to liver injury or cancer risk.

III. What are the major shortcomings of surgical therapy of gallstones and gallbladder disorders, and how might they be corrected?

Dr. Andersen called attention to an ongoing natural experiment that could provide information on the effects of gallstones and their formation versus the effects of a cholecystectomy. Of the 400,000 such operations performed annually in the United States, 100,000 proceed in patients with biliary dyskinesia but no gallstones—comprising a study population to compare bile salt metabolism and gut cancer. He highlighted the U.S. scenario of performing cholecystectomies when biliary dyskinesia is the diagnosis based upon cholecystokinin-cholescintigraphy (CCK-CS) and made several key points:

- The diagnosis of biliary dyskinesia is much more commonly made in the United States compared to Europe.
- Physicians in other countries are skeptical of the diagnosis of biliary dyskinesia and acalculous cholecystitis and cite lack of reproducibility of diagnostic tests using CCK-CS.
- Patients in Western Europe are treated symptomatically and rarely with cholecystectomy when presenting with right upper-quadrant warning signs but without detectable gallstones.

Dr. Andersen asked surgeons, Drs. Pugh, and Alseidi, and NIBIB bioimaging experts, Dr. Kirchner and Dr. George Zubal, to comment on this American scenario.

Dr. Pugh explained that the aim is to not operate on patients who do not have gallstones. Acalculous cholecystitis is a different disease, rarely requiring surgery. Surgeons can intraoperatively use drain insertion to overcome any disease process, such as sepsis or vascular issues, referring to the problem of acalculous cholecystitis. In the United States, patients with biliary dyskinesia have high levels of pain, affecting daily activities and resulting in long treatment schedules and work loss. Patients tend to be noncompliant of life-long medications and prefer having a procedure to relieve symptoms. The culture of American patients speaks to a desire for a "silver bullet" treatment. Collectively, these factors have contributed to use of surgery to treat biliary dyskinesia.

Dr. Kirchner asked how well established it is that individuals with acalculous cholecystitis have symptoms requiring treatment and inquired about the data relative to successful treatment, with or without a cholecystectomy. In his observation from the medical literature, the justification for such a surgery is that the symptoms are well relieved, with no other recourse. From her perspective, Dr. Pugh noted that there are two different conditions involved this discussion: (1) acalculous cholecystitis, where inflammation exists without the presence of gallstones, and (2) biliary dyskinesia, where there is biliary like pain without gallstones or inflammation, but where a cholecystectomy is often performed. Dr. El-Serag added that for biliary dyskinesia an appropriate term is "functional" pain.

Dr. Alseidi agreed that biliary dyskinesia should be defined as functional pain (an emptying problem without stones), and it should not be considered an accepted indication for surgery. In the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) definition—characteristic, symptomatic

pain, without gallstones, a CCK-CS indicating decreased dysfunction, and esophagogastroduodenoscopy negative for upper gastrointestinal disease—a cholecystectomy is likely to relieve a patient's pain only 50 to 60 percent of the time. The case is different if the patient has acalculous cholecystitis.

Regarding precision medicine, Dr. James asked Dr. Kim about data from long-term studies of outcomes of individuals without gallstones who had a cholecystectomy to relieve pain. He also inquired on how to identify the subset of patients who have had favorable outcomes (i.e., observable benefit). Dr. Kim noted that at his institution/clinic (a tertiary referral center), many patients return 6, 12, or 18 months after surgery with unresolved right upper quadrant pain, but he was not aware of any such long-term data. In his experience, patients without identifiable gallstone disease often receive surgery without viable benefit. He called for more objective evidence to support use of cholecystectomy for biliary dyskinesia such as discrete episodes of pain accompanied by elevations in liver enzymes. Developing a better diagnostic tool to define biliary dyskinesia might be the best option.

Dr. El-Serag called attention to a publicly available resource to explore gallstone disease, the VA's Million Veteran Program, a national research program that has enrolled more than 800,000 participants for germline DNA genotyping, with links to imaging, surgery, laboratory, and pharmacy databases. He also noted other VA resources, including new databases containing the entire medical record for a patient and machine learning applications, such as radiomics, and suggested that these were valuable resources with which to explore the natural history and mechanisms of gallstone disease.

In response to a question from Dr. Kirchner on studies that correlate gallbladder ejection fraction after stimulation with the incidence of symptoms (and whether the quantitative measurement of gallbladder ejection fraction can be used as an indicator of the abnormality), Dr. El-Serag replied that such studies have evaluated few patients and focused largely upon short-term outcomes. Dr. Sherker added that the NIDDK has funded a study (Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction [EPISOD]) investigating another functional disorder (sphincter of Oddi dysfunction) and an intervention, in which patient outcomes worsened, rather than improved.

Dr. Hoofnagle wondered whether the absence of gallstones in patients with biliary colic-like pain could be compatible with a history of passing the stones. Dr. Omary noted that the finding of super-saturated bile might be helpful in assessing such patients. Dr. Wang added that the biliary sludge can induce acalculous cholecystitis and may contain gallstones possibly passing from the body undetected. Dr. James remarked on the parallels in kidney stone formation and their passing from the body in painful syndromes throughout life and preventive measures used that could inform gallstone research.

When asked whether correlation studies have evaluated the quality of the bile in individuals experiencing abnormal gallbladder emptying, Dr. Andersen agreed that these investigations can be considered but was unaware of any that had been conducted, nor was he convinced that CCK-CS–determined ejection fraction correlates to bile constituents or to outcomes of cholecystectomies or is reproducible.
Dr. Kirchner reiterated the statement from his presentation that CCK-CS is a recommended method, but for which practitioners in this country have yet to establish a unform method for performance.

Dr. James noted the challenge in conducting double lumen studies, and Dr. Wang hypothesized that an imbalance in CCK-1 receptor and FGF-19 regulation/control—both of which are involved in gallbladder motility—could play a role.

Conclusions and the Way Forward
Dana K. Andersen, M.D.
NIDDK, NIH

Dr. Andersen summarized the key observations and conclusions regarding gallstone disease and research challenges, underscoring the way forward:

- The number of NIH research grants to study gallstone disease has significantly decreased during the past 10 years.
- While progress has been made in understanding the pathogenesis of cholesterol gallstone formation, there have been few advances in means of prevention and treatment.
- Although the incidence of gallstone disease has steadily increased in the past decades, especially in some U.S. populations, treatment options have remained limited.
- Research opportunities going forward include new drug therapy development, analysis of new comprehensive data collections, clinical trials in high-risk populations (such as the frail elderly, Native Americans, bariatric surgery patients, patients on therapies that induced rapid weight loss, and males with prostate cancer undergoing estrogen therapy) and newer methods to improve the safety and outcomes of cholecystectomy.
- Individuals receiving a cholecystectomy appear to be at risk of an increase in the severity of NASH and development of foregut cancers indicating that the adverse long-term outcomes of cholecystectomy merit ongoing studies on mechanisms.
- The outcomes of the Chile BiLS cohort will be valuable to inform future research on the natural history of gallstone disease and the relationship of gallstones and gallbladder cancer.

In closing, Dr. Andersen noted that questions remain on the correlation between gallbladder emptying and symptoms, on the mechanisms and consequences of biliary dyskinesia and the role of cholecystectomy for this disorder. He emphasized the overall goals of this meeting— to learn from one another to improve outcomes for gallstone patients and consider questions to propose for future NHANES surveys.

Adjournment

Dr. James thanked the presenters and attendees for their participation and adjourned the meeting.