International Journal of General Medicine

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COMMENTARY

Medical Therapies to Conquer Surgical Diseases: Gallstone Disease May Be the Next Frontier

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Abstract: Over the past half century, diseases that were predominantly treated surgically have transitioned to less invasive medical therapies. Such diseases that are now effectively treated with medicine are (1) peptic ulcer disease (PUD), (2) coronary artery disease (CAD), and (3) gastrointestinal stromal tumors (GISTs). Likewise, gallstone disease may soon follow this trend. Currently, the gold standard treatment of symptomatic gallstones is laparoscopic cholecystectomies. Though one of the most common surgeries in the United States, certain cases of acute and gangrenous cholecystitis can be some of the most difficult surgeries to perform. Advancements in neutrophil extracellular trap (NET) inhibitor medical therapies will alter gallstone disease management and the mainstream role of surgical interventions. This focus on less invasive therapies will greatly impact the quality of patient care, financial obligations, and even resident training opportunities.

Keywords: gallstone disease, medical therapies, NET inhibitor, invasive surgical therapy, drug discovery

Introduction

Over the last few decades, disease management has shifted focus towards novel medical therapies to treat traditionally surgically treated diseases. The efficacy of medical therapy over invasive surgical options can be highlighted with a few historical examples: (1) peptic ulcer disease (PUD), (2) coronary artery disease (CAD), and (3) gastrointestinal stromal tumors (GISTs) (Figure 1).

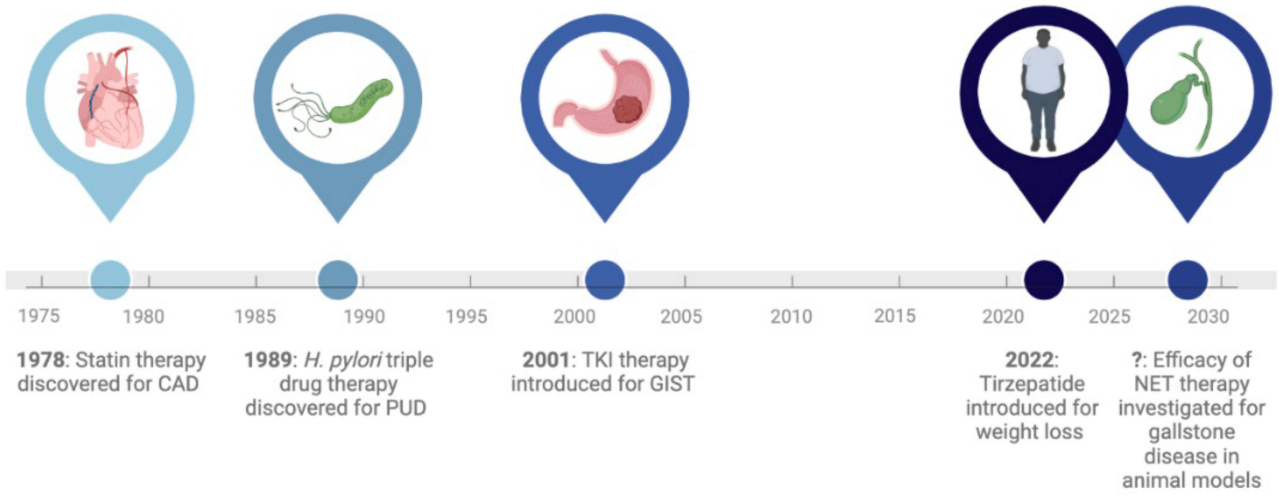

Figure 1 Timeline of troublesome diseases that have shifted to medical therapy treatment.

Received: 30 August 2023
Accepted: 18 December 2023
Published: 5 January 2024

Today, similar advancements are being made within gallstone disease management. The first successful surgical removal of a gallbladder with open cholecystectomy was in 1882. Since the early 1990s, laparoscopic cholecystectomies have largely replaced open cholecystectomies as the standard of care for the removal of the gallbladder.[1] Around 600,000 laparoscopic cholecystectomies are performed annually, making it the most common surgery in the United States.[2] These cholecystectomies are technically challenging surgical procedures resulting in high rates of iatrogenic complications such as bile duct injury, bleeding, infection, or death.[3] Due to the high morbidity of cholecystectomy complications, alternative medical therapies, such as neutrophil extracellular trap (NET) inhibitors, are being tested in animal studies. NET inhibitors are shown to impede gallstone formation. Therefore, gallbladders without gallstones will not have acute cholecystitis and the need for a cholecystectomy. This therapy will only be useful for gallstone disease management and not for acalculous cholecystitis or biliary dyskinesia. In general, NET inhibitors may reduce the incidence of gallstones, resulting in fewer surgeries required, therefore increasing the quality of patient care and decreasing the associated costs of the procedure and any complications that may arise. The frequency of open cholecystectomies has been declining since the introduction of laparoscopy, so NET inhibitors may demonstrate a similar trend once proven efficacious in human studies.

Statin Development's Impact on the Need for Coronary Artery Bypass Graft (CABG)

Statin therapy has revolutionized the management of CAD. Patients with CAD have narrowed coronary vessels due to the build-up of atherosclerotic plaques and carry the risk of obstructed blood flow to the heart. Disease management of CAD is continuously being refined and is currently divided into three categories based on level of severity: (1) medications and lifestyle modifications, (2) percutaneous intervention (PCI), and (3) CABG.[4] The once gold-standard surgical treatment of CAD first introduced in 1967 involving autografts is now only indicated for complete blockage.[5] Advances in medical therapy and PCI have led to a decrease in the number of CABGs performed.

Statins were accidentally discovered by Japanese microbiologist Akira Endo when he synthesized a substance with an inhibitory effect on HMG-CoA reductase which lowered plasma cholesterol (according to the NIH, an elevated LDL cholesterol, high-fat diet, and substance abuse increase the risk of coronary heart disease).[6] The CDC states that in 2013 about 71% of adults with cardiovascular disease used a cholesterol-lowering medication, and by 2011–2012, 93% of adults prescribed cholesterol-lowering medications were using statins.[7] Figure 2 depicts the increasing trend of statin use per data collected by Kantor et al.[8]

Statins are now used preoperatively and postoperatively and have resulted in greatly reduced cardiac mortality rates. In a meta-analysis of 15 different trials, the use of statins preoperatively correlated to a 38% reduction in mortality (1.9% vs 3.1%; $P = 0.0001$) after cardiac surgery and a 44% reduction in mortality rates (2.2% vs 3.2%; $P = 0.0001$) after non-cardiac surgery.[9] In a Scandinavian simvastatin survival study of 4444 patients, 383 patients who had coronary surgery with placebo reported a nonfatal cardiovascular event during a follow-up whereas only 252 who had coronary surgery with simvastatin reported a nonfatal cardiovascular event.[10] In a retrospective cohort study, the researchers identified 5205 patients who underwent single isolated CABG and were given a discharge regimen with statin therapy. An overall reduction in recurrent cardiac events in 30 days, 1 year, and long-term mortality was observed compared to those who underwent a CABG without a discharge regimen. Furthermore, transient ischemic attacks (TIA), strokes, and myocardial infarctions (MI) were also significantly lower in patients treated with statin therapy.[11]

However, new studies emerged in 2023 arguing that statin data is outdated and mostly limited to patients with prior cardiovascular events. Nissen et al underwent a randomized trial of 13,970 patients to understand the effects of bempedoic acid, a lipid-lowering adenosine triphosphate-citrate lyase inhibitor, on cardiovascular outcomes in patients without prior cardiovascular events. Results revealed a reduction in all-cause mortality from 109 patients (5.2%) to 75 patients (3.6%) and similar reductions in MI and cardiovascular death.[12] More research is still required to understand the effects of bempedoic acid within other populations and the impact it will have on statin use. However, such research demonstrates the efficacy of medical therapy, like statins and bempedoic acid, in cardiovascular surgical practice.

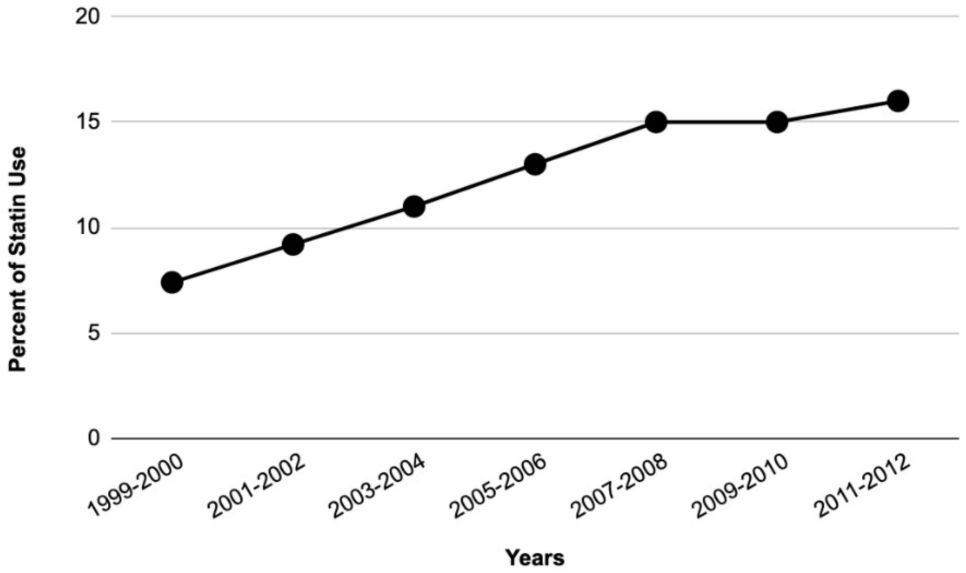

Figure 2 Trends in Statin Use Among US Adults from 1999–2012.
Note: Data from Kantor et al.[8]

Discovery of *H. pylori* Reduced Peptic Ulcer Surgery by 99.5%

In the early 20th century, PUD was the most common cause of gastric perforations requiring surgical repair.[13] Symptoms of PUD often include epigastric pain associated with bloating, dyspepsia, and/or nausea, however, two-thirds of patients are asymptomatic. Treatment regimes for PUD have evolved over multiple decades and can be understood as four distinct time periods. The first period (1972–1976) signifies the phase just before modern anti-ulcer medical treatment, during which surgery was the gold-standard treatment. In the second period (1977–1989), H2 Receptor Antagonists (H2RA) became the dominant treatment. It was during this period in 1984 that Barry J. Marshall and Robin Warren discovered *H. pylori*, a gram-negative microaerophilic bacillus, as the pathogen causing PUD. This discovery ultimately earned them the Nobel Prize in Physiology or Medicine in 2005. The mechanism of disease by this infectious agent primarily involves damage to the structure and function of the gastric mucosa, leading to hypochlorhydria or achlorhydria.[14] Since its discovery, *H. pylori* has been identified as a pathogenic factor in more than 90% of patients diagnosed with duodenal ulcers.[15]

The third period (1990–1994) then represents the shift to proton pump inhibitors (PPI) such as omeprazole. Finally, from 1995–2000, a full *H. pylori* eradication therapy of a PPI and two antibiotics became the gold standard PUD treatment.[16] As a result, the discovery of *H. pylori* has decreased the need for uncomplicated PUD surgical intervention to nearly negligible numbers.[14] Studies have shown that 90% of surgical cases are the result of complications such as hemorrhage, perforation, or obstruction.[17] Currently, the indications of ulcer perforation repairs are primarily due to malignancy or noncompliance to medical treatments for PUD.

Figure 3 depicts the number of duodenal ulcer elective surgeries as treatment methods were adjusted over the four time periods. The discovery of *H. pylori* as an etiology of PUD largely decreased the need for elective ulcer surgery and affirmed the efficacy of the triple *H. pylori* eradication therapy. In addition to improving PUD treatment, the use of *H. pylori* medical management also improved the success of elective surgical interventions. According to a randomized controlled trial by Ng et al, cases of perforated duodenal ulcers have a much lower recurrence rate when surgical closure of the perforation is performed in combination with an *H. pylori* eradication regimen.[18]

98% Recurrence-Free Survival with 1 Year of Adjuvant Tyrosine Kinase Inhibitor for Gastrointestinal Stromal Tumor (GIST)

The discovery of the c-kit gain-of-function mutations in GISTs represents another example of medical therapy successfully preventing the need for surgery.[19] Historically, surgical resection was the only therapy for a patient diagnosed with GIST.

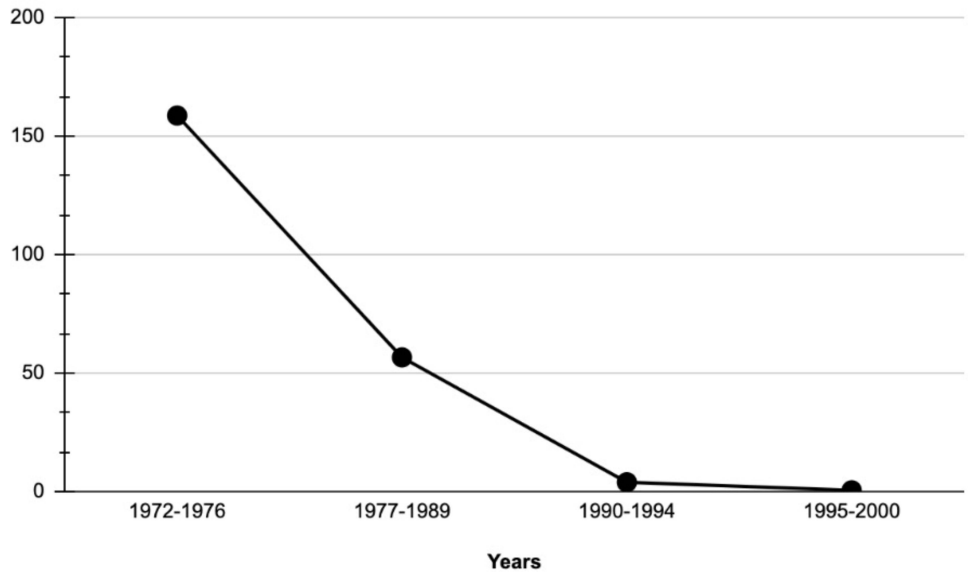

Figure 3 Elective duodenal ulcer surgery mean rates per million resident population per year in the Trent Region, UK.
Note: Data from Bardhan et al.[16]

However, even after surgical resection, up to 50% of patients still developed tumor recurrence.[20] Since the introduction of targeted therapy with tyrosine kinase inhibitors such as imatinib, the prognosis of GISTs has significantly improved. Neoadjuvant TKIs appear to downstage the average tumor size by 48.5%.[21] A decrease in tumor size improves tumor resectability and reduces surgical complications.[22] Postoperative therapy has also been shown to decrease tumor relapse. According to a multi-institutional cohort study by Tan et al, patients with metastatic GISTs have a significant increase in overall and progression-free survival (53.6 and 29.1 months respectively) after the introduction of imatinib. The median overall survival improved from 7.8 months in the period before imatinib was introduced to 61.4 months in the period after imatinib was introduced, an overall improvement of 56.3 months.[23]

Alternatives to Cholecystectomies: NET Inhibitors

Recently, in addition to cholesterol crystals, NETs were observed to be a vital component for gallstone generation and growth. First discovered in 2004, NETs are large web-like structures of decondensed chromatin, histones, and intracellular components (ie, elastase, myeloperoxidase, and proteinase) that enable neutrophils to entrap and destroy pathogens when activated during inflammation (Figure 4).[24] However, there is an imbalance between NET formation and degradation, as NETs are formed

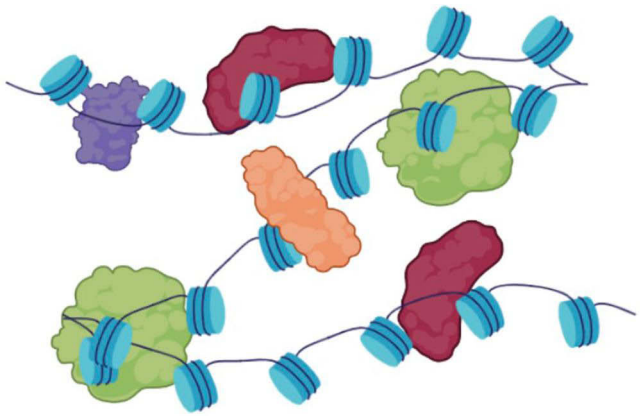

Figure 4 A Visualization of Neutrophil Extracellular Traps with Chromatin, Histones, and Protein Components.

much faster than they are degraded. Hence, researchers are interested in developing NET inhibitors as a more efficient way of moderating the growth of gallstones. Several compounds were tested against the processes that are essential for the formation of NETs (ie macropinocytosis and oxidative burst): Cl- amidine (PADI4 inhibitor), cytochalasin D (cytD), and diphenyleneiodonium (DPI). In the in vivo experiments involving mice, inhibition of ROS production by DPI and of NET formation by the PAD inhibitor Cl- amidine significantly inhibited the volume of aggregated NETs in the air pouches of mice. Compared to the wild-type, there were significantly ($p = 0.03$) less gallstones in PADI4-deficient mice. Also, the sizes of gallstones in each mouse ($p = 0.039$) and the diameters of individual stones ($p = 2.7*10^{-9}$) were significantly lower in mice that were PADI4-deficient. Though NET inhibitors seem promising, limited testing in humans signifies uncertainty about their safety and efficacy. Nevertheless, the development of these therapies continues to demonstrate the possibilities of medical management that can replace the need for surgery, similar to the trends seen with statins, *H. pylori* eradication therapy, and TKIs.

Earlier Medical Therapeutic Attempts for Treating Gallstones Have Not Become Standard of Care: Oral Litholysis

Given the complications associated with surgical management, an alternative medical therapy of oral bile acids that directly dissolves the gallstones has been proposed. Oral bile acids aim to decrease biliary cholesterol and increase unsaturated gallbladder bile, allowing for the dissolution of cholesterol crystals and gallstones. One such example is ursodeoxycholic acid (UDCA). UDCA is a hydrophilic bile acid that (1) reduces the absorption of cholesterol in the intestines, (2) decreases the amount of bile the gallbladder releases after a meal, and (3) sustains the contractility of the smooth muscle in the gallbladder.[24] Guarino et al found remarkable results with oral bile acids; gallstones with a diameter less than 5 mm were reported to have completely disappeared after 6 months of treatment with UDCA in 90% of the patients.[24] However, more abundant or large gallstones can decrease the chance of dissolution with UDCA. Other limitations of UDCA include the high rate of gallstone recurrence after dissolution, the negative cost-to-benefit ratio, the limited population that can utilize this treatment, and the performance of the gallbladder post-bile desaturation.

Impact on Clinical Care

With 20 to 25 million people in the United States suffering from gallstones, there is a significant need to enhance and expand treatment options.[25] The shift from open to laparoscopic cholecystectomies has already shown significant improvements in patient quality of life, including symptomatology, post-operative recovery, and emotional and psychological impact.[26] However, surgical complications leave much room for improvement.[27] Similar to the management of PUD, CAD, and GISTs, treatment options for gallstone disease may shift away from surgical therapies (NET inhibitors). If successful, the mainstream role of surgery in gallbladder disease management will greatly diminish.

Improvements in patient care illustrate the clear limitations of surgery and the reasons why researchers are investigating medical therapies. For example, NET inhibitors may eliminate the risk of operative complications such as blood loss, bile leak, intestinal perforation, hernias, pulmonary embolism, myocardial infarction, and even death. Other investigations suggest that NET inhibitors have been shown to have positive outcomes in various other diseases as well such as rheumatoid arthritis (RA), diabetes, multiple sclerosis (MS), colon cancer, atherosclerosis and spinal cord injury models.[28] Additionally, physical recovery (ie scars, pain, etc.), follow-up appointments, and added recovery time (approximately 1 week of recovery for laparoscopic cholecystectomy) will be reduced and improve patient quality of life.

Medical therapies can also be prescribed as neoadjuvant therapy prior to surgery to decrease complication rates and improve survival rates. For instance, Sjölund et al reported that neoadjuvant tyrosine kinase inhibitor therapy improved GIST resectability and organ-preserving surgery, and Hindler et al reported that preoperative statin use led to a 38% reduction of postoperative mortality risk.[9,22] NET inhibitors may have a similar impact by reducing cholecystectomy complications. This intervention would be especially useful for high-risk surgical populations, such as the elderly. It is important to note that increasing age also correlates to a higher incidence of gallstones (females > males) and a greater need for surgical intervention.[1] Thus, intervention with medical therapies may make surgery a safer option for risky populations.

In addition to improvements in patient quality of life, medical management has financial implications. Currently, gallstones are one of the leading causes of hospital admissions, with 30% of general surgeries being cholecystectomies. This translates to 6.2 billion US dollars being spent each year on gallstone disease management.[24] In Europe, the average cost of gallstone disease treatment from referral to discharge was £4697 (±2007) per patient, with costs varying anywhere from £3406 and £12,011. Surgery and inpatient costs comprised the majority of this expense at £2849 (±414) and £1527 (±1322), respectively. Additional expenses included preoperative outpatient consultations at £174 (±144) and at least one ultrasound at £81±29. While these costs vary in the United States, this example provides an overview of the additional medical expenses associated with surgery.[29] Thus, NET inhibitors can improve the financial burden associated with cholecystectomies.

Similar trends have been seen in the past with CAD management. Lipid-lowering pharmaceutical agents such as simvastatin have proven to be more cost-efficient than surgery by reducing the predicted cost of hospitalizations for vascular events by approximately 20% for 5 years. The net savings for participants with a 42% and 12% chance of vascular death in 5 years was $1300 and $216,500, respectively.[30]

While advancements in the medical management of gallstone disease may be a cost-effective method that increases patient quality of life, it can also have negative implications. More specifically, a decline in laparoscopic cholecystectomies can indicate fewer training opportunities for surgical residents. Today's residents already report difficulty in gaining experience with open cholecystectomies which have become less common with the adoption of laparoscopic techniques. Gallstone disease management is not the only area of medicine that has been impacted in this way. The discovery of *H. pylori* as a pathogen in ulcer disease has also led to a decrease in the number of vagotomies from 24% in 1990 to 7% in 2001. Chief surgical residents who are now graduating in the United States, as a whole, have performed less than 1 parietal cell vagotomy throughout their residency.[17] If these trends continue, residents will be forced to learn operative procedures from surgical textbooks and simulations rather than hands-on experience. As a consequence, fewer surgeons will be adequately trained to perform difficult operations and complication rates of already complicated surgeries will increase. Therefore, it is evident that higher rates of non-surgical management approaches will greatly influence surgical resident training opportunities and the practice of surgery in general.

Despite both positive and negative implications, medical management is also being investigated for obesity treatment. To this day, bariatric surgery has been the gold standard for treating diet and exercise-resistant obesity. According to the New England Journal of Medicine, a novel medical therapy called tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, could soon replace surgery as the gold standard. The drug has shown promising Phase 3 clinical trial results: 5mg, 10mg, and 15mg weekly doses correlated to 15%, 19.5%, and 20.9% weight loss, respectively.[31] There is still more research to be done, however, tirzepatide is yet another depiction of the vanishing role of surgery. Surgeries that were once thought to be mainstream treatment options are being replaced, and cholecystectomies may follow the same fate.

Disclosure

The authors report no conflicts of interest in this work.

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