Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/zm2ak371

RELATIONSHIP BETWEEN INFLAMMATORY BOWEL DISEASE AND CHOLELITHIASIS

Dr Shah Nawaz Khatti[1], Dr Talal Safdar[2*], Dr Saad Inayat Ullah[3], Dr Asim Shehzad[4], Dr Fareeha Naseer Syed[5], Farah Ali[6]

[1]Assistant Professor of General Surgery, Liaquat University of Medical and Health Sciences Jamshoro Pakistan
[2]*Assistant Professor of Medicine, Fauji Foundation Hospital Rawalpindi, Pakistan
[3]Trainee Medical Officer, Surgical B Unit, Hayatabad Medical Complex Peshawar, Pakistan
[4]Assistant Professor, Department of Gastroenterology, Fauji Foundation Hospital Rawalpindi, Punjab, Pakistan
[5]Assistant Professor of Pathology, Department of Pathology, CMH Multan Institute of Medical Sciences, Multan, Pakistan
[6]Senior House Officer, Hepato Pancreatico Biliary & Liver Transplant Unit, Shaikh Zayed Hospital Lahore, Pakistan

***Corresponding author:** Dr Talal Safdar
*Email: talal.safdar@fui.edu.pk

Abstract:
This review study was conducted to investigate the association between inflammatory bowel disease (IBD) and the development of cholelithiasis at Liaquat University of Medical and Health Sciences Jamshoro Pakistan in the duration from November, 2023 to April, 2024. Individuals with IBD, particularly those with Crohn's disease, may have an elevated risk of developing gallstones compared to the general population. Ulcerative colitis and Crohn's disease are both classified as inflammatory bowel diseases (IBD), which are chronic inflammatory disorders affecting the gastrointestinal tract. Studies have suggested that the risk of gallstones may be more prominent in individuals with Crohn's disease compared to ulcerative colitis. Researchers are still working that how different types of Inflammatory Bowel Disease (IBD) might be connected to the formation of gallstones. Gallstones are hard particles that can form in the gallbladder. The relationship between these digestive conditions is not completely clear, and studies have given different and sometimes unclear results. In other words, scientists are still working to understand how IBD and gallstones might be linked, and there's no clear answer just yet.

Key words: Inflammatory bowel diseases, Crohn's disease, ulcerative colitis, cholelithiasis

Overview of the inflammatory bowel disease and gall stone:

Cholelithiasis refers to the formation of gallstones in the gallbladder.(1) Gallstones are solid particles that form from the bile components, such as cholesterol, bilirubin, and calcium salts. Cholelithiasis encompasses gallbladder stone disease (GSD), intrahepatic stones (IHSs), and common bile duct (CBD) stones.(2) The distinction among these lies in the distribution of stones within the biliary trees. A number of research shows that people with inflammatory bowel disease (IBD), particularly those diagnosed with Crohn's disease, may be more prone to an elevated likelihood of developing

cholelithiasis.(3, 4)
The exact mechanisms linking IBD and cholelithiasis are not fully understood.(5) However, factors like inflammation, malabsorption, and changes in bile composition in individuals with IBD may contribute to the formation of gallstones.(5, 6)
IBD is a term that encompasses two main conditions: Crohn's disease and ulcerative colitis. Both of these conditions are chronic inflammatory disorders of the gastrointestinal tract.(7, 8) While they are not typically associated with high mortality rates, they can significantly impact an individual's quality of life and daily functioning due to the chronic and relapsing nature of the diseases. The incidence of IBD in Asia has seen a rapid increase due to heightened disease awareness, advancements in diagnostic tools, and the adoption of a more westernized lifestyle.(9) GSD represents the predominant form of cholelithiasis, and in Pakistan, the reported prevalence of cholelithiasis is approximately 8% in individuals over the age of 40 and 20% in those over the age of 60 years.(10) Cholelithiasis currently exhibits a prevalence rate of 10–15% in Western countries, whereas in Asian communities, the prevalence is reported to be lower, ranging from 3–4%.(11, 12) Although there is currently a lack of data from Pakistan, a previous study carried out in the Southern Sindh region found that cholelithiasis was the reason for 9.03 percent of procedures.(13) In the Pakistani population, the prevalence rate was reported to be 4.2% for men and 14.2% for women.(14) The occurrence of gallbladder stone disease (GSD) is reportedly associated with factors such as age, female sex, and metabolic disorders.
Both types of IBD such as Crohn's disease (CD) and ulcerative colitis (UC) are involve inflammation of the digestive tract, but they have distinct characteristics and can affect different parts of the digestive system.(15) Over the past few decades, there has been a noticeable increase in the incidence of inflammatory bowel disease (IBD) in Asia. The increasing prevalence of IBD in developing regions underscores the complex interplay between genetic, environmental, and lifestyle factors in the development of these conditions.(16) As a result, IBD is now recognized as a global health concern, and healthcare systems around the world are adapting to address the rising incidence of these chronic inflammatory disorders.

Clinical significance of the study:
The relationship between IBD and cholelithiasis (gallstones) has been recognized, and several studies have explored this association.(17) Clinical significance arises from the potential impact on the management and health outcomes of individuals with both conditions. Patients with IBD, including both Crohn's disease and ulcerative colitis, have been found to be at an increased risk of developing cholelithiasis compared to the general population. Various factors contribute to the development of gallstones in individuals with IBD. These may include malabsorption of bile salts, alterations in the composition of bile, and changes in gut motility. Surgical interventions, such as bowel resection, may further increase the risk of gallstone formation in IBD patients.

Objective: To investigate the association between inflammatory bowel disease (IBD) and the development of cholelithiasis.
The review study aims to contribute to the existing knowledge base, providing valuable insights into the relationship between inflammatory bowel disease and cholelithiasis and potentially informing clinical practices and patient care strategies.

Epidemic disease: Inflammatory bowel disease with cholelithiasis is considered a non-epidemic disease.(18) There is a well-recognized relationship between gallstones (GS) and Crohn's disease (CD) that has been acknowledged since the 1960s.(19) The prevalence of Crohn's disease in individuals with gallstones has been estimated to be around 13-14%, based on reports from different series.(20, 21)
However, the relationship may be subject to variability when assessing another type of inflammatory bowel disease, ulcerative colitis (UC). In other words, the association between gallstones and UC might not be as consistent or well-established as it is with Crohn's disease. The prevalence of IBD has

been increasing in some regions, but this is generally attributed to a combination of genetic, environmental, and immunological factors rather than being characterized as an epidemic.

IBD increases the incidence of disease:

Cholestasis refers to a condition where the flow of bile (a digestive fluid produced by the liver) is impaired, leading to a buildup of bile components in the liver or bloodstream. There is an association of IBD with an increased risk of gallstones (cholelithiasis) rather than cholestasis specifically.(22) The reasons for this association include factors such as malabsorption of bile salts, changes in bile composition, and alterations in gut motility. BAs as important aetiological agents in the pathogenesis of IBD.

There were studies exploring the changes in bile acid (BA) composition in patients with inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis. However, specific landmark studies may have been conducted since then. Studies have suggested that individuals with IBD may exhibit alterations in the composition of the bile acid pool. IBD patients may experience malabsorption of bile acids in the small intestine, leading to changes in the concentration and composition of bile acids in the gastrointestinal tract. Duboc et al. (23) illustrated that individuals diagnosed with colitis (n = 42: 12 with Crohn's disease, 30 with ulcerative colitis) exhibit compromised bile acid (BA) metabolism during active disease. This is distinguished by deficiencies in deconjugation, the conversion to secondary bile acids (SBAs), and desulphation, with a particular emphasis on these abnormalities in the context of active colitis. In a recent and extensive study (24) involving untargeted metabolomic and shotgun metagenomic profiling of stool samples, both in the discovery cohort (n = 155) and the validation cohort (n = 65) consisting of individuals with inflammatory bowel disease (IBD) and non-IBD controls, consistent patterns emerged. The study encompassed the analysis of over 8000 measured metabolites. The findings indicated a notable increase in the abundance of primary bile acids (PBAs) such as cholic acid (CA) and chenodeoxycholic acid (CDCA) among IBD patients. In parallel, there was a corresponding decrease in secondary bile acids (SBAs) such as lithocholic acid (LCA) and deoxycholic acid (DCA) in individuals with IBD. These observations provide valuable insights into the altered metabolic and metagenomic profiles associated with IBD. The research conducted by Jacobs et al.(25) in pediatric inflammatory bowel disease (IBD) patients has yielded comparable results. In their study, they noted heightened levels of primary bile acids (PBAs) and/or their conjugated forms, specifically cholic acid (CA), chenodeoxycholic acid sulphate (CDCA sulphate), and 7-sulphocholic acid (7-sulphoCA). Additionally, less familiar bile acids, such as 7-ketodeoxycholic acid and 3-sulfodeoxycholic acid, were observed at altered levels in individuals diagnosed with IBD (31). These findings further contribute to the understanding of the distinctive bile acid profiles associated with pediatric IBD. These findings imply a consistent impairment in bile acid (BA) metabolism among individuals with inflammatory bowel disease (IBD). This leads to an elevated presence of primary bile acids (PBAs) and/or their conjugated forms, accompanied by a decrease in secondary bile acids (SBAs) in patients with IBD.(26, 27) The study conducted by Lee et al.(28) observed an association between lower levels of fecal deoxycholic acid (DCA) and increased levels of intestinal inflammation in patients with inflammatory bowel disease (IBD). This suggests that reduced concentrations of DCA in fecal samples may be indicative of higher levels of inflammation within the intestinal tract among individuals diagnosed with IBD.

Relationship between gut microbe and bile acid metabolism:

The human gut is believed to harbor over 1,000 phylotypes, encompassing a gene count that is 100 times greater than that present in the human genome.(29) This collection of microorganisms, known as the gut microbiota (GM), comprises bacteria, archaea, viruses, and fungi, categorized into six divisions or phyla: Firmicutes, Bacteroidetes, Proteobacteria, Acinetobacteria, Fusobacteria, and Verrucomicrobia.(30, 31) The gut microbiota plays a crucial role in maintaining the health of its human host, and bile acids are among the metabolites that contribute to this symbiotic relationship. The gut microbiota further modulates the composition and function of bile acids through a process

known as bile acid metabolism. Primary bile acids, synthesized in the liver, can be transformed into secondary bile acids by the enzymatic activity of specific gut bacteria. These secondary bile acids have diverse biological activities and can influence host metabolism in several ways.

It is well known that bile acids (BA) function as signalling chemicals that act through the G protein-coupled membrane receptor 5 (TGR5) and the farnesoid X receptor (FXR). These receptors are essential for the start of signalling cascades that trigger the expression of genes linked to the metabolism of carbohydrates, lipids, and bile acids. Furthermore, they play a role in the control of inflammation and energy consumption, mostly in the tissues of the liver but also affecting other organs.(32, 33)

The bile acids (BA) found in the human body include primary ones like colic and chenodeoxycholic acids, and secondary ones like deoxycholic and lithocolic acids.(34, 35) Making these bile acids is a complex process that involves different enzymes found in various parts of cells, like the endoplasmic reticulum, mitochondria, cytosol, and peroxisomes. There are two ways the body can create bile acids from cholesterol. The first one, called the classical pathway, happens in liver cells and is often referred to as the neutral route. The second way, known as the alternative pathway, takes place in the gut.(35) The classical pathway is responsible for more than 90% of bile acid synthesis, making it the main route for creating these acids.(36) Under normal physiological conditions, the alternative pathway is responsible for the synthesis of secondary bile acids, contributing to less than 10% of the total bile acid synthesis.(37)

It has been noted that the GM participates in the deconjugation, dehydroxylation, and reconjugation of these molecules during the biotransformation of BA.(38) Furthermore, it has been acknowledged that bile acids (BA) possess antimicrobial properties capable of impairing bacterial cell membranes, thereby preventing excessive bacterial growth.(39) Bile acids also play a role in controlling the proliferation and makeup of the intestinal microbiota through interactions with FXR and TGR-5. This regulatory mechanism serves to safeguard the liver and intestine from inflammation. According to a study by David et al.(40), consuming an animal-based diet quickly changed the composition of the gut microbiota (GM). This change included an increase in the number of bile-tolerant bacteria, namely Bacteroides and B. wadsworthia, and a decrease in the number of Firmicutes. The results of this investigation suggested a link between dietary fat, bile acids (BA), and the growth of bacteria, which may have consequences for inflammatory bowel diseases (IBDs) such as Crohn's disease.

IBD related drugs may increase the incidence of disease:

IBD is a chronic inflammatory condition of the gastrointestinal tract, and managing it often involves the use of various medications. While medications can be effective in controlling symptoms and preventing flare-ups, some drugs may have side effects or complications associated with their use. There is evidence to suggest that certain medications used to treat inflammatory bowel disease (IBD), particularly corticosteroids, can increase the risk of cholelithiasis. Medications associated with the onset or exacerbation of conditions resembling Inflammatory Bowel Disease (IBD) include isotretinoin, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, mycophenolate mofetil, etanercept, ipilimumab, rituximab, and sodium phosphate. Isotretinoin is primarily used for severe acne and has been associated with the development or exacerbation of inflammatory bowel disease in some individuals. In the gastrointestinal tract (GIT), this inhibitory effect could potentially hinder the innate immune response to bacterial stimulation in the lumen, resulting in an amplified immune response. A recent study highlighted a case involving a 27-year-old female who exhibited chronic inflammation of the colon, including cryptitis, following isotretinoin treatment. About 1013–1014 bacteria are found in the gastrointestinal tract (GIT), and they are critical for immune system development because they promote immunological tolerance14. According to a recent study, these antibiotics change the gut flora and may be a factor in IBD. There is a relationship between the number of antibiotic dispensations and the risk of developing IBD. It mean as the dosage of antibiotic use increases, the risk of developing IBD also increases proportionally.

It has been stated that approximately 20-30% of individuals with IBD may experience arthritis. Therefore, there is a possibility that existing cases will worsen or possibly spark new ones19,20. They

function by preventing the production of prostaglandins, which are crucial for mucosal defence systems, by inhibiting cyclooxygenase (COX).
IBD includes conditions like Crohn's disease and ulcerative colitis, mycophenolate mofetil is sometimes considered as a treatment option. However, it is not a first-line therapy for IBD. Research on the use of mycophenolate mofetil in IBD is limited, and its efficacy can vary among individuals. Some studies suggest that it may be effective in inducing and maintaining remission in certain cases of Crohn's disease or ulcerative colitis. Rituximab, a monoclonal antibody, has been explored as a potential treatment for inflammatory bowel disease (IBD), encompassing conditions such as Crohn's disease and ulcerative colitis. This investigation has been particularly focused on cases where traditional therapies have proven ineffective.
Sodium phosphate is indeed used as a hyperosmotic solution in colorectal cleansing preparations for procedures such as colonoscopy. It works by causing water to be drawn into the colon, which helps to cleanse the bowel before the procedure. However, there have been reports of nonspecific aphthoid lesions, similar to those seen in Crohn's disease (CD), in some patients who have undergone colonoscopy preparation with sodium phosphate. These lesions are believed to be a result of the toxic effects of sodium phosphate on the mucosa. The relationship between sodium phosphate and the development of inflammatory bowel disease (IBD) is not well-established.

Demographic characteristics such as gender and age:
It has been stated in the literature that individuals with IBD, especially those with Crohn's disease, may have an increased risk of developing cholelithiasis. The risk of developing gallstones increases with age, especially after the age of 40. Older individuals are more prone to gallstone formation. The risk of developing gallstones increases with age, and the prevalence is higher in older adults compared to younger individuals. Aging can lead to changes in the composition of bile, making it more prone to forming solid particles and stones. As individuals with IBD age, the cumulative effects of inflammation and changes in bile composition may contribute to an increased risk of developing gallstones.
Gallstone disease is indeed a common disorder worldwide, and the composition of gallstones can vary. Hormonal factors in women, especially during reproductive years and pregnancy, can influence both IBD and cholelithiasis. Gender-specific considerations may affect the relationship between these conditions. Rates of gallstones are two to three times higher among women than men. Female hormones, such as estrogen, play a significant role in the formation of gallstones. Estrogen increases the concentration of cholesterol in bile and reduces gallbladder motility, both of which contribute to the formation of gallstones. The higher rates of gallstones among women compared to men are largely a phenomenon of the childbearing age, influenced by hormonal factors associated with menstruation, pregnancy, and the use of hormonal contraceptives. The risk tends to equalize after menopause when estrogen levels decline.

Nutritional status: Nutritional status can play a significant role in the relationship between inflammatory bowel disease (IBD) and cholelithiasis (gallstone formation). Both conditions are influenced by various factors, including dietary habits, nutrient absorption, and overall nutritional status. Individuals with IBD, such as Crohn's disease and ulcerative colitis, often experience inflammation in the gastrointestinal tract. This inflammation can lead to malabsorption of nutrients, including fat-soluble vitamins like A, D, E, and K.
Nutrition holds a crucial position in the clinical management of individuals with inflammatory bowel disease (IBD). Generally, nutritional therapy can be categorized as either supportive or primary treatment. Supportive therapy focuses on addressing malnutrition, correcting macronutrient deficiencies, and reversing associated metabolic or pathological consequences. Additionally, it involves offering guidance on specific dietary regimens. This approach should be considered for all patients diagnosed with inflammatory bowel disease.
Malabsorption of fats can result in changes in bile composition and a higher concentration of cholesterol, increasing the risk of gallstone formation. Nutrient deficiencies, common in individuals

with IBD due to malabsorption and inadequate dietary intake, may affect gallbladder function and increase the risk of gallstones. For example, deficiencies in fat-soluble vitamins may disrupt the metabolism of bile salts, contributing to the formation of gallstones. Certain dietary factors are associated with both IBD and gallstone formation. A diet high in refined carbohydrates, low in fiber, and rich in saturated fats may contribute to inflammation in the gastrointestinal tract and an increased risk of gallstones.

Nutrient-rich diets with an emphasis on fruits, vegetables, and whole grains can support overall health and potentially reduce the risk of both conditions.

Several factors contribute to malnutrition in inflammatory bowel disease (IBD). These include diminished oral intake, malabsorption, elevated nutrient losses from the gastrointestinal tract, drug–nutrient interactions, and heightened nutritional requirements. The reported prevalence of protein–energy malnutrition in individuals with inflammatory bowel disease varies and falls within the range of 20–85%. (41, 42) Hypoalbuminemia is observed in a significant percentage of hospitalized patients with Crohn's disease and ulcerative colitis, ranging from 25% to 80% for Crohn's disease and 25% to 50% for ulcerative colitis. (43) There is a lack of consensus regarding whether the basal metabolic rate is elevated in inflammatory bowel disease.

Site of lesion and degree of disease activity and duration:

IBD includes conditions like Crohn's disease and ulcerative colitis. The site of the lesion in the gastrointestinal tract can vary. Crohn's disease can affect any part of the digestive tract, from the mouth to the anus, while ulcerative colitis primarily affects the colon and rectum.

Inflammatory bowel diseases (IBD) exhibit a diverse array of extra intestinal manifestations, with hepatobiliary disorders (HD) being one of them.(44) HD are documented in both ulcerative colitis (UC) and Crohn's disease (CD), with a higher prevalence typically associated with UC.(45) The clinical progression of these disorders frequently occurs independently of the course of the concurrent inflammatory bowel disease (IBD). It is crucial to conduct regular screening for HD in individuals with IBD, as approximately 5% of adults with these conditions are at risk of developing liver disease.(46) Some studies have suggested an association between IBD and NAFLD, a condition characterized by the accumulation of fat in the liver.(45) NAFLD can progress to more severe forms, such as non-alcoholic steatohepatitis (NASH) and cirrhosis.(47)

IBD patients may also develop autoimmune hepatitis, a condition where the body's immune system mistakenly attacks the liver cells, leading to inflammation and liver damage.(48, 49) The exact mechanisms linking IBD and liver disease are not fully understood, but it is believed that inflammation and immune system dysregulation play key roles. Around 70% to 80% of individuals diagnosed with Primary Sclerosing Cholangitis (PSC) also experience concurrent Inflammatory Bowel Disease (IBD), while approximately 1.4% to 7.5% of those with IBD will go on to develop PSC.(50)

The duration and severity of IBD can vary significantly among individuals. Some people may experience only occasional flare-ups or short episodes of symptoms, while others may have a more chronic and persistent course of the disease. The unpredictable nature of IBD makes it challenging to predict the specific duration or course for any given individual.

Treatment:

The primary goal of treating inflammatory bowel disease (IBD) is to reduce inflammation in the gastrointestinal tract, which helps alleviate the signs and symptoms associated with the condition. Anti-inflammatory drugs, immunosuppressants, and biologics are commonly used to control inflammation and manage symptoms. These medications may include aminosalicylates, corticosteroids, immunomodulators, and drugs that target specific pathways involved in inflammation. In some cases, particularly when medications and other treatments are not effective or complications arise, surgery may be necessary. Surgery may involve removing damaged portions of the digestive tract. When it comes to treating inflammatory bowel disease (IBD), the medications mainly focus on two things: the immune system and the tiny living organisms (microbiota) in our gut.

For the microbiota, we use antibiotics to fight against harmful bacteria and probiotics to support the good ones. For the immune system, we use biologics and antibodies to control its overreaction, which is causing inflammation in the digestive tract. So, the drugs help by targeting these specific aspects related to the immune system and gut bacteria. In a recent study t has been stated that using biologics, especially a type called TNFα inhibitors, early on in the treatment of Crohn's disease (CD) can have some positive effects. Specifically, it showed that using these medications in the beginning can reduce the need for corticosteroids (another type of medication) and can also lower the chances of needing surgery for Crohn's disease later on.(51) This suggests that early use of biologics might be beneficial in managing and preventing certain complications associated with Crohn's disease.

Aminosalicylates:

Aminosalicylates are commonly used as the first line of treatment to maintain remission in ulcerative colitis (UC).(52) They work by acting on the cells lining the intestine (epithelial cells) in several ways. These medications help control the release of substances like lipid mediators, cytokines, and reactive oxygen species, which are involved in the inflammatory process. By doing so, aminosalicylates aim to keep the inflammation in check and maintain a state of remission in individuals with ulcerative colitis.(53) The drug mesalamine (also known as 5-aminosalicylic acid or 5-ASA) is a common treatment for conditions like ulcerative colitis. One of the earliest versions of this drug is sulfasalazine, which is made up of two parts: 5-ASA and sulfapyridine, connected by a link called an azo bond. When sulfasalazine reaches the colon, bacteria break the azo bond, releasing the active part (5-ASA) and an inactive part (sulfapyridine). However, sulfapyridine, even though inactive, can cause side effects. To address this, a new drug called olsalazine was developed. Olsalazine still has two 5-ASA molecules, but they are linked together differently (by an azo bond), aiming to reduce side effects and improve the effectiveness of the treatment. The typical dose of mesalamine is 4 grams per day.(54) This amount is usually divided into four separate doses, taken with food to minimize side effects. If necessary, the dose can be increased to a maximum of 6 grams per day, but as the dose goes up, the likelihood of side effects also increases.

When people with ulcerative colitis take sulfasalazine, 10–45% of them may experience side effects such as headaches, nausea, and fatigue. Serious allergic reactions like rash, fever, and more severe conditions (Stevens-Johnson syndrome, pancreatitis, agranulocytosis, or alveolitis) are rare but can occur.(53)

Additionally, sulfasalazine interferes with the absorption of folate in the intestine. Folate is an important vitamin for the body. So, individuals taking sulfasalazine are often given folate supplements to make sure they still get the necessary amount of this vital nutrient.(55)

Corticosteroids:

Corticosteroids are medications used to treat mild to moderate active cases of ulcerative colitis (UC) and Crohn's disease (CD).(56) To minimize the overall side effects and maximize the effectiveness in the colon, different formulations of corticosteroids have been created. Steroid-responsive patients (40%) exhibit clinical improvement and remission upon tapering their dose; steroid-dependent patients (20%) experience a resurgence of symptoms following an initial response to glucocorticoids; and steroid-independent patients (%) do not respond to steroid therapy due to up-regulated levels of the mdr gene or altered levels of corticosteroid binding globulin.(57) Prednisone is typically recommended with an initial dose ranging from 40 to 60 mg per day, and this amount is gradually reduced over several weeks to months. When the dosage exceeds 40 mg per day, individuals may experience side effects like a round and swollen face (moonface), acne, swelling (edema), and early sleep and mood disturbances. Prolonged use of prednisone can lead to health issues such as high blood sugar-induced visual problems (cataracts), bone conditions like osteoporosis and osteonecrosis, and an increased vulnerability to infections.

Immunosuppressants:

Immunosuppressants, originally designed as anticancer drugs, are now used to treat Inflammatory

Bowel Disease (IBD). These medications are typically given to patients who do not respond to steroids and aminosalicylates, or for those in whom the disease returns when steroids are stopped. While they can have notable side effects, they are generally considered safer and better tolerated compared to prolonged corticosteroid therapy. Immunosuppressants work by dampening the activity of the immune system, helping to reduce inflammation in conditions like IBD. Cyclosporine, Methotrexate, Azathioprine (AZA), and 6-mercaptopurine (6-MP) are immunosuppressive medications commonly used in the treatment of Inflammatory Bowel Disease (IBD), particularly in cases where other medications have not been effective or are not well-tolerated.

Methotrexate: Methotrexate is a medication commonly used as a disease-modifying anti-rheumatoid drug (DMARD) for treating rheumatoid arthritis. In the context of Crohn's disease (CD), it is effective in inducing remission or preventing relapses, especially in individuals who don't respond well to or cannot tolerate Azathioprine (AZA) or 6-mercaptopurine (6-MP). Methotrexate works by inhibiting dehydrofolate reductase, a key enzyme involved in DNA synthesis, leading to decreased inflammation and cell death. The typical dosage is an intramuscular injection of 15–25 mg once a week. However, it's important to note that overdose can lead to side effects like nausea, vomiting, diarrhea, stomatitis (inflammation of the mouth), leukopenia (low white blood cell count), and pneumonitis.(58) Therefore, the dosage is carefully managed to minimize these potential side effects.

Tacrolimus: Tacrolimus is an immunosuppressive medication that can be used in the treatment of severe Crohn's disease (CD). It belongs to a class of drugs known as calcineurin inhibitors and works by suppressing the immune system.

Conclusion:

The association between the different subtypes of Inflammatory Bowel Disease (IBD) and the subtypes of cholelithiasis (gallstone formation) is a topic of ongoing debate in epidemiological studies. The relationship between the two conditions is not yet fully understood, and research findings have been inconsistent or inconclusive. The subtypes of IBD, such as Crohn's disease and ulcerative colitis, may have different implications for the development of gallstones, and factors such as inflammation, altered bile composition, and medication use may contribute to this complex relationship. Further research is needed to clarify the association between specific subtypes of IBD and cholelithiasis.

References:

1. Littlefield A, Lenahan C. Cholelithiasis: Presentation and management. Journal of midwifery & women's health. 2019;64(3):289-97.
2. Chen C-H, Lin C-L, Kao C-H. Association between inflammatory bowel disease and cholelithiasis: a nationwide population-based cohort study. International journal of environmental research and public health. 2018;15(3):513.
3. Fagagnini S, Heinrich H, Rossel J-B, Biedermann L, Frei P, Zeitz J, et al. Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. PloS one. 2017;12(10):e0185193.
4. da Silva Gaspar SR, Mendonca T, Oliveira P, Oliveira T, Dias J, Lopes T. Urolithiasis and crohn's disease. Urology annals. 2016;8(3):297.
5. Hegyi P, Maléth J, Walters JR, Hofmann AF, Keely SJ. Guts and gall: bile acids in regulation of intestinal epithelial function in health and disease. Physiological reviews. 2018;98(4):1983-2023.
6. Pereira S, Bain I, Kumar D, Dowling R. Bile composition in inflammatory bowel disease: ileal disease and colectomy, but not colitis, induce lithogenic bile. Alimentary pharmacology & therapeutics. 2003;17(7):923-33.
7. Ramos GP, Papadakis KA, editors. Mechanisms of disease: inflammatory bowel diseases. Mayo Clinic Proceedings; 2019: Elsevier.
8. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology. 2005;129(3):827-36.
9. Ng SC, Bernstein CN, Vatn MH, Lakatos PL, Loftus EV, Tysk C, et al. Geographical variability

and environmental risk factors in inflammatory bowel disease. Gut. 2013:gutjnl-2012-303661.
10. KHAN R, PARI B. RISK FACTORS OF GALLBLADDER STONE IN LADY READING HOSPITAL PESHAWAR, PAKISTAN. Quantum Journal of Social Sciences and Humanities. 2023;4(5):195-213.
11. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut and liver. 2012;6(2):172.
12. Krawczyk M, Miquel JF, Stokes CS, Zuniga S, Hampe J, Mittal B, et al. Genetics of biliary lithiasis from an ethnic perspective. Clinics and research in hepatology and gastroenterology. 2013;37(2):119-25.
13. Naeem M, Rahimnajjad NA, Rahimnajjad MK, Khurshid M, Ahmed QJ, Shahid SM, et al. Assessment of characteristics of patients with cholelithiasis from economically deprived rural Karachi, Pakistan. BMC research notes. 2012;5(1):1-8.
14. Aslam HM, Saleem S, Edhi MM, Shaikh HA, Hafiz M, Saleem M. Assessment of gallstone predictor: comparative analysis of ultrasonographic and biochemical parameters. International archives of medicine. 2013;6(1):1-7.
15. Geboes K. Histopathology of Crohn's disease and ulcerative colitis. Inflammatory bowel disease. 2003;4:210-28.
16. Ho S-M, Lewis JD, Mayer EA, Bernstein CN, Plevy SE, Chuang E, et al. Challenges in IBD research: environmental triggers. Inflammatory bowel diseases. 2019;25(Supplement_2):S13-S23.
17. Zhang FM, Xu CF, Shan GD, Chen HT, Xu GQ. Is gallstone disease associated with inflammatory bowel diseases? A meta-analysis. Wiley Online Library; 2015. p. 634-41.
18. Paul J. Gastrointestinal Tract Infections. Disease Causing Microbes: Springer; 2024. p. 149-215.
19. Ellis H. Review of general surgery 1984-85. Postgraduate Medical Journal. 1985;61(721):941.
20. Lapidus A, Bångstad M, Åström M, Muhrbeck O. The prevalence of gallstone disease in a defined cohort of patients with Crohn's disease. The American journal of gastroenterology. 1999;94(5):1261-6.
21. Whorwell P, Hawkins R, Dewbury K, Wright R. Ultrasound survey of gallstones and other hepatobiliary disorders in patients with Crohn's disease. Digestive diseases and sciences. 1984;29:930-3.
22. Popper H. Cholestasis. Annual review of medicine. 1968;19(1):39-56.
23. Duboc H, Rajca S, Rainteau D, Benarous D, Maubert M-A, Quervain E, et al. Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. Gut. 2012:gutjnl-2012-302578.
24. Franzosa EA, Sirota-Madi A, Avila-Pacheco J, Fornelos N, Haiser HJ, Reinker S, et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. Nature microbiology. 2019;4(2):293-305.
25. Jacobs JP, Goudarzi M, Singh N, Tong M, McHardy IH, Ruegger P, et al. A disease-associated microbial and metabolomics state in relatives of pediatric inflammatory bowel disease patients. Cellular and molecular gastroenterology and hepatology. 2016;2(6):750-66.
26. Biagioli M, Marchianò S, Carino A, Di Giorgio C, Santucci L, Distrutti E, et al. Bile acids activated receptors in inflammatory bowel disease. Cells. 2021;10(6):1281.
27. Gallagher K, Catesson A, Griffin JL, Holmes E, Williams HR. Metabolomic analysis in inflammatory bowel disease: a systematic review. Journal of Crohn's and Colitis. 2021;15(5):813-26.
28. Lee JWJ, Plichta D, Hogstrom L, Borren NZ, Lau H, Gregory SM, et al. Multi-omics reveal microbial determinants impacting responses to biologic therapies in inflammatory bowel disease. Cell host & microbe. 2021;29(8):1294-304. e4.
29. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. nature. 2010;464(7285):59-65.
30. Sekirov I, Russell SL, Antunes LCM, Finlay BB. Gut microbiota in health and disease. Physiological reviews. 2010.

31. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell. 2006;124(4):837-48.
32. Cariou B, van Harmelen K, Duran-Sandoval D, van Dijk TH, Grefhorst A, Abdelkarim M, et al. The farnesoid X receptor modulates adiposity and peripheral insulin sensitivity in mice. Journal of Biological Chemistry. 2006;281(16):11039-49.
33. Abdelkarim M, Caron S, Duhem C, Prawitt J, Dumont J, Lucas A, et al. The farnesoid X receptor regulates adipocyte differentiation and function by promoting peroxisome proliferator-activated receptor-γ and interfering with the Wnt/β-catenin pathways. Journal of Biological Chemistry. 2010;285(47):36759-67.
34. Long SL, Gahan CG, Joyce SA. Interactions between gut bacteria and bile in health and disease. Molecular aspects of medicine. 2017;56:54-65.
35. Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. Annual review of biochemistry. 2003;72(1):137-74.
36. Arrese M, Trauner M, Sacchiero RJ, Crossman MW, Shneider BL. Neither intestinal sequestration of bile acids nor common bile duct ligation modulate the expression and function of the rat ileal bile acid transporter. Hepatology. 1998;28(4):1081-7.
37. Axelson M, Aly A, Sjövall J. Levels of 7α-hydroxy-4-cholesten-3-one in plasma reflect rates of bile acid synthesis in man. FEBS letters. 1988;239(2):324-8.
38. Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. Current opinion in gastroenterology. 2014;30(3):332.
39. Kurdi P, Kawanishi K, Mizutani K, Yokota A. Mechanism of growth inhibition by free bile acids in lactobacilli and bifidobacteria. Journal of bacteriology. 2006;188(5):1979-86.
40. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505(7484):559-63.
41. Han PD, Burke A, Baldassano RN, Rombeau JL, Lichtenstein GR. Nutrition and inflammatory bowel disease. Gastroenterology Clinics of North America. 1999;28(2):423-43.
42. Cabré E, Gassull MA. Nutrition in inflammatory bowel disease: impact on disease and therapy. Current opinion in gastroenterology. 2001;17(4):342-9.
43. Squirell E. Serum albumin as a measure of inflammation or malnutrition in inflammatory bowel disease: a cross sectional study: Memorial University of Newfoundland; 2021.
44. Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. Annals of medicine. 2010;42(2):97-114.
45. Gizard E, Ford A, Bronowicki JP, Peyrin-Biroulet L. Systematic review: the epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2014;40(1):3-15.
46. Mendes FD, Levy C, Enders FB, Loftus Jr EV, Angulo P, Lindor KD. Abnormal hepatic biochemistries in patients with inflammatory bowel disease. Official journal of the American College of Gastroenterology| ACG. 2007;102(2):344-50.
47. Martínez-Domínguez SJ, García-Mateo S, Laredo V, Gargallo-Puyuelo CJ, Gallego Llera B, López de la Cruz J, et al. Liver Fibrosis in Non-Alcoholic Fatty Liver Disease and Progression to Hepatocellular Carcinoma in Patients with Inflammatory Bowel Disease: A Systematic Review. Cancers. 2023;15(13):3367.
48. Muratori L, Lohse AW, Lenzi M. Diagnosis and management of autoimmune hepatitis. bmj. 2023;380.
49. Sivakrishnan S, Pharm M. Liver disease overview. World Journal of Pharmacy and Pharmaceutical Sciences. 2019;8(1):1385-95.
50. Halliday J, Chapman RW. Extraintestinal Manifestations of Inflammatory Bowel Disease: Primary Sclerosing Cholangitis. Crohn's Disease and Ulcerative Colitis: From Epidemiology and Immunobiology to a Rational Diagnostic and Therapeutic Approach. 2012:579-600.
51. Rubin DT, Uluscu O, Sederman R. Response to biologic therapy in Crohn's disease is improved with early treatment: an analysis of health claims data. Inflammatory bowel diseases. 2012;18(12):2225-31.

52. Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane database of systematic reviews. 2012(10).
53. Kondamudi PK, Malayandi R, Eaga C, Aggarwal D. Drugs as causative agents and therapeutic agents in inflammatory bowel disease. Acta Pharmaceutica Sinica B. 2013;3(5):289-96.
54. Singleton JW, Hanauer SB, Gitnick GL, Peppercorn MA, Robinson MG, Wruble LD, et al. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Gastroenterology. 1993;104(5):1293-301.
55. Ransford R, Langman M. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut. 2002;51(4):536.
56. Baron J, Connell A, Kanaghinis T, Lennard-Jones J, Jones FA. Out-patient treatment of ulcerative colitis. British medical journal. 1962;2(5302):441.
57. FN A. Corticosteroids and immunomodurators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology. 2003;125:320-7.
58. Fraser AG. Methotrexate: first-line or second-line immunomodulator? European journal of gastroenterology & hepatology. 2003;15(3):225-31.