



Extraintestinal Manifestations Of Ulcerative Colitis In Saudi Arabia: Systematic Review

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<i>Article History</i>	<i>Abstract</i>
Received: Revised: Accepted:	<p>Background: Inflammatory bowel disease (IBD), particularly ulcerative colitis (UC), exhibits varied clinical presentations and extraintestinal manifestations (EIMs) that impact the overall well-being of affected individuals. This systematic review aims to consolidate recent studies conducted in Saudi Arabia to comprehensively analyze the sociodemographic characteristics and clinical features of UC patients, with a specific focus on bone-related complications.</p> <p>Objective: To systematically review Extraintestinal Manifestations of Ulcerative Colitis in Saudi Arabia</p> <p>Methodology: Using the PRISMA guidelines, a comprehensive A systematic search was conducted to identify relevant studies published between 2014 and 2023 on PubMed in English that investigated UC in Saudi Arabia. resulting in the inclusion of seven studies with a collective participant count of 1580. Sociodemographic characteristics & Clinical characteristics, particularly the prevalence of bone-related complications, were examined across these studies.</p> <p>Results: The sociodemographic analysis of 1580 participants from seven studies highlighted variations in extraintestinal manifestations in IBD. Due to the inflammatory nature of the UC disease, and increased glucocorticoids concentrations, bone-related complications, including osteoporosis and osteopenia, were prevalent in UC patients, with distinct patterns observed in different studies. Arthropathy emerged as one of the most common extraintestinal manifestation. Moreover, renal stones are</p>

	<p>another issue for these patients. Finally, all of these manifestations contribute to the prevalence of anxiety and depression symptoms that was identified among UC patients, that indicated that fifth of these cohort suffer from, psychological disease.</p> <p>Conclusion: This systematic review provides a comprehensive overview of recent studies on UC in Saudi Arabia, emphasizing the prevalence of bone-related complications as predominant extra intestinal manifestations. The findings underscore the importance of addressing these complications in the management of UC patients, necessitating regular testing of the bone density in these patients and provide supplements and other necessary treatments for these patients. Moreover, it is important to consider the psychological impact of such disease on the quality of life of patients. Comprehensive multi-disciplinary medical teams need to work together to address various clinical aspects regarding Ulcerative colitis. This does not only include gastroenterologist, nephrologists and general internists, but also include psychologists/therapists to ensure all patients needs are addressed. Finally, further research is needed to have comprehensive view of UC in Saudi Populations and improve the overall quality of care.</p> <p>Keywords; <i>"Ulcerative colitis," "Extraintestinal manifestations," "Bone complications," "Osteoporosis," "Osteopenia," "Arthropathy," "Inflammatory bowel disease," "Saudi Arabia,"</i></p>
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Introduction:

Ulcerative colitis (UC), a chronic inflammatory bowel disease characterized by mucosal inflammation of the colon, is not confined solely to the gastrointestinal tract. Rather, it often manifests extraintestinal symptoms, impacting various organ systems and posing additional challenges for diagnosis and management. Understanding the prevalence and nature of extraintestinal manifestations (EIMs) is crucial for comprehensive patient care, particularly in diverse demographic and regional contexts.

Extraintestinal manifestations (EIMs) frequently occur in both ulcerative colitis (UC) and Crohn's disease (CD), encompassing various organ systems such as musculoskeletal, dermatologic, hepatopancreatobiliary, ocular, renal, and pulmonary. Dealing with these manifestations poses a considerable challenge for physicians overseeing patients with inflammatory bowel disease (IBD). While most IBD patients experiencing EIMs exhibit colonic inflammation, some may develop these manifestations before the onset of colonic symptoms. [1]

The frequency and intensity of extraintestinal manifestations (EIMs) and their connection to intestinal inflammatory bowel disease (IBD) activity vary. Many EIMs are directly linked to an ongoing flare-up in the intestine, encompassing conditions like aphthous ulcers, pauciarticular arthritis, erythema nodosum (EN), and episcleritis. On the other hand, extraintestinal manifestations such as ankylosing spondylitis (AS) and uveitis are not dependent on intestinal disease activity. These manifestations, whether singular or multiple, may manifest either before or after the onset of intestinal symptoms or the formal diagnosis of IBD. Research indicates that the presence of a solitary EIM heightens the likelihood of developing additional extraintestinal manifestations. [2-4]

In both Crohn's disease (CD) and ulcerative colitis (UC), extraintestinal manifestations (EIMs) predominantly affect the musculoskeletal system (including peripheral and axial arthritis, enthesitis), skin (such as pyoderma gangrenosum, erythema nodosum, Sweet syndrome, and aphthous stomatitis), hepatobiliary tract (notably primary sclerosing cholangitis), and eyes (episcleritis, anterior uveitis, and iritis). However, virtually any organ can be impacted, and these manifestations may not always be clinically evident or easily discernible. For instance, occurrences of acute or chronic pancreatitis associated with IBD (unrelated to IBD medications like azathioprine) are infrequent. Nonetheless, up to 18% of IBD patients exhibit asymptomatic exocrine insufficiency, pancreatic duct abnormalities, and hyperamylasemia. Antibodies against exocrine pancreatic tissue (PABs) can be identified in up to 29% of patients with CD but are absent in UC. Certain conditions, like pneumonitis or primary sclerosing cholangitis (PSC), may persist in patients with UC even after undergoing proctocolectomy. [5]

Despite the shared characteristics between ulcerative colitis (UC) and Crohn's disease (CD), considerable diversity exists in their clinical manifestations and histological pathologies. Recent advancements in technology have successfully identified single nucleotide polymorphisms associated with inflammatory bowel disease (IBD), confirming the involvement of 110 loci out of the 163 initially identified. The genetic underpinning of the disease involves mutations in the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) and autophagy-related genes. When combined with the dysregulation of host adaptive and innate immunity, this genetic susceptibility reduces the diversity of gut microbiota. Environmental factors such as drugs, dietary content, and stress further contribute to the development of IBD. Clinically, the predominant presentation involves the intestine, with common symptoms including fever, abdominal pain, weight loss, watery/bloody diarrhea, and anemia. [6]

This systematic review delves into the landscape of extraintestinal manifestations of ulcerative colitis within the unique setting of Saudi Arabia. The Kingdom's distinctive genetic, environmental, and cultural factors may contribute to variations in the presentation and prevalence of UC-associated extraintestinal manifestations. To illuminate these aspects, we draw upon a range of reputable studies and reviews that have explored the intricate interplay between ulcerative colitis and extraintestinal manifestations, with a specific focus on Saudi Arabia.

Methodology

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was followed for this systematic review.

Study Design and Duration: This was a systematic review conducted in November, 2023.

Search strategy: To retrieve the relevant research, a thorough search was conducted across major databases, Using PubMed Mainly as a search engine for studies. We only searched in English. The following keywords were converted into PubMed Mesh terms and used to find studies that were related; "Extraintestinal," "Manifestations," "Ulcerative," "Colitis," "Saudi" and " Arabia". The Boolean operators "OR" and "AND" matched the required keywords. Among the search results were publications in full English language, freely available articles, and human trials.

Selection criteria:

Inclusion criteria

We considered the following criteria for inclusion in this review:

- Studies that investigate the relationship between Ulcerative Colitis and Extraintestinal Manifestations
- Clinical Trials were included.
- Observational Studies were included.
- Controlled clinical trials.
- Comparative studies were included.
- Free accessible articles.

Exclusion criteria

- We excluded systemic reviews.
- We excluded studies that Conducted outside Saudi Arabia
- We excluded article reviews.
- We excluded meta-analysis.
- Studies before 2014
- Studies that did not study extraintestinal manifestations of UC
- Case reports, letters to the editors, and replies to conflicts were excluded.
- Non-English language.

Data extraction

Duplicates in the search strategy output were found using Rayyan (QCRI) [7]. To determine the titles and abstract relevance, the researchers used a set of inclusion/exclusion criteria to filter the combined search results. The reviewers carefully read each paper that matches the requirements for inclusion. The authors provided other methods of resolving disputes with some thought. The authors extracted data about the study titles, authors, study year, country, participants, gender, diagnostic tool, main outcomes, and conclusion.

Strategy for data synthesis

Summary tables were created using information from pertinent research to give a qualitative overview of the results and study components. Following data extraction for the systematic review, the most effective strategy for utilizing data from the included study articles was selected.

Risk of bias assessment

Using the ROBINS-I risk of bias assessment approach for non-randomized trials of therapies, the included studies' quality was assessed [8]. The seven themes that were assessed were confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choosing of the reported result.

Results

Search results

A total of 309 study articles resulted from the systematic search, and 237 were automatically removed. Title and abstract screening were conducted on 72 studies, and 26 studies were excluded. 46 studies were sought for retrieval, and only 19 articles were retrieved. Finally, 19 studies were screened for full-text assessment; 12 Studies were excluded for either having inappropriate study methodology or results. 7 eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1**.

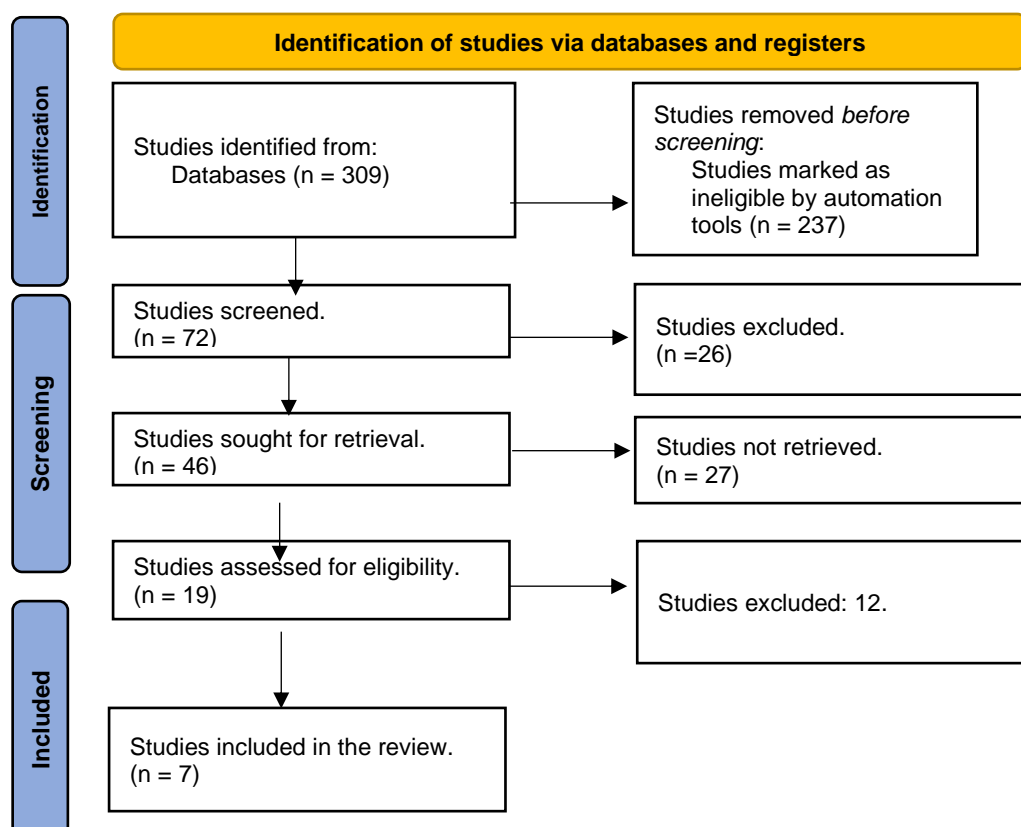


Figure (1): PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table 1: Sociodemographic Characteristics of Participants from Recent Studies

Table (1) delineates the sociodemographic specifics of the 1580 participants from seven different studies, [9-15] encompassing a diverse range of study designs and locations. The participant count from the studies is quite varied, with Alharbi, O. R., et al. 2014. [12] leading the list, having researched a substantial cohort of 394 participants. The studies are geographically restricted to Saudi Arabia with various region. 2 Studies has been conducted in King Abdulaziz Hospital, KSA. [10,11] and one in King Faisal. [14]m and the last in the King Fahd Specialist hospital. [15] In terms of male representation, majority of studies fair distributions of genders around the 50% percentage. [9-14] with one exception having high number of males at 60%. [15] Study designs have been predominately retrospective in design with only one cross-sectional. [15] Finally, when it comes to age disruption, except for 2 studies that focused on children population <14. [9,14]. Most studies focused on young adult population in their 20s and 30s, indicating the prevalence of UC disease in young populations.

Table (2) highlights various studies examining the clinical characteristics of UC in Saudi Arabia:

Several studies have explored various aspects of inflammatory bowel disease (IBD) in the Kingdom of Saudi Arabia (KSA), shedding light on its prevalence, extraintestinal manifestations (EIMs), and associated factors. Mosli and Saadah (2021) [9] aimed to assess the prevalence of metabolic bone disease in pediatric ulcerative colitis patients. Their study revealed that 29.7% of the 37 participants exhibited osteoporosis, and 40.5% showed osteopenia. Lumbar spine Z-scores were significantly associated with male gender.

Adam et al. (2020) [10] findings contradicted previous reports, indicating that EIMs occur more commonly in ulcerative colitis (UC) than Crohn's disease (CD), with an overall incidence of 52.3%. On the other hand, Mosli et al. (2021) [11] who aimed to estimate the prevalence of renal stones among IBD patients in Saudi Arabia. He radiologically detected nephrolithiasis in 3.6% of the cohort, with a higher prevalence in UC compared to CD. Older age at diagnosis and the presence of microscopic hematuria were identified as independent predictors for renal stones.

Alharbi et al. (2014) [12] study highlighted that UC predominantly affects young individuals, with a male preponderance. The disease course aligned with Western patterns, while similarities with Asian countries were observed in terms of disease extent and response to steroid therapy.

Al-Fawzan et al. (2023) [13] found that Arthropathy was the most common extraintestinal manifestation (5.8%). Additionally, Alreheili et al. (2018) [14] documented EIM in 32% of all patients, with bone involvement (osteopenia/osteoporosis) being the most common (16.7%). Sclerosing cholangitis was reported more in UC (14.8%) than CD (2.8%).

Finally on another approach, Alnafisah et al. (2023) [15] described the prevalence and risk factors of anxiety and depression symptoms among adult patients with IBD. The study found that almost one-fifth of IBD patients exhibited anxiety or depression. Female gender increased the risk of anxiety, extraintestinal manifestation increased the risk of depression, and intravenous (IV) medication was found to be a protective factor for depression.

Looking at these studies it is clearly that bone related complications such as osteoporosis, osteopenia and arthropathy are the most common manifestations in UC, which is probably linked to the malabsorption of calcium in such patients.

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Location	Participants	Age range (mean) in years	Males (%)
Mosli, M. H., & Saadah, O. I. (2021) [9]	Retrospective study	KSA	37	13.4±3.9	48.6%
Adam, H., et al. (2020). [10]	Retrospective study	King Abdulaziz Hospital, KSA	284	27.8 (±15)	44.4%
Mosli, M., et al. 2021. [11]	Retrospective study	King Abdulaziz University, KSA	363	32	47.1%
Alharbi, O. R., et al. 2014. [12]	Retrospective study	KSA	394	30.1	51%

Al-Fawzan, A. A., et al. 2023. [13]	Retrospective study	Qassim region, KSA	257	CD - 28.74 years, UC - 38.79 years	52.2%
Alreheili, K. M., et al. (2018). [14]	Retrospective study	King Faisal Specialist Hospital, KSA	66	<14	-
Alnafisah, K., et al. 2023. [15]	Cross-sectional descriptive study	King Fahad Specialist Hospital, KSA	179	-	60.9%

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Objective	Results
Mosli, M. H., & Saadah, O. I. (2021) [9]	Assess the prevalence of metabolic bone disease in pediatric ulcerative colitis patients and identify potential clinical predictors.	Of the 37 participants with UC, 29.7% exhibited osteoporosis, and 40.5% showed osteopenia. Lumbar spine Z-scores were significantly associated with male gender, while total body Z-scores correlated with body mass index Z-scores and duration of illness.
Adam, H., et al. (2020). [10]	estimate the incidence of extraintestinal manifestations (EIMs) in a Middle Eastern cohort of patients with inflammatory bowel diseases (IBD) and explore potential relationships among different EIMs.	It revealed an overall EIM incidence of 52.3%. Arthritis was the most common EIM (33%), followed by aphthous ulcers (16%). Notably, pyoderma gangrenosum was more specific to CD (p = 0.002), while Primary Sclerosing Cholangitis (PSC) was more specific to UC (p = 0.001). The co-occurrence of certain EIMs, such as arthritis with PSC, was observed (p = 0.001).
Mosli, M., et al. 2021. [11]	Estimate the prevalence of renal stones among inflammatory bowel disease (IBD) patients in Saudi Arabia.	Among 363 IBD patients, radiologically detected nephrolithiasis was found in 3.6% of the cohort, with a higher prevalence in UC (5.1%) compared to CD (2.7%). Older age at diagnosis and the presence of microscopic hematuria were identified as independent predictors for renal stones.
Alharbi, O. R., et al. 2014. [12]	determine the clinical, epidemiological, and phenotypic characteristics of ulcerative colitis (UC) in Saudi Arabia, focusing on the largest cohort of Arab UC patients.	In IBD patients, Extensive UC was prevalent in 42.7%, left-sided colitis in 35.3%, and proctitis in 29.2%. Disease severity varied, with 51.3% in remission and 8.6% having severe UC. Extraintestinal manifestations included arthritis (16.4%), osteopenia (31.4%), osteoporosis (17.1%), and cutaneous involvement (7.0%).
Al-Fawzan, A. A., et al. 2023. [13]	understand the demographics, prevalence, and manifestations of IBD in Qassim population.	UC patients were more likely to be diagnosed at an age over 40 years compared to CD patients. Perianal disease, particularly fistulizing Crohn's, was prevalent in CD patients (27.2%). Arthropathy was the most common extraintestinal manifestation of UC (5.8%).
Alreheili, K. M., et al. (2018). [14]	investigate the natural history of inflammatory bowel disease (IBD) in Saudi children, focusing on extraintestinal manifestations, changes in diagnosis, disease behavior, medical management, and surgical outcomes.	Among 66 children with IBD, 54.5% had Crohn's disease (CD), 41% had ulcerative colitis (UC), and 4.5% had indeterminate colitis (IC). Extraintestinal manifestations were documented in 32% of all patients, with bone involvement (osteopenia/osteoporosis) being the most common (16.7%). Sclerosing cholangitis was reported more in UC (14.8%) than CD (2.8%).
Alnafisah, K., et al. 2023. [15]	describe the prevalence and risk factors of anxiety and depression symptoms among adult patients with IBD, and to examine the relationship between mental illness and disease activity.	Among 179 IBD patients, 60.9% were males, with the majority in the 25-35 age group. Crohn's disease (CD) was the most prevalent IBD (73.2%), and perineal CD was detected in 45%. Prevalence of anxiety symptoms was 17.3%, while depressive symptoms were found in 19.6% of patients. Female gender was identified as a risk factor for anxiety, extraintestinal manifestation for depression, and intravenous (IV) medication as a protective factor for depression.

Discussion:

The studies conducted by various researchers across Saudi Arabia collectively contribute valuable insights into the prevalence and extraintestinal manifestations of inflammatory bowel disease (IBD) in the Saudi populations.

A comprehensive overview of the sociodemographic characteristics of 1580 participants across seven recent studies [9-15] on inflammatory bowel disease (IBD) in Saudi Arabia. The participant count varies among studies, with Alharbi et al. (2014) [12] leading with 394 participants. Geographically, the studies are concentrated in different regions of Saudi Arabia, including King Abdulaziz Hospital, King Faisal Specialist Hospital, and King Fahad Specialist Hospital. In terms of gender distribution, the majority of studies exhibit a fairly balanced representation, hovering around 50%, except for one study with a higher proportion of males at 60% [15]. Study designs predominantly lean towards retrospective, with only one adopting a cross-sectional approach [15]. Notably, the age distribution highlights a focus on young adults in their 20s and 30s in most studies, emphasizing the prevalence of ulcerative colitis in this demographic, while two studies specifically

targeted children's populations [9,14]. These sociodemographic insights contribute to a comprehensive understanding of the diverse participant profiles in recent IBD research in Saudi Arabia.

Mosli and Saadah's (2021) [9] investigation into metabolic bone disease in pediatric patients with ulcerative colitis revealed a significant prevalence, with 29.7% exhibiting osteoporosis and 40.5% showing osteopenia. The association between lumbar spine Z-scores and male gender, as well as the negative correlation with extraintestinal manifestations and biologic use, provides important clinical considerations.

In the context of inflammatory bowel disease (IBD), growth failure is observed more frequently in children with Crohn's disease (CD) compared to ulcerative colitis (UC). A meta-analysis of seven studies demonstrated a significant association between adulthood IBD and osteoporosis, particularly in CD. While previous research has reported high prevalence rates of metabolic bone disease (MBD) in children with CD, similar studies for UC are limited. Notably, the prevalence of MBD is influenced by the skeletal site and the type of score used, as shown by variations in t-scores or Z-scores. Previous studies have reported varying rates of osteopenia and osteoporosis in adults with IBD, associated with factors such as BMI, age, and calcium supplementation. Mosli and Saadah's (2021) study found rates of osteoporosis (29.7%) and osteopenia (40.5%) in adults with IBD, as determined by lumbar spine Z-scores, aligning broadly with previous reports. The diversity in bone density measurements across different parts of the skeleton underscores the non-homogeneous nature of bone loss in IBD patients. [9,16-18]

Adam et al. (2020) [10] challenge previous perceptions by highlighting a higher incidence of extraintestinal manifestations (EIMs) in ulcerative colitis (UC) compared to Crohn's disease (CD) in a Middle Eastern cohort. With an overall EIM incidence of 52.3%, the study emphasizes the prevalence of arthritis and aphthous ulcers. The specificity of certain EIMs to CD or UC and the co-occurrence of arthritis with Primary Sclerosing Cholangitis (PSC) underline the complexity of EIM patterns.

Almost half of the patients in Adam et al. (2020) [10] study (48.6%) experienced extraintestinal manifestations (EIMs), a notably high percentage compared to findings from three significant prospective cohort studies conducted in the USA, Switzerland, and India, where incidence rates ranged from 36% to 38%. The variations in these rates could be attributed to several factors, including differences in study design, criteria for inclusion and exclusion, and geographical diversity. Additionally, variations in diagnostic methods and definitions of EIMs, along with the completeness of patient data during follow-up, may contribute to the observed differences. Hypothesis testing indicated no significant difference in the overall incidence of EIMs between ulcerative colitis (UC) and Crohn's disease (CD) patients (48.5 vs. 49.2, $p = 0.70$), aligning with the findings of a cohort study in India. However, multiple regression analysis revealed a higher likelihood of developing EIMs in UC patients. [19-20]

Mosli et al.'s (2021) [11] retrospective study on the prevalence of renal stones in Saudi IBD patients revealed that 3.6% of the cohort had radiologically detected nephrolithiasis, with a higher prevalence in UC (5.1%) compared to CD (2.7%). Older age at diagnosis and the presence of microscopic hematuria were identified as predictors for renal stones. In cases of severe disease, the loss of extracellular fluid due to diarrhea and malabsorption may contribute to the development of renal stones. This finding revealed a greater prevalence of renal stone formation in ulcerative colitis (UC) patients compared to those with Crohn's disease (CD) (5.1% vs. 2.7%). This study underscores the importance of understanding the association between IBD and renal stones.

Alharbi et al. (2014) [12] provide a comprehensive view of the clinical, epidemiological, and phenotypic characteristics of ulcerative colitis (UC) in Saudi Arabia, utilizing data from the largest cohort of Arab UC patients. The study revealed that UC predominantly affects young individuals, with a male preponderance. The distribution of disease extent, severity, and extraintestinal manifestations showcased similarities with Western patterns, while parallels with Asian countries were observed in terms of disease extent and response to steroid therapy.

In a retrospective study by Al-Fawzan et al. (2023) [13], focusing on the Qassim region of Saudi Arabia, insights into the demographics, prevalence, and manifestations of Crohn's disease (CD) and ulcerative colitis (UC) were provided. Notably, UC patients were more frequently diagnosed at an age over 40 years compared to CD patients. The prevalence of perianal disease, particularly fistulizing Crohn's, in CD patients highlights the need for specialized management strategies. Arthropathy emerged as the most common extraintestinal manifestation, emphasizing the diverse clinical presentations in the Qassim population.

Alreheili et al. (2018) [14] focused on exploring the natural history of inflammatory bowel disease (IBD) in Saudi children, emphasizing extraintestinal manifestations. Approximately 25–47% of adults with inflammatory bowel disease (IBD) exhibit at least one extraintestinal manifestation, according to various studies. Recent investigations in pediatric patients reported extraintestinal manifestations in the range of 2–29%, with higher rates observed when including osteopenia and growth delay as extraintestinal manifestations.

The frequency of extraintestinal symptoms was higher in Crohn's disease (CD) compared to ulcerative colitis (UC). Alreheili et al. (2018) data aligns with international findings, as they report a similar rate of extraintestinal manifestations in both CD and UC (33%), considering osteopenia as an extraintestinal manifestation. Excluding osteopenia, the rate drops to 19.4% for CD and 11.1% for UC, comparable to global data. The study revealed that growth failure, complications, aggressive medical treatment, and surgery are predictive factors for the natural history of pediatric IBD. The prevalence of extraintestinal manifestations, particularly bone involvement, and the variation in medical management underscore the need for targeted therapy for bone manifestations, this can include calcium supplements to manage osteoporosis and osteopenia. [21-26]

Patients with inflammatory bowel disease (IBD) clearly face an elevated risk of experiencing bone loss compared to the general population. The persistent inflammation associated with IBD contributes to a decrease in bone mineral density (BMD), resulting in conditions like osteopenia and osteoporosis. [27] In the cross-sectional descriptive study by Alnafisah et al. (2023) [15] at King Fahad Specialist Hospital in Qassim, Saudi Arabia, investigating anxiety and depression symptoms among adult IBD patients. The study identified significant rates of anxiety (17.3%) and depression (19.6%) among the IBD population, with female gender emerging as an independent risk factor for anxiety and extraintestinal manifestations contributing to an increased risk of depression. Intriguingly, the study revealed that treatment with intravenous (IV) medication was associated with a protective effect against depression. This highlights the necessity for comprehensive care strategies that consider both physical and mental well-being in the management of inflammatory bowel disease.

Conclusion:

Collectively, these studies contribute to a nuanced understanding of IBD in the Saudi Arabian context, emphasizing the need for gender-specific monitoring of bone health, a multidisciplinary approach to managing extraintestinal manifestations, and further investigation into the association between IBD and renal stones. Prospective studies across diverse populations in Saudi Arabia are recommended to refine these insights and inform more targeted clinical interventions.

References:

1. Levine, J. S., & Burakoff, R. (2011). Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterology & hepatology*, 7(4), 235–241.
2. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. *World J Gastroenterol*. 2006 Aug 14;12(30):4819-31.
3. Trikudanathan G, Venkatesh PG, Navaneethan U. Diagnosis and therapeutic management of extra-intestinal manifestations of inflammatory bowel disease. *Drugs*. 2012 Dec 24;72(18):2333-49.
4. Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, Rogler G, Schoepfer AM. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol*. 2011 Jan;106(1):110-9.
5. Rogler, G., Singh, A., Kavanaugh, A., & Rubin, D. T. (2021). Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. *Gastroenterology*, 161(4), 1118–1132. <https://doi.org/10.1053/j.gastro.2021.07.042>
6. Sange, A. H., Srinivas, N., Sarnaik, M. K., Modi, S., Pisipati, Y., Vaidya, S., Syed Gaggatur, N., & Sange, I. (2021). Extra-Intestinal Manifestations of Inflammatory Bowel Disease. *Cureus*, 13(8), e17187. <https://doi.org/10.7759/cureus.17187>
7. Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Systematic reviews*, 5(1), 1-10.
8. Jüni, P., Loke, Y., Pigott, T., Ramsay, C., Regidor, D., Rothstein, H., ... & Shea, B. (2016). Risk of bias in non-randomized studies of interventions (ROBINS-I): detailed guidance. *Br Med J*
9. Mosli, M. H., & Saadah, O. I. (2021). Metabolic bone disease in children and adolescent patients with ulcerative colitis. *Jornal de pediatria*, 97(2), 242–247. <https://doi.org/10.1016/j.jpmed.2020.03.003>
10. Adam, H., Alqassas, M., Saadah, O. I., & Mosli, M. (2020). Extraintestinal Manifestations of Inflammatory Bowel Disease in Middle Eastern Patients. *Journal of epidemiology and global health*, 10(4), 298–303. <https://doi.org/10.2991/jegh.k.200330.001>
11. Mosli, M., Alzahrani, A. M., Bahafzalla, R. A., Gazzaz, T. A., Slaghour, R. M., Altabsh, G. Z., Aljadani, S. B., Alturkestani, R. N., Hussein, S. S., Kashgari, A., & Saadah, O. I. (2021). Prevalence of Renal Stones

- Among Patients With Inflammatory Bowel Disease in Saudi Arabia. *Cureus*, 13(6), e15787. <https://doi.org/10.7759/cureus.15787>
12. Alharbi, O. R., Azzam, N. A., Almalki, A. S., Almadi, M. A., Alswat, K. A., Sadaf, N., & Aljebreen, A. M. (2014). Clinical epidemiology of ulcerative colitis in Arabs based on the Montréal classification. *World journal of gastroenterology*, 20(46), 17525–17531. <https://doi.org/10.3748/wjg.v20.i46.17525>
 13. Al-Fawzan, A. A., Al-Radhi, S. A., Al-Omar, A. S., Al-Mutiri, N. H., Al-Ammari, A. M., El-Gohary, M., Shamsan, A. N., Al Shehri, H. M., & ALGhasab, N. S. (2023). A Study of the Epidemiology, Clinical, and Phenotypic Characteristics of Inflammatory Bowel Disease in the Northern-Central Region of Saudi Arabia. *Diagnostics (Basel, Switzerland)*, 13(13), 2135. <https://doi.org/10.3390/diagnostics13132135>
 14. Alreheili, K. M., Alsaleem, K. A., & Almehaidib, A. I. (2018). Natural history and outcome of inflammatory bowel diseases in children in Saudi Arabia: A single-center experience. *Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association*, 24(3), 171–176. https://doi.org/10.4103/sjg.SJG_490_17
 15. Alnafisah, K., Alsaleem, H. N., Aldakheel, F. N., Alrashidi, A. B., Alayid, R. A., Almuhayzi, H. N., & Alrebdi, Y. M. (2023). Anxiety and Depression in Patients With Inflammatory Bowel Disease at King Fahad Specialist Hospital, Qassim Region. *Cureus*, 15(9), e44895. <https://doi.org/10.7759/cureus.44895>
 16. Hidalgo D.F., Boonpheng B., Phemister J., Hidalgo J., Young M. Inflammatory bowel disease and risk of osteoporotic fractures: a meta-analysis. *Cureus*. 2019;11:e5810
 17. Tsai M.S., Lin C.L., Tu Y.K., Lee P.H., Kao C.H. Risks and predictors of osteoporosis in patients with inflammatory bowel diseases in an Asian population: a nationwide population-based cohort study. *Int J Clin Pract*. 2015;69:235–241.
 18. Neelis E., Rijnen N., Sluimer J., Olieman J., Rizopoulos D., Wijnen R., et al. Bone health of children with intestinal failure measured by dual energy X-ray absorptiometry and digital X-ray radiogrammetry. *Clin Nutr*. 2018;37:687–694.
 19. Vavricka SR, Brun L, Ballabeni P, Pittet V, Vavricka BMP, Zeitz J, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *The Am J Gastroenterol*. 2011;106:110–19. doi: 10.1038/ajg.2010.343.
 20. Singh B, Kedia S, Konijeti G, Mouli VP, Dhingra R, Kurrey L, et al. Extraintestinal manifestations of inflammatory bowel disease and intestinal tuberculosis: frequency and relation with disease phenotype. *Indian J Gastroenterol*. 2015;34:43–50. doi: 10.1007/s12664-015-0538-7
 21. Greenstein AJ, Janowitz HD, Sachar DB. The extraintestinal complications of Crohn's disease and ulcerative colitis: A study of 700 patients. *Medicine*. 1979;55:410–2.
 22. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: A population-based study. *Am J Gastroenterol*. 2001;96:1116–22
 23. Mendoza JL, Lana R, Taxonera C, Alba C, Izquierdo S, Díaz-Rubio M. Extraintestinal manifestations in inflammatory bowel disease: differences between Crohn's disease and ulcerative colitis. *Med Clin (Barc)* 2005;125:297–300
 24. Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldassano RN, et al. Development of Extraintestinal Manifestations in Pediatric Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2009;15:63–8.
 25. Grossman BJ, DeBenedetti CD. Extraintestinal manifestations of chronic inflammatory bowel disease in children. *Proc Inst Med Chic*. 1970;28:119.
 26. Stawarski A, Iwanczak B, Krzesiek E, Iwanczak F. Intestinal complications and extraintestinal manifestations in children with inflammatory bowel disease. *Pol Merkur Lekarski*. 2006;20:22–5
 27. Lima, C. A., Lyra, A. C., Rocha, R., & Santana, G. O. (2015). Risk factors for osteoporosis in inflammatory bowel disease patients. *World journal of gastrointestinal pathophysiology*, 6(4), 210–218. <https://doi.org/10.4291/wjgp.v6.i4.210>