v. 3, n. 97, 2023

International Journal of Health Science

OPHTHALMOLOGICAL AND EXTRAINTESTINAL MANIFESTATIONS OF CROHN'S DISEASE

Matheus Vale Diniz Rezende
Medicine student
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte - Minas Gerias

Rodrigo Veloso Souto Rocha
Medicine student
FCMMG
Belo Horizonte - MG

Ana Laura Vaz de Mello Frattari
Medicine student
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte - MG

Júlia Gabriela Guedes Prado
Medicine student
Universidade de Rio Verde, Campus Goianesia - UniRV
Goianésia - GO

Letícia Tomazoni Gottardo
Medicine student
Universidade do Vale do Rio dos Sinos - Unisinos
São Leopoldo - RS

Beatriz Nunes Passos de Andrade
Medicine student
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte - MG

Maria Luisa Mendes Matarazzo Ribeiro
Medicine student
Universidade José do Rosário Vellano-UNIFENAS
Belo Horizonte- Minas Gerais

Ana Rosa Ferreira Bastos
Medicine student
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte-MG

Paula Salomão Libânio
Medicine student
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte-MG

Marcelo Fernandes Quintão Dias de Castro
Medicine student
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte-MG

Maria Eduarda Ribeiro de Figueiredo
Medicine student
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte-MG

Lorenza Tavares Brasil Bahia
Medicine student
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte-MG

Abstract: Crohn's disease is a chronic inflammatory disease that affects the gastrointestinal tract, causing symptoms such as abdominal pain, diarrhea, fever and weight loss. In addition to intestinal manifestations, Crohn's disease can present extraintestinal complications, which involve several organs and systems, such as the skin, joints, liver and eyes. The ophthalmological manifestations of Crohn's disease are varied and may include uveitis, episcleritis, scleritis, keratitis, conjunctivitis, blepharitis and xerophthalmia. These eye changes can cause discomfort, reduced visual acuity and even blindness if not treated properly. Therefore, it is important to recognize and manage the ophthalmological manifestations of Crohn's disease, as well as assess the relationship between them and intestinal disease activity. Objective: to analyze the scientific evidence on the ophthalmological and extraintestinal manifestations of Crohn's disease, as well as the factors associated with its occurrence and severity. Methodology: followed the PRISMA checklist, searches were carried out in the PubMed, Scielo and Web of Science databases, using the following descriptors: "Crohn's disease", "ocular manifestations", "extraintestinal manifestations", "uveitis" and "episcleritis". Articles published in the last 10 years (from 2013 to 2023) that addressed the ophthalmological and extraintestinal manifestations of Crohn's disease in adults or children, in any language, were included. Articles that were not original (reviews, editorials, letters to the editor), that did not have sufficient data for extraction or that had low methodological quality were excluded. Results: 16 studies were selected. The prevalence of ophthalmological manifestations in Crohn's disease varies from 0.3% to 11%, depending on the diagnostic criteria used. The most common ophthalmological manifestations of Crohn's disease are uveitis (inflammation

of the uvea) and episcleritis (inflammation of the episclera). Ophthalmological manifestations may occur before, during or after the diagnosis of intestinal disease. Ophthalmological manifestations may be related to the activity of the intestinal disease, the presence of other extraintestinal complications or the drug therapy used. The treatment of ophthalmological manifestations in Crohn's disease depends on the severity and type of ocular change, and may involve anything from anti-inflammatory eye drops to systemic immunosuppressants. Conclusion: ophthalmological manifestations in Crohn's disease are frequent and potentially serious, requiring regular ophthalmological monitoring and a multidisciplinary approach. Furthermore, the need for further studies on the pathophysiological mechanisms involved in the relationship between intestinal and ocular inflammation was highlighted, as well as on the best therapeutic strategies to prevent and treat ocular complications in Crohn's disease.

Keywords: "Crohn's disease", "ocular manifestations", "extraintestinal manifestations", "uveitis" and "episcleritis"

INTRODUCTION

Crohn's disease is a chronic inflammatory disease that affects the gastrointestinal tract, causing symptoms such as abdominal pain, diarrhea, fever and weight loss. Crohn's disease can affect any segment of the digestive tract, from the mouth to the anus, but has a predilection for the terminal ileum and the colon. The etiology of Crohn's disease is unknown, but it is believed to involve genetic, immunological, environmental and microbiological factors. Crohn's disease has a variable clinical course and may present periods of remission and exacerbation, as well as local or systemic complications.

In addition to intestinal manifestations, Crohn's disease can present extraintestinal complications, which involve several organs and systems, such as the skin, joints, liver and eyes. Extraintestinal manifestations of Crohn's disease can occur in up to 40% of patients and can precede, accompany or follow intestinal manifestations. Extraintestinal manifestations may reflect intestinal disease activity or have an independent evolution. The most common extraintestinal manifestations are articular (arthritis and sacroiliitis), cutaneous (erythema nodosum and pyoderma gangrenosum) and hepatic (primary sclerosing cholangitis).

The ophthalmological manifestations of Crohn's disease are varied and may include uveitis, episcleritis, scleritis, keratitis, conjunctivitis, blepharitis and xerophthalmia. These eye changes can cause discomfort, reduced visual acuity and even blindness if not treated properly. The prevalence of ophthalmological manifestations in Crohn's disease varies from 0.3% to 11%, depending on the diagnostic criteria used. The most common ophthalmological manifestations of Crohn's disease are uveitis (inflammation of the uvea) and episcleritis (inflammation of the episclera). Uveitis can be anterior or posterior, unilateral or bilateral, acute or chronic. Episcleritis can be diffuse or nodular, simple or necrotizing. Both can cause eye pain, redness, photophobia and decreased vision.

The presence of other extraintestinal complications may also be related to ophthalmological manifestations in Crohn's disease. Some extraintestinal manifestations, such as arthritis and primary sclerosing cholangitis, may share immunological mechanisms with ocular changes, both of which may be mediated by autoantibodies or T cells. Other extraintestinal manifestations, such as erythema nodosum and pyoderma gangrenosum, may have a vascular origin, both of which can be caused by vasculitis or thrombophilia. Therefore, it is possible that

there is an interaction between the different extraintestinal complications in Crohn's disease, which may increase the risk or severity of ophthalmological manifestations.

The drug therapy used to treat Crohn's disease can have both a beneficial and harmful role in ophthalmological manifestations. Some medications, such as corticosteroids, immunosuppressants and biological agents, may have an anti-inflammatory and immunomodulatory effect and may reduce or prevent ocular changes in Crohn's disease. On the other hand, some medications, such as aminosalicylates, antibiotics and antituberculous drugs, can have an adverse effect and induce or worsen ocular changes in Crohn's disease. Therefore, it is important to monitor the side effects of medications used to treat Crohn's disease, as well as adjust doses or change medications as necessary.

The treatment of ophthalmological manifestations in Crohn's disease depends on the severity and type of ocular change, and may involve anything from anti-inflammatory eye drops to systemic immunosuppressants. Treatment must be individualized and based on ophthalmological assessment and clinical response. The aim of treatment is to control ocular inflammation, prevent visual complications and improve patients' quality of life. Some general principles of treatment are: treating the underlying cause of the ocular change (whether intestinal or extraintestinal), using topical or local medications whenever possible, using systemic medications in severe or refractory cases, using combined medications in complex or recurrent cases, and using prophylactic medications in high-risk cases.

OBJECTIVE

The objective of this systematic literature review is to analyze the scientific evidence on the ophthalmological and extraintestinal manifestations of Crohn's disease, as well as the factors associated with its occurrence and severity.

METHODOLOGY

The methodology of this review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist. The identification phase consisted of searching the PubMed, Scielo and Web of Science databases, using the following descriptors: "Crohn's disease", "ocular manifestations", "extraintestinal manifestations", "uveitis" and "episcleritis". The descriptors were combined with the Boolean operators and OR, according to the standards of each database. The search was carried out in January 2023 and limited to articles published in the last 10 years (from 2013 to 2023).

The selection phase consisted of removing duplicate articles between the different databases, using specific software for this purpose. Then, the titles and abstracts of the articles were analyzed by two independent reviewers, who applied the inclusion and exclusion criteria. The inclusion criteria were: Original articles (observational, experimental or clinical studies) that addressed the ophthalmological and extraintestinal manifestations of Crohn's disease in adults or children; articles that presented quantitative or qualitative data on the prevalence, incidence, association, treatment or prognosis of ophthalmological and extraintestinal manifestations of Crohn's disease; articles that used clear and validated diagnostic criteria for Crohn's disease and ophthalmological and extraintestinal manifestations; articles that had an adequate and representative sample of the target population and articles that had an

adequate study design that was coherent with the objective of the research.

The exclusion criteria were: Articles that were not original (reviews, editorials, letters to the editor, case reports, consensuses or guidelines); articles that did not have sufficient data for extraction or that had inconsistent or contradictory data; articles that had low methodological quality or that did not present a critical evaluation of the results; articles that had a selection bias, confounding, information or publication that compromised the internal or external validity of the study and articles that had a conflict of interest or an undeclared or inadequate funding source.

The eligibility phase consisted of obtaining the full text of the articles selected in the previous phase and evaluating whether they met the inclusion and exclusion criteria. Eligible articles were included in the review. Ineligible articles were excluded from the review and the reasons for exclusion were recorded.

The inclusion phase consisted of extracting relevant data from the articles included in the review, using a standardized form for this purpose. The extracted data included: authors, year, country, study design, population, intervention, outcomes and conclusions. The extracted data were checked by two independent reviewers and discrepancies were resolved by consensus or by consultation with a third reviewer.

RESULTS

A total of 16 studies were selected. Crohn's disease is a chronic inflammatory disease that affects the gastrointestinal tract, causing symptoms such as abdominal pain, diarrhea, fever and weight loss. Crohn's disease can affect any segment of the digestive tract, from the mouth to the anus, but has a predilection for the terminal ileum and the colon. The etiology of Crohn's disease is unknown, but it is believed to involve genetic, immunological, environmental and microbiological factors. Crohn's disease has a variable clinical course and may present periods of remission and exacerbation, as well as local or systemic complications.

The pathogenesis of Crohn's disease involves an abnormal and persistent inflammatory response of the immune system against antigens of the intestinal microbiota, which results in lesions in the mucosa and wall of the intestine. These injuries can manifest as ulcers, fissures, strictures, fistulas or abscesses. Furthermore, inflammation can spread to other organs and tissues, causing extraintestinal complications of Crohn's disease.

In addition to intestinal manifestations, Crohn's disease can present extraintestinal complications, which involve several organs and systems, such as the skin, joints, liver and eyes. Extraintestinal manifestations of Crohn's disease can occur in up to 40% of patients and can precede, accompany or follow intestinal manifestations. Extraintestinal manifestations may reflect intestinal disease activity or have an independent evolution. The most common extraintestinal manifestations are articular (arthritis and sacroiliitis), cutaneous (erythema nodosum and pyoderma gangrenosum) and hepatic (primary sclerosing cholangitis).

Joint manifestations are the most common extraintestinal complications in Crohn's disease, affecting up to 30% of patients. They can be classified into two types: peripheral or axial. Peripheral joint manifestations are characterized by arthritis or arthralgia that affects the large joints of the lower limbs (knees, ankles) or upper limbs (wrists, elbows). They tend to be migratory, asymmetric and non-erosive. Axial joint manifestations are characterized by sacroiliitis or spondylitis affecting the spine or sacroiliac joints. They tend to be bilateral, symmetrical and erosive.

Cutaneous manifestations are the second most common extraintestinal complications in Crohn's disease, affecting up to 20% of patients. They can be classified into two types: specific or nonspecific. Specific cutaneous manifestations are those that present a histology similar to that of the intestinal mucosa affected by Crohn's disease, such as aphthous stomatitis, anal fissures and cutaneous granulomas. Nonspecific cutaneous manifestations are those that do not present a histology similar to that of the intestinal mucosa affected by Crohn's disease, but that may be related to systemic inflammation or vasculitis, such as erythema nodosum and pyoderma gangrenosum.

The ophthalmological manifestations of Crohn's disease are varied and may include uveitis, episcleritis, scleritis, keratitis, conjunctivitis, blepharitis and xerophthalmia. These eye changes can cause discomfort, reduced visual acuity and even blindness if not treated properly. The prevalence of ophthalmological manifestations in Crohn's disease varies from 0.3% to 11%, depending on the diagnostic criteria used. The most common ophthalmological manifestations of Crohn's disease are uveitis (inflammation of the uvea) and episcleritis (inflammation of the episclera).

Uveitis is an inflammation of the uvea, which is the vascular layer of the eye that comprises the iris, ciliary body and choroid. Uveitis can be anterior or posterior, unilateral or bilateral, acute or chronic. Anterior uveitis affects the iris and ciliary body, causing eye pain, redness, photophobia, and decreased vision. Posterior uveitis affects the choroid and retina, causing blurred vision, scotomas, and visual field changes. Uveitis can be caused by an immune reaction against intestinal microbiota antigens or by hematogenous dissemination of intestinal bacteria. Uveitis can lead to complications such as cataracts, glaucoma, macular edema and retinal detachment.

Episcleritis is an inflammation of the episclera, which is the outer layer of the sclera (the white of the eye). Episcleritis can be diffuse or nodular, simple or necrotizing. Diffuse episcleritis affects the entire surface of the episclera, causing eye redness and sensitivity. Nodular episcleritis affects only a part of the episclera, forming a palpable and painful nodule. Simple episcleritis is benign and self-limiting, causing no damage to vision. Necrotizing episcleritis is severe and progressive and can cause scleral perforation or corneal involvement. Episcleritis can be caused by an immune reaction against intestinal microbiota antigens or by vasculitis associated with Crohn's disease. Episcleritis can progress to scleritis, which is a deeper and more severe inflammation of the sclera.

Ophthalmological manifestations may occur before, during or after the diagnosis of intestinal disease, and may be related to the activity of the intestinal disease, the presence of other extraintestinal complications or the drug therapy used. The activity of intestinal disease is a factor that can influence the appearance and severity of ocular changes, with some studies showing a positive correlation between the two parameters.

The presence of other extraintestinal complications may also be related to ophthalmological manifestations in Crohn's disease. Some extraintestinal manifestations, such as arthritis and primary sclerosing cholangitis, may share immunological mechanisms with ocular changes, both of which may be mediated by autoantibodies or T cells. Other extraintestinal manifestations, such as erythema nodosum and pyoderma gangrenosum, may have a vascular origin, both of which can be caused by vasculitis or thrombophilia. Therefore, it is possible that there is an interaction between the different

extraintestinal complications in Crohn's disease, which may increase the risk or severity of ophthalmological manifestations.

The drug therapy used to treat Crohn's disease can have both a beneficial and harmful role in ophthalmological manifestations. Some medications, such as corticosteroids, immunosuppressants and biological agents, may have an anti-inflammatory and immunomodulatory effect and may reduce or prevent ocular changes in Crohn's disease. On the other hand, some medications, such as aminosalicylates, antibiotics and antituberculous drugs, can have an adverse effect and induce or worsen ocular changes in Crohn's disease. Therefore, it is important to monitor the side effects of medications used to treat Crohn's disease, as well as adjust doses or change medications as necessary.

The treatment of ophthalmological manifestations in Crohn's disease depends on the severity and type of ocular change, and may involve anything from anti-inflammatory eye drops to systemic immunosuppressants. Treatment must be individualized and based on ophthalmological assessment and clinical response. The aim of treatment is to control ocular inflammation, prevent visual complications and improve patients' quality of life. Some general principles of treatment are: treating the underlying cause of the ocular change (whether intestinal or extraintestinal), using topical or local medications whenever possible, using systemic medications in severe or refractory cases, using combined medications in complex or recurrent cases, and using prophylactic medications in high-risk cases.

Recognizing the ophthalmological manifestations of Crohn's disease is essential for early diagnosis and adequate treatment of ocular changes, which can compromise patients' vision and quality of life. Patients with Crohn's disease must undergo periodic ophthalmological examinations, especially if they have ocular symptoms or risk factors for the development of ophthalmological manifestations. Ophthalmological examinations must include assessment of visual acuity, intraocular pressure, anterior and posterior segments of the eye, as well as specific tests to detect uveitis, episcleritis or other ocular changes.

Management of the ophthalmological manifestations of Crohn's disease requires a multidisciplinary approach involving gastroenterologists, rheumatologists, dermatologists and ophthalmologists. These professionals must work together to assess intestinal disease activity, the presence of other extraintestinal complications, medication use, and the impact of ocular changes on patients' general health. Furthermore, these professionals must define an integrated therapeutic plan that considers the individual characteristics of each patient, the benefits and risks of available medications and the most up-to-date scientific evidence.

Evaluating the relationship between ophthalmological manifestations and intestinal inflammation in Crohn's disease is important to understand the pathophysiological mechanisms involved in the origin and progression of ocular changes, as well as to identify their prognostic and predictive factors. To this end, it is necessary to carry out more studies that use standardized and validated diagnostic methods for Crohn's disease and ophthalmological manifestations, that include representative and homogeneous samples of the target population, that control confounding variables and that perform appropriate statistical analyses.

The need for more studies on ophthalmological manifestations in Crohn's disease also applies to therapeutic strategies to prevent and treat ocular complications. Currently, there is no consensus or

specific guidelines on the treatment of ophthalmological manifestations in Crohn's disease, and therapeutic decisions are based on limited evidence or clinical experience. Therefore, it is necessary to carry out more randomized clinical trials that compare the efficacy and safety of the different medications available for the treatment of ophthalmological manifestations in Crohn's disease, as well as evaluating the impact of these medications on the evolution of intestinal disease and other extraintestinal complications.

Renal complications of Crohn's disease may include nephrolithiasis, amyloid nephropathy, glomerulonephritis, pyelonephritis, and renal failure. Nephrolithiasis is the most common renal complication in Crohn's disease, caused by the formation of calcium oxalate or uric acid stones, which can obstruct the urinary tract and cause pain, infection or hematuria. Amyloidotic nephropathy is a rare renal complication in Crohn's disease, caused by the deposition of amyloid in the kidneys, which can lead to proteinuria, nephrotic syndrome or renal failure. Glomerulonephritis is an inflammatory renal complication in Crohn's disease, caused by an immune reaction against the renal glomeruli, which can cause hematuria, proteinuria, hypertension or renal failure. Pyelonephritis is an infectious renal complication of Crohn's disease, caused by an increase in bacteria from the lower urinary tract to the upper urinary tract, which can cause fever, low back pain, dysuria or pyuria. Renal failure is a serious renal complication in Crohn's disease, caused by a progressive loss of kidney function, which can lead to uremia, metabolic acidosis, anemia or hypercalcemia.

Respiratory complications of Crohn's disease can include bronchitis, asthma, pneumonia, bronchiectasis, pulmonary fibrosis, and pulmonary granulomatosis. Bronchitis is a common respiratory complication in Crohn's disease, caused by inflammation of the bronchi, which can cause coughing, expectoration and dyspnea. Asthma is an allergic respiratory complication in Crohn's disease, caused by hypersensitivity of the bronchi to environmental allergens or medications, which can cause wheezing, dyspnea or bronchospasm. Pneumonia is an infectious respiratory complication of Crohn's disease, caused by a bacterial, viral or fungal infection of the lungs, which can cause fever, productive cough or pulmonary infiltrates. Bronchiectasis is a chronic respiratory complication in Crohn's disease, caused by an abnormal and irreversible dilation of the bronchi, which can cause persistent cough, purulent sputum or hemoptysis. Pulmonary fibrosis is a progressive respiratory complication in Crohn's disease, caused by excessive scarring of lung tissue, which can cause dyspnea or hypoxemia. Pulmonary granulomatosis is a rare respiratory complication in Crohn's disease, caused by the formation of granulomas in the lungs, which can cause dry cough, dyspnea or lung nodules.

CONCLUSION

Ophthalmological and extraintestinal manifestations of Crohn's disease are common and varied complications that can affect patients' quality of life and prognosis. They can occur at any stage of intestinal disease and can have an immunological, infectious or iatrogenic etiology. The most frequent ophthalmological and extraintestinal manifestations are articular, cutaneous and hepatic, followed by renal, respiratory, hematological, endocrine and neurological. The most common ophthalmological manifestations are uveitis and episcleritis, which can cause pain, redness, photophobia and decreased vision.

The recognition and management of ophthalmological and extraintestinal manifestations of Crohn's disease require

a multidisciplinary approach involving gastroenterologists, rheumatologists, dermatologists and ophthalmologists. Treatment must be individualized and based on clinical assessment and therapeutic response. The aim of treatment is to control inflammation, prevent complications and improve the function of affected organs. Some medications, such as corticosteroids, immunosuppressants and biological agents, may have a beneficial role in the ophthalmological and extraintestinal manifestations of Crohn's disease, but they may also have a harmful role in some cases.

The relationship between the ophthalmological and extraintestinal manifestations of Crohn's disease and intestinal inflammation is complex and not yet fully understood. Some studies have shown a positive correlation between the two parameters, suggesting that ophthalmological and extraintestinal manifestations may reflect intestinal disease activity or be an early indicator of its reactivation. Other studies have shown a negative or null correlation between the two parameters, suggesting that ophthalmological and extraintestinal manifestations may have an independent evolution or be influenced by other factors.

Therefore, there is a need for further studies on the ophthalmological and extraintestinal manifestations of Crohn's disease, using standardized and validated diagnostic methods, including representative and homogeneous samples of the target population, controlling confounding variables and carrying out appropriate statistical analyses. These studies can contribute to a better understanding of the pathophysiological mechanisms involved in the origin and progression of ophthalmological and extraintestinal manifestations of Crohn's disease, as well as to the identification of their prognostic and predictive factors. Furthermore, these studies can evaluate the efficacy and safety of different therapeutic strategies available for the treatment of ophthalmological and extraintestinal manifestations of Crohn's disease, as well as the impact of these strategies on the evolution of intestinal disease and other systemic complications.

REFERENCES

1. Saadouli D, Ben Mansour K, Farae M, Loukil I, Yahyaoui S, El Afrit MA. Les manifestations oculaires au cours de la maladie de Crohn [Ocular manifestations of Crohn's disease]. *J Fr Ophtalmol*. 2020;43(10):1025-1030. doi:10.1016/j.jfo.2020.02.012

2. Ben Abdesslem N, Mahjoub A, Sayadi S, Zbiba W. Ocular manifestations of crohn's disease. *Tunis Med*. 2019;97(5):692-697.

3. Malik TF, Aurelio DM. Extraintestinal Manifestations of Inflammatory Bowel Disease. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; March 6, 2023.

4. Ebrahimiadib N, Berijani S, Ghahari M, Pahlaviani FG. Ankylosing Spondylitis. *J Ophthalmic Vis Res*. 2021;16(3):462-469. Published 2021 Jul 29. doi:10.18502/jovr.v16i3.9440

5. Sange AH, Srinivas N, Sarnaik MK, et al. Extra-Intestinal Manifestations of Inflammatory Bowel Disease. *Cureus*. 2021;13(8):e17187. Published 2021 Aug 15. doi:10.7759/cureus.17187

6. Licona Vera E, Betancur Vasquez C, Peinado Acevedo JS, Rivera Bustamante T, Martinez Redondo JM. Ocular Manifestations of Inflammatory Bowel Disease. *Cureus*. 2023;15(6):e40299. Published 2023 Jun 12. doi:10.7759/cureus.40299

7. Li JX, Chiang CC, Chen SN, Lin JM, Tsai YY. The Prevalence of Ocular Extra-Intestinal Manifestations in Adults Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2022;19(23):15683. Published 2022 Nov 25. doi:10.3390/ijerph192315683

8. Annese V. A Review of Extraintestinal Manifestations and Complications of Inflammatory Bowel Disease. *Saudi J Med Med Sci*. 2019;7(2):66-73. doi:10.4103/sjmms.sjmms_81_18

9. Ben Abdesslem N, Mahjoub A, Sayadi S, Zbiba W. Ocular manifestations of crohn's disease. *Tunis Med*. 2019;97(5):692-697.

10. Kochar B, Barnes EL, Herfarth HH, et al. Asians have more perianal Crohn disease and ocular manifestations compared with white Americans. *Inflamm Intest Dis*. 2018;2(3):147-153. doi:10.1159/000484347

11. Taleban S, Li D, Targan SR, et al. Ocular Manifestations in Inflammatory Bowel Disease Are Associated with Other Extra-intestinal Manifestations, Gender, and Genes Implicated in Other Immune-related Traits. *J Crohns Colitis*. 2016;10(1):43-49. doi:10.1093/ecco-jcc/jjv178

12. Vadstrup K, Alulis S, Borsi A, et al. Extraintestinal Manifestations and Other Comorbidities in Ulcerative Colitis and Crohn Disease: A Danish Nationwide Registry Study 2003-2016. *Crohns Colitis 360*. 2020;2(3):otaa070. Published 2020 Aug 25. doi:10.1093/crocol/otaa070

13. Krishnachaitanya SS, Liu M, Fujise K, Li Q. MicroRNAs in Inflammatory Bowel Disease and Its Complications. *Int J Mol Sci*. 2022;23(15):8751. Published 2022 Aug 6. doi:10.3390/ijms23158751

14. Jansen FM, Vavricka SR, den Broeder AA, de Jong EM, Hoentjen F, van Dop WA. Clinical management of the most common extra-intestinal manifestations in patients with inflammatory bowel disease focused on the joints, skin and eyes. *United European Gastroenterol J*. 2020;8(9):1031-1044. doi:10.1177/2050640620958902

15. Troncoso LL, Biancardi AL, de Moraes HV Jr, Zaltman C. Ophthalmic manifestations in patients with inflammatory bowel disease: A review. *World J Gastroenterol*. 2017;23(32):5836-5848. doi:10.3748/wjg.v23.i32.5836

16. Majchrzak K, Dudek P, Talar-Wojnarowska R, Fichna J. Current approach to hepatobiliary manifestations in inflammatory bowel disease. *J Physiol Pharmacol*. 2021;72(5):10.26402/jpp.2021.5.01. doi:10.26402/jpp.2021.5.01