Journal of Coloproctology

www.jcol.org.br

Review Article

Appendectomy and Crohn's Disease

Ana Catarina Caetano Fonseca Loureiro [a,*], *Laura Elisabete Ribeiro Barbosa* [a,b]

[a] *Universidade do Porto, Faculdade de Medicina, Porto, Portugal*
[b] *Centro Hospitalar São João, Serviço de Cirurgia Geral, Porto, Portugal*

ARTICLE INFO

Article history:
12 February 2018

Keywords:
Crohn's Disease
Appendectomy
Appendicitis
Appendix

ABSTRACT

Introduction: Crohn's Disease is a chronic and idiopathic inflammatory process with transmural invasion that can affect the entire gastrointestinal tract. The etiopathogenesis of this pathology is not fully understood and studies have been carried out to understand the influence of different kind of factors on its development, including appendectomy. This monograph aims to address the possible existence of a link between appendectomy and Crohn's Disease, and the possible causes and clinical consequences of this association.
Methods: This monograph was based on the research of original scientific articles in MEDLINE database via PubMed, restricted to articles in Portuguese and English during the period between 1991 and 2017.
Results: Appendectomy seems positively associated with the development of Crohn's Disease, especially in the first years of surgery, regardless of whether or not there is inflammation of the appendix. In fact, the appendix plays important roles in gastrointestinal integrity, acting in the development of an adequate immune response, maintaining and regulating the intestinal flora.
Conclusion: The appendix is important for intestinal homeostasis, preventing the development of certain pathologies. Its resection, regardless of whether or not there is an inflammation after surgery, increases the risk of Crohn's Disease and worsens the prognosis of this pathology, so appendectomy should be avoided in the absence of appendicitis.

Apendicectomia e Doença de Crohn

Palavras-chave:
Doença de Crohn
Apendicectomia
Apendicite
Apêndice

RESUMO

Introdução: A Doença de Crohn é um processo inflamatório crónico e idiopático com atingimento transmural que pode afetar todo o trato gastrointestinal. A etiopatogenia desta patologia não está completamente esclarecida pelo que se tem vindo a realizar estudos para perceber a influência de diferentes fatores no seu desenvolvimento, entre os quais a apendicectomia. Esta monografia visa abordar a existência de uma possível relação entre

* *Corresponding author.*
E-mail: loureiro_catarina@hotmail.com (A.C. Loureiro).
https://doi.org/10.1016/j.jcol.2017.12.004

apendicectomia e Doença de Crohn e as possíveis causas e consequências clínicas desta associação.

Métodos: Esta monografia foi elaborada com base em artigos científicos originais pesquisados na base de dados MEDLINE via PubMed, com restrição a artigos em português e inglês com limite temporal de 1991 a 2017.

Resultados: A apendicectomia parece associar-se positivamente ao desenvolvimento da Doença de Crohn, principalmente nos primeiros anos após a cirurgia, independentemente de haver ou não inflamação do apêndice. De facto, o apêndice desempenha importantes funções na integridade gastrointestinal, com influência no desenvolvimento de uma resposta imunológica adequada e na manutenção e regulação da flora intestinal.

Conclusão: O apêndice é importante na homeostasia intestinal, prevenido o desenvolvimento de determinadas patologias. A sua ressecção, independentemente do facto de haver ou não inflamação aquando da cirurgia, aumenta o risco de Doença de Crohn e piora o prognóstico desta patologia, pelo que a apendicectomia deve ser evitada na ausência da doença.

Introduction

Inflammatory Bowel Disease (IBD) includes Crohn's Disease (CD) and Ulcerative Colitis (UC) that are characterized by their inflammatory component. These diseases are thought to arise preferentially in genetically susceptible individuals when subjected to interactions between environmental, genetic, microbiological, and immunological factors. These entities continue to be a challenge for practitioners, since its etiology remains unclear, making it difficult to get more targeted treatments or preventive methods. These diseases affect several hundred thousand people worldwide, particularly 1.5 million Americans and 2.2 million Europeans.[1]

Some risk factors such as tobacco, infection, pharmacological agents, stress, pollution, and diet have been studied, contributing to a better understanding of the underlying causes of these pathologies.[2]

Lately, researchers have been interested in the influence of appendectomy in the course of these diseases. In fact, several studies have demonstrated a protective effect of this procedure on the onset and clinical course of UC. In CD, the studies are contradictory: some investigators found a negative association, others did not show any relation, and still others found that appendectomy plays a deleterious role in the onset and clinical course of the disease.

Material and methods

This monograph was elaborated based on original scientific articles searched in the MEDLINE database via PubMed, with a restriction made to articles in Portuguese and English with a time limit of 1991–2017.

The research was performed using different combinations of terms: *CD; IBD; Appendix, Appendectomy; Appendicitis*.

We selected the references taking into account their correspondence with the objectives sought in this review, with priority being given to the most recent and complete review articles. In addition, other articles were identified by cross-references of articles obtained in the initial research; articles considered pertinent to the work were included. In total, 39 publications were included in this study.

Results

Relationship between appendectomy and UC

The relationship between appendectomy and UC is relatively well understood; one of the most recent review studies concluded that despite the contradictory results sometimes observed in different case–control studies, most of them demonstrated a protective effect.[3] However, the mechanism underlying this association is still awaiting an explanation.[2]

Patients undergoing UC after an appendectomy have a less severe presentation of the disease, with lower colectomy rates compared to patients not undergoing an appendectomy.[4]

It was also been demonstrated in a case–control study that this relationship only applies to cases in which appendectomy was performed because of an inflammatory cause, e.g., appendicitis or mesenteric lymphadenitis. The relationship does not happen in cases of appendectomy performed by nonspecific abdominal pain. This finding suggests that what will actually influence the course of UC is the inflammatory state that precedes the surgery – not the appendectomy itself; and that, basically, the inflammation was caused by pathogenic factors different from those that gave rise to UC. Apart from this, the relationship will only be valid for surgeries performed before the age of 20; this indicates that the pathogenesis of appendicitis may be based on different causes, depending on the age group; and that the causal factors of this pathology in younger individuals may in some way contribute to the protective effect demonstrated with respect to UC.[5]

Appendicitis: differential diagnosis of ileal CD

Appendicitis is defined as an inflammation of the appendix mucosa, which subsequently affects the remaining layers of

the wall. Despite the diagnostic and therapeutic advances, this pathology continues to be a clinical emergency and is one of the most usual causes of acute abdominal pain and the most common cause of emergency surgery.[6]

Notably, appendicitis has an inconsistent clinical presentation. The classic history of anorexia, periumbilical pain with irradiation to the right iliac fossa, followed by nausea and vomiting occurs in only 50% of cases. At diagnosis, the physician should include medical history, physical examination, and laboratory tests with inflammatory markers at increased levels; however, one does not count with a result that is specific for appendicitis. Thus, in case of diagnostic doubt the clinician should use imaging studies (such as ultrasonography and computed tomography [CT]) and diagnostic laparoscopy.[7] Thus, it is clear why the overall precision in the diagnosis of acute appendicitis is approximately 80%. In fact, often the differential diagnosis of appendicitis is challenging, because its clinical picture is common to many pathologies that occur with abdominal pain, for example, CD, mesenteric lymphadenitis, enterocolitis, endometriosis, diverticulitis, and ischemic colitis, among many others.[8]

In 75% of cases, CD affects the terminal ileum. The characteristic presentation of this disease includes abdominal pain, non-bloody diarrhea, weight loss, fever, and sometimes obstructive symptoms, such as nausea and vomiting, occurring in the same age range as appendicitis, especially in its first peak. To diagnose the pathology, the physician must go beyond the clinical findings, using imaging and laboratory data, the results of which are not specific; its main importance lies in the evaluation of the patient's inflammatory and nutritional status.

Thus, considering the similarity of the clinical presentation of these two pathologies and the fact that they preferentially affect patients of the same age group (preferably affecting children and youngsters),[9] one can explain the frequent diagnostic errors that occur between these two nosological entities. Consequently, physicians should be aware of this possibility, when faced with patients with this symptomatology, to avoid errors of diagnosis.[10]

Despite the clinical similarities, the treatment of these pathologies is different. In appendicitis patients, the treatment is surgical[7]; on the other hand, in CD, the treatment is essentially clinical. Aside from this, studies show that patients with a history of appendicitis followed by a diagnosis of CD have a worse prognosis, with higher percentages of recession versus CD patients not undergoing an appendectomy.[11] But in many cases the similarities in clinical presentation cause the physician to perform an appendectomy as the first surgical approach in CD patients.[12] Thus, it is critical to establish the diagnosis of CD quickly so that the correct treatment is started as early as possible; this will contribute to an improvement in the quality of life of these patients.[9] For this reason, some preoperative evidence has been studied to diagnose CD more effectively: a history of abdominal pain or recurrent diarrhea, laboratory results compatible with the existence of a chronic process (e.g., microcytic anemia, hypoproteinemia, hypoalbuminemia, hypocholesterolemia)[13] and an increased platelet count.[9] It is also valid that the clinician uses imaging methods (ultrasonography and CT) to assist in the differentiation between these pathologies.[8]

Aside from the difficulty in differentiating the two pathologies, there are cases in which these entities are related in a more interconnected way, and there may even be a progression from granulomatous appendicitis to an aggressive CD.[14] According to the most recent guidelines regarding the diagnosis and treatment of appendicitis, postponing surgery in 12/24 h in the case of uncomplicated appendicitis does not increase the percentage of complications,[7] which gives the surgeon time for a more efficient diagnostic study with fewer errors.

CD in the appendix

Despite its proximity to the ileum, an inflammatory involvement of the appendix is uncommon[15]; However, this organ has been increasingly studied, in search of a better understanding of the pathogenesis of intestinal diseases.

It is important to differentiate acute appendicitis from CD versus CD with appendix involvement. The latter situation occurs more frequently in young patients, with a predominance of males.

Compared with CD found in other parts of the gastrointestinal tract, CD in the appendix has a lower percentage of recurrence and apparently with a better prognosis; in these cases, the first-line treatment is an appendectomy.[15]

Although the symptoms on CD with appendix involvement are very similar to the symptoms of appendicitis, they are more recurrent and with a longer course. Histologically, it is possible to easily differentiate these pathologies, since appendages with CD present specific characteristics such as transmural, focal or discontinuous inflammation, predominantly with histiocytic and lymphocytic features. It is possible to observe crypt distortion, granulomas and erosions or ulcers. In some cases, a fibrous obliteration of the appendix lumen is observed; this can be explained by the existence of a recurrent inflammation in the course of the disease, evolving to cicatrization. It has also been shown that patients with CD in the appendix exhibit a more diffuse involvement of the colon.[12]

Finally, in certain cases, granulomatous appendicitis may actually be a case of CD. However, it was observed that granulomatous appendicitis is a distinct entity from CD and that only 5–10% of patients with granulomatous appendicitis develop into CD.[16]

Appendectomy: risk factor for onset and aggravating factor in the clinical features of CD

As already mentioned, the relationship between appendectomy and UC is already relatively clear, and most studies show a protective effect. However, with regard to CD, the information about this association is still not very consistent. Some studies have shown a positive association between appendectomy and CD development.[11,17–22] Other studies failed to prove any association,[23] and there are even studies that have shown a negative association,[4] as in UC. The inconsistencies between studies may be explained by the heterogeneity of the protocols followed, or by the inherent differences between studies.[24] A recent meta-analysis of several studies has shown

that, despite heterogeneity, there is a higher relative risk of CD after an appendectomy.[24]

Time elapsed between appendectomy and CD

Some studies have stratified the risk of CD occurrence after an appendectomy, taking into account the time elapsed between surgery and the diagnosis of the disease.[11,17–19] In some of these studies, it was found that the risk of CD is significantly increased during the early stages after the appendectomy, but then this risk gradually decreases to a non-significant level.[17–19,22] Other studies state that the risk remains high even 10 years after surgery.[11] The aforementioned meta-analysis summarized that the time elapsed since appendectomy has implications for the development of CD and that the risk of CD occurrence after appendix removal is significantly increased in the first year after surgery (the risk increases sevenfold), remains increased 1–4 years after the intervention, and only after 5 years does the risk becomes statistically insignificant.[24]

Confounders

Although this possible association has been advocated in several studies, it must be borne in mind that, because CD is a multifactor entity, several factors may have made this conclusion fallacious, for example, the existence of confounders, among which tobacco stands out. In fact, a possible relationship between tobacco and appendicitis has been demonstrated.[25] Considering that this risk factor is also implicated in CD,[26] is, therefore, a confounding factor in these studies. In studies making adjustments for this factor, no statistically significant differences were found in their results.[4,20]

Diagnostic bias

Some authors state that, in fact, the increased risk of CD after an appendectomy, especially considering that this risk is increased, most clearly in the early times after surgery, with a decreased risk over time,[24] is due to a diagnostic bias.[18,22] As already mentioned, CD can be clinically similar to appendicitis; and the possible involvement of the appendix in a CD patient is a possibility that also contributes to the existence of a diagnostic bias. In the above-mentioned meta-analysis, the risk becomes elevated only in the first 5 years after an appendectomy.[24] But there is evidence that the risk remains increased if the follow-up is started 10 years after surgery – exceeding the prodromal period of appendicitis, thereby counteracting the hypothesis that this association is due only to a misdiagnosis of CD at the time of the appendicitis episode.

The same study revealed that the risk of CD was increased in patients whose appendix showed no inflammation at the time of appendectomy.[11] Although not presenting macroscopic inflammatory characteristics, inflammation can be evidenced in histological studies,[7] and may even have concordant characteristics with CD in a preclinical state, corroborating the diagnostic bias hypothesis.[11]

Diagnosis underlying acute appendicitis

By showing that the risk of developing CD was increased after appendectomy due to perforating appendicitis, mesenteric lymphadenitis, and non-specific abdominal pain, different studies showed that this association does not depend on the inflammatory or non-inflammatory nature of the underlying cause of the surgery.[11,22]

Age

An increased risk for CD occurs only when surgery is performed on adults; therefore, appendectomies performed in children are excluded,[11,22] contrary to what occurs in UC (in which there is a decreased risk of CD if appendectomy is performed in childhood).[5]

Location of CD

Studies evaluating the effect of appendectomy on CD localization have shown a lower incidence of colic involvement[27] and a greater probability of ileal involvement,[4,22,28,29] and that these cases mimic more closely appendicitis symptomatology.[22]

Prognosis

Regarding the effect of appendectomy performed prior to the diagnosis of CD, studies have demonstrated that this surgery is related to a worse prognosis of the disease, translated by the need of systemic steroids, immunosuppressive drugs, biological agents, and surgical treatment, namely, recession surgery.[27] Other studies have revealed no association,[4] and others still suggest that only a change in the course occurs, which translates into an increased probability of surgery in cases of perforated appendicitis.[11]

It appears that an appendectomy performed prior to CD diagnosis decreases the development of extraintestinal manifestations, particularly in the joints.[27]

Finally, there seems to be a relationship between previous appendectomy and a higher risk of stenosis and a lower risk of a fistulous disease and perineal involvement.[29]

Etiopathogeny of CD

Currently, the main factors involved in the etiopathogenesis of CD are environmental and genetic ones, associated with imbalances of the intestinal flora and with changes in the immune system promoting the genesis of a dysregulated immune response that is the basis of chronic intestinal inflammation.[30]

Immune response modification

Faced with an aggression, a vast group of cells (including macrophages, neutrophils, monocytes, and dendritic, mesenchymal, and epithelial cells) mediates an innate immune response. Initially, there is leukocyte infiltration of the mucosa – a finding observed throughout the course of the disease. In fact, these cells are responsible for oxidation processes, with

consequent destruction and perforation of tissues, leading to the release of inflammatory mediators. The process is at the basis of the dysfunction of the epithelial barrier, characteristic of CD.[30]

Likewise, adaptive immunity also appears to play an important role in the pathogenesis of CD. On the one hand, with regard to humoral immunity, in CD there occurs a generalized activation of the immune response, in which the production of the different subclasses of immunoglobulin shows alteration. It has been found that CD patients tend to develop antibodies against a number of antigens characteristic of certain bacteria such as *Saccharomyces cerevisiae* and *Escherichia coli*. Although there is no evidence of a direct association between the presence of these antibodies and the development of CD, it has been proven that higher levels of these antibodies are related to a worse prognosis and to a worsening of the clinical course. On the other hand, as regards to T cells, their ability to adapt to stimuli should be emphasized, which allows an adjustment of the response to the different characteristics of the organism (e.g., gender and age) and to the presence of microorganisms, thus ensuring immunological homeostasis. If this adaptive capacity is compromised, this will affect the reestablishment of this equilibrium after the occurrence of the damage, promoting the maintenance of immune response that is the basis of chronic inflammation. In fact, regulatory T cells (Treg) are critical in innate and adaptive immunity, being important both in the development of self and non-self-tolerance. Consequently, defects in these cells may be on the basis of autoimmune and inflammatory diseases, such as CD.

The function of Treg cells remains poorly defined; it is known only that the number and state of activation of these cells are sensitive to changes in the intestinal flora and in the inflammatory state of the disease. It was found that during the active phase, the amount of these cells increase in the lamina propria, with a concomitant decrease in peripheral blood.[30]

It is noteworthy that inappropriate immune responses may be based on a change in the balance between T-helper 1 (Th1) and T-helper 2 (Th2) lymphocytes, since CD is characterized by a Th1-cell-mediated response.[13] It has been shown that pregnancy status has a protective effect on the development of appendicitis, particularly during the third trimester of gestation. In pregnancy, there is a decrease in the Th1-cell-mediated inflammatory response with a predominance of Th2 cell action and an increase in humoral inflammatory response in favor of a decrease in cellular inflammatory response. These and other physiological changes characteristic of pregnancy may interfere with the pathogenesis of appendicitis.[31] Thus, because it is an inflammatory process and in view of the inverse relationship between this factor and pregnancy, it is possible to conclude that the inflammatory process of appendicitis may be mediated by a Th1-cell response. This may help explain the possible aggravating effect of appendicitis in CD patients.[13]

Other processes that may explain the importance of the appendix on the etiology of IBD have been described. Although apparently more related to UC, these pathways may in some way influence the pathogenesis of CD; but there is little information on this subject. Among these processes, we can highlight the production of immunoglobulin A (IgA), the significant presence of natural killer T-cells (NKT) in the appendix, and the action of Th17 cells, influenced by appendectomy.

The appendix is important in the production of IgA, which has a relevant role in the defense against pathogenic microorganisms. Thus, appendectomy will cause a decrease in this protective pathway, leading to pathological processes. In fact, experimental studies in animals reveal that performing an appendectomy at young ages may lead to decreased levels of immunoglobulin in the mucosa, interfering with humoral intestinal immunity.[32]

As far as NKT cells are concerned, these lymphocytes are present in a greater amount in the appendix compared to the other parts of the intestine. However, the true mechanism of these cells in intestinal pathophysiology has not yet been fully elucidated.[33]

Finally, a new pathway has been described that demonstrates the influence of a subtype of CD4+ cells (IL-17-secreting Th17 cells) on the inflammation characteristic of autoimmune and inflammatory diseases, such as CD. The action of these cells is recruited by the influence of CCL20 chemokine that binds to the CCR6 receptor; both are present at higher levels in the colon of patients with IBD. On the other hand, laboratory studies have revealed that, in relation to appendicitis and appendectomy, the genetic expression of CCL20 in the distal colon undergoes down-regulation, with subsequent suppression of this inflammatory pathway. Thus, these new findings may allow the development of techniques that allow the modeling of this inflammatory pathway, with repercussions in the discovery of new therapeutics for CD.[6]

Genetic susceptibility

Genetic susceptibility also influences the development of IBD; in total, 200 risk loci have been identified[34] that harbor genes with effects on the modulation of cytokine production, on the function of T cells and other components, and on the pathways present in inflammation.[30] Indeed, the intestinal flora can be influenced by the host genotype. Variants of NOD2 and ATG16L genes appear to impair the normal barrier function of the intestinal mucosa in protecting against bacteria, which causes a change in the intestinal microbioma – a thing which will have repercussions on the development of the immune system and, consequently, on the onset of CD, as will be discussed later.[35]

Intestinal microbioma interference

The gastrointestinal tract is the site of the human body where the largest amount of microorganisms is found,[30] representing a diverse set of agents that are related in a defined phylogenetic ratio and whose preservation allows the maintenance of homeostasis in the host.[36] On the one hand, the genotype of the microorganisms interferes with the genetic expression of the host; but on the other hand, the presence of these microorganisms in the gastrointestinal tract is essential for the development and subsequent maturation of the immune system by allowing the establishment of a symbiotic relationship that will develop tolerance and protection.[30]

Some factors, such as certain foods and food additives, tobacco, repeated exposure to antibacterial drugs, and acute events of gastroenteritis, cause changes in the composition and function of the intestinal flora. This modeling is most evident at younger ages.[37]

This change could be responsible for an imbalance that possibly will lead to a higher CD risk. In fact, epidemiological evidence has shown that the higher incidence of diseases due to chronic inflammation and autoimmune pathologies is related to lower percentages of infectious pathologies and to the use of antibiotics and vaccinations. This evidence speaks in favor of the hypothesis that intestinal microorganisms play a fundamental role in the development of the immune system in the first years of life.[30]

Bacterial translocation and microbial products from the intestinal lumen that cross the mucosa to the mesenteric lymph nodes allow for antigenic presentation. This contributes to the development of tolerance relative to endogenous microorganisms during childhood and its maintenance during adulthood, as well as to the development of gut-associated lymphoid tissue (GALT).[38] These bacterial antigens are necessary for the diversification of the repertoire of antibodies and also in the structuring of T- and B-cell areas in follicular centers, which have developed previously and independently of the antigenic presentation.[34]

Lastly, it was found that intestinal bacteria are arranged in colonies that develop in a mucous matrix adherent to the luminal membrane of epithelial cells of intestinal microvilli, forming biofilms. Thus, there is the generation of a symbiotic association in which the host confers advantages (mainly metabolic ones) to the bacteria, contributing to a longer survival of the microorganisms.[39] Likewise, commensal microbial agents protect the host by creating a physical barrier that hinders the entry of pathogens. In these biofilms, one can observe bacterial expulsion processes that allow the elimination of pathogenic microorganisms and the subsequent bacterial recolonization by commensal agents, with consequent biofilm regeneration.[34]

The influence of the appendix on intestinal pathophysiology

The appendix is a structure present in only a few mammals; in man, presents a peculiar architecture. Until recently, the function of this organ was not valued; it was thought that the appendix was nothing more than a vestigial and rudimentary remnant.[39] However, with the publication of some studies proposing that appendectomy was associated with the development and evolution of IBD, the appendix acquired some prominence, becoming the target of several studies.

First, the appendix has a specialized epithelium and houses cellular elements, such as B- and T-lymphocytes and dendritic cells, which allow the processing and presentation of antigens, with the subsequent genesis of an immune response.[32]

In relation to the conservation of the intestinal flora, the appendix plays a prominent role. In fact, thanks to its particular structural characteristics (such as a narrow lumen) and because of its location, this organ is relatively protected from the pathogens present in the fecal material, which cannot reach or disturb its integrity. Thus, in cases of diarrhea – and unlike the case in the large intestine – there are no very pronounced changes in the appendicular flora and epithelium. Therefore, a post-diarrhea recolonization capacity appears to be exclusive to the appendix. Finally, the bacterial density and biofilm continuity along the epithelium are comparatively superior in the appendix, progressively decreasing to the distal end of the large intestine. All these characteristics let us realize that this organ is a safe place, which allows the preservation of commensal bacteria and, in addition, provides support for their growth. Moreover, in pathological situations that occur with the elimination of the constituents of the gastrointestinal tract, this organ allows the reintroduction of bacteria in the colon, contributing to the maintenance of an intestinal flora that, as we have seen, is essential for the maintenance of an intestine without pathology.[34,39]

Thus, one can note the importance of the appendix in maintaining balance and avoiding gastrointestinal pathology. Changes in the function of the appendix can trigger changes in the intestinal flora, which may be the basis of certain pathologies. If, as already discussed, the appendix plays a preponderant role in the immunological integrity and maintenance of the intestinal flora (and consequently in the integrity of the mucosa), its removal will impair the intestinal dynamics, being in the base of pathologies like CD.

Conclusion

It seems that appendectomy is positively associated with CD, increasing the risk of its occurrence and worsening prognosis. This association was advocated in several studies; however, it should be borne in mind that such an assumption may be due to diagnostic errors explained by the clinical similarities between CD and appendicitis, and by the possible involvement of the appendix in CD patients.

According to the latest guidelines for the treatment of acute appendicitis, it is advisable to recess the appendix independently of its macroscopic characteristics, since in some cases it is possible to verify the presence of inflammation by histological analysis, even when no characteristic inflammatory conditions were observed during surgery.[7] However, considering that the possible association between appendectomy and CD does not seem to depend on the inflammatory nature of the pathology underlying the surgery, in clinical practice (especially in situations with possible presence of CD), the preservation of the appendix may be advantageous. The recession should be reserved for cases in which the physician is faced with a proven pathology, the treatment of which is necessarily surgical. In fact, the appendix has proved to be an essential component of intestinal homeostasis; thus, somehow the involvement or absence of this organ may contribute to the development of an intestinal pathology.

Thus, studies allowing a better understanding of the association of appendectomy with the clinical course of CD are justifiable. These studies may help to better understand the etiology and pathogenesis of this disease; this knowledge can be applied in the prevention, diagnosis, and treatment of CD, which, due to its characteristics, results in great deterioration of patients' quality of life.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

To Professor Elisabete Barbosa, for the willingness and teachings handed down during the elaboration of this monograph.

My sincere thanks also go to my parents for their fellowship and for the trust and support given to me throughout my academic journey.

REFERENCES

1. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol. 2015;2:205–17.
2. Abegunde AT, Muhammad BH, Bhatti O, Ali T. Environmental risk factors for inflammatory bowel diseases: evidence based literature review. World J Gastroenterol. 2016;22: 6296–317.
3. Gardenbroek TJ, Eshuis EJ, Ponsioen CI, Ubbink DT, D'Haens GR, Bemelman WA. The effect of appendectomy on the course of ulcerative colitis: a systematic review. Colorectal Dis. 2012;14:545–53.
4. Radford-Smith GL, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG, et al. Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. Gut. 2002;51:808–13.
5. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. N Engl J Med. 2001;344:808–14.
6. Cheluvappa R. Experimental appendicitis and appendectomy modulate the CCL20-CCR6 axis to limit inflammatory colitis pathology. Int J Colorectal Dis. 2014;29:1181–8.
7. Di Saverio S, Birindelli A, Kelly MD, Catena F, Weber DG, Sartelli M, et al. WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis. World J Emerg Surg. 2016;11:34.
8. Millet I, Alili C, Pages E, Curros Doyon F, Merigeaud S, Taourel P. Infection of the right iliac fossa. Diagn Interv Imaging. 2012;93:441–52.
9. Bass JA, Goldman J, Jackson MA, Gasior AC, Sharp SW, Drews AA, et al. Pediatric Crohn disease presenting as appendicitis: differentiating features from typical appendicitis. Eur J Pediatr Surg. 2012;22:274–8.
10. Hsu WF, Wu CS, Wu JM, Chung CS. Ileal Crohn's disease with perforation misdiagnosed as ruptured appendicitis: a case report. J Formos Med Assoc. 2013;112:652–3.
11. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy is followed by increased risk of Crohn's disease. Gastroenterology. 2003;124:40–6.
12. Stangl PC, Herbst F, Birner P, Oberhuber G. Crohn's disease of the appendix. Virchows Arch. 2002;440:397–403.
13. Oren R, Rachmilewitz D. Preoperative clues to Crohn's disease in suspected, acute appendicitis. Report of 12 cases and review of the literature. J Clin Gastroenterol. 1992;15:306–10.
14. Ho P, Law WL, Choy C, Chan GS, Chu KW. Granulomatous appendicitis progressing to Crohn's disease with bleeding complication. ANZ J Surg. 2003;73:554–6.
15. Han H, Kim H, Rehman A, Jang SM, Paik SS. Appendiceal Crohn's disease clinically presenting as acute appendicitis. World J Clin Cases. 2014;2:888–92.
16. Bronner MP. Granulomatous appendicitis and the appendix in idiopathic inflammatory bowel disease. Semin Diagn Pathol. 2004;21:98–107.
17. Frisch M, Gridley G. Appendectomy in adulthood and the risk of inflammatory bowel diseases. Scand J Gastroenterol. 2002;37:1175–7.
18. Kurina LM, Goldacre MJ, Yeates D, Seagroatt V. Appendicectomy, tonsillectomy, and inflammatory bowel disease: a case–control record linkage study. J Epidemiol Commun Health. 2002;56:551–4.
19. Frisch M, Johansen C, Mellemkjaer L, Engels EA, Gridley G, Biggar RJ, et al. Appendectomy and subsequent risk of inflammatory bowel diseases. Surgery. 2001;130:36–43.
20. Koutroubakis IE, Vlachonikolis IG, Kapsoritakis A, Spanoudakis S, Roussomoustakaki M, Mouzas IA, et al. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: case–controlled study in Crete. Dis Colon Rectum. 1999;42:225–30.
21. Firouzi F, Bahari A, Aghazadeh R, Zali MR. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: a case control study in Iran. Int J Colorectal Dis. 2006;21:155–9.
22. Kaplan GG, Pedersen BV, Andersson RE, Sands BE, Korzenik J, Frisch M. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. Gut. 2007;56:1387–92.
23. Reif S, Lavy A, Keter D, Broide E, Niv Y, Halak A, et al. Appendectomy is more frequent but not a risk factor in Crohn's disease while being protective in ulcerative colitis: a comparison of surgical procedures in inflammatory bowel disease. Am J Gastroenterol. 2001;96:829–32.
24. Kaplan GG, Jackson T, Sands BE, Frisch M, Andersson RE, Korzenik J. The risk of developing Crohn's disease after an appendectomy: a meta-analysis. Am J Gastroenterol. 2008;103:2925–31.
25. Montgomery SM, Pounder RE, Wakefield AJ. Smoking in adults and passive smoking in children are associated with acute appendicitis. Lancet. 1999;353:379.
26. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006;81:1462–71.
27. Riegler G, Caserta L, Esposito I, De Filippo FR, Bossa F, Esposito P, et al. Worse clinical course of disease in Crohn's patients with previous appendectomy. Eur J Gastroenterol Hepatol. 2005;17:623–7.
28. Caserta L, Filippo FR, Riegler G. Relationship between anamnestic evidence of appendectomy and onset and clinical course of Crohn's disease. Am J Gastroenterol. 2002;97:207–8.
29. Cosnes J, Seksik P, Nion-Larmurier I, Beaugerie L, Gendre J-P. Prior appendectomy and the phenotype and course of Crohn's disease. World J Gastroenterol. 2006;12:1235–42.
30. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. Nat Rev Gastroenterol Hepatol. 2016;13: 13–27.
31. Andersson RE, Lambe M. Incidence of appendicitis during pregnancy. Int J Epidemiol. 2001;30:1281–5.
32. Radford-Smith GL. What is the importance of appendectomy in the natural history of IBD? Inflamm Bowel Dis. 2008;14 Suppl. 2:S72–4.
33. Sahami S, Kooij IA, Meijer SL, Van den Brink GR, Buskens CJ, Te Velde AA. The link between the appendix and ulcerative colitis: clinical relevance and potential immunological mechanisms. Am J Gastroenterol. 2016;11:163–9.
34. Kooij IA, Sahami S, Meijer SL, Buskens CJ, Te Velde AA. The immunology of the vermiform appendix: a review of the literature. Clin Exp Immunol. 2016;186:1–9.
35. Øyri SF, Műzes G, Sipos F. Dysbiotic gut microbiome: a key element of Crohn's disease. Comp Immunol Microbiol Infect Dis. 2015;43:36–49.

36. Nagalingam NA, Lynch SV. Role of the microbiota in inflammatory bowel diseases. Inflamm Bowel Dis. 2012;18:968–84.
37. Cholapranee A, Ananthakrishnan AN. Environmental hygiene and risk of inflammatory bowel diseases: a systematic review and meta-analysis. Inflamm Bowel Dis. 2016;22:2191–9.
38. Gebbers JO, Laissue JA. Bacterial translocation in the normal human appendix parallels the development of the local immune system. Ann N Y Acad Sci. 2004;1029: 337–43.
39. Randal Bollinger R, Barbas AS, Bush EL, Lin SS, Parker W. Biofilms in the large bowel suggest an apparent function of the human vermiform appendix. J Theor Biol. 2007;249:826–31.