Review Article

Local Guidelines Regarding the Therapeutic and Diagnostic Management of Silent Crohn's Patients

Abstract

Crohn's disease is a chronic and progressive inflammatory disease of the gastrointestinal tract; whose symptoms recur and subside. This disease mainly affects the ileum and terminal colon and usually causes segmental, asymmetric, and transmural inflammation. Its clinical symptoms are variable, including diarrhea, abdominal pain, rectal bleeding, weight loss, and skin lesions. Due to the unknown causes of this disease, it is difficult to diagnose and manage it, especially in cases of silent Crohn's disease that does not have clear symptoms, and this has made the diagnosis of silent Crohn's a serious challenge for specialists. Unfortunately, today there is no specific guideline for the diagnosis and management of silent Crohn's disease, and the purpose of this research is to provide such a guideline. Two separate approaches were adopted: firstly, the evaluation of international articles (researchers' point of view) and the second part, the evaluation of the opinions of Iranian specialists active in the field of diagnosis and treatment of Crohn's patients (experts' point of view). in terms of Therefore, the opinions and discussions raised in international articles regarding diagnostic methods, clinical indicators, alternative methods in diagnosis, treatment methods, methods of monitoring treatment, and follow-up are reviewed, summarized, and compared with the opinions and performance of experts. Internally placed. According to experts' opinions, questions were designed based on scenarios of patients with special conditions. Then, the opinions of the country's most prominent internal medicine and gastroenterology specialists were recorded in person or by phone. Finally, the opinions were summarized and a proposed recommendation was created for the diagnosis of silent Crohn's disease. Mainly for the initial diagnosis of silent Crohn's depending on the condition of the disease, the diagnosis of aphthous lesions similar to Crohn's, in patients with high CRP and other inflammatory indicators or fecal calprotectin, the diagnostic recommendations were based on colonoscopy-based methods. Endoscopy (capsule) and especially ileocolonoscopy, fecal calprotectin assay, but no diagnosis is superior to histopathological findings. For treatment, steroid immunosuppressive drugs, mesalazine, budesonide, azathioprine, and sometimes surgery are useful. In cases where the intensity of the lesions is low, the use of non-steroidal anti-inflammatory drugs and acetylsalicylate recommended. However, there is often no need for therapeutic intervention and the lesions may have resolved spontaneously during follow-up. For the diagnosis of silent Crohn's disease, our proposed guideline can be of great help to physicians, as the most available tools are identified in diagnosis, disease monitoring, treatment, and follow-up. We recommend that the effectiveness of this guideline in the diagnosis and treatment of silent Crohn's disease be investigated by other researchers.

Keywords: *Anti-inflammatory drugs, calprotectin, ileocolonoscopy, inflammatory bowel disease, silent Crohn's disease*

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Introduction

Crohn's disease is a chronic inflammatory disease of the digestive system that can be progressive and lead to intestinal damage, especially the ileum and colon. The inflammation is usually segmental, asymmetric, and transmural. The most important symptoms of Crohn's disease include diarrhea, abdominal pain, rectal bleeding, and weight loss.[1-3]

There is no significant difference in Crohn's disease in adult men and women. Usually, Crohn's disease occurs more often in the second to fourth decade of life, and the chance of its occurrence is less in the ages of 50 to 60 years. The incidence of Crohn's disease is higher in developed countries than in developing countries, and it is higher in urban areas than in rural areas. According to Karami H (Iran, 2022), the average global incidence rate of Crohn's disease is 29 cases per 100,000 persons in the

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world, while the incidence rate in the Middle East is 5 cases per 100,000.[1,4]

Diagnosis of Crohn's disease relies on a combination of clinical symptoms, radiological findings, endoscopy, and histological indicators. Endoscopy is the gold standard for diagnosing Crohn's disease, in which segmental inflammation, aphthoid, longitudinal, and serpiginous ulcers are common findings. Serpiginous ulcers, which are scattered in the intestinal tissue with nodular edematous mucosa, create the so-called cobblestone pattern. Since mucosal recovery is considered an important therapeutic goal, colonoscopy plays an important role in monitoring the condition of the disease by the doctor. Also, colonoscopy plays an important role in monitoring the condition of colorectal neoplasia and in managing the complications of the disease such as strictures.[5,6]

Silent Crohn are generally defined as clinical conditions without obvious symptoms or signs. However, to detect silent cases of inflammatory bowel disease, the same classical evaluations should be performed first, which include serological measurements of inflammatory activity (such as C-reactive protein or CRP, erythrocyte sedimentation rate or ESR test, stool tests (to evaluate fecal calprotectin), radiologic imaging (eg, small bowel CT scan, MRI) and endoscopic evaluation (colonoscopy or esophagogastroduodenoscopy, capsule enteroscopy). Some measures, such as the Mayo Clinic Disease Activity Index, include both symptoms and objective observations (such as observations during endoscopy).[7-10]

No study to date has shown that silent inflammatory bowel disease is more common in a specific subgroup of inflammatory bowel disease, whereas one investigator (Sakata) and colleagues[11] showed that most groups with the silent inflammatory bowel disease that was examined by them were diagnosed with colon disease. In addition, most researchers do not consider the role of age and sex indicators for the rate of Crohn's disease, although a few studies also consider Crohn's disease or silent inflammatory bowel disease to be more common at older ages.[11-14]

The exact impact of silent Crohn is difficult to determine, but patients may appear to be at risk for several serious sequelae. Among these consequences are the occurrence of intra-abdominal fistulas, lack of micronutrients and their complications (for example, iron deficiency); anemia, osteoporosis, precancerous changes of the gastrointestinal tract or the occurrence of intestinal cancer, intestinal obstruction, and intra-abdominal fistula alone or together with enterocutaneous.[12-15]

Therefore, considering the importance mentioned about silent Crohn's disease, its symptoms, and the possibility of the disease progressing to more serious complications; in the present study, an attempt has been made to determine the treatment strategies and patient follow-up using experts' opinions. Let us reach a guideline and a common opinion.

Materials and Methods

As mentioned in the previous chapter, the lack of a suitable guideline for the diagnosis and management of silent Crohn's disease is the main problem of the present study. To develop an appropriate guideline, it is necessary to review and evaluate the views of experienced experts and active researchers in the field of diagnosis and treatment of silent Crohn's disease. Therefore, in the current research, our approach is to evaluate the views and performance of experts in this field. For this purpose, the current research method is divided into two main parts: one part is the evaluation of articles published by researchers at the international level and the other part is the evaluation of the opinions of Iranian experts active in the field of diagnosis and treatment of Crohn's patients.

The first part is an evaluation of articles published internationally

To evaluate the articles published at the international level, the most important sources were searched based on the inclusion criteria of studies in reliable scientific sources and reliable databases using appropriate keywords. The most important keywords used were:

1. Silent Crohn's disease.
2. Diagnosis of Crohn's disease.
3. Management of Crohn's disease.
4. Approach to diagnosing or treating Crohn's disease.

Criteria for selecting articles

The most important criteria for the selection of articles to be included in the study were the language of the article should be English or Persian, the subject of the article should be centered on inflammatory bowel disease (IBD), preferably IBD should be Crohn's type, preferably Crohn's disease should be categorized as silent Crohn's. The focus of the article is solely and minimally on diagnosis or treatment or both; the article is not about diagnostic molecular markers or future therapeutic targets and is focused on clinical rather than molecular message transmission pathways and findings that are currently unavailable or cannot be applied at present.

The most important aspects of attention in the articles

The most important aspects of attention in the articles included PICO criteria, and most of the articles that considered PICO indicators (patient or population, intervention, comparison, and outcome) were considered.

Specifically, clinical questions related to the management of lower GI bleeding were formulated in the PICO format. A systematic keyword search was performed in databases (including EMBASE, Ovid MEDLINE, and ISI Web of Science). For each article, it was determined

whether the PICO components are fully present in the text of the article or only a part of the PICO is included. Finally, the most relevant citations for each PICO question were identified and summarized in an Excel file.

Second part is an opinion of specialists and experts

In the present study, the pivotal arms in diagnosis and determining the therapeutic approach based on the opinion of experts included the following:

The first clinical case is a young asymptomatic patient who had an aphthous lesion similar to Crohn's disease during colonoscopy (especially in the terminal ileum in isolation), and in pathology, the evidence is in favor of Crohn's disease, but the patient has no clinical symptoms.

The second clinical case is a patient with mild and nonspecific symptoms of Crohn's, who had high calprotectin, but there were no special findings in colonoscopy and endoscopy, and there was no significant lesion in pathology.

The third clinical case: is a patient with mild and nonspecific symptoms of Crohn's disease, who had evidence of Crohn's disease in colonoscopy, but the evidence of Crohn's disease was not confirmed in pathology. Mild symptoms mean a CDAI of less than 220.

Each of the above assessment arms was presented to experts in the form of open questions and they were asked to answer the following three questions for each diagnostic arm:

a) Does the mentioned patient need more diagnostic procedures?
b) Does the mentioned patient need treatment, and if so, what medicine is used?
c) Which diagnostic measures and at what intervals do you suggest for the follow-up of patients?

The method of evaluating the opinions or recommendations of elites regarding the diagnosis and treatment of silent Crohn's patients.

Regarding the recommendations, it should be mentioned that each of the recommendations included an evaluation of the strength of the recommendation and the quality of the evidence based on the GRADE methodology[16] followed by a summary of the evidence. Therefore, the categories of recommendations were as follows:

1. Elite recommendation strength was graded as a strong recommendation when the evidence showed that the benefit of the intervention or treatment outweighed any risk.
2. When the risk–benefit ratio is uncertain, the power of elite recommendation is graded under the title of conditional recommendation.
3. If it seemed that further research could not add anything to the certainty of the evidence, the evidence was classified as high-grade evidence.
4. If further research was likely to have a significant impact on the evaluations and change the estimates, it would be marked with a moderate grade.
5. Evidence was categorized as low if further research was very likely to change the estimates.
6. Also, key concepts included terms that were not subject to the GRADE categorization process due to question structure or limited evidence. Most of the key concepts express expert opinion based on an external understanding of the available evidence.

After collecting the responses of experts, finally, the summary obtained from the review of the most important articles related to the research topic and the opinions of experts was used to formulate a suitable guideline for the diagnosis and management of silent Crohn's disease.

Results

First scenario

Asymptomatic patient who has an aphthous lesion similar to Crohn's disease in the colonoscopy examination, and pathology, the evidence is in favor of Crohn's disease, but there is no clinical or laboratory evidence of the disease.

Tables 1 and 2 presents the articles related to the first scenario, the results of which are explained below.

In a randomized single-center study based on the placebo-control model, Ingvar Bjarnason *et al*. (2019) examined 250 suspected Crohn's patients with the aim of to determine whether the probiotic Symprove can improve the quality of life of these patients and the condition Change intestinal inflammation in patients with silent or overt Crohn's disease? They have noted that by evaluating the changes in IBD status based on the Guyatt index, which included 4 aspects of the patients' lives, 32 patients (out of 250 patients) were identified as definite Crohn's patients. These researchers consider the evaluation of systemic symptoms, emotional and social functioning secondary measures, differences in clinical disease activity scores between active treatment and placebo, or changes in laboratory measures including fecal calprotectin useful in examining patients. They consider fecal calprotectin measurement helpful for diagnosing latent Crohn's disease. They consider probiotic use to reduce FCAL values and inflammation in latent Crohn's patients. However, the consumption of probiotics examined by him in patients with clear Crohn's disease did not cause a significant change.[17]

Benjamin Click *et al*. (2015) reported 351 asymptomatic Crohn's patients and mentioned that endoscopy, pathological, and radiological diagnosis can be used for routine diagnoses. However, measuring CRP is not very appropriate and will be useful when the inflammation in the mucous tissue is severe. FCAL measurement is not very useful and not available everywhere. The method of

Table 1: This table is in response to the first scenario, which includes an asymptomatic patient who has an aphthous lesion similar to Crohn's disease in colonoscopy, and in pathology, the evidence is in favor of Crohn's disease, but there is no clinical and laboratory evidence of the disease

Study	Publication year	Publication Type	Number of patients	Does the patient need more diagnostic measures? What action do you suggest?	Do the mentioned patients need treatment and if so, what medicine is used?	Which diagnostic measures and at what intervals do you suggest for the follow-up of patients?	conclusion
Ingvar Bjarnason, *et al*.[17]	2019	single-center, randomized, double-blind, placebo-controlled trial	250	Fecal Calprotectin helps to diagnose latent Crohn's disease	Probiotic use reduces calprotectin levels and inflammation in latent Crohn's patients, but it does not cause obvious changes in Crohn's patients.	Check fecal calprotectin	Probiotic diets can probably be used to treat Crohn's
Benjamin Click, *et al*.[13]	2015		351	Routine diagnoses include endoscopy, pathology and, radiological diagnosis. CRP measurement is not very suitable and will be useful when the inflammation in the mucous tissue is severe. Also, FCAL measurement is not very useful and is not available everywhere	Treatment of IBD is preferable to treatment of mucosal inflammation rather than symptom-based treatment.	Evaluation of objective criteria periodically (clinical examination), and paying attention to the identification of new subtypes of Crohn's disease can provide a unique diagnosis process for each individual.	CRP measurement is probably not useful for diagnosing latent Crohn's disease, but it can be helpful in clearing Crohn's disease. Corticosteroids and their combination therapy with sulfasalazine can be useful for the treatment of overt Crohn's disease
Cristina Bezzio *et al*.[18]	2017		51	Colonoscopy methods, endoscopic findings, histological findings. The diagnosis of Crohn's disease should be as definite as possible and not based only on mild and non-specific intestinal endoscopic lesions, which are often observed in healthy individuals.	Not mentioned	In the presence of suspicious clinical conditions and/or in the absence of definite criteria for the diagnosis of Crohn's disease, people with clear and non-specific ileitis should be closely monitored clinically. Repeat ileocolonoscopy may be helpful if signs and symptoms persist (or appear new).	To diagnose Crohn's disease, focus on imaging and histological methods
Hye-Sook Chang, *et al*.[19]	2010	A single-center retrospective study	148	It can be important to evaluate the clinical course and check isolated ileal terminal ulcers by colonoscopy in asymptomatic people.	Asymptomatic patients usually do not need treatment	At this time, we cannot make any definitive recommendations on how to evaluate and manage Crohn's patients.	Colonoscopy should be used to diagnose and follow up with silent Crohn's patients, and there is usually no need for special drug treatment to treat this group of patients.

Contd...

Table 1: Contd...

Study	Publication year	Publication Type	Number of patients	Does the patient need more diagnostic measures? What action do you suggest?	Do the mentioned patients need treatment and if so, what medicine is used?	Which diagnostic measures and at what intervals do you suggest for the follow-up of patients?	conclusion
Elizabeth L. Courville, *et al*.[20]	2009		29	In patients with clear ileitis, whose clinical symptoms appear in addition to histopathological findings, it indicates progress toward Crohn's disease; Therefore, histopathological findings are important along with clinical symptoms	Patients with asymptomatic ileitis do not require any inflammatory bowel treatment and show mild Crohn's disease. Only patient follow-up is recommended	Statistical average of about 3.5 years of follow-up; For follow-up, serological tests and molecular genetic tests, which are used to diagnose inflammatory bowel disease, are recommended.	Mild ileitis does not require treatment; Simply following up patients with serological tests is sufficient to rule out asymptomatic patients
Young Mo Kang, *et al*.[21]	2018		5	A Colonoscopy is required for diagnosis	Treatments should be considered if the patient shows signs of serious inflammation of the intestinal tissue; In such cases, tuberculosis may require treatment	The average follow-up time was 23.3 months	In patients whose colonoscopy evidence does not indicate serious inflammation, treatment is not required
Manasi Agrawal, *et al*.[22]	2021	Systematic review	6408	Diagnosis of the disease based on clinical symptoms, colonoscopy findings, and pathological and serological results should be given and then treatment should be carried out.	Asymptomatic cases do not require treatment.	Every 6 months, calprotectin excretion should be checked	Regarding the progression of ileitis to Crohn's disease, little information is available; Various diagnostic methods and various treatments are available for Crohn's disease.

diagnosing and differentiating the patient in his research was as follows. According to him, treatment based on symptoms is not very useful because it makes correct and timely diagnosis difficult and exposes the person to a high risk of disease complications. Therefore, for the treatment of IBD, instead of symptom-based treatment, the treatment of mucosal inflammation is preferable. They have recommended the use of immune system modulators (corticosteroids), opiates, or their combination for treatment; For biologic therapy, combination therapy is appropriate in individuals with elevated or normal CRP. In general, the discussion of these researchers summarizes that CRP measurement is probably not useful for diagnosing latent Crohn's disease, but it can be helpful in clearing Crohn's disease.[13]

Cristina Bezzio *et al*. (2017) have identified 5 Crohn's patients out of a total of 51 evaluated patients. Regarding the diagnosis of Crohn's disease, they have mentioned that colonoscopy methods, endoscopic findings, and histological findings are suggested methods. The diagnosis of Crohn's disease should be as definite as possible and should not be based only on mild and non-specific endoscopic lesions of the intestine, which are often observed in healthy individuals. Early diagnosis of Crohn's disease is important because it can lead to a better outcome for the disease. Also, they have advised to avoid overestimating Crohn's disease. In the presence of suspicious clinical conditions or the absence of definite criteria for the diagnosis of Crohn's disease, people with clear and non-specific ileitis should be strictly followed up clinically. In this situation, bowel ultrasound is not very useful (probably because of very superficial and insignificant ileal involvement). Conversely, ileocolonoscopy may be helpful if signs and symptoms persist (or appear new). They have not discussed the issue of treatment, but regarding the diagnosis, their conclusion

is to focus on imaging and histological methods to diagnose Crohn's disease.[18]

Hye-Sook Chang *et al*. (2010) reviewed 148 patients in a retrospective study, of which 62 patients had suspected and only 1 had clear Crohn's disease. Regarding their diagnosis, they describe the evaluation of the clinical course and examination of isolated ileal terminal ulcers in asymptomatic people as important. In addition, they consider it useful to follow up the patient with a colonoscopy. They mention that currently, we cannot provide any definitive recommendations on how to evaluate and manage Crohn's patients. Long-term follow-up studies are needed to answer these questions. Most of the lesions that are accidentally observed in asymptomatic people resolve without any treatment and usually do not require special drug treatment.[19]

Elizabeth L. Courville *et al.* (2009) have reviewed 29 patients with silent Crohn's disease and believe that in patients with clear ileitis, whose clinical symptoms appear in addition to histopathological findings, the disease will progress to Crohn's disease. Was. Therefore, histopathological findings are important for diagnosis along with clinical symptoms. In terms of treatment, patients with asymptomatic ileitis do not need any intestinal inflammation treatment and show mild Crohn's disease. Only patient follow-up is recommended. In the follow-up of patients with diagnostic methods, serious diseases may be discovered. Therefore, he concludes that the histopathological findings, along with the symptoms of the disease, indicate the patient's condition; Mild ileitis does not require treatment; Simply following up patients with serological tests in asymptomatic patients is sufficient.[20]

Young Mo Kang *et al*. (2018) reported the number of 5 patients with Crohn's disease and emphasized the colonoscopy method to diagnose their disease. They believe that there is no need for treatment in many asymptomatic patients who only have Crohn's symptoms in colonoscopy; Treatments should be considered if the patient shows signs of serious inflammation of the intestinal tissue; In such cases, tuberculosis may require treatment. In his research, the average follow-up time was 23.3 months. Therefore, the result of his discussion is that in patients whose colonoscopy evidence does not indicate serious inflammation, treatment is not needed.[21]

Manasi Agrawal *et al*. (2021) during a review research on patients with ileitis who were randomly identified and are likely to progress to Crohn's disease, mentioned that for the diagnosis of Crohn's, it is necessary to evaluate the following: clinical findings, biomarkers Blood samples, endoscopic findings, histology and imaging are important. to follow up with the patient, according to the results of the research, they have recommended that calprotectin excretion be checked every 6 months. Therefore, his discussion summarized that there is little information available about the progression of ileitis to Crohn's disease; There are various diagnostic methods and various treatments for Crohn's disease in the literature, and there is no procedural unity in diagnosis and treatment.[22]

Varun Mehta *et al*. (2016) have mentioned in a prospective study on 18 patients with silent Crohn's that the most important findings that should be looked for in the diagnosis of silent Crohn's are: chronic focal or spotty lymphoblastic inflammation, structure Irregular villi, crypt distortion, granuloma. Colonoscopy findings and histological diagnosis have been relatively accurate in most patients, and patients respond positively to treatment. They have suggested pentaza and budesonide for treatment. Finally, his opinion is that ileocolonoscopy should be used for diagnosis, and depending on the type and severity of inflammation, drug treatments can be suitable.[23]

Summary of the IBD research team of Isfahan Gastroenterology and Liver Research Center

Recommendation-1

1.1 Obtain a complete medical history again regarding medication use, especially NSAIDs, KCl, or recent chemotherapy

1.2 In the case of taking these drugs, they have recommended that the drug be discontinued or changed to another class.

1.3 To follow up with the patient and evaluate the treatment effect, they have also recommended that ileocolonoscopy be performed within 4-8 weeks after changing the treatment regimen and implementing the recommendations.

Recommendation-2

The patient should be examined again according to the history and other tests in terms of other differential diagnoses such as lymphoma, TB, Yersinia, salmonella, and vasculitis including Behcet.

Recommendation-3

Tests for anti-neutrophil nuclear antibody or ANCA, anti-Saccharomyces cerevisiae antibody or ASCA, anti-bacterial outer membrane protein C antibody or Anti-OMPC, and anti-flagellin type C/Bir1 antibody or Anti-CBIR should be performed. He has mentioned that these antibodies are mostly reported in non-Crohn-negative cases.

Recommendation-4

After rejecting the differential diagnosis of drugs and other diseases, the experts do not consider the need for drug treatment necessary.

Recommendation-5

If these patients need treatment according to the doctor's discretion, they should take 5-ASA, and if they take

5-ASA, they should only take one course of treatment and do not need maintenance treatment.

Recommendation-6

The recommendation of the experts was to repeat the colonoscopy and measure biomarkers 6-12 months later.

Second scenario:

A patient with mild and non-specific Crohn's symptoms, who had high calprotectin, but there was no special point in colonoileoscopy, and there was no special lesion in pathology:

Tables 3 and 4 is in response to the questions of the second scenario, whose detailed description is described below:

Cristiana Sequeira, *et al*. (2022) reported a patient who had Crohn's disease (a rare case). They have noted that the use of calprotectin as a screening test to detect inflammation of the small intestine and the need for a sequential approach (continuous measurement and evaluation) in diagnosing the pathological cause of small intestine involvement is recommended. Also, capsule endoscopy of the small intestine has a high diagnostic sensitivity for diagnosing this group of patients (Crohn's disease of the jejunum). The patient in question was treated with adalimumab and his condition was followed up for 1 year. In his opinion, the presence of serious symptoms, infectious agents, and neoplasms, which are necessary to prove the results of histopathological evaluation, should be considered by the doctor during follow-up.[24]

Ming Hui Chang *Et al*. (2014) showed in a case-control study that fecal calprotectin can be used to differentiate inflammatory bowel disease from inflammatory bowel syndrome. Fecal calprotectin can be considered a useful marker for the diagnosis and follow-up of patients with inflammatory bowel disease. Therefore, the discussion of these researchers concludes that: Fecal calprotectin

Table 2: Summary of recommendations regarding the first scenario

Question	Scenario	Power of recommendation	Quality of Evidence
Question	The first scenario: the advice of the elite regarding that A young asymptomatic patient who had an aphthous lesion similar to Crohn's disease in the colonoscopy examination (especially in the terminal ileum in isolation) and pathology, the evidence is in favor of Crohn's disease, but the patient has no clinical symptoms.	Power of recommendation	Quality of evidence
Does the mentioned patient need more diagnostic measures?	Regarding the diagnostic procedure, a complete medical history should be taken from the patient, especially NSAID, KCl, or recent chemotherapy, and if he is taking the abovementioned items, he should be advised to stop the medication or change to a new class. Do it again To follow up with the patient and evaluate the treatment effect, it is recommended to repeat the ileocolonoscopy for three months after changing the treatment regimen and implementing the recommendations.	Conditional recommendation	Moderate quality evidence
	According to the history and other tests, the patient has been examined for other differential diagnoses such as lymphoma, TB, Yersinia, salmonella, and vasculitis, including Behcet's disease.	Conditional recommendation	Moderate quality evidence
	Examining tests of anti-neutrophil nuclear antibody or ANCA, anti-Saccharomyces cerevisiae antibody or ASCA, anti-bacterial outer membrane protein C antibody or Anti-OMPC, and anti-flagellin type C/Bir1 antibody or Anti-CBIR, which These antibodies are mostly reported negative in non-Crohn cases	Conditional recommendation	Low-quality evidence
Does the mentioned patient need treatment, and if so, what medicine is used?	After rejecting the differential diagnosis of case A (drug and other diseases), most of the team members have recommended not to treat the patient, and not treating the patient is preferred over drug treatment.	Conditional recommendation	Low-quality evidence
	If these patients need treatment according to the doctor's discretion, they should take 5-ASA, and if they take 5-ASA, they should only take one course of treatment, and no maintenance treatment is required.	Conditional recommendation	Low-quality evidence
Which diagnostic measures and at what intervals do you recommend for the follow-up of patients?	It is recommended to repeat the colonoscopy and measure biomarkers 6-12 months later	Conditional recommendation	Low-quality evidence

Table 3: This table is in response to the second scenario, which includes a patient with mild symptoms (CDAI <220) and non-specific Crohn's disease, who had high calprotectin, but there was no special point in the colonoileoscopy, and there was no special lesion in the pathology

Study	Publication year	Publication Type	Number of patients	Does the patient need more diagnostic measures? What action do you suggest?	Do the mentioned patients need treatment and if so, what medicine is used?	Which diagnostic measures and at what intervals do you suggest for the follow-up of patients?	conclusion
Ming Hui Chang, *et al*.[25]	2014	Case-control	162	Excretory calprotectin assay is a more direct and useful diagnostic marker than CRP and ESR for the diagnosis of intestinal inflammation in patients with inflammatory bowel disease.	Not mentioned.	Excreted calprotectin can be considered a useful marker for the diagnosis and follow-up of patients with inflammatory bowel disease	Calprotectin is a more sensitive marker than CRP and ESR for the diagnosis and differentiation of inflammatory bowel disease
D.R. Gaya, *et al*.[27]	2005	Cross sectional	37	Excretory calprotectin measurement has several advantages in diagnosing and evaluating the status and activity of Crohn's disease.	Not mentioned.	For follow-up of Crohn's patients using 99mTc-HMPAO imaging (Ceretec) in the method Radiolabeled white cell scanning (WCS) Used. Several studies have indicated the high diagnostic value of this method	Excretory calprotectin assay is a safe method with high sensitivity to detect intestinal inflammation in Crohn's patients

is a sensitive and useful indicator for the differentiation of inflammatory bowel disease and can be a suitable marker for identifying these cases. Calprotectin is a more sensitive marker than CRP and ESR for diagnosing and differentiating inflammatory bowel disease.[25]

D. R. Gaya *et al*. (2005) in a cross-sectional study on 37 Crohn's patients, examined the measurement of excretory calprotectin and stated that the measurement of this index has several advantages in diagnosing and evaluating the status and activity of Crohn's disease. This test is inexpensive, non-invasive, directly performed, has good diagnostic sensitivity, and requires a small amount of stool that can be easily sent to the laboratory.[26]

Henrik Hovstadius *et al*. (2021) conducted a cross-sectional study on 585 colonoscopy patients, 202 of whom had calprotectin levels of more than 50 micrograms per gram of stool despite a normal colonoscopy. The drugs prescribed for the patients in this study included NSAIDs, acetylsalicylate, and proton pump inhibitors. In patients with normal colonoscopy results, calprotectin measurement during 3 years of follow-up did not indicate an increased risk of gastrointestinal disease progression. Therefore, his emphasis is that the existence of a serious disease can be rejected in patients who have normal colonoscopy findings despite having calprotectin excretion.[27]

In a report on Crohn's disease, Priyanka Ramphul *et al*. (2016) noted that periodic measurements of calprotectin allow the identification of patients at high risk of intestinal wall damage, abscess formation, and stricture formation. They have intestines. These researchers believe that considering the cutoff point of 250 micrograms per gram of stool, calprotectin excretion has 90% diagnostic sensitivity and 76% diagnostic specificity for silent Crohn's disease. Therefore, he concludes that calprotectin is useful for diagnosing intestinal inflammation and the complications caused by this inflammation; It has high sensitivity and diagnostic specificity in diagnosing Crohn's disease.[28]

Summary of the IBD research team of Isfahan Gastroenterology and Liver Research Center.

Recommendation-7

A complete medical history and concomitant diseases, especially chronic diarrhea, vasculitis should be taken from the patient.

Recommendation-8

Examination of the small intestine should be done with MR-Enterography or CT-Enterography.

If the involvement of the small intestine is seen by the imaging method, sampling should be done through

Table 4: Summary of recommendations regarding the second scenario

Question	Scenario	Power of Recommendation	Quality of Evidence
Question	The second scenario: the advice of the elite regarding that A patient with mild and non-specific symptoms of Crohn's, who had high calprotectin, but there was no special point in colonoscopy and eososcopy, and there was no significant lesion on pathology.	Power of recommendation	Quality of evidence
Does the mentioned patient need more diagnostic measures?	A complete medical history and concomitant diseases, especially chronic diarrhea, vasculitis should be taken from the patient	Conditional recommendation	Low-quality evidence
	Examining the small intestine with MR- Enterography or CT- Enterography methods	Conditional recommendation n	Moderate quality evidence
Does the mentioned patient need treatment, and if so, what medicine is used?	If the involvement of the small intestine is seen by the imaging method, sampling should be done through enteroscopy.	Conditional recommendation n	Moderate quality evidence
	If the involvement of the small intestine is proven through imaging and pathology, it is recommended that the patient be treated with anti-TNF or budesonide.	Conditional recommendation n	Moderate quality evidence
	If small bowel involvement is proven by imaging and pathology, the recommendations are against the use of 5-ASA; That is, it is recommended not to use 5-ASA.	Conditional recommendation n	Moderate quality evidence
Which diagnostic measures and at what intervals do you recommend for the follow-up of patients?	Recommend repeat colonoscopy along with measurement of fecal calprotectin, CRP, and ESR during the next 6-12 months.	Conditional recommendation	Low-quality evidence

Table 5: Summary of recommendations regarding the third scenario

Question	Scenario	Power of Recommendation	Quality of Evidence
Question	The third scenario: the advice of the elite regarding that A patient with mild and non-specific symptoms of Crohn's disease who had evidence of Crohn's disease in colonoscopy, but the evidence of Crohn's disease was not confirmed in pathology.	Power of recommendation	Quality of evidence
Does the mentioned patient need more diagnostic measures?	MR- Enterography or CT- Enterography is recommended	Conditional recommendation	Low-quality evidence
	It is recommended that Lam pathology be read by a second skilled pathologist	Strong recommendation	Moderate quality evidence
Does the mentioned patient need treatment, and if so, what medicine is used?	If the presence of Crohn's is not confirmed in the pathology and the patient has mild symptoms, most of the elite team members have recommended not to treat with drugs.	Conditional recommendation	Low-quality evidence
Which diagnostic measures and at what intervals do you recommend for the follow-up of patients?	Check fecal calprotectin every 6-12 months	Strong recommendation	Low-quality evidence

enteroscopy. if the conflict is proven, the second recommendation should be implemented.

Another recommendation is that if small bowel involvement is proven by imaging and pathology, it is recommended not to use 5-ASA. (No new recommendation).

Recommendation-9

The recommendation of experts is to repeat the colonoscopy along with measurement of fecal calprotectin, CRP, and ESR during the next 6-12 months.

Third scenario:

A patient with mild and non-specific Crohn's symptoms had evidence of Crohn's disease in colonoscopy, but definitive evidence of Crohn's disease was not confirmed in pathology [Table 5].

Charlotte Delattre *et al*. concluded that regarding the differential diagnosis of aphthous lesions of the lower gastrointestinal tract, before confirming Crohn's disease, other diseases such as vasculitis should be taken into

consideration, and aphthous lesions are not specific for Crohn's diagnosis.[29]

T Matsumoto *et al*. mentioned that Aphthous lesions have been considered as one of the diagnostic lesions in Crohn's diagnosis. The location of aphthous lesions (only colon, only terminal ileum, or a combination of colon and terminal ileum) and their number can also be effective in the patient's prognosis.[30]

The conclusion of the IBD research team of Isfahan Gastroenterology and Liver Research Center was as follows

Recommendation-10

Regarding the diagnostic procedure, MR-Enterography or CT-Enterography is recommended.

Recommendation-11

Examination of pathology slides by a skilled pathologist was the second.

Regarding whether the patient needs treatment for this patient and what medicine should be taken:

Recommendation-12

It is recommended that if the presence of Crohn's is not confirmed in the pathology and the patient has mild symptoms, there is no need for treatment.

Regarding the follow-up of such a disease and follow-up intervals:

Recommendation-13

Fecal Calprotectin evaluation and colonoscopy are recommended 6 to 12 months later.

Discussion

Since silent Crohn's disease does not have characteristic symptoms, we expect a challenging diagnostic process for it. Other diseases such as inflammatory bowel diseases, both genetic and non-genetic, transient infections, and inflammations close to the digestive tissues, can all be related to the possibility of Crohn's disease, until the diagnosis is reached certainly, there is a wide range of diagnoses or diagnostic challenges in front of the clinicians. The lack of specificity of clinical symptoms or even paraclinical findings is an ambiguous issue for the diagnosis of silent Crohn's disease.[1-4]

In the current research, we have tried to use the information available in valid scientific articles and the opinions of elites to reach a conclusion based on which a suitable approach can be found in the diagnosis and management of silent Crohn's disease. In this regard, we reviewed related articles, diagnostic and treatment methods and solutions, care, and follow-up of patients. Also, we got the help of experts in the diagnosis and treatment of Crohn's patients to benefit from their valuable opinions and experiences in the diagnosis and management of silent Crohn's disease and to determine what forward-looking strategies can be used in the management of Crohn's disease treatment as a guideline.

In the previous chapters, we presented detailed and comprehensive opinions and recommendations of various diagnostic and treatment teams whose results were published in articles or had valuable experiences in the field of silent Crohn's disease.

In this research, three main groups of patients were defined, the first group included patients who had aphthous lesions similar to Crohn's disease in the colonoscopy examination, and the pathology, the evidence was in favor of Crohn's disease, but they did not have convincing clinical and laboratory evidence. The most important recommendations from the articles were:

1. Taking advantage of the patient's history, and family history of gastrointestinal diseases, using screening methods such as fecal calprotectin, CRP, ESR, lactoferrin
2. Use of more definitive and invasive diagnostic methods such as colonoscopy, endoscopy, biopsy and pathology diagnosis, ileocolonoscopy, capsule endoscopy of the small intestine
3. Evaluation of other possible causes and diseases such as tuberculosis, and infectious inflammations
4. Evaluation and attention to the type of lesions and inflammations in imaging or pathology diagnoses

For the treatment of patients included in the first scenario, there are also articles on drug treatments such as oral mesalamine, topical mesalamine, corticosteroids, thiopurines, methotrexate, TNF inhibitors, corticosteroids followed by vedolizumab, or corticosteroids followed by azathioprine, 5-aminosalicylate. have recommended pentaza and budesonide.[7,31,32] Or even in research, the use of probiotics has been recommended.[33,34]

For this scenario, the summary of the elite recommendations was:

1. Performing ileocolonoscopy, and a complete history of the use of various drugs and chemotherapy
2. Changing the drug regimen and following up with the patient with ileocolonoscopy after one
3. Check for other differential diagnoses according to the symptoms and findings
4. Evaluation of ANCA, ASCA, Anti-OMPC, etc.
5. If the symptoms are not severe and the disease is not progressive, no special treatment is needed; If drug treatment is needed, 5-ASA can be used for a treatment period.
6. Colonoscopy can also be performed to follow up such patients.

Regarding the diagnosis of silent Crohn's disease in the second scenario: for screening, articles have suggested the use of calprotectin, while experts have suggested

MR-Enterography or CT-Enterography methods. In this regard, it can be said that calprotectin can only be used in diagnoses with low probability, and therefore, for a doctor who intends to diagnose Crohn's disease, and for whom microbial or parasitic inflammations, for example, are not considered, it is better than imaging methods. It is safer to use. Therefore, to diagnose silent Crohn's, the opinion of experts is preferred. In any case, the description and family history of the patient are a part of any usual process of taking a patient's history, and the explanation is clear and does not need to be discussed.

In this regard, articles and experts agree. Therefore, 5-ASA can be prescribed for the treatment of this group of patients on the condition that the small intestine is not involved, and in case of small intestine involvement, Anti-TNF or budesonide, NSAIDs can be prescribed.

In this case, the articles and elites have a common opinion and it is recommended to measure fecal calprotectin, CRP, and ESR or lactoferrin within 6-12 months.

Regarding the third scenario, a patient with mild and non-specific symptoms of Crohn's disease who had evidence of Crohn's disease in colonoscopy but definitive evidence of Crohn's disease was not confirmed in pathology, the summary of recommendations of the articles are:

1. Diagnosis by colonoscopy and esophagogastroduodenoscopy, evaluation of family history of intestinal diseases, and detailed clinical history
2. Treatment is not needed unless the disease is progressive.

For this scenario, the summary of the elite recommendations was:

1. Examining the patient with MR- Enterography or CT- Enterography
2. Examining the pathology slide by a second skilled pathologist
3. In the absence of serious symptoms, treatment is not required
4. For patient follow-up, Fecal Calprotectin and colonoscopy are recommended 6 to 12 months later.

Conclusions

In the current research, an attempt has been made to reach a basic summary by examining the diagnostic, therapeutic, and management trends of silent Crohn's disease in the articles and opinions of elites so that appropriate guidelines can be proposed. However, if the evidence at the patient's bedside, family history, or other findings indicate that more serious intervention measures are necessary for the patient, these measures should not be withheld from the patient at the appropriate time. Let's not forget that in applying these recommendations, neither exaggerating the disease nor ignoring important evidence and symptoms is useful for patient management.

However, it should be noted that the recommendations that we consider in the present study as a suitable guideline for the management of silent Crohn's disease, should be implemented in the hospital and the feedback should be determined during subsequent studies. Hence, it is recommended that treating physicians implement this guideline, test its quality and shortcomings, and improve it during subsequent studies if necessary.

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Conflicts of interest

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