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Editorial

Subclinical Inflammation in Crohn's Disease

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1. Introduction

Crohn's disease is one of the major types of inflammatory bowel disease (IBD), and results in chronic progressive inflammation of the gastrointestinal tract [1]. Treatment for several decades has centred on controlling inflammation and trying to provide symptomatic relief/benefit to patients. With an increasing number of treatment options and a greater move towards earlier initiation of effective therapies, clinical management has rapidly advanced in Crohn's disease. However, despite this progress, many patients have ongoing subclinical inflammation, which can be persistent for several years and often results in either minimal or no symptoms for patients [2]. However, there is emerging evidence that ongoing subclinical inflammation can drive structural bowel damage and complications [3]. In this article, we will cover contemporary approaches for detecting subclinical inflammation, the evidence base for targeting subclinical inflammation, potential proactive therapeutic strategies, and offer insights into future research directions.

2. Scale of Problem

The transmural and "skipping" nature of Crohn's disease, as well as the well-recognised disconnect between symptoms and objective disease activity, remain some of the principal reasons that subclinical inflammation can be hard to detect. Since the disease can affect the full thickness of the bowel and extend into the mesentery, inflammation can persist deep within the intestinal wall even when the mucosa appears endoscopically healed [1]. This means that aiming for endoscopic remission alone may allow ongoing transmural activity to remain undetected. The multinational IBD PODCAST study provided insights into the scale of this problem, with more than 50% of patients reporting suboptimal disease control [2]. A large proportion of these patients had ongoing active subclinical inflammation which typical symptom-based follow-up appointments had failed to capture.

3. Detecting Subclinical Inflammation

One of the major challenges of Crohn's disease management has been the recognition that symptoms correlate poorly with underlying tissue inflammation. Given the realisation that symptom-based monitoring is insufficient in Crohn's disease, there has been much focus on what would constitute appropriate, patient-centred, and accurate objective measures of disease activity.

4. Biochemical Activity

Serum C-reactive protein (CRP) is a widely accessible marker of systemic inflammation. However, its utility is limited by CRP-negative phenotypes, with several patients not mounting a CRP response even in the presence of widespread endoscopic activity. As a result, faecal calprotectin (FCAL) has emerged and, in many settings, has become the non-invasive monitoring tool of choice, as it correlates more accurately with endoscopic inflammation than CRP. Normalisation of FCAL has also been associated with reduced disease progression [3].

One challenge of using both CRP and FCAL has been an appreciation that these tests may have variable sensitivity for different phenotypes of Crohn's disease. Approximately one third of patients with Crohn's disease do not mount a CRP response, even in the context of moderate or severe inflammation [4]. Although FCAL is a more sensitive marker, its performance has been shown to be higher for detecting colonic inflammation than for terminal ileal or proximal small bowel inflammation [5]. Therefore, although somewhat reassuring, abnormal CRP and FCAL do not fully exclude active inflammation in patients who otherwise have symptoms and signs that might be consistent with ongoing disease activity. Moreover, uncertainties regarding cutoff values still exist e.g., whether clinicians would be reassured with values of <250 µg/g or <50 µg/g for subclinical inflammation. In parallel, there has been growing understanding that longitudinal FCAL response may be a better marker than any isolated value. Therefore, further studies are still required to accurately quantify and evaluate appropriate FCAL cutoff values and longitudinal changes/trajectories.

5. Endoscopic Activity

Ileocolonoscopy remains the standard for detecting ongoing mucosal inflammation, including patients who are in remission. Notably, achieving endoscopic remission has been associated with a reduction in long-term disease pro-

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gression of Crohn's disease [6]. Although evidence is still emerging, it appears that even low levels of ongoing endoscopic activity are associated with worse outcomes for patients [7]. However, a major limitation of ileocolonoscopy is that it can only reach the terminal ileum; therefore, it may miss ongoing disease activity in more proximal bowel segments.

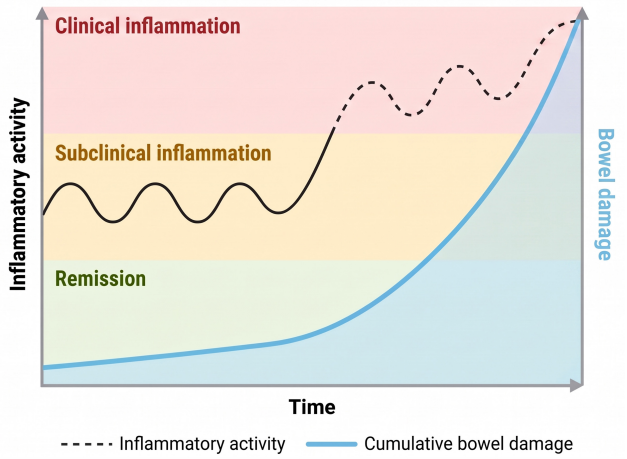


Fig. 1. Subclinical inflammation and progressive disease complications. Schematic representation of the natural history of Crohn's disease in the absence of proactive therapeutic intervention. Created with BioRender (https://app.biorender.com).

6. Transmural Activity

Magnetic resonance imaging (MRI) has historically been the main cross-sectional modality in Crohn's disease, given that it offers transmural assessment without the drawback of ionising radiation. However, MRI can be of limited availability in many countries and carries other disadvantages such as needing poorly palatable oral contrast. With regard to the colon, it also has a reduced sensitivity for superficial mucosal inflammation. In this regard, intestinal ultrasound (IUS) has emerged as a simple and non-invasive alternative for identifying transmural inflammation, and there is emerging evidence that it is able to detect subtle changes, consistent with ongoing subclinical activity [8].

7. Gastrointestinal Impact of Subclinical Inflammation

Persistent inflammatory activity driving subclinical disease, if left unchecked, can lead to cumulative and often irreversible damage to the bowel wall (Fig. 1). This typically leads to fibrogenesis and stricture formation, and then downstream penetrating complications such as abscesses and fistulae. Indeed, a prospective real-world study showed that subclinical persistent inflammation was an independent risk factor for development of Crohn's disease complications [9]. Persistent inflammation was also found to be common in asymptomatic patients [9], illustrating just why detection and management of subclinical inflammation might be important to drive better gastrointestinal outcomes for patients with Crohn's disease.

8. Systemic Impact of Subclinical Inflammation

The consequences of unresolved inflammation are not confined to the gut. Subclinical inflammatory activity has also been linked to a variety of extraintestinal manifestations (EIMs), including a key role in driving spondyloarthritis. In addition to joint manifestations, chronic inflammation in Crohn's disease has also been strongly associated with a prothrombotic state, with a near two-fold increase in the risk of venous thromboembolism (VTE) with active disease [10]. This VTE risk includes peripheral deep vein thrombosis, pulmonary embolisms, and central cerebral venous sinus thrombosis. There is emerging evidence that extends vascular risk even to arterial disease, with high rates of major cardiovascular events such as strokes and myocardial infarctions being reported particularly in patients with active disease [11]. It has been proposed that subclinical inflammation might affect production of microbial metabolites, which can then drive plaque formation and vascular inflammation. However, data on arterial risk is still lacking, and thus further prospective studies are needed to help quantify this relationship and determine how significant the influence of subclinical inflammation might be.

Beyond vascular risk, subclinical inflammation has also been associated with mental health manifestations including higher levels of depression, anxiety, and fatigue for patients [12]. Poorer sleep quality has also been noted in patients with ongoing inflammatory disease activity, with some association that poor sleep quality itself might also worsen inflammatory disease activity. However, it remains unclear to what extent these mental health manifestations are attributable to subclinical inflammation, as they may also occur in patients with Crohn's disease who have no evidence of ongoing inflammation and whose disease is otherwise well controlled.

9. Proactive Therapeutic Strategies

Historically, most management strategies in Crohn's disease have been reactive, typically in response to patient-reported symptoms. However, there has been an increasing shift towards early and proactive management to ensure better outcomes for patients. One of the major advances in recent years has been a move towards early and effective treatment from the point of diagnosis to ensure a more durable remission before the damage accumulates [13,14]. The second principle is proactive monitoring after treatment initiation. This is where therapy is altered in response to objective evidence of inflammation rather than waiting for symptoms to emerge. In this regard, the CALM trial es-

tablished that a proactive approach, of acting on raised inflammatory biomarkers, even in the absence of symptoms, resulted in better outcomes for patients [15]. This proactive approach is now widely recommended, and collectively, early detection and early treatment offer a practical method to tackle subclinical inflammation.

10. Future Research Directions

Emerging molecular markers such as transcriptomic, proteomic, and microbial signatures or digital data from wearable devices may enable the detection of deeper levels of healing and eventually identify persistent subclinical inflammatory pathways even beyond the objective measures of disease activity described above. However, future research studies will need to demonstrate improved performance over current clinical tools such as FCAL, endoscopy, or imaging. It is also important that definitions for the optimal biomarker thresholds and how often to perform monitoring are clearly defined, in order to detect (and treat) subclinical inflammation.

11. Conclusion

In summary, subclinical inflammation in Crohn's disease is far from a benign state, even though patients may only have minimal symptoms or be asymptomatic. Subclinical inflammation contributes to future disease progression and potential structural damage. The inflammatory process in subclinical inflammation can drive not only structural bowel damage but also systemic complications, which can lead to long-term impact and disability for patients. Effective management for subclinical inflammation requires looking beyond clinical symptoms alone and seeking to normalise more objective targets, including aiming for biomarker normalisation, endoscopic healing and/or transmural healing. Early detection and early treatment appear to be the highly effective strategies to manage subclinical inflammation, and by placing greater emphasis on this, it is hoped that more optimal outcomes can be delivered and quality of care can be improved for a large number of people living with Crohn's disease.

Key Points

• Subclinical inflammation is common in patients living with Crohn's disease, even for patients reporting minimal or no symptoms.

• There are gastrointestinal complications of ongoing and uncontrolled subclinical inflammation, including risks of structural complications and Crohn's disease progression.

• There are also several potential systemic associations of subclinical inflammation in Crohn's disease, including extraintestinal manifestations affecting joints and vasculature, and the presence of mental health symptoms.

• Proactive therapeutic strategies have emerged to tackle subclinical inflammation, notably early detection and early treatment, including use of tight control monitoring strategies.

• Future research should seek to establish optimal monitoring intervals, tools and treatment goals for patients with subclinical inflammation in Crohn's disease.

Abbreviations

CRP, C-reactive protein; EIMs, extraintestinal manifestations; FCAL, faecal calprotectin; IBD, inflammatory bowel disease; IUS, intestinal ultrasound; MRI, magnetic resonance imaging; VTE, venous thromboembolism.

Availability of Data and Materials

Not applicable.

Author Contributions

PK and NMN made substantial contributions to conception and design of this article. PK wrote the initial manuscript draft. NMN provided additional critical review and input. Both authors contributed to revising the manuscript critically for important intellectual content. Both authors have read and approved the final version of this manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

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