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Crohn's Disease and Periodontal Manifestations: A Review of Current Evidence

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Abstract

Objective: Crohn's disease (CD) is a chronic inflammatory bowel condition of unknown cause, with rising prevalence. Oral manifestations, ranging from 0.5% to 80% of cases, are frequently associated with the disease. This review examines the association between CD and periodontal disease, underlying mechanisms, and therapeutic strategies to improve oral and systemic health.

Methods: A review was conducted using the keywords ((Crohn's disease OR inflammatory bowel disease) AND periodontal) across multiple databases. Relevant studies were analyzed to investigate the relationship between CD and periodontal health and identify effective treatments.

Results: Evidence suggests a bidirectional relationship between CD and periodontal disease. CD patients exhibit microbial dysbiosis, with significant similarities between oral and intestinal microbiomes. Elevated levels of cytokines like TNF-α, IL-1β, and IL-10 in oral fluids are correlated with poor periodontal outcomes (e.g., pocket depth, attachment loss) and increased CD severity. CD patients are about three times more likely to develop periodontal disease [OR = 3.64 (95% CI: 2.33–5.67)] and nearly eight times more prone to early implant failure [OR = 7.95 (95% CI: 3.47–18.24)]. These findings emphasize the need for further large-scale studies to elucidate these interactions and refine management.

Conclusions: Effective CD management requires a multidisciplinary approach, combining pharmacotherapy, nutrition, psychological support, and regular monitoring. Anti-TNF agents are effective but need careful supervision. Dentists play a critical role in identifying oral manifestations as early indicators of CD. Collaborative care between medical and dental professionals is vital for early diagnosis, timely intervention, and improved patient outcomes.

Keywords: Crohn's disease; Periodontal disease; Biological agents; Microbiome; Cytokines

Introduction

Crohn's disease (CD) is one of the two primary forms of inflammatory bowel disease (IBD), alongside ulcerative colitis (UC) [1]. It is a chronic inflammatory condition of the gastrointestinal tract (GIT) characterized by alternating periods of exacerbation and remission [2]. CD can affect any part of the GIT, from the oral cavity to the anus, but most commonly involves the small intestine and terminal ileum. Histopathologically, CD is distinguished

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by granulomatous inflammation [3], which can affect all layers of the intestinal wall (transmural inflammation), unlike UC, which is confined to the intestinal mucosa [4,5].

The pathogenesis of CD is multifactorial and complex, with its precise etiology yet to be fully elucidated. A combination of genetic, microbial, environmental, immunological, and psychological factors is believed to contribute to the onset and progression of the disease. Among infectious agents, Mycobacterium avium ssp. paratuberculosis (MAP) has been extensively studied as a potential trigger, but its exact role remains controversial [6]. Genetic predispositions, particularly mutations in the CARD15/NOD2 gene, are among the most well-documented risk factors, impairing innate immune responses to microbial stimuli [7]. Other genetic abnormalities linked to CD involve disruptions in autophagy and immune regulation [8]. Environmental factors such as smoking-recognized as a significant aggravating factor-are associated with more severe disease progression and an increased likelihood of surgical intervention [9]. Additionally, gut microbiota imbalances (dysbiosis) play a critical role in initiating inflammatory responses, with dietary patterns, particularly Western diets high in processed foods and low in fiber, considered a contributing factor.

From an immunological standpoint, CD is characterized by an excessive immune response to normal gut flora, resulting in chronic inflammation. This dysregulated response is driven by overactivity of Th1 cells and heightened production of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), a key mediator in the inflammatory cascade [10,11]. The success of biological therapies targeting TNF-α underscores the centrality of this mechanism in CD pathophysiology [12]. Psychological factors such as stress, anxiety, and depression [13], while not direct causes, are known to exacerbate symptoms, impact quality of life, and contribute to disease progression.

The diagnosis of CD requires a multimodal approach that integrates clinical, endoscopic, radiologic, and histopathological assessments [14,15]. Colonoscopy and endoscopy are gold-standard techniques, allowing direct visualization of the mucosa and enabling biopsy for histopathological confirmation. Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) offer detailed imaging of the intestinal wall and surrounding structures. While CTE provides high accuracy, concerns about radiation exposure make MRE a safer option for long-term monitoring. Capsule endoscopy is invaluable for assessing small intestine pathology but lacks biopsy capability. Non-invasive methods like intestinal ultrasound, hematological markers (e.g., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]), and stool tests offer supplementary diagnostic information but lack disease specificity.

CD has a global distribution, with the highest incidence and prevalence rates reported in developed countries. A 2017 systematic review estimated a prevalence of 0.32% in Europe and North America, with rates stabilizing or declining in these regions [16]. Conversely, since 1990, developing nations have experienced an 11% increase in incidence, likely linked to urbanization and Westernized dietary practices that disrupt gut microbiota and immune homeostasis. While CD can occur at any age, it is most frequently diagnosed in young adults between 15 and 30 years, with a secondary, smaller incidence peak between 50 and 70 years. The disease affects men and women equally, though some studies suggest a slightly higher prevalence in women.

Objective

The present paper aims to review the existing literature on the relationship between CD and oral, specifically periodontal, manifestations, emphasizing their potential role as diagnostic indicators of the disease. The paper presents clinical findings related to the intraoral manifestations of CD and discusses the diagnostic approaches and therapeutic strategies essential for the holistic care of patients. Special attention is given to the role of biological agents, recognized as the most modern and effective therapeutic practice. The overall goal is to improve understanding of the connection between CD and periodontal issues to facilitate early diagnosis, enhance patient management, and ultimately improve the quality of life for affected individuals.

Materials and Methods

A comprehensive literature search was conducted across several databases, including Medline (PubMed), CENTRAL (Cochrane Library), Cochrane Database of Systematic Reviews (Cochrane Library), Scopus, and EMBASE (Elsevier), up to August 2024. The search was performed using the following combination of keywords: ((Crohn's disease OR inflammatory bowel disease) AND periodontal).

Clinical features of Crohn's disease

CD can manifest at any point along the GIT, with symptoms varying depending on the affected area. When the small intestine is involved, the primary symptoms include mild abdominal pain, diarrhea, and weight loss, though the clinical presentation can become more pronounced, with noisy abdominal tenderness that may mimic acute appendicitis [17]. When the colon is affected, anal fissures and perianal fistulas are frequently observed, often causing severe discomfort and pain. Patients may also experience intestinal obstructive conditions [18].

In addition to gastrointestinal symptoms, CD is associated with a variety of extraintestinal manifestations that can significantly impact the patient's quality of life. Common extraintestinal manifestations include enteropathic arthritis,

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pyoderma gangrenosum, and erythema nodosum [19]. Ophthalmic lesions, such as iritis and conjunctivitis, are also common and can affect the patient's overall health and well-being. Additionally, anemia, weight loss, and stunted growth are often consequences of impaired nutrient absorption due to inflammation and intestinal lesions [20]. Recent research has also highlighted that patients with CD have an increased risk of developing other autoimmune conditions, such as thyroiditis and psoriasis.

Oral manifestations of CD can occur in a range from 0.5–20% (21,22) to 60% [23] in adults, with a more recent study reporting a prevalence of 0–9% [24]. In children and adolescents, the rates are higher, reaching 10–80% [25-32). In pediatric patients, oral lesions often appear early and may be the only manifestation of the disease, which makes them critical for early diagnosis, especially since gastrointestinal symptoms may be absent for years [33,34].

The clinical presentation of CD in the oral cavity is classified into specific and non-specific lesions. Specific lesions include sclerotic lesions resembling tag lesions, mucosal hyperplasia that resembles cobblestones, lip swelling, gingivobuccal mucositis, deep linear ulcers, and polyps in the gingivobuccal groove. Non-specific lesions may include aphthae, granulomatous stomatitis, cheilitis, submandibular lymphadenopathy, abscesses, perioral erythema, and glossitis [35].

Histopathologically, specific lesions are characterized by multilayered squamous parakeratinized epithelium, with subepithelial non-caseating granulomas containing epithelial cells, Langerhans-type giant cells, blood vessels, and hemorrhage. Additionally, spongiosis, ulceration of connective tissue, and infiltration by chronic inflammatory cells are commonly observed [36,37].

Oral facial granulomatosis, which exhibits similar clinical and histopathological features to oral CD, arises from chronic immune system inflammation of unknown etiology. It is characterized by lip swelling and erythematous, edematous gingiva, with histopathological findings of granulomatous inflammation [38]. Although oral facial granulomatosis may be associated with CD or other conditions such as sarcoidosis and Melkersson-Rosenthal syndrome, it was initially described in 1985 as a separate entity without intestinal manifestations [39]. However, Freysdottir et al. [40] argue that a large percentage of patients with oral facial granulomatosis may represent a different expression of CD. They found elevated levels of CD4+ cells, IFN-γ and IL-12 cytokines, RANTES and MIP-1α chemokines, and CCR5 and CXCR3 receptors in immunohistopathological analysis of oral biopsies from lesions of oral facial granulomatosis. These findings suggest a Th1 cell environment, which is also observed in CD, supporting the hypothesis that oral facial granulomatosis could be another expression of CD.

Crohn's disease and Periodontal manifestations

In recent years, the association between periodontitis and CD has attracted increasing attention. Several studies have investigated the potential migration of pathogenic periodontal bacteria to the gut microbiome in CD patients. For example, Imai J. et al. [41] found a significant similarity between the oral and intestinal microbiomes in CD patients compared to healthy controls, suggesting an increased colonization of the gut by oral bacteria. While periodontal disease did not significantly affect the clinical outcomes of CD patients, those with periodontal disease exhibited a higher "short CD activity index," indicating that periodontal disease might play a role in the onset and progression of CD. However, further research is needed to clarify the exact mechanisms underlying this relationship.

Similarly, Xun Z. et al. [42] reported microbial dysbiosis in the oral microbiome and differentiated ecological types (ecotypes) in CD patients compared to healthy individuals, highlighting changes in specific bacterial populations. Their analysis showed an increase in the Veillonellaceae family and a decrease in Neisseriaceae and Haemophilus, along with a higher Firmicutes/Bacteroidetes ratio in the saliva of CD patients using 16S rRNA gene analysis. These findings underscore the potential of the oral microbiome as a diagnostic tool and a non-invasive method for monitoring gut health in patients with IBD.

Enver A. et al. [43] further explored the role of specific inflammatory cytokines in oral fluids, showing different levels of TNF-α, IL-1β (interleukin-1β), and IL-10 (interleukin-10) in saliva and gingival crevicular fluid (GCF) of CD patients compared to non-IBD patients with periodontal disease. Specifically, CD patients exhibited elevated TNF-α levels and reduced IL-1β and IL-10 levels, with probing depth and clinical attachment loss being significantly correlated with IL-1β levels in saliva. These findings suggest that oral cytokine profiles may serve as biomarkers for both the diagnosis and monitoring of CD.

The meta-analysis by She Y. et al. [44] supports the idea of an association between periodontitis and CD, suggesting that periodontal disease may contribute to the onset or exacerbation of IBD. The analysis found that CD patients have approximately three times the risk of developing periodontitis compared to healthy controls, with an odds ratio (OR) of 3.64 (95% CI: 2.33–5.67). Conversely, patients with periodontitis had a higher incidence of CD. The meta-analysis also identified shared factors that contribute to both conditions, including smoking, medication use, and changes in the microbiota of both the mouth and gut. Smoking and the active clinical phase of CD were found to increase the risk of periodontitis, while in UC, smoking appeared to have a protective role. The use of immunosuppressive drugs in IBD patients was also linked to an increased need for periodontal

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therapy. Moreover, CD patients exhibited changes in their oral microbiota, including an increased presence of pathogenic bacteria such as Treponema denticola. The systemic inflammation characteristic of CD was found to interact with local oral inflammation, leading to elevated levels of pro-inflammatory cytokines, such as TNF-α, in patients with both periodontitis and CD.

A systematic review by Ozayzan FI. et al. [45] found that 78% of the studies (21 out of 27) confirmed the association between periodontitis and IBD through both in vitro and in vivo research. Many studies suggest a bidirectional relationship between these two conditions, where periodontitis may exacerbate IBD and vice versa [46]. Some studies propose that shared pathological processes, such as abnormal immune responses and microbial dysbiosis, may contribute to the development of both periodontitis and CD. Pathogenic microorganisms in the mouth, including Porphyromonas gingivalis and Fusobacterium nucleatum, have been associated with intestinal inflammation and worsening of CD. Animal studies have shown that transplanting periodontal pathogenic bacteria into the gut can induce intestinal inflammation, further supporting the role of microbial dysbiosis in the development of IBD. Factors such as age, smoking, and oral hygiene were found to significantly influence the interaction between periodontitis and IBD, with smoking particularly increasing the risk of developing UC in patients with periodontitis [47].

In conclusion, while a growing body of evidence supports the bidirectional relationship between periodontitis and CD, the exact mechanisms linking these two conditions remain unclear. The findings suggest that oral health, particularly the status of the microbiome and inflammatory markers, plays a significant role in the onset and progression of IBD. Further research is needed to fully understand these mechanisms and to explore how the management of periodontal disease may improve the overall health and quality of life of patients with CD. The involvement of both gastroenterologists and dental professionals in the comprehensive care of CD patients is crucial, as maintaining good oral health may help mitigate the impact of periodontitis on the progression of CD and improve patient outcomes.

Crohn's disease and Dental implant therapy

The literature regarding the impact of CD on implant survival and success is limited but suggests a heightened risk of early implant failure in CD patients. A retrospective study [48] explored the relationship between various systemic conditions, including CD, and early dental implant failure. Despite the study's design limitations, the results indicated a significantly increased risk of implant failure in CD patients, with an OR of 7.95 (95% CI: 3.47–18.24). This suggests that CD patients are nearly eight times more likely to experience early implant failure compared to those without the disease.

The increased risk of implant failure in CD patients can be attributed to several disease-related factors. Chronic inflammation can impair the body's ability to heal effectively after dental procedures. In addition, the immunosuppressive therapies commonly prescribed to manage CD can hinder wound healing and increase the risk of postoperative infections, which may further complicate the success of dental implants. Furthermore, the oral manifestations of CD, such as gingivitis, periodontitis, and bone loss (exacerbated by corticosteroid use), can compromise the stability of implants by affecting both soft and hard tissues in the oral cavity.

While CD does not necessarily preclude the placement of dental implants, it is crucial for patients to be in clinical remission prior to undergoing the procedure. Active disease can elevate the risk of complications, including delayed wound healing, infections, and subsequent implant failure. Therefore, a thorough evaluation by both gastroenterologists and dentists is recommended before implant placement. This collaborative approach is essential to assess the patient's overall health and ensure that any disease activity is properly managed. Additionally, periodontal health must be closely monitored and treated, as existing oral infections or periodontal disease could interfere with implant success.

Therefore, while dental implants can generally be safely placed in CD patients, careful management is essential before, during, and after the procedure. Ensuring that patients are in remission, addressing any periodontal issues, and fostering a multidisciplinary approach involving both gastroenterologists and dentists are critical factors in improving implant success and minimizing potential complications.

Therapy

The management of CD requires a multidimensional approach that combines pharmacological treatment, nutritional and psychological support, and continuous monitoring to prevent and manage potential complications early [49,50]. Pharmacological therapy plays a central role in the management of CD, aiming to reduce inflammation and achieve clinical remission.

First-line therapy typically includes corticosteroids, which are highly effective in rapidly reducing inflammation. However, due to significant side effects such as osteoporosis, hypertension, and an increased risk of infections, long-term use of corticosteroids is not recommended. As a result, corticosteroids are usually combined with other therapies for better management. Immunosuppressive agents, such as azathioprine and methotrexate, are crucial for maintaining remission and preventing relapses.

Biological agents have revolutionized the treatment of CD, offering targeted therapies that suppress inflammation and help achieve remission in patients who do not respond adequately to traditional treatments. These immunomodulatory drugs are

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widely used for managing systemic inflammatory diseases like CD and are characterized by their effectiveness. Biological agents are protein molecules, often monoclonal antibodies, targeting specific mediators such as IL-17, IL-12, TNF-α, IL-1, and CD20. By inhibiting the action of these mediators, they reduce inflammation and disease activity [51]. The route of administration varies based on the drug selected and the severity and location of the disease, with subcutaneous and intravenous methods being the most common. Biological agents are classified into two main categories: cytokine inhibitors and inhibitors of B and T lymphocytes, with anti-TNF agents being the most widely used.

TNF-α is found in elevated concentrations in the blood, stool, and mucosa of patients with CD. It is an inflammatory protein primarily produced by macrophages but also by T and B lymphocytes, mast cells, and epithelial cells. TNF-α is key in the chemotaxis and activation of immune cells such as dendritic cells, neutrophils, monocytes, macrophages, and T lymphocytes. It also activates endothelial cells and fibroblasts, contributing to inflammation by inducing the expression of cell adhesion molecules (VCAM-1, ICAM-1) and the production of chemokines, which lead to the recruitment of leukocytes to the intestines. The strongest stimuli for TNF-α activation include lipopolysaccharide (LPS), IL-2, macrophage colony-stimulating factor (GM-CSF), and various bacteria [52,53].

Currently, five biological agents are FDA-approved for the treatment of idiopathic IBD: infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), certolizumab pegol (Cimzia), and vedolizumab (Entyvio).

Infliximab is one of the first and most well-studied biological agents for CD. It is a chimeric monoclonal antibody (human-mouse) that binds with high affinity to both soluble and membrane-bound types of TNF-α, but not to lymphotoxin α (TNF-β) [54,55]. It acts as an antibody against TNF-α, reducing inflammation in the gastrointestinal system through multiple mechanisms. In immune cells, infliximab induces apoptosis in activated T lymphocytes and monocytes that express the membrane form of TNF-α (mTNF-α), activating caspases and mitochondrial pathways, while simultaneously reducing the production of interferon-γ (IFN-γ) and CD40L expression, leading to reduced inflammation. In epithelial cells, infliximab restores the increased intestinal permeability seen in CD, reduces epithelial cell apoptosis, and helps restore the intestinal barrier, further reducing inflammation. In endothelial cells, infliximab reduces the expression of adhesion molecules such as VCAM-1 and ICAM-1, which are involved in the recruitment of T lymphocytes to inflamed tissues, while suppressing the interaction between endothelial cells and T lymphocytes via the CD40/CD40L pathway. In fibroblasts, it increases the production of the protein TIMP-1, limiting collagen production and promoting healing of intestinal damage without inducing fibroblast apoptosis. Additionally, infliximab reduces cytokines associated with fibrosis and angiogenesis, such as fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), while also reducing inflammatory cytokines such as IL-6 and CD40L. Overall, infliximab is a multifunctional anti-inflammatory drug that restores immune system balance and intestinal tissue integrity [56]. Recent studies confirm its effectiveness in achieving and maintaining clinical remission, alleviating symptoms, and preventing complications.

The typical dosing regimen for both adults and children involves 5 mg/kg intravenously at weeks 0, 2, and 6, followed by a maintenance infusion every 8 weeks. Some studies suggest that increasing the dosage to 10 mg/kg may result in a longer duration of remission [57].

Other biological agents, such as adalimumab, golimumab, and certolizumab pegol, also target TNF-α and offer flexibility in treatment. These agents can be administered through subcutaneous injections, allowing patients to self-administer the drug at home. Research shows that adalimumab is effective in achieving remission, improving quality of life, and reducing hospital stays.

There are additional biological agents that are not yet FDA-approved for IBD treatment but show promise. Ustekinumab (Stelara), an inhibitor of interleukin-12 and -23, targets both IL-12 and IL-23, which play key roles in enhancing the inflammatory response in CD. Studies show that ustekinumab is effective in achieving remission and reducing symptoms, particularly in patients who do not respond to other therapies. Guselkumab (Tremfya), initially developed for psoriasis, has shown promising results in CD by reducing inflammatory activity and maintaining remission in patients who have not responded to other biological treatments. Finally, tofacitinib, a JAK receptor inhibitor primarily used for rheumatoid arthritis, has shown positive results in treating CD, especially in cases where other therapies have failed.

The use of biological agents not only effectively reduces inflammation and disease activity but also decreases the need for surgical interventions. Personalizing treatment, along with other therapeutic strategies, can significantly improve disease outcomes and patients' quality of life.

However, biological agents are associated with certain adverse reactions, particularly with long-term use. The most common issue is the development of antibodies against the drug, usually when it is administered at incorrect or insufficient dosages, leading to reduced effectiveness. Patients receiving biological agents are also at increased risk of lichenoid reactions in the oral mucosa, as well as demyelinating, cardiovascular, and dermatological disorders. Furthermore, these patients are more susceptible to opportunistic infections, especially when biological agents are combined with corticosteroids, with candidiasis being the most frequent [58,59].

Conclusions

Periodontal diseases are commonly observed in patients with CD. The majority of studies support the idea that there is a bidirectional relationship between periodontitis and CD, with shared pathogenic pathways and inflammatory mechanisms playing a significant role in the connection between these two conditions. However, some literature questions the existence or clinical significance of this relationship. As such, more research, particularly randomized clinical trials, is needed to better understand how these two conditions interact and to refine strategies for managing patient health.

Furthermore, it is essential for dentists to be aware of CD and its oral manifestations. Early diagnosis and effective management of oral symptoms can play a critical role in the holistic care of CD patients and contribute significantly to the overall management of the disease.

Conflicts of interest

The authors declare no conflicts of interest related to this work.

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