# Oral manifestations in Inflammatory Bowel Diseases

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# ORAL MANIFESTATIONS IN INFLAMMATORY BOWEL DISEASES

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# Chapter 1

## General introduction and thesis outline

# General introduction

Inflammatory bowel diseases (IBD) are chronic idiopathic immune-mediated disorders causing relapsing and remitting inflammation of the gastrointestinal tract.[1] The two major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease was first described in 1932 as a chronic granulomatous inflammation of the intestinal wall of the terminal ileum.[2] It can however affect any part of the gastrointestinal tract from the oral cavity to the anus, but mainly involves the end of the small intestine (terminal ileum) and colon. It usually appears in patches, affecting some areas of the gastrointestinal tract while other parts are unaffected, and may extend through the entire thickness of the bowel wall from mucosa to serosa. Ulcerative colitis was first described in 1859 and it was suggested that idiopathic colitis should be considered in a different category from specific epidemic dysentery.[3] UC, characterised by diffuse and more superficial mucosal inflammation of the colon and the rectum, usually begins in the rectum and ultimately extends proximally in a continuous pattern involving the entire colon (pancolitis). In UC, the inflammation occurs only in the innermost layer of the lining of the intestine (mucosa). In some cases, when it is difficult to discriminate between CD or UC, the patients are given the diagnosis of IBD undetermined (IBD-U).

## Global burden of IBD

The global burden of IBD is increasing worldwide, with the highest prevalence in North America and Europe. In 2017, over 6.8 million individuals were diagnosed with IBD.[4] While the incidence of IBD has stabilised in the Western world since 1990, the adoption of a "Western-like" lifestyle in newly industrialised countries has contributed to a rising incidence in these regions, analogous to trends previously seen in the Western world in the 20$^{th}$ century. Together with improved survival of patients with IBD, this results in a worldwide increasing prevalence.[5]

IBD are lifelong diseases with a significant impact on quality of life[6]. In approximately half of the employed IBD population, there is work productivity loss with fatigue as the most important reason for work related absence.[7] As a consequence, the indirect costs of IBD play a significant role in the global burden.[8] The treatment and disease management have evolved significantly in recent decades in which the direct health care costs have shifted from surgery and hospitalization to (targeted) drug therapy with the use of biological treatment.[9,10] Since the majority of the healthcare cost are driven by medication and considering the increasing prevalence of IBD, the direct cost will rise in the future.

## Etiology and pathogenesis

While the exact etiology of IBD is not entirely understood, IBD is believed to result from an inappropriate inflammatory response to intestinal microbes and other environmental factors in a genetically susceptible host.[11] A genetic component in the development of IBD was initially demonstrated by epidemiological data, including differences in prevalence between different ethnic groups, familial aggregation, concordance in twins and associations with certain genetic syndromes.[12] At least 242 susceptible loci have been identified, of which 45 have been statistically fine-mapped to conclusive causal variants and 50 have been associated with very-early-onset IBD.[13,14] Most of these genes are involved in the control of the epithelial barrier function or the immunological (innate) host defence.[15]

The higher prevalence rate in the industrialised world suggests that environmental factors could also play a role in the etiology of IBD.[16] This suggestion is supported by the observation that incidence rates increase when people migrate from low incidence regions to more developed regions, and the correlation of the incidence rates with the level of industrialisation.[17] The gut microbiome seems to be another important player in the pathogenesis of IBD, as a different composition of faecal microbiota has been found in patients with CD and UC compared to healthy individuals.[18–21] Smoking cigarettes increases the risk for CD and worsens its clinical course, while it seems to be a protective factor against developing UC.[22] However, given the well-known negative side-effects of smoking cigarettes, non-smoking UC patients should obviously not be advised to start smoking cigarettes. Appendectomy for appendicitis is associated with a reduced risk of having UC and with a less severe course of UC[23] but may increase the risk of developing CD.[24] Other described (potential) environmental factors triggering IBD are increased consumption of antibiotics, vitamin D deficiency and lifestyle habits such as insufficient diet, poor sleep, physical inactivity, and excessive stress.[25]

## Symptoms, diagnosis and complications

IBD is slightly more prevalent in females than in males, and generally manifests in early adulthood between 15-30 years of age, but may also occur later in life.[4,26] The symptoms of IBD differ from person to person, may vary from mild to severe and can change over time. The clinical presentation often includes abdominal pain, diarrhea, rectal bleeding and painful defecation. Children with IBD may have a reduced linear growth and delayed pubertal development. Consequently, full assessment of children presenting with potential IBD is essential for early identification of the disease to determine and optimize related short and long term outcomes.[27] The variability of the symptoms can make diagnosing IBD challenging. To date, diagnosis is based on a

combination of patient anamnesis, family disease history, exclusion of gastrointestinal infections, biochemical analyses of blood and stool, radiological imaging, endoscopy and histologic assessment of intestinal mucosa biopsies.[28] Both CD and UC patients often suffer from a lack of iron because of gastrointestinal blood loss causing an iron deficiency anemia which is associated with a reduced quality of life.[29,30] Complications of CD include the formation of gastrointestinal internal or external fistulas, strictures, abscesses and malabsorption causing malnutrition. Internal fistulas can develop between the gastrointestinal tract and other organs, such as vagina or bladder, while external fistulas drain intestinal content to the (often perianal) skin. The development of strictures is caused by scarring and narrows the intestinal lumen, which may lead to obstructive complaints and even a complete intestinal blockage.[31] Anal and perianal fissures, abscesses, or fistulas are frequently observed in patients with CD and cause perianal pain, itching, and/or fecal incontinence. Complications of UC include heavy persistent diarrhea with rectal bleeding and pain. In more severe cases a perforated bowel and toxic megacolon as a consequence of severe inflammation that leads to rapid non-obstructive dilation of the colon can occur. Patients with CD of the colon and patients with UC have an elevated risk of developing colorectal dysplasia and cancer compared to the general population. The risk increases the longer a person lives with the disease and is also related to the severity of the disease, the length of colon segment involved, the family history of colorectal cancer and the presence of primary sclerosing cholangitis (PSC).[32] It is therefore important to enroll these patients into coloscopy screening programs to detect and remove possible pre-cancerous dysplastic changes.[33]

## Treatment

Since IBD is currently neither medically nor surgically curable, treatment is pragmatically aimed at suppressing the chronic intestinal inflammation leading to symptomatic relief, reduction of inflammation, improve the quality of life, maintenance of remission, preventing complications and prevention of surgical intervention.[34,35] In general, IBD patients with mild disease are initially treated with corticosteroids and, when initial remission is reached, maintenance therapy can start. For maintenance therapy, CD patients may receive immunomodulators such as thiopurines and methotrexate, while UC patients are typically treated with 5-aminosalicylic acid (mesalazine) first and thiopurines as a second (immunosuppressive) step. If the effect is insufficient or adverse reactions occur, TNF-alfa inhibitors (e.g. infliximab, adalimumab or golimumab) are often initiated, while IL-12/23 blockers (e.g. ustekinumab), IL-23 p19 inhibitor (e.g. risankizumab[36]), alfa4-beta7 integrin inhibitors (e.g. vedolizumab), JAK-

inhibitors (e.g. tofacitinib, filgotinib[37] or upadacitinib[38]) or sphingosine-1-phosphate receptor modulator (e.g. ozanimod[39]) are usually considered after anti-TNF-alfa therapy failure.[40,41] Generally, the accelerated step-up strategy (with tight control) is applied, but when severe inflammation is present, early aggressive top-down treatment is indicated which can result in decreased complications. When patients develop fistulas usually TNF-alfa inhibitors are primarily started, often in combination with azathioprine (or another immunomodulator) as the SONIC study found that combination therapy was more effective in achieving remission.[42] However, for some patients with IBD, medication does not adequately control the symptoms and surgical intervention is needed. About 60% of the CD patients will eventually undergo surgery after 20 years of disease[43] and up to 15% of people with UC will require surgery after 20 years of disease.[44]

### Extra-intestinal manifestations

Although IBD primarily involves the bowel, they can be associated with extra-intestinal manifestations (EIM). These manifestations may follow the clinical course of IBD and involve osseous (such as spondyloarthropathy or arthritis), oral (e.g. aphthous stomatitis), ocular (such as episcleritis or uveitis), cutaneous (e.g. erythema nodosum), hepato-pancreato-biliary (e.g. PSC), neurological and pulmonary tissues (e.g. chronic obstructive pulmonary disease).[45] In the literature, varying prevalence rates of EIM have been reported depending on geographic region, definitions, and methods of data capture.[46,47] A recent study with 1249 patients, performed in Switzerland, reported that 29.3% of the IBD patients had one to five EIM, with the highest prevalence for peripheral arthritis (70.0%), followed by aphthous stomatitis (21,6%). This study also reported that 25.8% of the patients had their first EIM before IBD was diagnosed (median time 5 months before IBD diagnosis with a range from 0-25 months).[48]

## Outline of the thesis

In 1969, oral lesions in a patient with CD were described for the first time.[49] Since then, varying prevalence rates of oral manifestations in both CD and UC have been reported. The oral manifestations in IBD include a wide range of specific and non-specific lesions which can significantly impact the quality of life of IBD patients. Moreover, oral manifestations may precede or coincide with intestinal symptoms which, when recognized, may contribute to diagnose IBD at an earlier stage which is important to minimize complications, especially in children.

The aim of this thesis is to investigate the oral manifestations of IBD in general and its association to bowel surgery, salivary function and composition, and quality of life. Furthermore, we wanted to study the current knowledge and interdisciplinary communication between gastroenterologists and oral health care professionals and whether and how the communication between these professional groups could be improved for better patient care.

**Chapter 2** and **Chapter 3** provide a review of the literature about oral manifestations in respectively CD and UC. In **Chapter 4** and **Chapter 5**, two clinical studies are presented. The purpose of the study in **Chapter 4** was to explore the potential association between salivary function and oral and dental problems in CD patients. The study described in **Chapter 5** evaluated oral health problems and salivary function and composition in UC patients and its correlation with disease activity. In addition, it also evaluated whether quality of life and oral health problems differed between UC patients with active and inactive disease activity. The retrospective study presented in **Chapter 6** investigates the prevalence of dental caries and periodontal disease in patients with CD and UC compared to an age and gender-matched control group of patients without IBD. The aim of the study presented in **Chapter 7** was to investigate whether resection of (a part of) the inflamed intestine may be related to self-reported oral health problems in patients with IBD and, secondly, whether there is an association between IBD-specific health-related quality of life (IBD-HQOL) and oral health problems. A final prospective study, on the knowledge of gastroenterologists and dentists in the Netherlands about gastrointestinal diseases with oral manifestations, is presented in **Chapter 8**. This study also assessed the frequency, extent, content and value of the communication between gastroenterologists and oral health care professionals in the Netherlands. The findings are summarized and evaluated in the general discussion in **Chapter 9**, which ends with future study perspectives.

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# Chapter 2

## Oral manifestations in Crohn's disease

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## Abstract

Widely varying prevalence rates of oral lesions in patients with Crohn's disease have been reported, ranging from 0.5% to 37%. These manifestations may coincide with or precede intestinal symptoms. Oral manifestations can be classified as specific lesions, when macroscopic examination shows similar changes to those observed endoscopically in the intestine, and non-specific lesions including aphthous ulcerations. The most frequently observed oral lesions are oedema, ulcers and hyperplastic lesions on the buccal mucosa. In most patients these lesions are asymptomatic, however, some patients may experience discomfort. In this review we describe the most relevant oro-dental manifestations observed in patients with Crohn's disease and discuss the potential implications for oro-dental management.

# Introduction

Crohn's disease and ulcerative colitis represent the two main types of inflammatory bowel disease, which is a broad term that describes conditions with chronic and recurring inflammation of the gastrointestinal tract. Bowel symptoms are predominant, but extra-intestinal manifestations may occur, including involvement of the oral cavity. In this review we will focus on the oral manifestations of Crohn's disease.

Burrill Crohn and co-workers first described a chronic granulomatous inflammation of the intestinal wall (*enteritis regionalis*) in 1932.[1] This chronic bowel inflammation was later named Crohn's disease (CD). CD usually has a patchy, rather than continuous distribution throughout the gut ('skip lesions') and may affect any part of the gastrointestinal tract from the oral cavity to the anal canal, but mainly involves the terminal ileum and colon (Figures 2.1 and 2.2). The diagnosis of CD depends on the demonstration of typical clinical, endoscopical, radiological, histopathological and/or biochemical findings.[2]

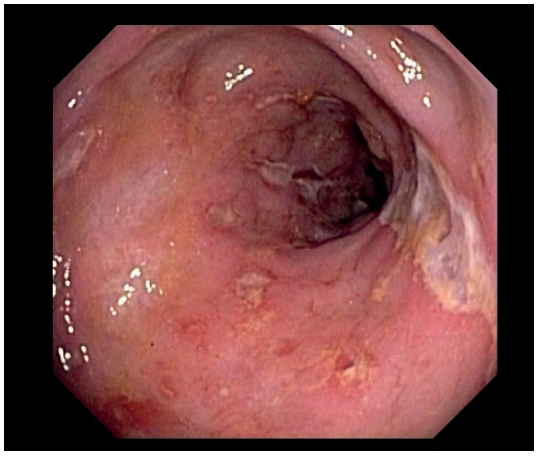

Figure 2.1 Endoscopy of the colon shows ulceration of the mucosa.

The incidence of CD differs between geographical regions. The disease is relatively infrequently diagnosed in developing countries but is increasing.[3] The age-standardised incidence rates in the Netherlands between 1991 and 2002 in males and females were respectively 4.84 and 7.58 per 100,000 person-years.[4] Symptoms can start at any age with peaks in early and late adulthood.[5,6]

Clinical symptoms include abdominal pain, diarrhoea, rectal blood loss, decreased appetite, weight loss, fever and growth failure in children.[2] The disease usually shows

episodes of clinical activity (exacerbations or flares) interspersed with asymptomatic intervals or remissions.

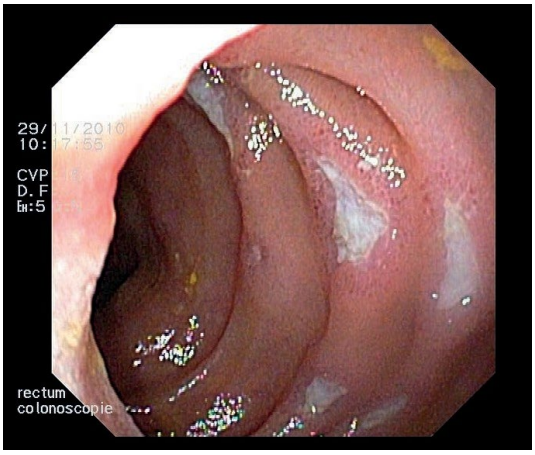


Figure 2.2 Endoscopy of the terminal ileum shows typical skip lesions.

There are three phenotypes of CD: the stricturing, penetrating and non-stricturing non-penetrating types.[7] In the stricturing type of CD, gradual thickening of the intestinal wall will lead to stenosis or obstruction of the bowel lumen with subsequent pain, vomiting and weight loss (Figure 2.3). The penetrating disease pattern is characterised by formation of internal fistulas between the gastrointestinal tract and other organs, such as vagina or bladder, as well as external fistulas draining intestinal contents to the skin. Anal and perianal fissures, abscesses, or fistulas are frequently observed in patients with CD and cause perianal pain, itching, or faecal incontinence.[22]

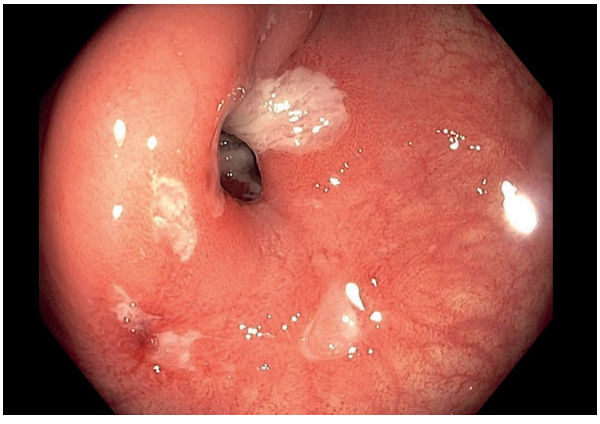

Figure 2.3 Endoscopy showing stenosis of the colon with ulcera.

Although the exact underlying pathogenesis has not been clearly elucidated, increasing evidence suggests that CD results from an inappropriate inflammatory response to intestinal microbes and other environmental factors in a genetically susceptible host.[8] The influence of genetic factors was initially demonstrated by epidemiological data, including differences in prevalence between different ethnic groups, familial aggregation, concordance in twins and association with genetic syndromes. In total, over 150 risk genes/loci that might play a role in susceptibility for CD have been reported.[9]

Several authors have described the potential role of environmental factors in the aetiology. An increase in carbohydrate intake, particularly simple carbohydrates, has been suggested as a risk factor for the development of CD.[10] Smoking cigarettes clearly increases the risk for CD and worsens its clinical course.[11] Some ingredients of toothpaste, such as tricalcium phosphate, magnesium trisilicate and quartz, are capable of penetrating the epithelium and creating enteric lesions similar to CD.[10,12]

Since CD is neither medically nor surgically 'curable', treatment is pragmatically aimed at symptomatic relief, reduction of inflammation during exacerbations, increasing quality of life, maintenance of remissions and prevention of surgical intervention or complications. Therapeutic approaches depend on the disease location, disease severity, and disease-associated complications.[13] The main drugs used in therapy are glucocorticoids, immunomodulators and biologicals.[14] Thiopurines and methotrexate are primarily used as maintenance immunosuppressive therapy to minimise the risk of future exacerbations. Glucocorticoids, given systemically or locally, are mainly prescribed to induce a remission, as long term usage leads to unacceptable high rates of steroid-induced adverse events. The most frequently administered biologicals in CD patients comprise two monoclonal antibodies directed against tumour necrosis factor-α (TNF-α). Many patients with CD ultimately require surgical intervention with intestinal resection because of intractability of symptoms, obstruction, or perforation.

## Epidemiology of oral manifestations

Oral lesions in a patient with CD were initially described by Dudeney in 1969.[15] Since then, widely varying prevalence rates of oral lesions have been reported, ranging from 0.5% to 37% per cent.[5,16–20] This variation in the prevalence of oral lesions might be related to a variety of factors, including age and ethnicity of the population studied, experience of the examiner, definition of disease-specific lesions, and whether the patients received medication for CD at the time of the study.[17]

Oral lesions are more prevalent in children compared to adults – a prospective three year study showed oral lesions in 41.7% of the children with CD.[21] Oral lesions are also more prevalent in CD patients with proximal gastrointestinal tract and/or perianal involvement.[21,22]
Oral lesions may precede intestinal involvement. A retrospective study of 40 patients found that 42% had orofacial lesions 1 to 39 years before they were diagnosed as having CD, and 50% developed oral lesions 1 to 45 years after gastrointestinal involvement.[23] Oral lesions might be more severe during active intestinal disease, but approximately 30% of the patients continue to manifest oral lesions despite control of their intestinal disease activity.[17,24]

## Oral manifestations

CD may present with several types of oral manifestations.[23] An evaluation of 147 patients with CD showed that 42 patients (29%) presented with one lesion only, whereas 12 patients (8%) presented more than one lesion simultaneously.[18] Oral manifestations can be classified as specific lesions, when macroscopic examination shows similar changes to those observed endoscopically in the intestinal tract, and non-specific lesions[25] (Box 2.1). The non-specific lesions may be related to nutritional deficiency, resulting from chronic diarrhoea, reduced oral feeding, overgrowth of intestinal flora, intestinal resection, malabsorption, or to adverse reactions of drug therapy.[25,26] The most frequently observed oral lesions are oedema, ulcers and hyperplastic lesions on the buccal mucosa.[18] These lesions may be painful, impair proper oral function and hygiene, and even lead to psychological problems.[24,27]

### Specific lesions

*Diffuse labial and buccal swelling*

One of the most obvious and common presentations of oral CD is diffuse swelling.[23] This swelling is usually persistent, firm on palpation, painless and tends to involve the lips, buccal mucosa, and facial soft tissues[28,29] (Figure 2.4). Most commonly the swelling involves the lips, but it may extend to the perioral area and involve other parts of the face. The lip swelling can be diffuse and symmetrical or localised. In most cases it involves only one lip, but it can also affect both lips. The prevalence of upper and lower lip involvement is similar.[23,30] Lip involvement can lead to vertical fissuring.[6,24,29]

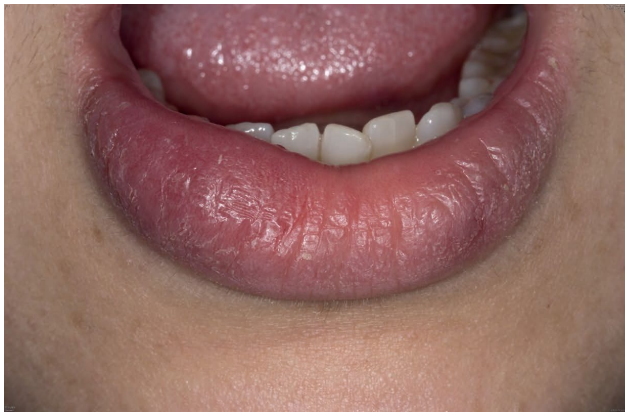

Figure 2.4 Swelling of the lower lip.

Box 2.1 Specific and non-specific oral lesions in Crohn's disease.

| |
|---|
| Specific lesions: |
| Diffuse labial and buccal swelling |
| Cobblestones |
| Other specific lesions |
| mucosal tags |
| deep linear ulcerations |
| mucogingivitis |
| granulomatous cheilitis |
| Non-specific lesions: |
| Aphthous ulcerations |
| Pyostomatitis vegetans |
| Dental caries |
| Gingivitis and periodontitis |
| Other non-specific lesions |
| angular cheilitis |
| glossitis |
| gingival hyperplasia |
| lichen planus |
| halitosis |
| dysphagia |
| altered taste perception |
| reduced salivation |
| lymphadenopathy |
| secondary fibrosis |
| candidiasis |

### *Cobblestones*

Granulomatous swelling in the oral cavity sometimes may resemble the swelling of the intestinal mucosa at endoscopy and give a similar 'cobblestone' appearance[23] (Figures

2.5 and 2.6). The mucosal nodularity consists of papules forming firm plaques. These plaques may have a hyperplastic appearance with corrugation and a fissured swollen mucosa. These lesions are usually observed in the buccal mucosa and may be alternated with mucosal folds with normal epithelium.[24,31] Cobblestoning may be painful and interfere with speaking and eating.[19]

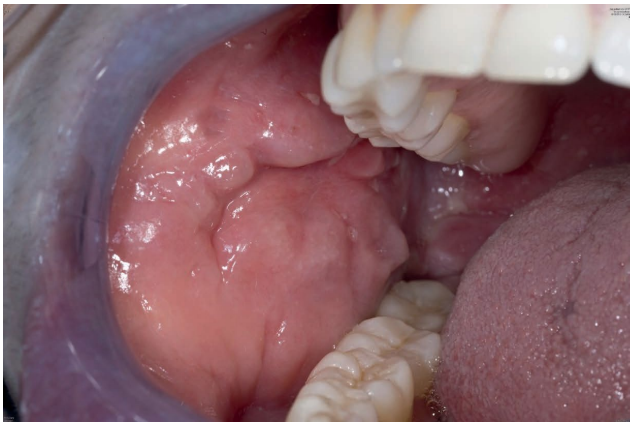

Figure 2.5 Folded and swollen buccal mucosa known as cobblestoning.

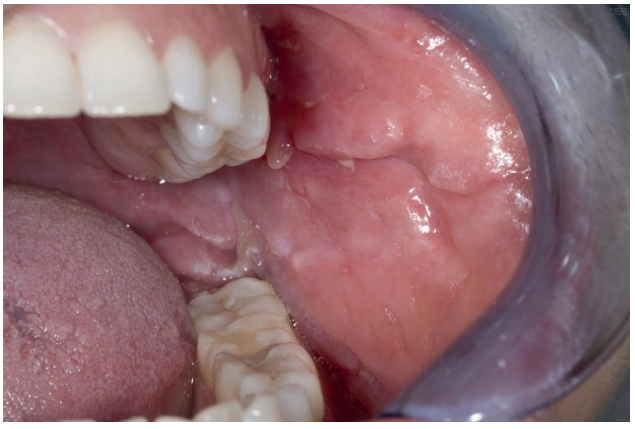

Figure 2.6 Typical cobblestone appearance of the buccal mucosa.

*Other specific lesions*

Mucosal tags can be observed at various locations in the oral cavity. They are small, localised swellings and often asymptomatic.[23,32,33] (Figure 2.7). Deep linear ulcerations

may be surrounded by hyperplastic margins and are usually seen at the buccal vestibule[28] (Figure 2.8). These ulcers are not only linear and deep, but also persistent and could be confused with aphthous ulcers.[34] Mucogingivitis might affect the whole gingiva up to the mucogingival line. The gingiva may become oedematous and hyperplastic and may be associated with ulceration.[24] A prospective three year study of 49 children with CD shows that mucogingivitis was the most common oral finding.[17,21] Granulomatous cheilitis is a swelling of the lip due to granulomatous inflammation. It is a rare condition and the onset is usually in young adulthood.[35]

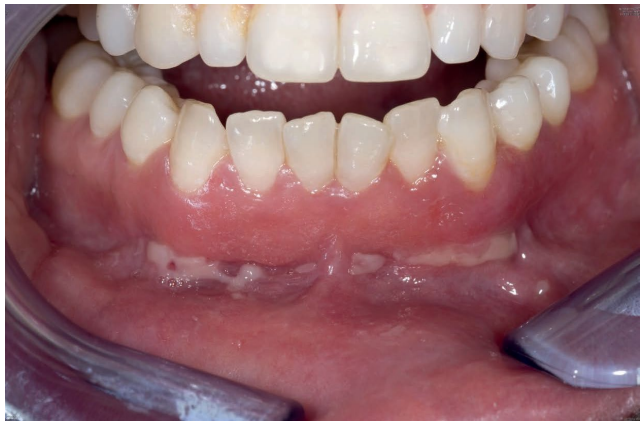

Figure 2.7 Linear ulceration with mucosal tag.

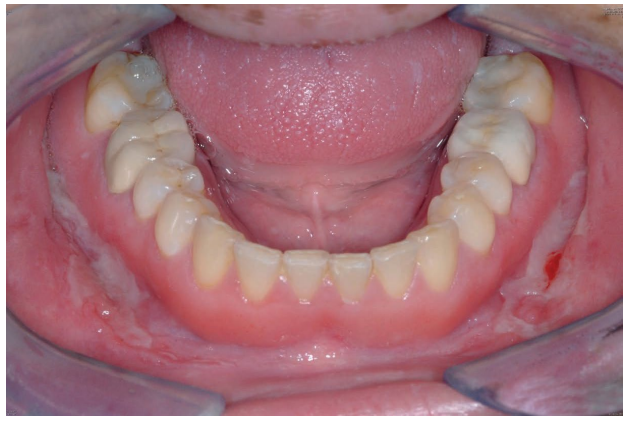

Figure 2.8 Linear ulceration of the mandibular buccal vestibule.

## Non-specific lesions

*Aphthous ulcerations*

Oral ulcerations are one of the most common lesions associated with CD and occur in about 20–30% of the CD patients,[23,24,36] however, these ulcerations also frequently occur in the general population with a prevalence of approximately 20%.[24] Aphthous ulcers are shallow round to oval shaped lesions and may feel granular below the epithelium on palpation.[34] They are often painful and can have negative effects on daily activities.[23] Their onset is usually sudden and they may occur with or precede intestinal disease activity.[5] The association with flare-ups of intestinal disease is unclear.[37]

*Pyostomatitis vegetans*

Pyostomatitis vegetans can occur in CD, but is more frequently associated with ulcerative colitis.[19,24,26] The lesions are characterised by multiple pustules, erosions, vegetative plaques and mucosal folds.[17,19,26,27,38] They appear mostly on the buccal and gingival mucosa but can also appear on the tongue or the floor of the mouth. The pustular lesions may easily rupture and fuse, leading to linear or 'snail track' ulcerations.[19,38] The histologic features of these lesions are dominated by eosinophilic micro abscesses.[39]

*Dental caries*

A number of studies have reported higher caries prevalence rates in CD patients compared to controls.[40–42] One study did not report any differences in the decay-missing-filled-surface (DMF-S) index but found a significantly higher prevalence of dentine caries amongst IBD patients compared to controls. A possible explanation could be the difference in study groups, since the latter group also included patients with ulcerative colitis.[43] The levels of lactobacilli and *Streptococcus mutans* were higher in CD patients compared to control groups.[42] Szymanska *et al.* revealed in a study with 235 CD patients that patients who had undergone resective surgery had higher DMF-S scores compared to the control group, while there was no difference between CD patients who had not undergone resective surgery and the control group. They also found more dental plaque in the CD groups, and male CD patients had a significantly higher prevalence of dental plaque than females. The study also showed a higher consumption of sweetened drinks between meals. This is in agreement with a study that showed a higher sugar intake in CD patients.[41,42]

*Gingivitis and periodontitis*

Gingival bleeding is common in patients with CD and occurs in approximately 20%.[40] A study of 53 patients with long-standing CD did not reveal any statistically significant

differences in gingival index between patients with active and inactive disease. Patients with active disease more often had high counts of lactobacilli and mutans streptococci compared to patients with inactive disease.[44]

Several studies have revealed that the prevalence of periodontitis is higher among patients with CD compared to controls.[18,40,45] Brito *et al.* found periodontitis in 81.8% of the CD patients compared to 67.6% in the controls.[40] Stein *et al.* suggest that CD patients have a moderate severity of periodontitis with a community periodontal index of treatment needs (CPITN) score 3 in 57.8% of the patients.[18] Periodontitis in the primary dentition may be indicative for CD and could precede intestinal symptoms.[46]

*Other non-specific lesions*

Some of the other non-specific oral lesions include angular cheilitis, glossitis due to nutritional deficiencies, gingival hyperplasia, lichen planus, halitosis, dysphagia, altered taste perception, reduced salivation, lymphadenopathy, secondary fibrosis and candidiasis.[25,28,40,41,47]

## Orofacial granulomatosis

The term orofacial granulomatosis (OFG) is used to describe patients with orofacial signs and symptoms similar to those seen in Crohn's disease but in absence of any evident intestinal involvement.[48] It is an uncommon chronic inflammatory disorder with lip and facial swelling as the most common clinical signs. Less commonly, it may also affect gingivae, buccal mucosa, tongue, floor of the mouth and other sites in the oral cavity. OFG may occur at any age but appears to be more prevalent in children and young adults. Childhood onset has a higher risk to be related to systemic disease, which can manifest years after initial presentation.[49,50] A systematic review showed that concurrent CD is described in about 40% of the children diagnosed with OFG and suggests that OFG may be a subtype of CD.[51] However, the debate about whether OFG is just an oral manifestation of CD or rather a separate inflammatory disease is still open.[30]

Observational studies have shown that dietary elimination of some provoking elements is an effective treatment. A cinnamon- and benzoate-free diet provides benefit in 54-78% of the patients with 23% not requiring adjunctive therapy so this is recommended as primary treatment, especially in younger patients.[52]

## Dental management

As described above, CD can have negative effects on oral health and therefore CD patients need special attention from dental clinicians. A study of 2085 CD patients demonstrates that there is a significantly higher total number of dental procedures compared to the control group. The most pronounced difference were for removable dentures, front teeth fillings and endodontic treatments.[53] Clinical implications include frequent dental check-ups with oral hygiene instruction and application of fluoride varnishing.[25] It is important to advise the patients to reduce the amount and frequency of sugar- and carbohydrate-containing consumptions. In addition, sugar substitutes are relatively contra-indicated because of the risk of gastrointestinal disturbances.[25] In patients treated with the immunomodulator methotrexate, use of non-steroidal anti-inflammatory drugs and penicillin is contraindicated because combination increases the risk of bone marrow depression caused by an impaired renal methotrexate clearance.[54]
In most patients, the oral lesions are asymptomatic and in these patients no special treatment is necessary.[24] However, some patients may experience discomfort and for them there are several treatment options. The first and foremost step in treatment of the specific and non-specific oral lesions is gastrointestinal disease control,[34] so referring to a gastroenterologist is recommended at this point. To relieve the pain of aphthous ulcerations, topical agents such as lidocaine and/or topical steroids such as triamcinolone 0.1% can be used. Topical application of 0.1% dexamethasone seems also effective. Severe and recurrent cases of aphthous ulceration can be treated with systemic or intra-lesional steroids. Lip swelling and deep linear ulcerations can be treated with topical tacrolimus (0.5 mg/kg) and intra-lesional steroid injections. Treatment of cobblestoning consists of application of topical steroids.[17,24,25]
As described previously, oral manifestations may precede gastrointestinal symptoms of CD. General practitioners may suspect CD in patients with the aforementioned oral lesions, especially when combined and with a positive family history of CD and/or clinical symptoms such as frequent abdominal pain, diarrhoea, unwanted weight loss and failure to thrive in children. In these cases, referral to a gastroenterologist for further investigation seems warranted.

## Conclusion

Crohn's disease may have negative effects on oral health and therefore patients with CD need special attention from dental clinicians. In complex cases, dedicated specialist teams consisting of dental clinicians and gastroenterologists are to be consulted.

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# Chapter 3

## Oral manifestations in ulcerative colitis

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# Abstract

Ulcerative colitis is a rather common inflammatory bowel disease, especially in the industrialised world. A limited number of studies have reported the prevalence of oral signs and symptoms in these patients, and widely varying prevalence rates have been reported ranging from 2 to 34%. Pyostomatitis vegetans is the most pathognomonic oral sign but also other abnormalities as oral ulcerations, caries and periodontitis are more often seen in patients with ulcerative colitis. In this review we describe the oral manifestations of ulcerative colitis and their potential dental implications.

# Introduction

Ulcerative colitis (UC) was first described by Sir Samuel Wilks in 1859[1] and is characterised by diffuse mucosal inflammation of the colon.[2] The rectum is always involved but the colitis may extend proximally in a contiguous pattern up to the entire colon (pancolitis).[2–5] Histological findings include inflammation limited to the mucosal layers with varying degrees of infiltration by plasma cells, lymphocytes and granulocytes.[4] Active disease is characterised by ulcerations, loss of goblet cells and crypt abscesses[6] (Figure 3.1). Distortion of the crypt architecture with shortening and disarray of the crypts, crypt branching, atrophy and Paneth cell metaplasia is indicative of a chronic inflammatory process.[7,8]

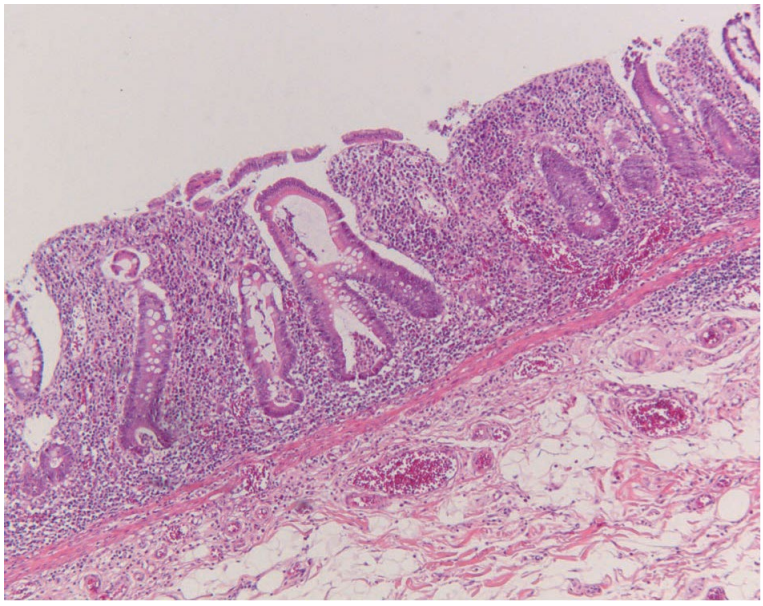

Figure 3.1 Histologic slide of the colon mucosa during active disease shows typical crypt abscesses and crypt irregularities. The inflammation is limited to the mucosa, the submucosa is not involved. H&E staining (original magnification 100×) courtesy of A. Neefjes-Borst, department of Pathology, VU Medical Centre, Amsterdam, The Netherlands.

The clinical presentation varies in severity but typically includes abdominal pain, intermittent bloody diarrhoea and painful defecation. The symptoms are also dependent on the localisation and extension of disease. Children with UC may have a reduced linear growth and a delayed pubertal development. Therefore, full assessment of children presenting with potential UC is essential for early identification of the

disease, to optimise short and long term outcomes.[4] Patients with UC have an increased risk to develop colorectal cancer. The extent and duration of UC, presence of concomitant primary sclerosing cholangitis and family members with colorectal cancer are the important risk factors for the development of colonic dysplasia and subsequent cancer.[6,9] Although UC primarily involves the bowel, it may be associated with extra intestinal manifestations (EIM). The most common EIMs involve the skin, eyes, joint and liver[5] and tend to follow the clinical course of the colitis. Less than 10% of the patients have EIMs at the initial presentation of UC, but approximately 25% of the patients will develop an EIM in their lifetime.[10]

The diagnosis of UC is made on the typical clinical symptoms combined with endoscopic and histologic evidence.[5] Colonoscopy with biopsies is currently the diagnostic gold standard. Characteristic observations during endoscopy are exudates, ulcerations, loss of the typical vascular pattern, friability, and granularity in a continuous, circumferential pattern[2,11] (Figures 3.2–3.4). Superficial inflammation associated with loss of haustration suggests UC, whereas non-continuous patches of inflammation would support Crohn's disease.[12] Particularly in the early stage of the disease, differentiating UC from CD can be challenging, but it is important as appropriate treatments and potential complications vary for these two diseases.[2]

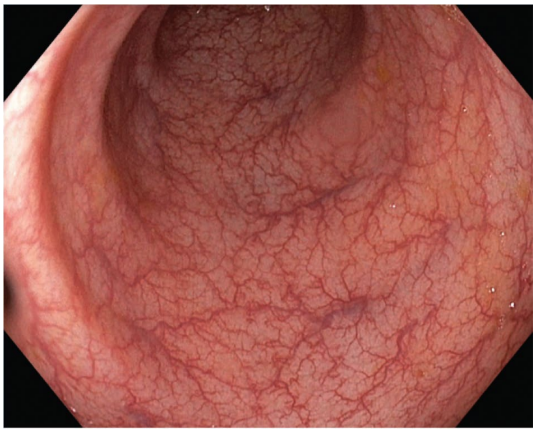

Figure 3.2 Endoscopy of normal colon mucosa.

## Epidemiology

Ulcerative colitis is rather common in the developed countries of the world, particularly in North America and Western Europe, with an overall incidence of 10.4 per 100,000

persons in Europe.[13] Several studies have shown that the incidence is decreasing from North to South and that the incidence values in high incidence areas are increasing.[14]

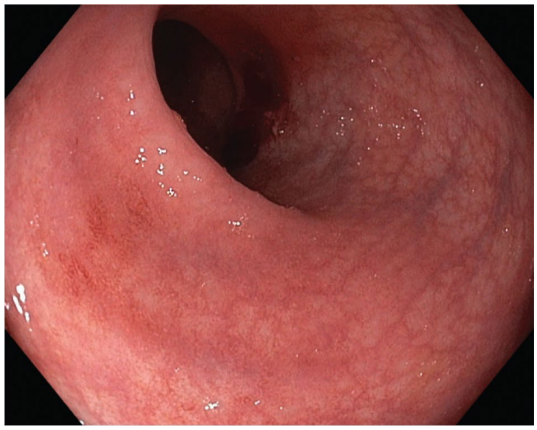

Figure 3.3 Endoscopy shows loss of normal vascular pattern and erythematous colon mucosa in a mild case of UC.

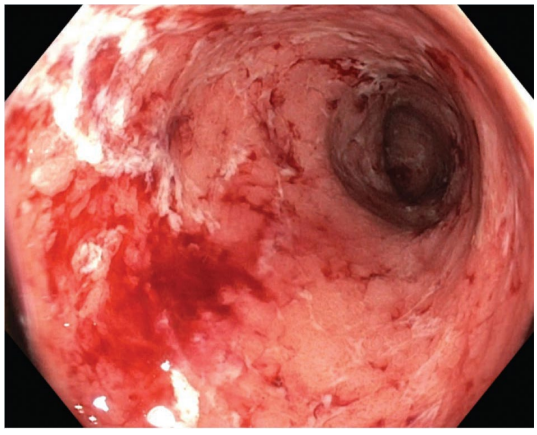

Figure 3.4 Endoscopy of colon mucosa with ulceration and spontaneous bleeding in a severe case of UC.

## Aetiology

The pathogenesis of UC is still not completely resolved. The most accepted hypothesis is that a dysregulated interaction between the mucosal immunology in the intestinal microflora leads to inflammation in a genetically predisposed host. Many studies have

focused on the intestinal flora, without clear evidence for a specific pathogen. A considerable number of genes have been associated with UC. Most of these genes control the epithelial barrier function or the (innate) host defence.[4,15]
A positive family history is the largest independent risk factor for UC. People with UC with a first-degree relative have a 10-15-fold risk of developing the disease.[16] UC is more common in patients of Jewish origin and less frequently observed in Afro-Americans or Hispanics.[5,17,18] The strongest evidence of genetic factors contributing to susceptibility to UC comes from concordance studies in twins. The concordance for UC was 10% for monozygotic twins compared to 3% for dizygotic twins.[19,20]
The higher incidence and prevalence rates of UC in the industrialised world suggest that environmental factors could also play a role in the aetiology.[21] This suggestion is supported by the observation that incidence rates increase when people migrate from low incidence regions to more developed countries, and the correlation of the incidence rates with the level of industrialisation in Hong Kong and mainland of China.[22] It is also supported by a study in Europe that shows a west-east gradient of UC.[23]
Smoking cigarettes is a protective factor against developing UC, as smokers have approximately 40% lower risk of UC than non-smokers.[24–26] However, compared with those who never smoked, former smokers are approximately 70% times more likely to develop the disease, which is often more extensive and refractory than those who have never smoked.[27,28] The beneficial effects of nicotine in UC are due to increased mucus production, decreased production of pro-inflammatory cytokines and nitric oxide and improvement of intestinal barrier function.[29] A study among 205 patients showed a protective effect in patients smoking fewer than ten cigarettes/day and the effect disappeared in patients smoking more than 20 cigarettes/day.[24] Appendectomy performed for appendicitis at an early age might also be protective against UC.[30–32]

## Treatment

Ulcerative colitis is currently not curable. Therefore, the primary aims of therapy are to induce and maintain clinical remission, decrease the risk of complications and improve quality of life.[5,33] Important additional aims in children with UC include optimisation of nutrition and growth. Ensuring that the child is able to resume normal psychological development is important.[4]
The initial treatment of UC is based upon the severity and extent of the disease. The first line therapy in mild to moderate disease activity is administration of 5-aminosalicylic acid (5-ASA), which can be given orally or locally by suppository or enema.[34] For patients who do not respond or cannot tolerate 5-ASA, oral steroid

therapy should be considered.[35] Patients with severe disease activity should be treated directly with oral steroids in combination with a high oral dose of 5-ASA. Antibiotics are recommended in patients with signs of systemic toxicity, such as high grade fever, inflammation of the peritoneum and megacolon.[36] Patients who fail to improve with this intensive treatment should be treated with induction therapy with anti-TNF or cyclosporine.[37,38] The treatment options for maintenance of remission in UC include 5-ASA derivatives, thiopurine compounds (azathioprine or mercaptopurine) or biologicals (including infliximab, adalimumab, golimumab and vedolizumab).[39–43]
Approximately 9% of the UC patients will eventually require surgical treatment.[44] Surgical treatment is indicated in UC patients who fail medical therapy or who develop acute severe colitis or cancer.[45] As previously described, longstanding UC is associated with an increased risk of developing colorectal cancer. Therefore, in UC patients screening (chromo) colonoscopies should be initiated several years after the onset of the disease.

# Oral signs and symptoms

## Epidemiology

A limited number of studies have reported the prevalence of oral signs and symptoms in adult patients with UC. In a group of 50 patients who had an oral examination and completed an oral health questionnaire, 2 to 34% of the patients had oral signs and symptoms compared to 2 to 10% in a control group.[46] Another study found oral lesions in 32% of 121 patients with UC compared to 24% in the control group.[47]
Ulcerative colitis is associated with a variety of oral signs and symptoms. Oral signs include pyostomatitis vegetans, aphthous ulcerations, tongue coating, gingivitis and periodontitis while symptoms include halitosis, acidic taste and taste change, which also may be related to use of medication. The oral manifestations seem related to the severity of UC. Severe UC is associated with a higher prevalence of oral ulceration, tongue coating and halitosis.[46] In patients with active UC, a prevalence up to 50% was found for halitosis.[48]

# Pyostomatitis vegetans

Pyostomatitis vegetans (PV) was first described in 1949.[49] The lesions are relatively rare but they are consistently associated with inflammatory bowel disease (IBD) and more frequently associated with UC than with Crohn's disease.[50,51] The oral lesions are benign

and consist of multiple small white and yellow pustules on an erythematous and oedematous mucosal background. The pustules can rupture and fusion of the ruptured pustules can lead to a scattered, clumped or typical 'snail-track' appearance (Figure 3.5).[52–60] Histological features are intraepithelial and subepithelial microabscesses with large numbers of eosinophils and neutrophils. Hyperkeratosis and acanthosis can also be present.[50,53,59,61]

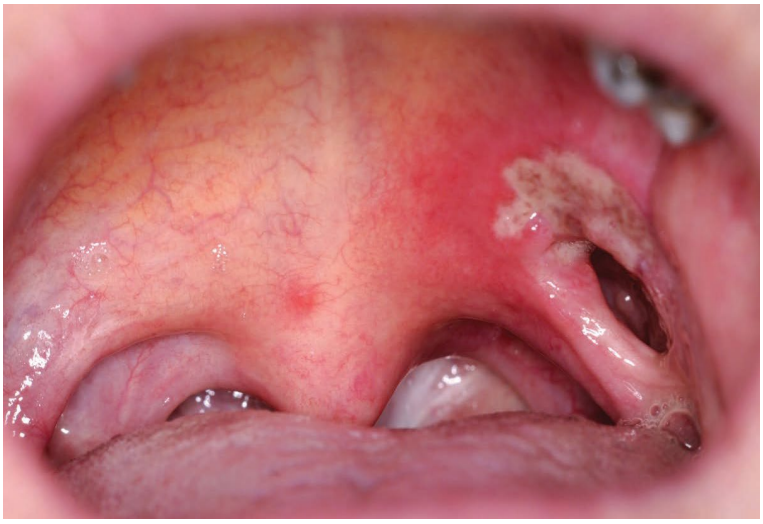

Figure 3.5 Pyostomatitis vegetans (courtesy of Dr J. R. Mekkes, department of dermatology, Academic Medical Centre, Amsterdam, the Netherlands).

Patients may experience severe oral discomfort, which is not related to clinical activity of UC, but PV lesions may also be painless.[52,61] There is a predilection for males with a male:female ratio of nearly 3:1. The lesions can occur at any age but are more prevalent between 20 and 59 years old with an average age of 34 years.[53,60,62]
Pyostomatitis vegetans can involve almost any part of the oral cavity but are most frequently observed on the labial attached gingiva, soft and hard palate, buccal mucosa and vestibular gingivae. The least affected locations are the floor of the mouth and the tongue.[52,53,58,61,62] The intestinal symptoms usually precede oral PV by several months or years.[50,63]

## Oral ulceration

Oral ulceration is the most common oral sign of UC.[46,64,65] These ulcers can present simultaneously with flare-ups of intestinal disease but can also present without intestinal disease activity.[66] The ulcers can be painful and cause discomfort. They usually heal within a couple of weeks, but new ulcers may develop resulting in a prolonged period of ulceration (Figure 3.6).[52]

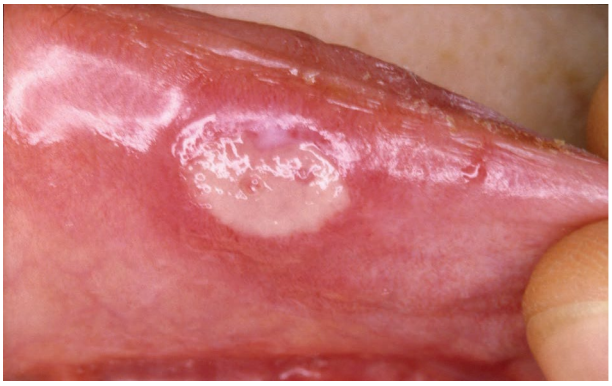

Figure 3.6 Ulcer located at the lower lip.

## Caries

To our knowledge, only one study investigated the correlation of caries and UC specifically. UC patients had a significantly higher mean Decayed-Missing-Filled-Teeth (DMFT) index compared to controls (15.3 versus 12.1).[67] Other investigators have studied the correlation of caries and IBD and found that patients with IBD have a significantly higher prevalence of dentine caries compared to controls with an odds ratio of 2.37. They also found that the plaque scores in the IBD group were significantly higher due to altered dietary habits and assume this to be the reason for the higher prevalence of dentine caries.[68]

## Periodontitis

A study of 80 UC patients observed significantly more frequently periodontitis, deeper pocket depths and fewer teeth in patients with UC compared to controls. Periodontitis

was also more common among smoking UC patients compared to smoking controls. Furthermore, UC patients had more clinical attachment loss ≥3 mm compared to CD patients, although there was no statistical difference in dental plaque scores. This finding may indicate that the response to dental plaque may differ between the two subtypes of IBD.[67,69] Another case control study with 101 UC patients also showed a much higher prevalence of periodontitis among UC patients compared to controls for the age group <45 years with an odds ratio of 7.00. The severity of the periodontitis, measured by average pocket depth and average clinical attachment loss, was also significantly greater among UC patients compared to CD patients and controls.[69] This is in contrast with the study of Grössner-Schreiber who found that IBD subjects had more generalised but less severe periodontal disease than the general population.[68]

## Other oral observations

Several studies show that halitosis is more frequent in UC patients compared to controls.[46,48] Regurgitation is also significantly more prevalent in UC patients compared to controls.[48] In a study of 50 UC patients, 20% reported a change in taste. Acidic taste and taste change were more commonly reported by patients suffering from pancolitis.[46].

## Dental management

Patients with UC have an increased risk of several oral problems. The causes are multifactorial, with the patient's altered immune status and medication as important factors. Preventive dental care of these patients with frequent dental check-ups, strict oral hygiene and the use of fluoride treatment seems recommended.[46,68]
The most important step in the treatment of the oral signs and symptoms is intestinal disease control.[64,66] Specific treatment of the oral signs and symptoms is usually not necessary, but can be indicated when the patient suffers from severe oral discomfort. Pyostomatitis vegetans can be treated with topical corticosteroids but this treatment is not always successful and usually systemic treatment is required. Successful use of azathioprine, dapsone, cyclosporine and adalimumab have been described in case reports.[50,53,60,63] The pain from aphthous ulcerations can be relieved with 2% viscous lidocaine. Use of a corticosteroid gel or mouthwash one to three times per day may stimulate healing of the ulcerations.[63]

The use of immunosuppressants for the treatment of UC is associated with a reduced number of white blood cells in approximately 5% of the patients, which subsequently may increase the risk of oral infections, like candida overgrowth. Prescribing non-steroidal anti-inflammatory drugs (NSAID) should be avoided, when possible, in patients with UC as they may trigger a flare-up of the gastrointestinal symptoms. Paracetamol can be used as an alternative for pain control.[70]

## Conclusion

Patients with ulcerative colitis may develop oral health problems. Dental clinicians need to be aware of these problems to provide personalised dental care with special attention for prevention. In complex cases, special teams consisting of dedicated dental clinicians and gastroenterologist are to be consulted.

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# Chapter 4

## Salivary function and oral health problems in Crohn's disease patients

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# Abstract

**Background**

In Crohn's disease (CD) patients, many oral complaints have been reported. The aim of this study was to determine whether salivary function is contributing to reduced oral health in CD. Oral and dental complaints in patients were explored. The prevalence of xerostomia in conjunction with salivary flow rates and biochemical saliva composition was studied.

**Methods**

The Xerostomia Inventory score (XI-score), the salivary flow rates, the concentrations of salivary amylase and mucin 5B, and the type of oral and dental complaints were evaluated. These outcomes were stratified by disease activity, using the Harvey Bradshaw Index (HBI) and the Inflammatory Bowel Disease Questionnaire (IBDQ-9).

**Results**

Fifty-three CD patients in a Dutch tertiary referral hospital were included. Of the patients evaluated, 9.4% had hyposalivation under resting conditions, and 28.3% had hyposalivation under chewing stimulated conditions. Saliva secretion rates were not correlated to XI-scores. Median XI-score was 25 (11–45). XI-scores were correlated to the IBDQ scores (r=−0.352, *P*=0.010). Salivary mucin 5B was correlated to disease activity (r=0.295, *P*=0.04). Regarding the number of oral complaints, a correlation with disease activity (HBI r=0.349, *P*=0.011) and experienced xerostomia (r=−0.554, *P*=0.000) was observed. Oral and dental problems like oral ulcers (37.7%) and cavities (46%) occurred more frequently in CD patients, especially when compared with a non-IBD population.

**Conclusions**

Oral and dental complaints are common in CD patients. Xerostomia is correlated with disease activity–associated quality of life and with the number of oral and dental complaints. Changes in salivary function may contribute to reduced oral health in CD patients.

# Introduction

Approximately one third of patients with Crohn's disease (CD) suffer from at least 1 extraintestinal manifestation during their disease.[1] A wide spectrum of oral complaints and abnormalities has been identified in CD, which can be divided into disease-specific and nonspecific symptoms.[2] Specific oral lesions resemble the characteristics of intestinal changes observed in CD, and upon histological inspection, these lesions often contain granulomas.[3,4] All tissues of the oral cavity can be affected, including teeth and salivary glands.[3,5] Both reduced saliva secretion rate and xerostomia have been reported as non-specific oral symptoms.[5-7] CD patients consider their oral health as less compared with healthy individuals, and several studies found a higher consumption of dental treatment by CD patients.[8,9]

Saliva has an important protective function against bacteria and fungi, has a maintaining function for teeth and oral mucosa, and is also important for the transport of enzymes and nutrients. Hyposalivation may lead to an increased risk of developing cavities, periodontal disease, and other oral inflammation normally prevented by antimicrobial peptides present in saliva.[10,11] This makes it essential to determine whether salivary gland hypofunction is a contributing factor to reduced oral health in CD patients.

Salivary dysfunction can be categorized into xerostomia (the subjective feeling of a dry mouth), hyposalivation (an objective reduction of salivary flow rate), and changes in salivary composition.[10] Xerostomia may be a manifestation of reduced salivary flow, but can also be a symptom on its own. Studies have shown that xerostomia can also be related to changes in the biochemical composition of saliva.[12] Mucins have an important role in the lubrication and microbial protection of the mouth. Mucin 5B (MUC5B) is the component that mainly determines the viscoelasticity of saliva.

The perception of dry mouth is thought to be influenced by MUC5B as well because it retains water in the oral mucosa.[13] Mucin 5B is mostly produced by the sublingual gland, and amylase is mainly produced by the parotid gland.[14] Amylase plays an important role in the processing of carbohydrates and contributes to the immunity of the mucosa. In periodontal disease, higher concentrations of both mucin 5B and amylase have been found, suggesting that salivary glands increase their secretion during inflammation to protect the oral cavity.[15]

The purpose of this study is to explore the potential relation between salivary function and oral and dental problems in Crohn's disease patients.

# Materials and methods

This cross-sectional study was performed at the outpatient clinic of the VU University medical center in Amsterdam, an academic tertiary referral center for inflammatory bowel disease. Patients with Crohn's disease visiting their physician were invited to participate in this study. Inclusion criteria were an established diagnosis of CD and an age of 18 years or older.[16] Non-Dutch speakers, patients with current gastrointestinal infections, and pregnant patients were excluded. Subjects were invited to stay an additional 30 minutes to determine salivary flow and fill out questionnaires concerning oral and dental complaints and CD-related gastrointestinal complaints. After collection, the saliva was stored at −18°C until biochemical analysis. The protocol was approved by the local ethics committee (number 2016.165).

## Questionnaire

The xerostomia experienced by patients was assessed with the Xerostomia Inventory (XI).[17] This internationally validated questionnaire contains 11 statements related to xerostomia, each on Likert scale, ranging from 1 (never) to 5 (often). The Harvey-Bradshaw index (HBI)[18] was used to measure CD activity in each patient. A secondary index for disease activity, the shortened and validated version of the Inflammatory Bowel Disease Questionnaire (IBDQ-9),[19,20] was used to measure disease activity and its influence on quality of life.

The number and type of oral and dental complaints were determined with an oral questionnaire of the Dutch organization for applied scientific research (TNO).[21] Because this questionnaire for oral health has been used in a large epidemiologic project in the Netherlands previously, our results could be compared with historic data.[22]

## Saliva secretion

Salivary flow rates (SFR) were measured with the spitting method.[23,24] Unstimulated whole saliva (UWS) and chewing-stimulated whole saliva (CWS) were measured separately. Subjects were asked to not eat, drink, or smoke 1 hour prior to the collection of saliva. The patients were instructed not to speak, to rinse their mouth with water, or to swallow saliva still present in their mouth, and then subsequently to drool produced saliva in a preweighted container for 5 minutes. To determine the chewing-stimulated SFR, the procedure was repeated with a second container while the patient chewed on a piece of "parafilm" of 5 x 5 cm (American National CAL, Chicago, USA). After the collection the saliva samples, the containers were reweighted, and the salivary flow rates were calculated in milliliters per minute, assuming 1 g was

considered equal to 1 mL. An UWS <0.10 mL/minute or a CWS <0.70 mL/minute was considered hyposalivation.[10,24]

## Saliva samples

The chewing-stimulated whole saliva samples were used to determine the amylase and mucin 5B concentrations. The samples were first vortexed, and centrifugation (at 4°C for 10 minutes, 10,000 g) was used to clarify the samples of any residues. The samples were then 1:1 diluted with 500 mM NaCl and divided in several aliquots. For both biochemical analyses, polystyrene microtiter plates with 96 wells were used (Greiner Bio-One microlon nr. 655151 and 655092), using a Multiscan FC microplate photometer (Thermo Scientific).

## Amylase

Human amylase was obtained from Sigma-Aldrich. Different dilutions of this amylase standard were made with amylase CNPG3 buffer (pH 6.0) to create an 8-point standard curve. The saliva samples were diluted 1:50 in amylase CNPG3 buffer to a final concentration of 1:100. Ten microliters of the samples was added in duplicate to the plate. Subsequently, 90 µl of amylase CNPG3 was added to the wells, as a direct substrate. The plate was then analysed every minute for 20 minutes at 405 nM to determine enzyme concentrations.

## MUC5B

Salivary MUC5B concentrations were determined using a previously described enzyme-linked immuno sorbent assay.[25]

The saliva samples were diluted 1:100 in 0.1 M Na CO coating buffer (pH 9.6) to a final concentration of 1:200. Then 100 µl was added in duplicate to the wells of the microtiter plate. A reference sample that contained pooled saliva of 10 different healthy volunteers was used as standard, and the concentration of MUC5B in this standard was defined as 1 arbitrary unit per milliliter. Two-fold serial dilutions, with coating buffer, were made in 7 rows of the plate. The plates were then left to incubate overnight at 4°C. The next day, monoclonal antibodies F2 (mAb F2) diluted in a PBS Tween buffer were added and incubated at 37°C for 1 hour. Subsequently antimouse HRP conjugate (P0260, DAKO) was added, and finally, o-Phenylenediamine dihydrochloride (0.4 mg/mL, Sigmafast) was also added as a substrate. The reaction was stopped after 10 minutes with 2 M H2SO4, and the color was measured at 492 nm. The outcomes will be presented as the amylase and MUC5B output; this parameter illustrates the milligrams per minute and the units per minute, respectively.

## Statistical analysis

Demographic- and disease-related outcomes were tabulated. SPSS statistics (version 22.0) was used to analyse the data. Shapiro-Wilk tests showed that the determinants, and most outcomes were not normally distributed.
The HBI scores were used to dichotomise the study population into a group with active disease and a group with inactive disease. HBI scores of 5 or higher reflect active CD.[26] Fisher exact tests were used to compare patient characteristics and complaints between patients with active and inactive disease. To compare the mean number of oral complaints, a Mann-Whitney U test was used. Correlations were explored with Spearman rank correlation tests. All levels of significance were set at $P<0.05$.

# Results

## Population characteristics

Primarily, 54 patients were included, of which 1 was excluded because of a gastrointestinal infection which severely overestimated disease activity scores. In total, 53 consecutive patients with Crohn's disease were analyzed (Table 4.1). Due to logistical reasons, 1 subject was not able to perform salivary flow tests, 1 subject's saliva samples were stored incorrectly, and another subject did not perform the CWS. These data were registered as missing.

## Salivary function

The median XI-score of the study population was 25 (11-45). The median XI-score of the active group and the nonactive group did not differ significantly.
The distribution of the UWS flow rate was skewed, with a median UWS of 0.24 mL/minute (ranging from 0.02-1.04). In 9.4% of the subjects, the UWS was less than 0.10 mL/minute, so it could be considered hyposalivation under resting conditions. The median CWS flow rate was 1.03 mL/minute (0.14-2.46), and in 28.3% it was considered hyposalivation under chewing-stimulated conditions (<0.70 mL/minute). No significant correlations were observed between the XI score and either unstimulated whole saliva or chewing-stimulated whole saliva secretion.
Median amylase concentration was 1.38 mg/mL (0.11-3.58), with a median output of 1.09 mg/minute (0.16-4.97). The median of the MUC5B concentrations was 0.22 AU/mL (0.001-1.271). The median output of MUC5B was 0.24 AU/ minute (0.00-1.43). The median ratio of amylase:MUC5B was 5.00 (0.29–14). The XI score was not significantly correlated to MUC5B output or amylase output.

Table 4.1 Patient characteristics, stratified according to their HBI score into patients with active disease (HBI≥5) and inactive disease (HBI<5).

| | All | Active (HBI≥5) | Inactive (HBI<5) | *P* |
|---|---|---|---|---|
| Total | 53 | 19 | 34 | — |
| Gender | — | — | — | 0.273 |
| Male | 22 | 6 | 16 | — |
| Female | 31 | 13 | 18 | — |
| Age (SD) | 38.2 (14.2) | 39.4 (12.2) | 37.4 (15.6) | 0.475 |
| Smoking | — | — | — | 0.465 |
| Smoker | 10 | 5 | 5 | — |
| Nonsmoker | 43 | 14 | 29 | — |
| Localization (Montreal classification) | — | — | — | 0.693 |
| Ileitis (L1) | 19 | 8 | 11 | — |
| Colitis (L2) | 10 | 4 | 6 | — |
| Ileocolitis (L3) | 24 | 7 | 17 | — |
| Uppertract | 9 | 4 | 5 | 0.706 |
| Behaviour (Montreal classification) | — | — | — | 0.343 |
| Nonstricturing, nonpenetrating (B1) | 16 | 4 | 12 | — |
| Stricturing (B2) | 11 | 3 | 8 | — |
| Penetrating (B3) | 26 | 12 | 14 | — |
| Perianal disease | 21 | 10 | 11 | 0.241 |
| Medication | — | — | — | 0.035 |
| Untreated | 12 | 2 | 10 | — |
| Corticosteroids | 1 | 0 | 1 | — |
| Immunosuppressants | 9 | 1 | 8 | — |
| Biologicals | 31 | 15 | 16 | |
| Previous surgical resection | 24 | 10 | 14 | 0.566 |
| Stoma | 7 | 2 | 5 | 1.000 |
| EIM as defined by HBI (1 or more) | 18 | 9 | 9 | 0.143 |
| Dentures | 3 | 2 | 1 | 0.290 |

* Samples were tested with Fisher exact and Mann Whitney U tests.

## Correlation between disease activity and salivary function

Disease activity (HBI) did not correlate significantly with XI-scores, UWS, and CWS. The HBI also did not correlate to the concentration of amylase and the amylase output, the MUC5B concentration, or the ratio of amylase:MUC5B. A statistical significant correlation was, however, observed with the MUC5B output (r=0.295, *P*=0.04).

Using IBDQ-9 as a secondary outcome for disease activity, a significant correlation was observed between the IBDQ score and the XI-score (r=−0.352, *P*=0.010). The IBDQ scores did not correlate significantly with the salivary secretion rates nor with MUC5B and amylase concentrations and ratio.

## Oral and dental complaints

Oral and dental problems reported by CD patients are presented in Table 4.2. Frequently reported oral health problems were oral blisters or ulcers (37.7% of patients), angular cheilitis (30.2%), bad taste (28.3%), and halitosis (20.8%).
Frequently mentioned dental problems were cavities (46.0%), gum problems (44.0%), and sensitive root surfaces (38%).

Table 4.2 Oral complaints reported by patients with Crohn's disease, stratified according to their HBI scores into patients with active disease (HBI≥5) and inactive disease (HBI<5).

| | All | Active (HBI≥5) | Inactive (HBI<5) | p |
|---|---|---|---|---|
| **Oral** | **n=53** | **n=19** | **n=34** | |
| Problems with eating or drinking | 5 (9.4) | 3 (15.8) | 2 (5.9) | 0.336 |
| Temporomandibular joint complaints | 9 (17.0) | 4 (21.1) | 5 (14.7) | 0.706 |
| Oral blisters or ulcers | 20 (37.7) | 10 (52.6) | 10 (29.4) | 0.140 |
| Red or white discolouring of mouth mucosa | 6 (11.3) | 2 (10.5) | 4 (11.8) | 1.00 |
| Angular cheilitis | 16 (30.2) | 7 (36.8) | 9 (26.5) | 0.536 |
| Irritated mouth mucosa | 7 (13.2) | 2 (10.5) | 5 (14.7) | 1.00 |
| Bad taste | 15 (28.3) | 3 (15.8) | 12 (35.3) | 0.205 |
| Reduced taste | 9 (17.0) | 4 (21.1) | 5 (14.7) | 0.706 |
| Halitosis | 11 (20.8) | 3 (3.9) | 8 (23.5) | 0.726 |
| Difficulty speaking | 1 (1.9) | 0 (0,0) | 1 (2.9) | 1.00 |
| Oral fungal infection/thrush | 5 (9.4) | 2 (10.5) | 3 (8.8) | 1.00 |
| Pain | 7 (13.2) | 3 (15.8) | 4 (11.8) | 0.691 |
| Tongue burning | 8 (15.1) | 4 (21.1) | 4 (11.8) | 0.436 |
| Median number of oral complaints (range) | | 2.0 (0.0–10.0) | 1.0 (0.0 -9.0) | 0.405 |
| **Dental** | **n=50** | **n=17** | **n=33** | **—** |
| Cavities | 23 (46.0) | 5 (29.4) | 18 (54.5) | 0.136 |
| Gum problems | 22 (44.0) | 6 (35.3) | 16 (48.5) | 0.548 |
| Loosening, missing or broken teeth | 5 (10.0) | 1 (5,9) | 4 (12.1) | 0.650 |
| Teeth malposition | 8 (16.0) | 1 (5.9) | 7 (21.2) | 0.237 |
| Sharp edges of teeth | 7 (14.0) | 2 (11.8) | 5 (15.2) | 1.000 |
| Sensitive rootsurfaces | 19 (38,0) | 7 (41.2) | 12 (36.4) | 0.767 |
| Median number of dental complaints (range) | — | 1.00 | 2.00 | 0.112 |

Data are expressed as the number of patients and in percentages.

## Relation disease activity versus oral or dental complaints

When the HBI was used to compare oral complaints of patients with active and inactive disease, patients in an active phase showed a higher prevalence of most problems, but none of these differences reached statistical significance (Table 4.2). The number of oral complaints showed a significant correlation with both HBI (r=0.349, *P*=0.011) and IBDQ (r=0.403, *P*=0.003). Dental complaints were not significantly related to HBI scores (r=−0.092, *P*=0.524) or IBDQ-9 scores (r=−0.023, *P*=0.876).

## Salivary function in relation to oral and dental complaints

XI-scores were significantly correlated to oral (r=−0.554, *P*=0.000) and dental (r=0.372, *P*=0.008) complaints (Table 4.3). UWS and CWS were not significantly correlated to oral or dental problems. No significant correlations were seen when oral and dental complaints were compared with amylase output or MUC5B output.

Table 4.3 Correlation coefficients between oral and dental complaints and salivary functions.

| | XI-score | UWS mL/min | CWS mL/min | MUC5B output mg/min | Amylase output mg/min |
|---|---|---|---|---|---|
| Oral complaints correlation coefficient | −0.554 | −0.236 | 0.014 | −0.094 | −0.201 |
| Sig. (2-tailed) | 0.000 | 0.095 | 0.921 | 0.521 | 0.150 |
| Dental complaints correlation coefficient | 0.372 | −0.208 | −0.067 | −0.212 | −0.123 |
| Sig. (2-tailed) | 0.008 | 0.155 | 0.654 | 0.158 | 0.396 |

## Oral and dental complaints in patients versus healthy subjects

For several oral and dental complaints, a comparison could be made with the TNO cohort of 1407 healthy Dutch inhabitants (Table 4.4). A considerable higher prevalence of cavities (46.0% vs. 25.0%), gum problems (44.0% vs. 24.0%), temporomandibular joint complaints (17.0% vs. 7.0%), oral blisters or ulcers (37.7% vs. 9.0%), bad taste (28.3% vs. 5.0%), and halitosis (20.8% vs. 10.0%) was observed in CD patients.

Table 4.4 Oral and dental complaints reported by patients with Crohn's diseases in comparison to healthy controls of the TNO cohort.

| **Patients** | | **Controls** |
|---|---|---|
| Oral | n=53 | n=1407 |
| Problems with eating or drinking | 9.4% | 17% |
| Temporomandibular joint complaints | 17% | 7% |
| Oral blisters or ulcers | 37.7% | 9% |
| Red or white discolouring of mouth mucosa | 11.3% | — |
| Angular cheilitis | 30.2% | — |
| Irritated mouth mucosa | 13.2% | — |
| Bad taste | 28.3% | 5% |
| Reduced taste | 17% | — |
| Halitosis | 20.8% | 10% |
| Difficulty speaking | 1.9% | — |
| Oral fungal infection/thrush | 9.4% | — |
| Pain | 13.2% | 13% |
| Tongue burning | 15.1% | — |
| Dental | n=50 | n=1407 |
| Cavities | 46% | 25% |
| Gum problems | 44% | 24% |
| Loosening, missing or broken teeth | 10% | 22% |
| Teeth malposition | 16% | 14% |
| Sharp edges of teeth | 14% | 13% |

| | | |
|---|---|---|
| Sensitive rootsurfaces | 38% | — |

## Discussion

This study investigated salivary function in patients with CD in relation to oral and dental health problems, while taking the role of intestinal disease activity into account. Regarding salivary function, surprisingly no relation between the severity of xerostomia and salivary flow rates or salivary composition was seen. Disease-associated quality of life was correlated to the severity of xerostomia experienced. Clinical disease activity had a correlation to mucin 5B output in saliva, indicating a difference in salivary composition in patients with active disease. Patients with more active disease had a higher number of oral problems, which might be attributed to salivary dysfunction. However, of the measured salivary functions in this study, only xerostomia scores were of influence on the number of oral and dental problems in patients.

Previous studies reported percentages of dry mouth symptoms in 29%-38% of Crohn's disease patients and in 4%-16% of controls, indicating a higher prevalence of dry mouth symptoms experienced by CD patients.[6,11,27–29] In our CD cohort, an XI-score of 25 was measured, being higher than the value of 16.8 in healthy controls in a previous study.[30] This indicates that CD patients experience more severe xerostomia. No significant correlation was found between the severity of xerostomia and the HBI score for clinical disease activity, which is in line with other studies.[6,7] However, the IBDQ-9 score, which takes disease-related quality of life into account was significantly correlated to the severity of xerostomia. The difference in outcome between these scores might be explained by a difference in perception in patients and a lower tolerance for any additional symptoms. Another possible explanation is that patients with xerostomia experience a lower quality of life. Additionally, it is known that clinical disease activity scores for Crohn's disease do not always portray the disease hindrance in daily life or the severity of bowel involvement.[31] Almost 10% of the CD patients suffered from hyposalivation under resting conditions, which is similar to a general population sample.[27] For CWS, hyposalivation was 28% in patients compared with 0%-5% in the general population.[32] This suggests a higher prevalence of hyposalivation under chewing-stimulated conditions in patients with CD. Previously, a relation between a very low CWS and young patients with a systemic disease was observed.[30] It is in concordance with previously performed CD studies that the salivary flow is not correlated to disease activity.[32,33] In the present study population, no significant correlation was found between the XI score and either unstimulated whole saliva or chewing-stimulated whole saliva. A potential explanation for patients experiencing

xerostomia without having reduced saliva secretions can be a difference in composition of saliva. It has been reported that saliva of IBD patients differs in composition and has different immunologic properties.[34] MUC5B is especially thought to be of influence for xerostomia because of its moisture retaining properties in saliva.[13] This study shows that there is a correlation between the MUC5B output and disease activity, meaning that saliva might become more viscous during active disease and thus during inflammation.[15] However, mean and median MUC5B concentrations are lower than found in previous studies.[28] These different results may be related to the use of the chewing-stimulated samples instead of unstimulated saliva. Further research on differences in salivary parameters of CD patients in both stimulated and unstimulated saliva seems warranted.

Patients with higher disease activity experienced a higher number of oral complaints, which is in line with previous findings.[6,7,29] Although no correlation between dental and gum related problems and disease activity was found, the incidence of oral health problems differed from healthy Dutch controls. Dental complications might take long to evolve and be caused by nutritional deficiencies, medication, oral hygiene habits or dietary factors, rather than recent disease activity.[29,35,36]

The present study has several potential limitations. The study design did not include data collection of healthy subjects. Comparison with the large TNO cohort and data from prior studies shows that a difference in occurrence of dental and oral complaints is more evident when patients and healthy individuals are compared.[6,7,35,37-39] However, it should also be noted that in the questionnaire of the TNO project, subjects were asked if these complaints occurred within the previous 6 months, instead of the 12 months used in the present study.

Secondly, this study took place in a tertiary referral center, which influences the extent of the disease and the type of medication used by patients that were included. Correction for effect modification and confounding was not included in the analysis because of the sample size. Nutritional state, type of medication, and additional comorbidity with concomitant medication may have influenced the outcomes of the study.

Despite these limitations, the present study concludes that patients with CD experience an increased severity of xerostomia and have more oral complaints. Xerostomia is not related to clinical disease activity, but is associated with quality of life. Relatively many patients suffer from hyposalivation under chewing-stimulated conditions. Salivary flow does not correlate with xerostomia complaints, indicating that patients experiencing dry mouth complaints do not necessarily have reduced saliva secretion rates. However, composition of saliva might be different, as indicated by increased mucin 5B output during active disease. Further studies on the potential contribution of an altered

salivary function to the reduced oral health of patients with Crohn's disease seem warranted.

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# Chapter 5

## Oral health and salivary function in ulcerative colitis patients

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# Abstract

**Background**

Although ulcerative colitis primarily involves the colon, extra-intestinal manifestations are common and oral and dental complaints are no exception.

**Objective**

This study aims at evaluating oral and dental health problems and salivary function and composition in ulcerative colitis patients and its correlation with disease activity.

**Methods**

Xerostomia Inventory score, (unstimulated/stimulated) salivary flow rates, salivary amylase and mucin/Mucin 5B levels, self-reported oral and dental complaints, the oral health related quality of life, Simple Clinical Colitis Activity Index and inflammatory bowel disease-specific health related quality of life were determined.

**Results**

The cohort consisted of 51 ulcerative colitis patients. Hyposalivation was experienced by 16% of patients under resting conditions and 24% under chewing-stimulated conditions. Xerostomia was not correlated with salivary flow rates. Disease activity did not influence salivary amylase and Mucin 5B concentrations. The Xerostomia Inventory score was correlated with the Simple Clinical Colitis Activity Index ($P$=0.042) and inflammatory bowel disease-specific health related quality of life ($P$=0.001). Most reported oral health problems were halitosis (29%) and aphthae (28%). Frequently reported dental problems were cavities (35%) and gum problems (31%). Patients with active disease experienced significantly more oral and dental complaints. The number of oral problems was positively correlated with the Simple Clinical Colitis Activity Index ($P$=0.045) and negatively correlated with the inflammatory bowel disease-specific health related quality of life (P=0.005).

**Conclusion**

The subjective feeling of a dry mouth (xerostomia) is related to disease activity and disease activity-associated quality of life in ulcerative colitis patients, whereas the objective saliva secretion rate is not. Oral and dental health problems are frequently observed in patients with ulcerative colitis, especially during active disease.

# Key summary

## Summarise the established knowledge on this subject

- Extra-intestinal manifestations are frequently encountered in patients with ulcerative colitis. The most common sites include the skin, eyes, joints and liver. The oral cavity is also considered as an extraintestinal site but far less studied.
- Ulcerative colitis is associated with specific and nonspecific oral signs and symptoms as halitosis, dry mouth, aphthous ulcers, pyostomatitis vegetans and lichen planus.
- Saliva is important for the maintenance of oral and general homeostasis. It has a crucial function in the digestion, hydration of the oral mucosa and protection of the teeth.

## What are the significant and/or new findings of this study?

- Patients with active ulcerative colitis experienced significantly more oral and dental complaints with a negative impact on the quality of life.
- Xerostomia, the subjective feeling of a dry mouth, was not correlated with salivary flow rates.
- Disease activity did not influence salivary amylase and MUC5B concentrations.

# Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract, which, together with Crohn's disease (CD), belongs to the family of inflammatory bowel diseases (IBD). The aetiology is considered to be a combination of genetic predisposition, environmental factors and a dysbiotic microbiota with an excessive host response.

Although the clinical presentation of patients with UC primarily involves intestinal symptoms such as abdominal pain, diarrhoea and rectal bleeding, extraintestinal manifestations (EIM) are frequently encountered. The most common EIM are located in the skin, eyes, joints and liver. The oral cavity is also considered an extra-intestinal site of involvement in UC.[1-3]

In the literature, limited studies have reported inconclusive results on the prevalence of oral and dental complaints in patients with UC.[4,5] UC is associated with specific and nonspecific oral signs and symptoms such as halitosis, dry mouth, aphthous ulcers, pyostomatitis vegetans and lichen planus.[6] Some oral manifestations seem specifically correlated with disease activity.[6]

Saliva is important for the maintenance of oral and general homeostasis. It has a crucial function in digestion, hydration of the oral mucosa and protection of the teeth. Caries, periodontal disease and other oral inflammation may be caused by a lack of antimicrobial peptides present in saliva, sometimes due to hyposalivation.[7-9]

Salivary dysfunction might result in a reduced salivary flow rate (SFR, hyposalivation), the subjective feeling of a dry mouth (xerostomia) and/or an altered biochemical composition of saliva. Although xerostomia is frequently a manifestation of reduced salivary flow, it can also be a symptom on its own. Hyposalivation can be a disabling condition, as it may cause problems with eating, speaking and sleeping and can, therefore, have a significant negative effect on a patient's quality of life.[9]

Saliva is mainly secreted by three pairs of salivary glands: parotid, submandibular and sublingual.

Mucins, mainly secreted in saliva by the submandibular and sublingual glands, are large glycoproteins that provide lubrication and microbial protection to the oral cavity. The visco-elasticity of saliva is mainly dependent on the concentration of Mucin 5B (MUC5B).[10] MUC5B retains water in the oral mucosa and therefore has an important influence on the perception of a dry mouth.[11] Amylase in saliva is particularly secreted by the parotid glands and splits high molecular-weight carbohydrates into lower molecular weight sugars.[12] Amylase also has an important role in maintaining mucosal immunity.[12,13]

Previous studies observed higher salivary concentrations of MUC5B and amylase during inflammation, possibly to protect the oral cavity by decreasing the flow rate of the salivary glands.[14] A comparable study in CD patients found a significantly higher concentration of MUC5B during active intestinal disease. This indicates a difference in salivary composition in patients with active disease.[15]
The aim of this study was to evaluate oral health problems and salivary function and composition in UC patients and its correlation with disease activity. Secondary, we wanted to evaluate the correlation between quality of life and oral health problems in UC patients with active and inactive disease activity.

# Materials and methods

## Study design and participants

This was a cross-sectional cohort study in a tertiary referral center for IBD. The study population consisted of consecutive patients with UC who visited the outpatient IBD clinic or day care unit of the Amsterdam UMC (location VUmc). Due to the absence of literature data, no power analysis could be performed. It was estimated that at least 50 subjects would be sufficient.
Inclusion criteria were a confirmed diagnosis of UC and an age of 18 years or older. Exclusion criteria were inability to read or speak Dutch and pregnancy. Subjects were asked to stay an additional 30 minutes to participate in salivary flow test and fill in five (inter) nationally validated questionnaires about their oral health, intestinal disease activity and oral health and IBD-specific health-related quality of life.

## Healthy controls

A formal control group was not included in the study. However, data from oral and dental health were obtained from a study by Kalsbeek in 2003.[16] This study investigated in detail the oral and dental health in a large cohort of healthy Dutch individuals (n=1407) after a change in the insurance system after 1995 (so-called Nederlandse Organisatie voor Toegepast-Natuurwetenschappelijk Onderzoek (TNO) cohort).

## Whole saliva secretion rates

Saliva was collected from all participating subjects. Unstimulated whole saliva (UWS) and chewing-stimulated whole saliva (CWS) were collected with the spitting method.[17] The subjects were instructed to refrain from eating, smoking and drinking during at least 1 hour prior to the collection of saliva; tap water was allowed. Before the

collection of UWS, subjects were informed to swallow saliva still present in their mouth and then to drool produced saliva for 5 minutes in a pre-weighed container. The subjects were not allowed to talk, swallow or move the tongue during these 5 minutes. To obtain CWS the procedure was repeated while the patients were asked to chew on a piece of tasteless Parafilm (5x5 cm; 0.03 g). By re-weighing the containers, we calculated the SFR, assuming 1 gram is 1 millilitre.[9] Cut-off values for hyposalivation were 0.1 mL/minute for resting whole saliva and 0.7 ml/minute for CWS.[18]

## Questionnaires

Five different questionnaires were used in this study. To quantify the xerostomia experienced by patients the Xerostomia Inventory (XI) was used. This is a validated and frequently used questionnaire that consists of 11 items, each on a five-point Likert scale.[19] The presence of oral- and dental complaints was determined by an oral health questionnaire (OHQ). The OHQ contains questions about different oral and dental complaints experienced by patients during the last 12 months. The questions need to be answered with yes or no. The Oral Health Impact Profile (OHIP-14) has been developed to assess the quality of life in relation to oral health.[20] It consists of 14 items, each on a five-point Likert scale from 0 (never) to 4 (very often) according to the frequency of the impact on the quality of life. The Simple Clinical Colitis Activity Index (SCCAI) was used to measure intestinal disease activity. A disease activity score of five or higher indicates active disease and a disease activity score under five means inactive disease.[21] To measure intestinal disease activity and its influence on the patient's quality of life the shortened and validated IBD Questionnaire (IBDQ-9) was used.[22] Responses to each item of the IBDQ-9 were scored on a seven-point Likert scale, where a score of one indicates the worst and a score of seven the best possible condition. The scores of the individual items are summed resulting in a total IBDQ-9 score ranging from nine to 63 with higher scores reflecting a better wellbeing of patients.

## Amylase and MUC5B activity in saliva

The collected UWS and the CWS saliva samples were vortexed and centrifugated. The samples were then 1:1 diluted with 500 mM NaCl and stored at –70°C until biochemical analysis. To determine the amylase activity, EnzChekVR Ultra Amylase Assay Kit was used according to the manufacturer's instructions. The saliva samples were used in a dilution of 1:100 amylase CNPG3 buffer. The reaction was measured every minute for 20 minutes and enzyme activity per minute was determined using a calibration curve. MUC5B concentration was determined by enzymelinked immunosorbent assay, using pooled saliva of healthy persons as standard reference.[23] For both biochemical analyses, polystyrene microtiter 96 wells plates were used (Greiner Bio-One microlon

nr. 655151 and 655092), using a Multiscan FC microplate photometer (Thermo Scientific). The amylase and MUC5B activity are expressed in unit/millilitres (U/mL).

### Statistical analyses

SPSS-Statistics version 25 was used for statistical analyses. The significance level was set at $P<0.05$. The primary outcomes were the XI-score, UWS and CWS. To analyse whether data were normally distributed, Kolmogorov-Smirnov and Shapiro-Wilks tests were used. The Spearman correlation test was used to analyse the correlation between the primary outcomes and IBDQ-9, SCCAI and number of oral and dental problems. Based on the SCCAI score, the study population was dichotomized into a group with active and a group with inactive disease (SCCAI score of ≥5 and <5, respectively). Chi-square tests were used to compare individual oral and dental complaints in active and inactive disease.

## Ethical considerations

The study design was reviewed and approved prior to the start of the study by the Medical Ethic Committee of the Amsterdam UMC, location VUmc (number 2018.624 and date November 2018). All subjects gave informed written consent preceding their participation in the study.

## Results

### Cohort characterization

Demographic and disease specific characteristics of the cohort of UC patients are depicted in Table 5.1. A total of 51 patients were included in the study. One patient was not able to perform the CWS and therefore registered as missing for this part of the study.

The average age of the cohort was 43.4±16.5 years, the minimum age was 18 years old and the maximum age was 77 years old. In total, 27 patients were female (52.9%) and 24 (47.1%) were male. Six of the subjects were smokers (12%). Based on the SCCAI score, 14 of the included 51 patients had active disease, whereas 37 patients were in remission. Of the cohort, 60% had a history of corticosteroid treatment and 40% had not.

Table 5.1 Demographic data of included ulcerative colitis patients.

| Characteristics | Total n=51 | Active (SCCAI≥5 n=14 | Inactive (SCCAI<5) n=37 | *P* |
|---|---|---|---|---|
| Age | 43.8 ± 16.3 | 49.64 ± 18.2 | 40.92 ± 15.4 | 0.094 |
| Participants | | | | |
| Female | 27 (52.9%) | 8 (57.1%) | 19 (51.4%) | 0.762 |
| Male | 24 (47.1%) | 6 (42.9%) | 18 (48.6%) | |
| Smoking | | | | 0.533[a] |
| Yes | 6 (11.8%) | 1 (7.1%) | 5 (13.5%) | |
| Medication (three missing data) | n=48 | n=12 | n=36 | 0.852[a] |
| None | 5 (10.4%) | 2 (16.7%) | 3 (8.3%) | |
| Aminosalicylates | 17 (35.4%) | 4 (33.3%) | 13 (36.1%) | |
| Corticosteroids | 0 | 0 | 0 | |
| Immunosuppressants | 9 (18.8%) | 1 (8.3%) | 8 (22.2%) | |
| Anti-TNF treatment | 16 (33.3%) | 5 (41.7%) | 11 (30.6%) | |
| Combination Aminosalicylates and Anti-TNF | 1 (2.1%) | 0 (0%) | 1 (2.8%) | |
| Disease extent (Montreal classification) (four missing data) | n=47 | n=12 | n=35 | 0.494[a] |
| E1 Ulcerative proctitis | 9 (19.1%) | 2 (16.7%) | 7 (20.0%) | |
| E2 Left-sided colitis | 19 (40.4%) | 4 (33.3%) | 15 (42.9%) | |
| E3 Pancolitis | 19 (40.4%) | 6 (50.0%) | 13 (37.1%) | |

Data are presented as mean ± standard deviation or number and percentage (%). Chi-square tests for categorical variables and students t test for continuous variables. [a]Mann-Whitney U test. UC: ulcerative colitis; SCCAI: Simple Clinical Colitis Activity Index.

## Disease activity associated with oral and dental complaints

In Table 5.2 the SCCAI was used to compare the frequency of oral and dental problems of the patients with active and inactive UC. Patients with active disease reported significantly more complaints of bad taste, reduced taste, halitosis and missing or broken teeth compared to patients in remission.

## Oral and dental complaints in patients versus healthy subjects

The oral and dental complaints reported by the UC patients are presented in Table 5.2. Commonly reported oral health problems were aphthae, angular cheilitis, bad taste and halitosis. Frequently witnessed dental problems were cavities, gum problems and sensitive root surfaces. Compared with a control group of 1407 healthy Dutch inhabitants (Table 5.3) differences in prevalence were found for aphthae, temporomandibular joint complaints, bad taste, halitosis and cavities.

Table 5.2 Oral and dental complaints stratified according to disease activity scores.

| | Total n=51 | Active (SCCAI2:5) n=14 | Inactive (SCCAI<5) n=37 | *P* |
|---|---|---|---|---|
| Oral complaints | | | | |
| Problems with eating or drinking | 6 (11.8%) | 2 (14.3%) | 4 (10.8%) | 0.731 |
| Temporomandibular joint complaints | 9 (17.6%) | 3 (21,4%) | 6 (16.2%) | 0.663 |
| Aphthae | 14 (27.5%) | 3 (21.4%) | 11 (29.7%) | 0.553 |
| Red or white discolouring of mouth mucosa | 4 (7.8%) | 2 (14.3%) | 2 (5.4%) | 0.292 |
| Angular cheilitis | 11 (21.6%) | 3 (21.4%) | 8 (21.6%) | 0.988 |
| Irritated mouth mucosa | 7 (13.7%) | 2 (14.3%) | 5 (13.5%) | 0.943 |
| Bad taste | 11.0 (21.6%) | 7 (50.0%) | 4 (10.8%) | 0.002[a] |
| Reduced taste | 9 (17.6%) | 5 (35.7%) | 4 (10.8%) | 0.037[a] |
| Halitosis | 15 (29.4%) | 7 (50.0%) | 8 (21.6%) | 0.047[a] |
| Difficulty speaking | 5 (9.8%) | 3 (21.4%) | 2 (5.4%) | 0.086 |
| Oral fungal infection/thrush | 2 (3.9%) | 1 (7.1%) | 1 (2.7%) | 0.466 |
| Pain | 10 (19.6%) | 4 (28.6%) | 6 (16.2%) | 0.321 |
| Burning tongue | 5 (9.8%) | 2 (14.3%) | 3 (8.1%) | 0.508 |
| Dental complaints | | | | |
| Cavities | 18 (35.3%) | 5 (35.7%) | 13 (35.1%) | 0.969 |
| Gum problems | 16 (31.4%) | 3 (21.4%) | 13 (35.1%) | 0.346 |
| Loosening, missing or broken teeth | 8 (15.7%) | 6 (42.9%) | 2 (5.4%) | 0.001[a] |
| Teeth malposition | 6 (11.8%) | 3 (21.4%) | 3 (8.1%) | 0.188 |
| Sharp edges of teeth | 7 (13.7%) | 3 (21.4%) | 4 (10.8%) | 0.325 |
| Sensitive root surfaces | 13 (25.5%) | 3 (21.4%) | 10 (27.0%) | 0.682 |

[a]Statistically significant, P<0.05. UC: ulcerative colitis, SCCAI: simple clinical colitis activity index.

Table 5.3 Oral and dental complaints compared to healthy controls.

| | UC patients | Controls |
|---|---|---|
| Oral | n=51 | n=1407 |
| Problems with eating or drinking | 11.8% | 17% |
| Temporomandibular joint complaints | 17.6% | 7% |
| Oral blisters or ulcers | 27.5% | 9% |
| Red or white discolouring of mouth mucosa | 7.8% | - |
| Angular cheilitis | 21.6% | – |
| Irritated mouth mucosa | 13.7% | – |
| Bad taste | 21.6% | 5% |
| Reduced taste | 17.6% | – |
| Halitosis | 29.4% | 10% |
| Difficulty speaking | 9.8% | – |
| Oral-fungal infection/thrush | 3.9% | – |
| Pain | 19.6% | 13% |
| Burning tongue | 9.8% | – |
| Dental | | |
| Cavities | 35.3% | 25% |
| Gum problems | 31.4% | 24% |
| Loosening, missing or broken teeth | 15.7% | 22% |
| Teeth malposition | 11.8% | 14% |
| Sharp edges of teeth | 13.7% | 13% |
| Sensitive root surfaces | 25.5% | - |

UC: ulcerative colitis.

## Saliva and hyposalivation

The XI-score was normally distributed with a mean XI-score of 23, ranging from 11 to 44.

The UWS flow rate was not normally distributed, with a median UWS of 0.26 mL/minute ranging from 0.04 to 1.40 mL/minute. Hyposalivation under resting conditions was observed in eight of the 51 patients (16%). The CWS flow rate was normally distributed.

The mean CWS rate was 1.31 mL/minute ranging from 0.06 to 3.42 mL/minute. Hyposalivation under chewing-stimulated conditions was observed in 12 of 50 patients (24%). No statistically significant correlations were detected between XI and UWS (r=-0.009, *P*=0.953) and between XI and CWS (r=-0.186, *P*=0.196), respectively.

## Correlations of intestinal disease activity with salivary function

The correlations between SCCAI and XI, UWS, CWS, salivary MUC5B and salivary amylase were analysed. A positive correlation was observed between SCCAI and XI-score (r=0.285, *P*=0.042), indicating that subjects with active disease had a more severe feeling of a dry mouth. SCCAI did not correlate with the unstimulated and stimulated saliva secretion rates (UWS r=0.139, *P*=0.332 and CWS r=-0.17, *P*=0.237). The SCCAI also did not correlate with the salivary amylase activity, the MUC5B concentrations or the ratios of amylase:MUC5B in both stimulated and unstimulated saliva, respectively.

A significant correlation was found between the IBDQ-9 score and the XI-score (r=-0.527, *P*=0.001). No correlation was observed between IBDQ-9 scores and the salivary amylase activity, the MUC5B concentrations or the ratios of amylase: MUC5B in both stimulated and unstimulated saliva.

## Correlations of disease duration and salivary function

The disease duration in this cohort ranged from 0–39 years, with a mean duration of 14 years. No statistically significant correlation was found between disease duration and the XI-score (r=-0.099, *P*=0.523). Also, no statistically significant correlations were found between disease duration and UWS (r=-0.76, *P*=0.622) and between disease duration and CWS (r=0.103, P=0.507), respectively.

## Amylase and MUC5B

The median amylase activity for UWS was 87.3 U/mL (range 0.7-836.3). The median amylase activity for CWS was 99.3 unit/mL (range 0.2-444.5). The median of the MUC5B concentration for UWS was 0.7 unit/mL (range 0-4.4) and for CWS 0.3 unit/mL (range 0-2.3). The median of the amylase:MUC5B ratio was 52.4 (range 0-2566.9) for UWS and

182.9 (range 8.3-14,821) for CWS. The XI score was not significantly correlated to the salivary amylase activity, MUC5B concentration or the amylase:MUC5B ratio.

### Oral health-related quality of life in UC patients with active and inactive disease

A near significant correlation of the OHIP-14 scores with SCCAI and IBDQ-9 was observed (r=0.280, *P*=0.051 and r=-0.274, *P*=0.057, respectively). A positive relation was found between the number of oral and dental complaints of patients and the IBDQ-9 score (r=0.393, *P*=0.005). A significant correlation was also observed between the number of oral problems and SCCAI (r=-0.285, *P*=0.045).

## Discussion

As far as we know, this is the first study that explored oral health problems and salivary function in correlation with intestinal disease activity in patients with UC. Active disease was associated with more xerostomia and a diminished quality of life, but not with objective oral dryness. No correlation was observed between the volume of secreted unstimulated and stimulated whole saliva with xerostomia. Moreover, we observed that oral and dental problems are frequently present in patients with UC, especially during active disease.

We found that the median XI-score of our cohort was 22. In a previously reported study, the median score of the healthy controls was almost 17.[24,25] In the UWS sample group, 15.7% experienced hyposalivation, which is more than in a general healthy cohort (10%) and in the CWS group 24% experienced hyposalivation, compared with 0-5% in a general population. We therefore assume that UC patients experience more severe xerostomia. A possible explanation for the xerostomia without objective oral dryness might be due to alterations during active disease in the visco-elastotic properties of the patients' whole saliva, possibly by diminished minor salivary gland secretion, failing to lubricate the mouth properly.[24] Contrary to our expectations, no relation was found between the severity of xerostomia and salivary composition. Also, no correlation was found between intestinal disease activity and MUC5B or amylase, respectively.

A higher percentage of several oral complaints was observed when we compared our UC cohort with the cohort of healthy controls. Patients with active disease reported bad taste, reduced taste, halitosis and missing or broken teeth more often when compared to patients with UC in remission. These findings are roughly in line with current literature. In a comparative Iranian cohort of 50 patients, a significant statistical

relationship was found among tongue coating, halitosis and oral ulceration in patients with severe UC compared to the control group.[4]

Recently, a similarly designed study examined xerostomia, salivary function and oral health problems among a cohort of 53 Dutch patients with CD.[15] In patients with CD no significant correlation between disease activity and xerostomia was observed. In contrast, in CD patients salivary MUC5B correlated with disease activity whereas in UC patients no correlation was found. These opposite observations might be related to the unique rheological properties of MUC5B. It contributes to the formation of the thin salivary film on the oral mucosa, which plays an important role in dry mouth perception.[26] Patients treated with radiotherapy for head-and-neck cancer with higher salivary MUC5B levels suffer less from xerostomia than patients with low levels of MUC5B in saliva.[27] Similarly, in CD patients the disease-associated increase in salivary MUC5B concentration could counteract the expected increase in the severity of xerostomia.

We also found that patients in the UC group experienced more frequent oral complaints compared to previously described CD patients.[15] This is in line with a previous review that concluded oral involvement is more pronounced in CD than UC[28] and that active inflammation has a negative influence.[29] A systemic review of nine cross-sectional studies including 1297 IBD patients also concluded that UC patients had worse oral health compared to CD patients.[30] The difference in oral health might be related to differences in immunological responses in both diseases. CD is considered to be a Th1 disease whereas UC has more characteristics of a Th2-type disease.[31]

As mentioned in the introduction, the aetiology of UC is considered to be a combination of genetic predisposition, environmental factors and a dysbiotic microbiota with an excessive host response. Proteobacteria are one of the most common phyla in the human gut microbiota and are found at different body sites, such as skin, tongue, vaginal tract and in the oral cavity.[32] Proteobacteria are often found to be increased in UC, indicating these microorganisms may carry proinflammatory characteristics.[33] There might be a relationship between oral health problems, disease activity of UC and proteobacteria.

Recently, Nanki and co-workers[34] demonstrated by exon sequencing that somatic PIGR mutations in UC result in concomitant depletion of secretory IgA in the intestinal epithelium. Immunoglobulin IgA contributes to the maintenance of the mucosal homeostasis in the colon[35] and regulates the composition and function of gut microbiota.[36]

Only a limited number of studies have investigated salivary IgA in UC and their results are inconclusive. Two studies reported that salivary IgA concentration did not differ between UC and healthy subjects.[37,38] However, another study reported a significant

negative correlation between disease activity and the concentration of IgA in whole saliva.[39] Therefore further studies on the salivary IgA concentration and its possible role in oral health problems in UC seem warranted.

The results of our study should be interpreted with some caution as we included a relatively small number of patients. The oral cavity was not inspected by a professional, instead we used questionnaires to gain an insight into the oral and dental health of UC patients. This could be considered a limitation, because patients might not be aware of all their oral and dental problems, therefore we could have missed some problems or overestimated others.

Also, we could not correct for potential effect modification and confounding, because of the small sample size. Comorbidities, medication, age, site of involvement, gender and nutritional state were not taken into account.

Another limitation of the present study is that it did not include a cohort of age- and gender-matched healthy subjects as a control group, but historical data from a large Dutch cohort from the general population. [16] However, this historical cohort appears to be quite comparable with regard to mean age (40 years) and the gender distribution (58% female, 42% male) with the cohort of UC patients in the present study (mean age 43.8 years, 53% female). Also, this study took place in a tertiary referral center, which may influence the complexity of the disease and the type of medication used by the included patients.

Our study underlines that oral health problems are common in patients with UC, especially during active disease, therefore we plea for a better communication and collaboration between gastroenterologists and dentists to strive for optimal care for UC patients. Moreover, understanding of the oral presentation of UC may improve early diagnosis and may even prevent pain and discomfort of the oral cavity and teeth. It is essential to inform the patient about the possible consequences of UC for the oral cavity.

## Conclusion

The subjective feeling of a dry mouth (xerostomia) is related to disease activity and disease activity associated quality of life in UC patients, whereas the objective saliva secretion rate is not. Oral and dental health problems are frequently observed in patients with UC, especially during active disease.

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# Chapter 6

## Dental and periodontal disease in patients with Inflammatory Bowel Disease

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# Abstract

**Objectives**

Although bowel symptoms are often predominant, inflammatory bowel disease (IBD) patients can have several oral manifestations. The aim of this study was to investigate the prevalence of dental caries and periodontal disease in patients with Crohn's disease (CD) and ulcerative colitis (UC) compared to an age and gender-matched control group of patients without IBD.

**Material and methods**

The DMFT (Decayed, Missing, Filled Teeth) scores and the DPSI (Dutch Periodontal Screening Index) of 229 IBD patients were retrieved from the electronic health record patient database axiUm at the Academic Centre for Dentistry Amsterdam (ACTA) and were compared to the DMFT scores and DPSI from age and gender-matched non-IBD patients from the same database.

**Results**

The total DMFT index was significantly higher in the IBD group compared to the control group. When CD and UC were analyzed separately, a statistically significant increased DMFT index was observed in CD patients but not in UC patients. The DPSI did not differ significantly between the IBD and non-IBD groups for each of the sextants. However, in every sextant, IBD patients were more frequently edentulous compared to the control patients.

**Conclusion**

CD patients have significantly more dental health problems compared to a control group. Periodontal disease did not differ significantly between IBD and non-IBD groups as determined by the DPSI.

**Clinical relevance**

It is important that IBD patients and physicians are instructed about the correlation between their disease and oral health problems. Strict oral hygiene and preventive dental care such as more frequent checkups should be emphasized by dental clinicians.

# Introduction

Inflammatory bowel diseases (IBD) are chronic, immune-mediated diseases of the gastrointestinal tract.[1] The exact pathogenesis is unknown, but an interaction of host susceptibility and environmental triggers appears likely.[2] The two major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any part of the gastrointestinal tract, while UC primarily affects the rectum and may extend proximally up to the entire colon.[3] The overall worldwide incidence of CD and UC ranges depending on the region from 0.0 to 29.3 and 0.15 to 57.9 per 100.000 person-years respectively.[4] Bowel symptoms are predominant, but also a variety of extra-intestinal manifestations including those affecting the oral cavity can appear. Oral manifestations reported in IBD patients are aphthous ulcerations, cobblestoning of the oral mucosa, orofacial swelling, and pyostomatitis vegetans (mainly in UC), but IBD patients also appear to have an increased risk for dental caries, periodontitis, and xerostomia.[5-8] These manifestations may coincide, precede, or follow at any time during the intestinal symptoms.[9-11]

Little is known about the dental and periodontal status of patients with IBD. The aim of this study was to investigate the prevalence of dental caries and periodontal disease in patients with CD and UC compared to an age and gender-matched control group of patients without IBD.

# Materials and methods

## Patient selection

In this retrospective study, data were retrieved from the electronic health record patient database axiUm (Exan group, Coquitlam, British Columbia, Canada) at the Academic Centre for Dentistry Amsterdam (ACTA). This database contains individual records of patients registered at ACTA since January 1, 1998. All patients visiting ACTA are obligated to fill in questionnaires including their medical history according to the European Medical Risk-Related History (EMRRH) questionnaire.[12] These data were used to retrieve patients having CD or UC. For every patient with either CD or UC, a non-IBD patient with the same age and gender was randomly selected from the electronic health record database. This non-IBD patient was matched with regard to age and gender, differed maximally 1 month of age from the IBD patient, and visited ACTA in the same year as the matched IBD patient.

## Data extraction

*Dental assessment*

The DMFT index (Decayed, Missing, Filled Teeth) was extracted from the dental charts according to the criteria of the World Health Organization.[13] The DMFT index is the sum of the number of decayed (D), missing (M), and filled (F) teeth (T). Missing and filled teeth as a result of trauma were not included. In addition to the total DMFT index, the DMFT index was registered for 6 subregions: upper front region, upper premolar region, upper molar region, lower front region, lower premolar region, and lower molar region. Edentulous IBD patients were excluded from the dental assessment.

*Periodontal assessment*

The DPSI (Dutch Periodontal Screening Index) was retrieved from the most recent checkup note or from the last periodontal chart and was registered for each sextant.[14] The DPSI is a scoring system where the severity of periodontitis is scored for each sextant on a scale from 0, 1, 2, 3−, 3+, 4, and X (see Table 6.8). Edentulous IBD patients were excluded from the periodontal assessment.
If the DMFT index or DPSI of a patient with IBD was not retrievable, this information was also left out for the matching control subject. Several potential covariates were extracted from the medical assessment form: age, gender, diabetes mellitus, xerostomia, smoking, daily intake of alcohol, and the use of IBD-related medication (corticosteroids, biologicals, immunosuppressants, and aminosalicylates). Details on medication are given in Table 6.9.

## Statistical analysis

Data are presented as means ± SD or as percentages and were statistically analyzed using SPSS Statistics for Windows, V.23.0 (Armonk, New York, USA). Data between the groups were compared using the Pearson Chi-square test. For the comparison of DMFT indices between groups, the Mann Whitney U test was used. The significance level was set at 0.05.

## Study population

A total of 229 patients with IBD were identified in axiUm and consisted of 133 females (58%) and 96 males (42%), with a mean age of 51 ± 16 years (Table 6.1). In the IBD group, 148 (65%) had CD, 80 (35%) had UC, and 1 (0.5%) reported to have IBD undetermined. The DMFT index of 17 patients was not retrievable (CD n=13, UC n=4), and in 18 cases, the DPSI was unknown (CD n=12, UC n=6). There were no significant

differences in the prevalence of diabetes mellitus between the IBD and non-IBD groups; in both groups, the percentage of patients with diabetes mellitus was 6.6%.
Subjects in the non-IBD group smoked significantly more frequently than subjects in the IBD group. There was no significant difference in the daily intake of alcohol between IBD patients and controls. More than half of the IBD patients used IBD-related medication while the control subjects seldom used these medications. A total of 36 IBD patients used corticosteroids, 27 biologicals, 25 immunosuppressants, and 59 aminosalicylates. In the control group, 1 patient used an immunosuppressant, 2 corticosteroids, and 1 patient used a biological (Table 6.1).

Table 6.1 Demographic characteristics of IBD patients (n=229) and non-IBD controls (n=229).

| | **IBD** | **Non-IBD** | ***P* value** |
|---|---|---|---|
| Male | 96 | 96 | |
| Female | 133 | 133 | |
| Mean age (years) | 51 ± 16 | 51 ± 16 | |
| Crohn's disease | | | |
| Male | 60 | | |
| Female | 88 | | |
| Total | 148 | | |
| Ulcerative colitis | | | |
| Male | 36 | | |
| Female | 44 | | |
| Total | 80 | | |
| IBD undetermined | 1 | | |
| Diabetes mellitus | 15 | 15 | |
| Smoking | 53 | 72 | 0.046 |
| Daily intake of alcohol | 19 | 17 | 0.728 |
| Use of IBD-related medication | 125 | 4 | <0.0005 |

# Results

## Dental assessment

The total DMFT index was significantly higher in the IBD group compared to the control group (Table 6.2). When stratified for 4 dental subregions in the upper and lower jaw, this difference remained significant for 3 subregions except for the upper premolar and molar region. In CD patients, the total DMFT index and the DMFT scores of the upper front, lower front, and lower premolar and molar regions were significantly higher than in the control group (Table 6.3). For the upper premolar and molar region, this difference almost reached statistical significance (*P*=0.076). There were no significant differences in total DMFT index and in DMFT scores for the 4 dental subregions in UC patients compared to the control group (Table 6.4). There were no significant differences in DMFT scores in patients with or without the use of IBD-related medication.

Table 6.2 Total DMFT indices of IBD patients (n=212) and controls (n=212), stratified for all and 4 oral regions.

| DMFT | IBD | Non-IBD | *p*-value |
|---|---|---|---|
| DMFT total | 14.3 ± 7.8 | 12.3 ± 7.0 | 0.012 |
| DMFT upper front region | 2.5 ± 2.4 | 1.9 ± 2.3 | 0.013 |
| DMFT upper (pre)molar region | 5.6 ± 2.6 | 5.3 ± 2.6 | 0.135 |
| DMFT lower front region | 1.0 ± 1.9 | 0.5 ± 1.3 | <0.0005 |
| DMFT lower (pre)molar region | 5.2 ± 2.4 | 4.7 ± 2.5 | 0.023 |

DMFT data are presented as mean ± SD.

Table 6.3 DMFT indices of CD patients (n=135) and controls (n=135), stratified for all and 4 oral regions.

| DMFT | CD | Non-IBD | *p*-value |
|---|---|---|---|
| DMFT total | 14.6 ± 8.0 | 11.8 ± 7.1 | 0.002 |
| DMFT upper front region | 2.6 ± 2.5 | 1.8 ± 2.2 | 0.004 |
| DMFT upper (pre)molar region | 5.7 ± 2.7 | 5.1 ± 2.7 | 0.076 |
| DMFT lower front region | 1.1 ± 1.9 | 0.4 ± 1.3 | 0.001 |
| DMFT lower (pre)molar region | 5.3 ± 2.5 | 4.5 ± 2.5 | 0.016 |

DMFT data are presented as mean ± SD.

Table 6.4 DMFT indices of UC patients (n=76) and controls (n=76), stratified for all and 4 oral regions.

| DMFT | UC | Non-IBD | *p*-value |
|---|---|---|---|
| DMFT total | 13.8 ± 7.5 | 13.2 ± 6.8 | 0.643 |
| DMFT upper front region | 2.2 ± 2.4 | 2.0 ± 2.3 | 0.628 |
| DMFT upper (pre)molar region | 5.5 ± 2.6 | 5.6 ± 2.4 | 0.748 |
| DMFT lower front region | 0.9 ± 1.8 | 0.6 ± 1.4 | 0.287 |
| DMFT lower (pre)molar region | 5.2 ± 2.4 | 4.9 ± 2.4 | 0.591 |

DMFT data are presented as mean ± SD

## Periodontal assessment

The DPSI did not differ significantly between the IBD and non-IBD groups for each of the sextants (Table 6.5). However, in every sextant, IBD patients were more frequently edentulous compared to the control patients. There was no significant difference in DPSI for both CD and UC patients when compared to their respective control patients (Tables 6.6 and 6.7).

The incidence of edentulism in CD patients was significantly higher compared to controls in the 1st, 2nd, 3rd, 4th, and 6th sextant (Table 6.6). UC patients did not demonstrate a significantly higher incidence of edentulism for any sextant when compared to control patients (Table 6.7). There were no significant differences in DPSI and edentulism in patients with or without the use of IBD-related medication. Xerostomia was significantly more frequently reported in IBD patients compared to the control group (8.8% vs. 2.6%, *P*=0.005). This difference was significant for CD (8.8% vs. 2.0%, *P*=0.010), but not for UC (8.6% vs. 3.7%, *P*=0.192). Xerostomia was not significantly related with the use of IBD-related medication (*P*=0.815).

Table 6.5 DPSI scores of IBD patients (n=211) compared to the control group (n=211).

| DPSI | ≤2 | 3– | 3+ | 4 | *P*-value | Edentulous | *P*-value |
|---|---|---|---|---|---|---|---|
| 1st sextant control | 83 (39%) | 61 (29%) | 17 (8%) | 34 (16%) | 0.539 | 16 (8%) | 0.040 |
| 1st sextant IBD | 78 (37%) | 50 (24%) | 11 (5%) | 43 (20%) | | 29 (14%) | |
| 2nd sextant control | 137 (65%) | 39 (19%) | 15 (7%) | 11 (5%) | 0.409 | 9 (4%) | 0.003 |
| 2nd sextant IBD | 129 (61%) | 32 (15%) | 8 (4%) | 16 (8%) | | 26 (12%) | |
| 3rd sextant control | 88 (42%) | 59 (28%) | 18 (9%) | 32 (15%) | 0.955 | 14 (7%) | 0.016 |
| 3rd sextant IBD | 79 (37%) | 61 (29%) | 16 (8%) | 26 (12%) | | 29 (14%) | |
| 4th sextant control | 100 (47%) | 60 (28%) | 15 (7%) | 31 (15%) | 0.664 | 5 (2%) | 0.001 |
| 4th sextant IBD | 82 (39%) | 64 (30%) | 19 (9%) | 24 (11%) | | 22 (10%) | |
| 5th sextant control | 166 (79%) | 18 (9%) | 12 (6%) | 12 (6%) | 0.087 | 3 (1%) | 0.018 |
| 5th sextant IBD | 155 (74%) | 25 (12%) | 5 (2%) | 14 (7%) | | 12 (6%) | |
| 6th sextant control | 103 (48%) | 55 (26%) | 13 (6%) | 35 (17%) | 0.574 | 5 (2%) | 0.005 |
| 6th sextant IBD | 90 (43%) | 62 (29%) | 14 (7%) | 27 (13%) | | 18 (9%) | |

DPSI scores 0, 1, and 2 were combined because these categories indicate no clinical attachment loss. The DPSI scores and the percentage of edentulism in each sextant were compared using Chi-square tests.

Table 6.6 DPSI scores of CD patients (n=136) compared to the control group (n=136).

| DPSI | ≤2 | 3– | 3+ | 4 | *P*-value | Edentulous | *P*-value |
|---|---|---|---|---|---|---|---|
| 1st sextant control | 57 (42%) | 43 (32%) | 9 (7%) | 19 (14%) | 0.903 | 8 (6%) | 0.017 |
| 1st sextant CD | 48 (35%) | 36 (27%) | 8 (6%) | 24 (18%) | | 20 (15%) | |
| 2nd sextant control | 90 (66%) | 27 (20%) | 8 (6%) | 6 (4%) | 0.578 | 5 (4%) | 0.008 |
| 2nd sextant CD | 80 (59%) | 22 (16%) | 7 (5%) | 10 (7%) | | 17 (13%) | |
| 3rd sextant control | 59 (43%) | 42 (31%) | 10 (7%) | 18 (13%) | 0.754 | 7 (5%) | 0.013 |
| 3rd sextant CD | 48 (35%) | 41 (30%) | 11 (8%) | 17 (13%) | | 19 (14%) | |
| 4th sextant control | 65 (48%) | 43 (32%) | 6 (4%) | 19 (14%) | 0.125 | 3 (2%) | 0.003 |
| 4th sextant CD | 52 (38%) | 43 (32%) | 15 (11%) | 11 (8%) | | 15 (11%) | |
| 5th sextant control | 110 (81%) | 13 (10%) | 5 (4%) | 6 (4%) | 0.522 | 2 (2%) | 0.053 |
| 5th sextant CD | 101 (74%) | 15 (11%) | 4 (3%) | 8 (6%) | | 8 (6%) | |
| 6th sextant control | 63 (46%) | 42 (31%) | 11 (8%) | 17 (13%) | 0.817 | 3 (2%) | 0.028 |
| 6th sextant CD | 58 (43%) | 44 (32%) | 10 (7%) | 13 (10%) | | 11 (8%) | |

DPSI scores 0, 1, and 2 were combined because these categories indicate no clinical attachment loss. The DPSI scores and the percentage of edentulism in each sextant was compared using Chi-square tests.

Table 6.7 DPSI scores of UC patients (n=74) compared to the control group (n=74). DPSI scores 0, 1, and 2 were combined because these categories indicate no clinical attachment loss.

| DPSI | ≤2 | 3– | 3+ | 4 | *P*-value | Edentulous | *P*-value |
|---|---|---|---|---|---|---|---|
| 1st sextant control | 25 (34%) | 18 (24%) | 8 (11%) | 15 (20%) | 0.245 | 8 (11%) | 0.797 |
| 1st sextant UC | 30 (41%) | 14 (19%) | 2 (3%) | 19 (26%) | | 9 (12%) | |
| 2nd sextant control | 46 (62%) | 12 (16%) | 7 (10%) | 5 (7%) | 0.398 | 4 (5%) | 0.147 |
| 2nd sextant UC | 48 (65%) | 10 (14%) | 1 (1%) | 6 (8%) | | 9 (12%) | |
| 3rd sextant control | 29 (39%) | 16 (22%) | 8 (11%) | 14 (19%) | 0.659 | 7 (10%) | 0.439 |
| 3rd sextant UC | 30 (41%) | 20 (27%) | 5 (7%) | 9 (12%) | | 10 (14%) | |
| 4th sextant control | 35 (47%) | 16 (22%) | 9 (12%) | 12 (16%) | 0.492 | 2 (3%) | 0.085 |
| 4th sextant UC | 29 (39%) | 21 (28%) | 4 (5%) | 13 (18%) | | 7 (10%) | |
| 5th sextant control | 55 (74%) | 5 (7%) | 7 (10%) | 6 (8%) | 0.149 | 1 (1%) | 0.172 |
| 5th sextant UC | 53 (72%) | 10 (14%) | 1 (1%) | 6 (8%) | | 4 (5%) | |
| 6th sextant control | 39 (53%) | 13 (18%) | 2 (3%) | 18 (24%) | 0.511 | 2 (3%) | 0.085 |
| 6th sextant UC | 31 (42%) | 18 (24%) | 4 (5%) | 14 (19%) | | 7 (10%) | |

The DPSI scores and the percentage of edentulism in each sextant was compared using Chi-square tests.

## Discussion

This study investigated dental and periodontal disease in patients with IBD. Dentate CD patients had a higher DMFT index than the control group. There were no significant differences in the DMFT index of UC patients compared to the control group. There were no significant differences in periodontal disease as determined by the DPSI between dentate IBD patients and the control group. Both CD and UC patients did not show any significant differences in DPSI when compared to the control group.

As a small dental restoration equally contributes to the DMFT index as a missing tooth, this could mean that IBD patients potentially still have the same number of functional teeth as control subjects. However, analyzing the DPSI data, it was shown that IBD patients had significantly more edentulous sextants than control subjects (Table 5). This is in contrast with a reported study that found no significant difference in the number of teeth present between IBD and non-IBD patients.[8] A possible explanation may be that their patient group was considerably younger than the IBD population in the present study (mean age 38.4 ± 10.2 vs. 51 ± 16 years), which may have contributed to the differences in missing teeth. An additional argument for that is that the same study found a higher prevalence of dentine caries in IBD patients (40% vs. 22% in the controls) which might be a reason for tooth loss with aging. A more recent study investigated a cohort more similar in age to the present study (mean age; CD 53.1 ± 10.3 years, UC 57.0 ± 8.2 years) and reported that IBD patients needed more treatments to prevent tooth loss.[15] This is in accordance with findings in the present study.

Several studies have reported an increased DMFT index for CD patients.[16-19] It has been suggested that patients with CD may have a higher incidence of dental caries because of nutritional deficiencies, changes in salivary conditions, and oral microflora.[20] CD patients have increased numbers of Lactobacilli and Streptococcus mutans in the oral cavity which seems to be related to a more frequent intake of refined sugars by CD patients.[8,16,20-22] In the present study, xerostomia was significantly more frequently reported by CD patients compared to the controls. Although xerostomia is not always related to hyposalivation, previous studies have shown that CD and UC patients can have hyposalivation in resting and chewing-stimulated conditions and that the composition of the saliva in CD patients may be correlated to bowel disease activity.[7,23] A decreased salivary flow increases the risk of developing dental caries and might have contributed to the increased DMFT index in patients with CD.[24]

Only three previous studies reported a significantly higher DMFT index in UC patients.[17-19] These studies were performed in China, Brazil, and Greece, so dissimilarities in comparison to a western European population cannot be excluded.

Furthermore, in the Greek study, only children and adolescents were investigated while in the present study, only adult patients were included.[18] The Brazilian study adjusted in the statistical analysis for plaque levels.[17] In the Greek study, no significant differences in plaque scores were found. As plaque scores were not included in the present study, we cannot exclude the possibility that the control subjects may had higher plaque scores than UC patients. Another study reports higher caries treatment needs in UC patients when compared with controls, but the differences were less clear than in patients with CD and it was speculated that this was caused by a higher sugar intake in CD patients compared to UC patients.[15,21,25]

Periodontitis and IBD are both considered to be a disproportionate mucosal inflammatory response to microorganisms in susceptible patients. Recent reviews of epidemiological studies conclude that there seems to be increasing evidence for a correlation between IBD and periodontal disease.[19,26-28] The present study failed to produce evidence for a correlation between IBD and periodontal disease. When CD and UC groups were compared separately with the controls, there was no significant difference in the DPSI between the patients and their controls. Also, the clinically higher scores 3+ and 4, which indicate clinical attachment loss and thus indicate periodontitis, were not significantly different. A higher prevalence of periodontitis was reported in IBD patients; however, smoking turned out to be an effective modifier since there was no difference in the prevalence of periodontitis among non-smoking control patients and non-smoking patients with IBD.[17] It was found that clinical signs of gingivitis and periodontitis were higher among IBD patients, but that not smoking decreased the risk of periodontitis.[29] In the present study, control patients smoked significantly more than IBD patients which might explain why the DPSI is not significantly different. As smoking is a known risk factor for periodontitis, we have to interpret the findings of this study regarding the DPSI with caution.[30,31] An increased prevalence and severity of periodontal disease for IBD patients was reported; however, this study was performed in a Middle-Eastern population with a poor average level of oral hygiene, as more than 20%of the included IBD patients stated that they never had brushed their teeth.[32] Other studies found results comparable to the present study and also showed no significant differences in periodontal disease between IBD and non-IBD groups.[8,15] It should be taken into consideration that various other factors such as oral hygiene, poorly controlled diabetes, and smoking history are also risk factors for periodontal disease[33,34] and these factors differed considerable between the previously discussed studies. Furthermore, different methods were used for the assessment of the absence, and presence, and the degree of periodontal disease. To our knowledge, the present study is the first that used DPSI scores in IBD patients. The DPSI is a relatively easy and fast screening method to determine periodontal disease which makes it ideal

for routine dental checkups but due to its low specificity, it is not well suited for epidemiological studies.[14] This is because the site with the highest probing depth determines the score for the whole sextant. A patient who has only one site with a periodontal pocket depth of e.g., 6 mm per sextant therefore has the same score as someone who has multiple sites per sextant with the same pocket depth. A full periodontal status would give much more detailed information about the actual severity of periodontal disease.

The present study has several limitations. One of the most important is the retrospective design. The data extracted from the patient records had not been gathered specifically for this study. The dental records were not complete for all patients with IBD and in many cases did not contain information about the current oral hygiene status, plaque index, and dietary habits of the patient. Although registered whether a patient was smoking or not, the number of pack-years was not registered. Oral hygiene has a crucial impact on the DMFT index and the DPSI. For instance, the use of interdental cleaning aids has a huge role in preventing dental decay and periodontal diseases. Some studies have suggested a higher plaque index and bad dietary habits in IBD patients.[8,16,32] A higher plaque index in IBD patients was attributed to insufficient oral hygiene because of painful oral manifestations.[8] Therefore, future studies on the influence of oral hygiene habits on dental and periodontal diseases of IBD patients seem warranted.

Statistical significance depends on sample size and expected effect. Recent studies reported statistically significant differences for DMFS and periodontal disease in patients with UC compared to healthy controls.[19,28] The fact that no significant differences were observed for patients with UC in the present study might be related to the relatively small size of this subgroup of IBD patients. Therefore, a multi-center trial to explore DMFS and periodontal disease in patients with UC seems warranted.

Another possible limitation is that the presented periodontal data are based on the most recent dental evaluation rather than the initial periodontal evaluation during the initial visit of the patients. It could be possible that patients with periodontal disease already had received periodontal therapy and were under supportive therapy during the periodontal evaluation on the last dental checkup. However, as this also applies to non-IBD group, both groups are comparable in this aspect. Nevertheless, it will be interesting to investigate the initial periodontal evaluation with full-mouth measurements of pocket depth, clinical attachment loss, bleeding on probing, and plaque index in future clinical studies.

ACTA is an academic dental school, where most dental checkups are performed by a large number of students. As formal clinical calibration between these students is lacking, this could also have introduced for some inconsistencies in the data.

Despite the limitations, the present study did show that CD patients had a significantly higher DMFT index compared to a control group. IBD exhibits how a systemic disease can complicate and provoke predisposing factors. Hence, it is important that these patients are instructed about the correlation between their disease and dental health problems. Strict oral hygiene and preventive dental care such as more frequent checkups should be emphasized by dental clinicians.

# Appendix 1

Table 6.8 The Dutch Periodontal Screening Index scoring system.

| **DPSI** | |
|---|---|
| 0 | - Probing depth ≤3mm<br>- No bleeding on probing<br>- No dental tartar<br>- No overhanging restorations |
| 1 | Same as 0, but bleeding on probing |
| 2 | Same as 1, but with dental tartar and/or overhanging restorations |
| 3– | Probing depth of 4-5 mm without gingival recession |
| 3+ | Probing depth of 4-5 mm with gingival recession |
| 4 | Probing depth ≥6mm |
| X | Edentulous |

1st sextant: right upper (pre)molar region, 2nd sextant: upper front region, 3rd sextant: left upper (pre)molar region, 4th sextant: left lower (pre)molar region, 5th sextant: lower front region, 6th sextant: right lower (pre)molar region

# Appendix 2

Table 6.9 List of medication used in treatment of inflammatory bowel disease in the Netherlands

| **Corticosteroids** | **Biologicals** | **Immunosuppressants** | **Aminosalicylates** |
|---|---|---|---|
| Beclometasone | Adalimumab | Azathioprine | Mesalazine |
| Betamethasone | Golimumab | Mercaptopurine | Olsalazine |
| Budesonide | Infliximab | Tioguanine | Sulfasalazine |
| Dexamethasone | Vedolizumab | Methotrexate | Salazopyrine |
| Methylprednisolone | Ustekinumab | Tacrolimus | |
| Prednisolone | | Ciclosporine | |
| Prednisone | | | |
| Triamcinolone | | | |
| Triamcinolonacetonide | | | |
| Hydrocortisone | | | |
| Cortiment | | | |
| Entocort | | | |

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# Chapter 7

## A self-reported survey on oral health problems in patients with inflammatory bowel disease with a stoma

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# Abstract

**Objectives**

Patients with inflammatory bowel disease have an increased risk of developing oral health problems. The aim of this study was to investigate whether oral diseases in these patients are related to inflammation of the intestine and if there is a correlation between inflammatory bowel disease-specific health-related quality of life (IBD-HR-QOL) and oral health problems.

**Study design**

The study was a cross-sectional survey and analysis of self-reported oral health of individuals with a stoma for Crohn's disease (CD), ulcerative colitis (UC), and treated colon cancer (CC). Validated international questionnaires were sent to members of the Stoma Federation of The Netherlands. Because there was an unequal distribution of male and female patients with CD and CC, data of 169 age-matched female patients with CD, UC, and CC with a stoma were analyzed.

**Results**

Patients with CD had significantly more oral health problems compared with those with UC or CC. Patients with CD and UC both had significantly more gingival-related problems compared with patients with CC. There was a significant negative correlation between IBD-HR-QOL and oral health problems.

**Conclusions**

In the 3 distinguishable groups of patients with a stoma, patients with CD had an increased risk for oral health problems, independently from surgical removal of (a part of) the inflamed intestine, suggesting a general increased susceptibility of patients with CD for oral health problems.


## Statement of Clinical Relevance

Patients with inflammatory bowel disease, particularly those with Crohn disease, have an increased risk for oral health problems, which remains after surgical removal of (a part of) the inflamed intestine, necessitating special attention to their oral health from gastroenterologists and dentists.

# Introduction

Inflammatory bowel disease (IBD) is a chronic, recurring and often disabling disorder of the gastrointestinal (GI) tract. The 2 main types of IBD are Crohn disease (CD) and ulcerative colitis (UC).[1] CD can affect any part of the GI tract, whereas UC mainly affects the rectum and may extend proximally up to the entire colon.[2,3] Clinical symptoms involve abdominal pain, cramps, diarrhea, melena, vomiting, fatigue, weight loss, and sometimes fistula.[4,5] Both types of IBD usually show episodes of clinical activity, characterized by exacerbations or flares interspersed with asymptomatic intervals or remissions. The overall worldwide incidence of CD and UC, depending on the region, ranges from 0.0 to 29.3 and 0.15 to 57.9 per 100,000 person-years, respectively.[6] IBD is currently not curable, and treatment is aimed at symptomatic relief, reduction of inflammation during exacerbations, maintenance of remission, and increasing quality of life. Surgical treatment is indicated in patients who fail drug treatment or develop severe complications, and approximately 20% of patients with UC and 80% of patients with CD will eventually require surgery.[7]

Although IBD primarily involves the bowel, patients also have a risk of developing oral health problems. The prevalence of oral health problems is higher in patients with CD than in those with UC.[8] Oral diseases that have been reported in patients with IBD are, among others, mucosal ulceration, mucosal swelling and cobblestoning, orofacial granulomatosis, xerostomia, and an increased risk for dental caries, gingivitis, and periodontitis.[9-12] Patients with active CD suffer more from xerostomia[13] and have higher salivary levels of Streptococcus mutans, a microorganism that is highly associated with origin of dental caries.[14] In 2011, in a case report published in the patient magazine of the Stoma Federation of The Netherlands, the patient stated that she had fewer oral health problems after surgical removal of the inflamed part of her intestine.[15]

The aim of this study was to investigate whether resection of (a part of) the inflamed intestine may be related to self-reported oral health problems in patients with IBD and, secondary, if there is an association between IBD-specific health-related quality of life (IBD-HRQOL) and oral health problems.

# Materials and methods

The study was a cross-sectional survey of self-reported oral health status in 2 groups of patients with a stoma for chronic intestinal inflammation (CD and UC). Patients with a stoma for a noninflammatory cause (surgically treated colon carcinoma [CC]) served as control group. The first part of the questionnaire was related to the presence of a

stoma and contained the 9 items of the shortened IBDQ-9 (Inflammatory Bowel Disease Questionnaire-9).[16,17] Responses to each item of the IBDQ-9 were scored on a 7-point Likert scale, in which a score of 1 indicates the worst and a score of 7 the best possible condition. The scores of the individual items were summed, resulting in a total IBDQ-9 score ranging from 9 to 63, with higher scores reflecting a better health status of patients.

The second part of the questionnaire contained the oral health problems of the Toegepast-Natuurwetenschappelijk Onderzoek (TNO) oral health questionnaire,[18] with 2 additional questions about the oral hygiene practices of the participants. The TNO oral health questionnaire consisted of 21 questions about oral health practices in the last 12 months, with the answer options being “yes” or “no.” A group without a stoma was not included in the study. However, data on oral health was obtained from a study by Kalsbeek et al. That study had investigated the differences in oral health in the general population in The Netherlands (n=1407) after the change in the insurance system in 1995 (TNO-cohort).[18]

The third part of the questionnaire was the Xerostomia Inventory (XI),[19] an internationally validated questionnaire to quantify the severity of xerostomia. The XI comprises 11 items on a Likert scale of 1 to 5, corresponding to the answers “never”, “hardly ever”, “occasionally”, “fairly often”, and “very often”. The responses to the individual items were summed to a total XI score ranging from 11 (no xerostomia) to 55 (extreme xerostomia).

The final part of the questionnaire related to information about the frequency of visits to the dental office during the past 12 months and contained general questions on age, gender, work experience, and educational level.

The questionnaire was programmed in NewCom Research & Consultancy software version 3.38, and a “closed” web link to the questionnaire was distributed to all 2180 resident members of the Stoma Federation of The Netherlands. Completion of the questionnaire was on a voluntary base and completely anonymous. After a week, the members were sent a reminder via email, and in addition, a public access “open link” was created and made available through social media: Facebook, Twitter, and a digital newsletter. The questionnaire was closed exactly 3 weeks after the initial access date. Members of the Dutch Stoma Association without online access could request a printed version of the questionnaire. The collected data were downloaded into an Excel spreadsheet.

This study followed the tenets of the Declaration of Helsinki on medical protocol and ethics, and the data were collected in accordance with the guidelines of the Medical Ethical Committee of the VU University Centre. The Ethics Review Committee of the VU University confirmed that the Medical Research Involving Human Patients Act (WMO)

did not apply to this study, and therefore, institutional review board approval was not required.

## Statistical analysis

Data were expressed as mean ± standard deviation (SD) or percentages and were analyzed statistically with SPSS Statistics for Windows version 25.0 (SPSS Inc., Chicago, IL). $\chi^2$ tests were used to determine whether sample frequencies differed significantly. Differences between median values were established by using the Kruskal-Wallis test, followed by Mann-Whitney tests as a post hoc procedure, where appropriate. Correlations were explored by using Spearman's rank order correlation tests. Statistical significance was set at $P<0.05$.

The total number of returned questionnaires was 773. Of these, 125 questionnaires were incomplete, and 7 members reported that they did not have a stoma, resulting in 641 respondents, with equal numbers of male and female respondents. Of the respondents, 171 had other reasons for their stoma (e.g., bladder dysfunction, preventive removal because of a genetic disorder, or removal as a result of an accident). In the CD group, there were far more females than males; in the UC group, males and females were equally distributed; and in the CC group, there were more males than females (Table 7.1). With regard to age and gender differences ($\chi^2$ test: males vs females: $P<0.001$), we decided to analyze age-matched female patients with CD, UC, or CC with a stoma.

Table 7.1 Reason for stoma, stratified according to gender.

| | **All (n=470)** | **Males (n=259)** | **Females (n=211)** |
|---|---|---|---|
| Crohn disease | 78 | 16 | 62 |
| Ulcerative colitis | 120 | 64 | 56 |
| Colon cancer | 272 | 179 | 93 |

$\chi^2$ test: males versus females: $P<0.001$.

# Results

Female patients with CD had a significantly higher total XI score compared with patients with UC or CC. Statistical differences between the groups were found for the following individual items of the XI: "The skin of my face feels dry" and "My lips feel dry". Female patients with CD reported more that their skin and lips felt dry compared with patients with CC, but not those with UC. Female patients with UC also reported dry skin of the face more than did CC patients. Female patients with CD had a significantly lower IBDQ-

9 score compared with those with UC or CC, reflecting the poorer health status of patients with CD (Table 7.2).

Table 7.2 Age-matched groups of female patients with CD, UC, or CC and XI and IBDQ-9 scores.

| | CD (n=60) | UC (n=54) | CC (n=55) | *P* value |
|---|---|---|---|---|
| Age | 53.8 ± 11.9 | 53.2 ± 11.8 | 57.6 ± 6.5 | 0.080 |
| XI score | 30.9 ± 7.4 | 28.1 ± 6.3* | 26.7 ± 6.5* | 0.004 |
| IBDQ-9 | 44.1 ± 12.0 | 48.8 ± 10.0* | 50.3 ± 7.9* | 0.003 |

*Chi-square test: *P*<0.05 versus CD.*CC,* colon cancer; *CD,* Crohn disease; *IBDQ-9,* Inflammatory Bowel Disease Questionnaire-9; *UC,* ulcerative colitis; *XI,* Xerostomia Inventory.

Table 7.3 shows the results of self-reported oral health problems in age-matched female patients with CD, UC, or CC with a stoma and in the general population. Female patients with CD reported a significantly higher mean number of oral health problems compared with the other 2 groups, in which the patients experienced discolorations of the oral mucosa, irritated oral mucosa, and pain significantly more frequently than patients with UC and CC. Bad taste was more frequently reported by patients with CD than by those with UC but did not differ significantly from patients with CC. Female patients with CD suffered from angular cheilitis and oral blisters or aphthae significantly more frequently than did patients with CC, but not significantly more than patients with UC.

Table 7.3 Self-reported oral health problems in age-matched female patients with CD, UC, or CC with a stoma.

| | CD (n=60) | UC (n=54) | CC (n=55) | *P* value | General population (n=1407) |
|---|---|---|---|---|---|
| Problems with eating/drinking | 10 (17%) | 8 (15%) | 5 (9%) | 0.473 | 17% |
| Temporomandibular joint complaints | 11 (18%) | 8 (15%) | 7 (13%) | 0.700 | 7% |
| Oral blisters or aphthae | 27 (45%) | 18 (33%) | 10 (18%)* | 0.009 | 9% |
| Discolorations of the oral mucosa | 16 (27%) | 2 (4%)* | 2 (4%)* | 0.000 | - |
| Angular cheilitis | 20 (33%) | 10 (19%) | 7 (13%)* | 0.022 | - |
| Irritated oral mucosa | 18 (30%) | 4 (7%)* | 7 (13%)* | 0.003 | - |
| Bad taste | 18 (30%) | 6 (11%)* | 10 (18%) | 0.039 | 5% |
| Decreased taste | 15 (25%) | 9 (17%) | 9 (16%) | 0.412 | - |
| Halitosis | 10 (17%) | 11 (20%) | 9 (16%) | 0.829 | 10% |
| Bad odor | 12 (20%) | 10 (19%) | 9 (16%) | 0.880 | - |
| Problems with speaking | 6 (10%) | 2 (4%) | 2 (4%) | 0.248 | - |
| Oral fungus | 7 (12%) | 2 (4%) | 2 (4%) | 0.131 | - |
| Pain | 17 (28%) | 7 (13%)* | 3 (6%)* | 0.003 | 13% |
| Burning tongue | 9 (15%) | 4 (7%) | 7 (13%) | 0.442 | - |
| Other mouth problems | 14 (23%) | 12 (22%) | 7 (13%) | 0.298 | - |
| Mean of number of oral health problems (+ SD) | 3.5 ± 3.3 | 2.1 ± 1.8† | 1.7 ± 2.6† | 0.001 | |

*$\chi^2$ test: *P*<0.05 versus CD. †Kruskal-Wallis test: *P*<0.05 versus CD.*CC,* colon cancer; *CD,* Crohn disease; *SD,* standard deviation; *UC,* ulcerative colitis.

Table 7.4 shows the results of self-reported dental problems of dentate female patients with CD, UC, or CC with a stoma and of the general population. Dentate female patients with CD or UC with a stoma experienced gingival problems both significantly and more frequently than did patients with CC. No differences in frequency of gingival problems were observed between patients with CD and those with UC. There were significant differences among the 3 groups with regard to other tooth-related problems.

Table 7.4 Self-reported dental problems of dentate female patients with CD, UC, or CC with a stoma.

| | **CD (n=55)** | **UC (n=51)** | **CC (n=50)** | ***P* value** | **General population (n=1407)** |
|---|---|---|---|---|---|
| Cavities | 16 (29%) | 20 (39%) | 17 (34%) | 0.546 | 25% |
| Gingival problems | 34 (62%) | 25 (49%) | 13 (26%)* † | 0.001 | 24% |
| Missing/loose teeth | 6 (11%) | 7 (14%) | 6 (12%) | 0.906 | 22% |
| Malposition of teeth | 3 (6%) | 7 (14%) | 4 (8%) | 0.316 | 14% |
| Sharp teeth | 10 (18%) | 7 (14%) | 5 (10%) | 0.483 | 13% |
| Sensitive exposed root surfaces | 32 (58%) | 25 (49%) | 21 (42%) | 0.250 | - |
| Other problems | 5 (9%) | 14 (28%) | 6 (12%) | 0.023 | - |
| Mean of total number of tooth problems (+ SD) | 1.9 ± 1.4 | 2.0 ± 1.7 | 1.4 ± 1.4 | 0.102 | |

*$\chi^2$ test: *P*<0.05 versus CD. †$\chi^2$ test: *P*<0.05 versus UC.*CC,* colon cancer; *CD,* Crohn disease; *SD,* standard deviation; *UC,* ulcerative colitis.

Table 7.5 shows the results of self-reported swelling of the orofacial areas of female patients with CD, UC, or CC with a stoma. Female patients with UC less frequently reported swelling of the lips and a significantly lower number of orofacial swelling problems compared with patients with CD or CC.

Table 7.5 Self-reported swelling of the orofacial area of female patients with CD, UC, or CC with a stoma.

| | **CD (n=60)** | **UC (n=54)** | **CC (n=55)** | ***P* value** |
|---|---|---|---|---|
| Swelling of lips | 8 (13%) | 0 (0%)* | 2 (4%) | 0.007 |
| Swelling of buccal oral mucosa | 6 10%) | 3 (6%) | 3 (6%) | 0.553 |
| Swelling of the face | 5 (8%) | 1 (2%) | 2 (4%) | 0.239 |
| Mean number of orofacial swelling problems (+ SD) | 0.3 ± 0.7 | 0.0 ± 0.3† | 0.1 ± 0.5 | 0.040 |

*$\chi^2$: *P*<0.05 versus CD. †Mann-Whitney U test: *P*<0.05 versus CD.*CC,* colon cancer; *CD,* Crohn disease; *SD,* standard deviation; *UC,* ulcerative colitis.

Tables 7.6 and 7.7 show that there were no statistical differences in the frequency of tooth brushing and use of interdental cleaning devices among the 2 groups for females.

Table 7.6 Frequency of tooth brushing of female patients with CD, UC, or CC with a stoma.

| Times a day | CD (n=55) | UC (n=51) | CC (n=50) |
|---|---|---|---|
| 1 | 9 (16%) | 9 (18%( | 9 (18%) |
| 2 | 38 (69%) | 31 (61%) | 35 (70%) |
| 3 | 7 (13%) | 9 (18%) | 4 (8%) |
| Ø3 | 1 (2%) | 2 (4%) | 2 (4%) |

$\chi^2$ test: *P*=0.084. *CC,* colon cancer; *CD,* Crohn disease; *UC,* ulcerative colitis.

Table 7.7 Use of interdental cleaning devices by female patients with CD, UC, or CC.

| | CD (n = 55) | UC (n = 51) | CC (n = 50) | *P* value |
|---|---|---|---|---|
| Tooth picks | 24 (44%) | 23 (45%) | 30 (60%) | 0.187 |
| Floss | 22 (40%) | 21 (41%) | 20 (40%) | 0.990 |
| Interdental brushes | 31 (56%) | 25 (49%) | 26 (52%) | 0.748 |
| Other devices | 1 (2%) | 3 (6%) | 5 (10%) | 0.199 |
| No devices | 6 (11%) | 7 (14%) | 4 (8%) | 0.653 |

*CC,* colon cancer; *CD,* Crohn disease; *UC,* ulcerative colitis.

Table 7.8 shows the relationship among the IBDQ-9 score and the total number of oral health problems, total number of orofacial swelling problems, and XI scores in female patients with a stoma.

Table 7.8 Spearman's rank order correlations between IBDQ-9 score and total number of oral health problems (TNOHP), total number of orofacial swelling problems (TNSP) and XI score in female stoma patients.

| | Crohn's disease (n = 60) | Ulcerative colitis (n = 54) | Colon cancer (n = 55) |
|---|---|---|---|
| IBDQ-9 score and TNOHP | r=-0.638 *P*<0.001 | r=-0.358 *P*<0.001 | r=-0.380 *P*=0.004 |
| IBDQ-9 score and TNSP | r=-0.301 *P*=0.019 | r=0.066 *P*=0.638 | r=0.144 *P*=0.300 |
| IBDQ-9 score and XI-score | r=-0.657 *P*<0.001 | r=-0.327 *P*<0.001 | r=-0.312 *P*=0.020 |

*IBDQ-9,* Inflammatory Bowel Disease Questionnaire-9; *XI,* Xerostomia Inventory.

There was a significant negative correlation between the IBDQ-9 score and the total number of oral health problems in female patients with CD or UC, reflecting more oral health problems in patients with lower well-being scores. There was a significant correlation between the IBDQ-9 score and the number of orofacial swelling problems in female patients with CD, reflecting more orofacial swelling problems in those with lower well-being scores. For patients with UC or CC, no significant correlation between the number of orofacial swelling problems and the IBDQ-9 score was observed. There was a negative correlation between the IBDQ-9 score and the total XI score in female patients with CD, UC, or CC, reflecting more severe xerostomia in patients with lower well-being scores. There was a significant negative correlation between the IBDQ-9 score and the total number of dental problems, reflecting more dental problems in

female patients with lower well-being scores, especially in patients with CD or CC with a stoma.

## Discussion

As far as we know, this is the first study that compared the oral health of patients with IBD with a stoma. In this study, we found that female patients with CD with a stoma report more oral health problems compared with patients with UC or CC with a stoma. Further clinical studies are warranted to confirm whether the self-reported oral problems are, indeed, associated with an increased incidence of oral abnormalities. Previous studies have shown a higher prevalence of oral health problems in patients with IBD compared with the normal population.[9,10,13,14,20] The present study also showed that patients with CD have an increased risk for oral health problems, independent of surgical removal of (a part of) the inflamed intestine, suggesting a generally increased susceptibility of patients with CD for oral health problems.

Another finding of the present study is that female patients with IBD experience more gingival problems compared with those with CC. Previous studies have also reported an increased risk of gingival and periodontal problems in patients with IBD and that compared with controls, patients with CD experience more mouth-related problems, including significantly more gingival bleeding,[21] significantly more periodontitis in patients with IBD,[22] and a significantly higher severity of periodontitis among IBD patients.[23] The increased risk of periodontitis in patients with IBD might be related to larger numbers of pathogens, such as Campylobacter rectus, Porphyromonas gingivalis, and Tannerella forsythia found in those with CD.[24] Immunologic mechanisms might also play a role because the co-occurrence of IBD and periodontitis in animals with specific immune disorders suggests that both conditions are at least partly caused by common immunologic mechanisms.[25,26] The increased risk of gingivitis and periodontitis in patients with IBD could potentially lead to premature tooth loss. However, this suggestion was not supported by the present study, as the percentages of (partly) edentulous patients among the 3 groups did not differ significantly.

Xerostomia is a subjective feeling of a dry mouth and is not necessarily associated with a reduced saliva secretion rate.[13,14] In this study, patients with CD had a significantly higher total XI score compared with those with UC or CC. This is in line with studies on xerostomia in patients with IBD, in which an increased prevalence of dry mouth was found in patients with IBD[27] and in those with active CD.[28]

The compromised oral health that was found in patients with CD cannot be explained by reduced oral hygiene because there were no statistical differences in frequency of

tooth brushing and use of interdental cleaning among the 3 groups. It has been reported that there were no differences in oral hygiene habits between patients with CD and controls with regard to frequency of tooth brushing and the use of approximal cleaning aids,[29] and the frequency of tooth brushing and the use of dental floss and breath freshener was even higher in patients with IBD at disease onset compared with control groups.[27]

An analysis of the results from male patients with a stoma showed a pattern similar to that of the results of female patients, but because of the small number of male patients in the CD group (16 individuals), the differences frequently failed to reach statistical significance.

The present study has several limitations. There was a relatively low response rate of 26% from the members of the stoma panel. In a study on the quality of life in a large group of Finnish patients with IBD, there was a response rate of 63%,[30] and in a survey on the prevalence of halitosis among members of another panel, the response rate was 62%.[31] A probable cause of the low response rate in the present study may be the lack of interest in the topic of the study among patients with a stoma. As a result of the low response rate, a bias may have been introduced because patients suffering from oral health problems might have been more likely to participate. It can also be questioned whether members of the Stoma Federation of The Netherlands are representative of all patients with a stoma because members of this patient federation may have a more-than- average interest in their general and oral health.

The study was limited to patients with a stoma, but one should realize that approximately 20% of patients with UC patients but greater than 80% of patients with CD require surgical treatment.[32,33] Although surgical treatment in patients with CD does not always involve intestinal resection, this may also have introduced a bias of the results because the patients in the UC group may have represented those who had relatively severe UC.

In this study, no differentiation was made between the different types of stoma. Patients with UC usually have an ileostoma and those with CC usually have a colostoma, whereas we did not know whether there was a colostomy or ileostomy in our CD population, and we also did not know if an inflamed intestinal trajectory was removed or if an ostomy was placed above the inflamed intestine to induce remission of disease. We assume that the (diverted) active disease becomes quiescent after creation of the osteomy. The colon is very important for uptake of water, so the type of stoma might play a significant role in oral health. It should also be considered that patients with UC are in remission after colectomy, whereas those with CD may experience exacerbations in other parts of the GI tract after removal of a part of the intestine. Because the disease activity and the use of medication were not determined when the patients

filled out the questionnaires, it may be possible that some patients with CD had active disease at that time. Future studies should take this into consideration.
Another limitation of this study is that the obtained information on oral health was limited to self-reported data. Although several studies have concluded that self-reported oral health may provide reasonable estimates of clinical measures[34-37] and (inter)nationally validated questionnaires, such as the TNO-oral problems questionnaire, the shortened IBDQ-9 questionnaire, and the XI questionnaire, were used in this study, the accuracy of information provided by patients through a questionnaire may be questioned. Accuracy may vary for different items of oral health questionnaires. For example, a study on self-reported data with regard to periodontitis found that self-perceived periodontal disease had sensitivity of 49% and specificity of 67%, whereas self-reported information on bone loss, tooth loss caused by periodontal disease, and mobility of teeth had specificity of greater than 90%.[38] Future studies on the oral health of patients with IBD should not be limited to self-reported data but should also include an oral examination by an expert.

## Conclusions

The findings of the present study show that the increased risk of oral health problems in patients with IBD, particularly those with CD, remains after surgical removal of (a part of) the inflamed intestine, necessitating special attention to their oral health from gastroenterologists and dentists.

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# Chapter 8

## Knowledge and interdisciplinary communication of gastroenterologists and dentists in the Netherlands about gastrointestinal diseases with oral manifestations

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# Abstract

**Background**
Gastrointestinal diseases can have oral manifestations. The aim of this study was to investigate the knowledge of gastroenterologists and dentists about gastrointestinal diseases with oral manifestations and to assess the frequency, extent and content of communication between gastroenterologists and oral healthcare professionals.

**Methods**
Separate questionnaires were developed and sent to all 523 gastroenterologists and a random selection of 500 dentists in the Netherlands. Both questionnaires contained questions about demographic characteristics of the participants, 10 statements about gastrointestinal diseases with possible oral manifestations and questions about the communication between gastroenterologists and oral healthcare professionals. Additionally, the questionnaire for gastroenterologists contained 9 statements about general dentistry and the questionnaire for dentist had 9 questions about gastrointestinal diseases.

**Results**
Gastroenterologists answered 47.6% ± 31.9% of the questions correct about gastrointestinal diseases with possible oral manifestations and 57.5% ± 27.9% of the questions correct about general dentistry. Dentists answered 26.6% ± 20.5% of the questions correct about possible oral manifestations of gastrointestinal diseases and 50.3% ± 18.7% of the questions correct about gastrointestinal diseases. Gastroenterologists and dentists valued interdisciplinary consultation as very useful with scores of 4.07 ± 0.70 and 4.67 ± 0.49 on a 5-point Likert scale, respectively, but the frequency of consultation was considered insufficiently with a mean score of 2.88 ± 1.01 and 2.24 ± 1.05 on a 5-point Likert scale, respectively.

**Conclusions**
This study suggests that the knowledge of gastroenterologists and dentists about gastrointestinal diseases with oral manifestations could be improved. Interdisciplinary consultation was considered valuable for the optimal treatment of their patients but was assessed as insufficient.


## Lay summary

Knowledge of gastroenterologists and dentists about gastrointestinal diseases with oral manifestations is limited. Both gastroenterologists and dentists feel that the communication between one another should be improved for better treatment of patients with signs and symptoms of gastrointestinal diseases with oral manifestations.

# Introduction

Crohn's disease, ulcerative colitis, Peutz–Jeghers syndrome, and celiac disease are gastrointestinal diseases that may be associated with oral manifestations. There is a wide variety of more or less specific oral conditions including aphthae, cobblestones in the buccal mucosa, diffuse swelling of the lips, buccal mucosa and face, pyostomatitis vegetans, hyperpigmentation on the lips and oral mucosa, enamel defects, and xerostomia. Some or a combination of these oral diseases can have a long-time negative impact on the quality of life in patients.[1–5] Since gastrointestinal symptoms are often predominant, the first consultation is usually by a gastroenterologist where awareness of the possible presence of associated oral health problems is important. Oral manifestations may sometimes precede intestinal disease[6] and approximately 30% of the patients continue to manifest oral lesions despite control of their intestinal disease activity.[7,8]

Previous studies have shown that dental professionals were knowledgeable about oral–systemic health associations, but had mixed feelings about translating this information into the dental practice.[9,10] On the other hand, recent surveys among general practitioners concluded that their knowledge about the relation between periodontal diseases and systemic disorders needed to be improved.[11,12] Medical consultations by dentists still seem to be rare. However, when such consultations take place they frequently result in an alteration of the dental treatment plan.[13] This suggests that knowledge about oral manifestations of gastrointestinal diseases is important for both dentists and gastroenterologists, and good communication between these healthcare professionals is essential for optimal patient care.

Therefore, the aim of this study was to investigate the knowledge of gastroenterologists and dentists in the Netherlands about gastrointestinal diseases with oral manifestations. Secondary, we wanted to assess the frequency, extent and content of the communication between gastroenterologists and oral healthcare professionals in the Netherlands and what value is attached to this.

# Materials and methods

## Questionnaires

Two separate questionnaires were developed, 1 for gastroenterologists and 1 for dentists. Both questionnaires consisted of 4 parts and participants were asked to answer the questions with their current knowledge without consulting scientific literature or internet. The first part was the same for both professions and

contained general questions about demographics, work conditions, and the extent and content of patient care. The second part for gastroenterologists contained questions regarding the frequency, content, and their opinion on the importance and value of the communication between gastroenterologists and various oral healthcare professionals (dentists, oral hygienists, and oral and maxillofacial surgeons). The second part for dentists had questions about various aspects of the communication with gastroenterologists. The third part of the questionnaire for gastroenterologists explored their knowledge about dentistry in general and gastrointestinal diseases with oral manifestations, while the third part of the questionnaire for dentists explored their knowledge about gastrointestinal diseases in general and gastrointestinal diseases with oral manifestations. These statements could be answered with "correct", "incorrect", or "don't know". The final part of the questionnaire explored the opinion of the gastroenterologists and dentists regarding the knowledge of, respectively, oral health and gastrointestinal diseases and about the sources of information they use. The answers for these items were based on recent reviews of the relation between oral health and gastrointestinal diseases. Preliminary versions of the questionnaires were tested on 3 gastroenterologists and 4 dentists for understanding and clarity. Their feedback led to some minor adjustments of the questionnaires.

## Study population

The final versions of the self-developed questionnaires were distributed by mail among all 523 gastroenterologists in the Netherlands. For the dentists, a random selection of 500 dentists was taken from the member guide of the dental association in the Netherlands (about 9000 members). When a randomly selected member was an oral and maxillofacial surgeon or an orthodontist, this member was not included but replaced by another general dentist. The envelopes contained the questionnaire, a letter with an explanation of the study and a prepaid envelope to return the questionnaire free of charge and anonymously. The questionnaires were mailed only once.

## Statistical analysis

Data are expressed as mean ± SD or percentages and were analyzed statistically with IBM SPSS Statistics for Windows Version 25.0 (IBM) using Chi2 tests, Mann–Whitney *U*-tests, and ANOVA tests. For statistical analysis of the answers to statements, the gastroenterologists were dichotomized based on the median year of graduation, 2006, into 2 subgroups (≤2006 versus >2006), and stratified according

to gender and whether they consulted an oral healthcare professional or not. The dentists were stratified into subgroups according to gender and the way they obtained their current knowledge (their studies at dental school, textbooks, or scientific articles). Answers on a Likert scale of 1–5 were divided into insufficient (scores 1 and 2), neutral (score 3), and sufficient (scores 4 and 5). All significance levels were set at 0.05.

### Ethical considerations

This study followed the Declaration of Helsinki on medical protocol and ethics and the data were collected in accordance to the guidelines of the Medical Ethical Committee of the VU University Centre. The Medical Ethical Review Committee of the VU University confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study and therefore an institutional review board approval was not applicable.

## Results

### Gastroenterologists

A total of 107 gastroenterologists returned the questionnaire, resulting in a response rate of 20.5%. There were 32.7% females and 67.3% males and the average age of the respondents was 48.2 ± 9.7 years (range 32–65 years). The average year of graduation was 2005 ± 9 years ranging from 1984 to 2018. On average, the gastroenterologists worked 42.3 ± 9.3 hours per week (range 16–80 hours) and the mean number of patients consulted per week was 72 ± 32 (range 1–180). These data are summarized in Table 8.1.

**Table 8.1** Demographic characteristics of gastroenterologists (n=107) and dentists (n=93).

| | Gastroenterologists | Dentists |
|---|---|---|
| Male | 72 (67.3%) | 56 (60.2%) |
| Female | 35 (32.7%) | 36 (38.7%) |
| Gender not reported | 0 (0.0%) | 1 (1.1%) |
| Mean age (years) | 48.2 ± 9.7 | 48.3 ± 12.8 |
| Year of graduation | 2005 ± 9 | 1993 ± 13 |
| Working hours per week | 42.3 ± 9.3 | 32.8 ± 7.7 |
| Consulted patients per week | 72 ± 32 | 88.5 ± 44 |

In the period of the last 5 years, 52.4% (n=58) of the gastroenterologists contacted an oral health professional; 86.2% of these 58 gastroenterologists consulted an oral and maxillofacial surgeon, 37.9% a dentist and 5.2% an oral hygienist (multiple answers were possible). The mean number of contacts in the last 5 years (n=56) was 11.9 ± 23.8 with a range of 1–125. 67.2% of the consultations were because of oral symptoms which could be related to gastrointestinal diseases and 34.5% of the consultations were initiated to discuss the possible influence of these oral symptoms on the treatment plan. 8.4% of the gastroenterologists always asked patients about oral manifestations during the first consultation whereas 5.6% never asked patients about oral manifestations. 6.5% of the gastroenterologist always examined the oral cavity during the first consultation while 80.4% of the gastroenterologist examined the oral cavity only when the patient reported complaints. When oral disease was present, the gastroenterologists valued consultation of an oral healthcare professional as very useful for the treatment of their patients with a mean score of 4.07 ± 0.70 on a 5-point Likert scale. Gender and year of graduation had no significant effect on these scores (Mann–Whitney *U*-test *P*=0.130 and *P*=0.633, respectively). Gastroenterologist noted that there was not enough structured contact between gastroenterologists and oral healthcare professionals with a mean score of 2.88 ± 1.01 on a 5-point Likert scale and they indicated that communication between the 2 disciplines is useful for optimal treatment of their patients (4.37 ± 0.71). 46.5% of the gastroenterologists suggested that the curricula of dental schools and medical schools should be more aligned to improve the communication between the 2 disciplines.

Table 8.2 shows the answers of the gastroenterologists on 9 statements about general dentistry. They answered 57.5% ± 27.9% of the questions correct and 23.9% ± 19.1% were answered with “don’t know”. The percentages of correct answered questions varied considerable for the different questions. Statements on function of dentures and lack of saliva were frequently answered correctly whereas statements on the number of teeth of children and the potential role of bacteria in dental erosion were answered poorly. Table 8.3 shows the answers of the gastroenterologists on 10 statements about gastrointestinal diseases with possible oral manifestations. They answered 47.6% ± 31.9% of the questions correct and 34.5% ± 19.3% of the questions were answered with “don’t know”. Gastroenterologists who had graduated after 2006 answered more statements correct about gastrointestinal diseases with possible oral manifestations than their colleagues who had graduated in 2006 or before, but this difference did not reach statistical significance (Mann–Whitney *U*-test, *P*=0.796).

Gastroenterologists rated their knowledge about oral diseases with a mean score of 2.20 ± 0.00, on a 5-point Likert scale. Most (58.8%) reported that they had obtained their knowledge about gastrointestinal disease-related oral problems during their specialization, followed by textbooks (43.1%) and scientific articles (28.4%).

Table 8.2 Answers of gastroenterologists on statements about general dentistry.

| | True | False | Don't know |
|---|---|---|---|
| Dental caries is caused by acid producing bacteria. | **84 (78.5%)** | 11 (10.3%) | 12 (11.2%) |
| Dental erosion in caused by acid producing bacteria. | 68 (63.6%) | **22 (20.6%)** | 17 (15.9%) |
| Smoking has a positive effect on periodontitis. | 9 (8.4%) | **89 (83.2%)** | 9 (8.4%) |
| A complete adult dentition has 28 teeth (wisdom teeth excluded). | **54 (50.9%)** | 19 (17.9%) | 13 (31.1%) |
| A complete children's dentition has 24 teeth. | 36 (34.3%) | **20 (19.0%)** | 49 (46.7%) |
| The function of a conventional denture is comparable with the natural dentition. | 3 (2.8%) | **93 (86.9%)** | 11 (10.3%) |
| Decreased salivation increases the chance of developing dental caries. | **92 (86%)** | 2 (1.9%) | 13 (12.1%) |
| Dental erosion is caused by an acid rich diet. | **63 (58.9%)** | 26 (24.3%) | 18 (16.8%) |
| Removal of a molar in the lower jaw can cause damage to the inferior alveolar nerve. | **36 (33.6%)** | 4 (3.7%) | 67 (62.6%) |

The correct answer to the statement is indicated in bold (*n* = 105–107, not every question was answered by all gastroenterologist).

Table 8.3 Answers of gastroenterologists on statements about gastrointestinal diseases with possible oral manifestations.

| | True | False | Don't know |
|---|---|---|---|
| The prevalence of dental caries is higher in patients with Crohn's disease than in patients with ulcerative colitis. | **7 (6.8%)** | 37 (35.9%) | 59 (57.3%) |
| Pyostomatitis vegetans is more prevalent in patients with ulcerative colitis. | **11 (10.7%)** | 52 (50.5%) | 40 (38.8%) |
| Cobblestoning in the oral cavity occur in patients with ulcerative colitis. | 3 (2.9%) | **76 (73.1%)** | 25 (24%) |
| Linear ulcerations in the oral cavity can occur in patients with Crohn's disease. | **93 (89.4%)** | 2 (1.9%) | 9 (8.7%) |
| The prevalence of gingivitis/periodontitis is higher in patients with ulcerative colitis. | **21 (21%)** | 23 (23%) | 56 (56%) |
| Diffuse swelling of the lips and buccal mucosa occur in patients with Crohn's disease. | **52 (50.5%)** | 7 (6.8%) | 44 (42.7%) |
| Halitosis and changes in taste is a common symptom in patients with celiac disease. | 32 (31.1%) | **26 (25.2%)** | 45 (43.7%) |
| Enamel defects are more common in patients with celiac disease. | **42 (40.4%)** | 8 (7.7%) | 54 (51.9%) |
| Aphthous ulcerations are more common in patients with celiac disease than in patients with Crohn's disease. | 20 (19.2%) | **68 (65.4%)** | 16 (15.4%) |
| Oral characteristics of Peutz–Jeghers syndrome are distinct mucocutaneous pigmentations on the lips and oral mucosa. | **97 (93.3%)** | 0 (0%) | 7 (6.7%) |

The correct answer to the statement is indicated in bold (n=100–104, not every question was answered by the gastroenterologists).

## Dentists

A total of 103 dentists returned the questionnaire, resulting in a response rate of 20.6%. Four questionnaires were incomplete and 6 were returned by retired dentists, resulting in 93 questionnaires for statistical analysis. There were 38.7% females and 60.2% males and the average age of the respondents was 48.3 ± 12.8 years (range 25–78 years). The average year of graduation was 1993 ± 13 years ranging from 1967 to 2016. On average, the dentists worked 32.8 ± 7.7 hours per week and the mean number of patients consulted per week was 88.5 ± 44.0. These data are summarized in Table 8.1.

89.2% of the dentists consulted a general practitioner, an oral and maxillofacial surgeon, or a medical specialist about all kinds of medical issues during the last 5 years; 91.6% a general practitioner, 76.8% an oral and maxillofacial surgeon, 76.8% a cardiologist, and 13% a gastroenterologist. The mean number of contacts with a general practitioner, an oral and maxillofacial surgeon, or a medical specialist during the last 5 years was 20.7 ± 44.4. Fifty percent of the dentists who consulted a gastroenterologist did this for additional information, 41.7% because of symptoms in the mouth that were possibly related to a gastrointestinal disease, 33.3% because of questions about medication, and 25% to discuss the dental treatment plan (multiple answers were possible). The dentists valuated consultation of gastroenterologists as very useful with a mean score of 4.67 ± 0.49 on a 5-point Likert scale. There were no statistically significant differences with regard to gender (male 4.80 ± 0.45 versus female 4.50 ± 0.55, Mann–Whitney *U*-test, *P*=0.353). Dentist indicated that there was not enough contact between gastroenterologists and dentists with a mean score of 2.24 ± 1.05 on a 5-point Likert scale whereby 92% of the dentists felt that communication with gastroenterologists should be improved, preferably through postgraduate courses about gastrointestinal diseases (71.7%), whereas 45.7% suggested to align the curricula of the dental and medical schools more closely.

Table 8.4 presents the answers of the dentists on 9 statements about gastrointestinal diseases. Dentists answered 50.3% ± 18.7% of the questions correct, 36.4% ± 22.3% of the questions were answered with “don’t know.” There were no statistically significant differences in number of correct answers with regard to gender (Mann–Whitney *U*-test, *P*=0.546). Table 8.5 shows the answers from the dentists on 10 statements about possible oral manifestations of gastrointestinal diseases. Dentists answered 26.6% ± 20.5% of the questions correct, 50.5% ± 26.1% of the questions were answered with “don’t know”. There were no statistically significant differences in number of correct answers with regard to gender (Mann–Whitney *U*-test, *P*=0.853).

Table 8.4 Answers of dentists (*n* = 93) on statements about gastrointestinal diseases.

| | True | False | Don't know |
|---|---|---|---|
| The first symptoms of Crohn's disease and ulcerative colitis often start at early and late adulthood. | **67 (72.0%)** | 10 (10.8%) | 16 (17.2%) |
| Clinical symptoms of Crohn's disease and ulcerative colitis include abdominal pain, diarrhea, and rectal blood loss. | **79 (84.9%)** | 4 (4.3%) | 10 (10.8%) |
| Smoking protects against developing ulcerative colitis. | **16 (17.2%)** | 36 (38.7%) | 41 (44.1%) |
| Patients with long lasting ulcerative colitis have an increased risk of developing colorectal cancer. | **69 (74.2%)** | 2 (2.2%) | 22 (23.7%) |
| Celiac disease patients can have diarrhea based on malabsorption. | **67 (72.0%)** | 5 (5.4%) | 21 (22.6%) |
| Prednisone is used in the treatment of celiac disease. | **19 (20.4%)** | 32 (34.4%) | 42 (45.2%) |
| Gastrointestinal fistulas can occur in patients with Crohn's disease. | **36 (38.7%)** | 17 (18.3%) | 40 (43.0%) |
| Crohn's disease can lead to failure to thrive in children. | **26 (27.9%)** | 12 (12.9%) | 55 (59.1%) |
| Peutz–Jeghers syndrome is an inherited condition. | **31 (33.3%)** | 2 (2.2%) | 60 (64.5%) |

The correct answer to the statement is indicated in bold.

Table 8.5 Answers of dentists (n = 93) on statements about possible oral manifestations of gastrointestinal diseases.

| | True | False | Don't know |
|---|---|---|---|
| Prevalence of dental caries is higher in patients with inflammatory bowel disease. | **31 (33.3%)** | 26 (27.9%) | 36 (38.7%) |
| Pyostomatitis vegetans is more frequently associated with ulcerative colitis than with Crohn's disease. | **21 (22.6%)** | 5 (5.4%) | 67 (72.0%) |
| "Cobblestone" appearance of the buccal mucosa in the mouth is a clinical symptom of ulcerative colitis. | 19 (20.4%) | **12 (12.9%)** | 62 (66.7%) |
| Linear ulcerations can occur in Crohn's disease patients. | **34 (36.6%)** | 7 (7.5%) | 52 (55.9%) |
| The prevalence of gingivitis and periodontitis is higher in ulcerative colitis patients compared to the normal population. | **42 (45.2%)** | 9 (9.7%) | 42 (45.2%) |
| Diffuse labial and buccal swelling can occur in Crohn's disease patients. | **22 (23.7%)** | 10 (10.8%) | 71 (76.3%) |
| Halitosis and altered taste change are common in Celiac disease patients. | 28 (30.1%) | **12 (12.9%)** | 53 (56.9%) |
| Dental enamel defects are common in Celiac disease patients. | **19 (20.4%)** | 23 (24.7%) | 51 (54.8%) |
| Aphthous ulcerations are more common in Celiac disease patients compared to Crohn's disease patients. | 17 (18.3%) | **20 (21.5%)** | 56 (60.2%) |
| Oral characteristics of Peutz–Jeghers syndrome are distinct mucocutaneous pigmentations on the lips and oral mucosa. | **34 (36.6%)** | 3 (3.2%) | 56 (60.2%) |

The correct answer to the statement is indicated in bold.

Dentists rated their knowledge about gastrointestinal diseases with a mean of 2.10 ± 1.07 on a 5-point Likert scale. Most dentists (73.1%) reported that they had obtained their knowledge about gastrointestinal diseases during their studies at dental school, followed by textbooks (26.9%) and scientific articles (20.4%). Dentists who reported that they obtained their knowledge from scientific articles rated their knowledge about gastrointestinal diseases significantly higher than dentists who had used other sources (2.53 ± 0.96 versus 1.99 ± 1.08, Mann–Whitney *U*-test *P*=0.016) whereas dentists who obtained their knowledge from textbooks had higher scores for both questions about gastrointestinal diseases in general (56.0% ± 16.2%) and questions about gastrointestinal diseases with possible oral manifestations (39.6% ± 17.4%).

## Discussion

The results of this study show that the knowledge and the frequency, extent and content of the interdisciplinary communication between gastroenterologists and dentists in the Netherlands about gastrointestinal diseases with oral manifestations are limited and that there is a need for additional and adequate education. Limited knowledge of oral diseases is not restricted to gastroenterologists, but has previously also been reported for other medical specialists. Pediatricians and general practitioners are reported to have moderate awareness and knowledge of the signs and symptoms of common oral diseases.[14,15] A recent study from London showed that foundation year 1 doctors and general practitioner trainees lacked knowledge and confidence regarding the management of oral health issues or signposting patients appropriately, and they acknowledged that there is a need to know more about oral health.[16] This may be because education on oral health is probably not part of the standard curriculum of medical schools in many countries. Most dentists (73.1%) reported that they had obtained their medical knowledge during dental school. This is in line with a study performed in the Netherlands where 91% of the dentists stated that they had obtained most of their medical knowledge during dental school.[17] The results presented in this study indicate that more postgraduate courses on gastrointestinal diseases and probably also on other medical topics as well are recommended for dentists.

The interdisciplinary communication between gastroenterologists and dentists was valuated as very useful, but both gastroenterologists and dentist felt that it needs improvement. Aligning of medical and dental schools more closely and postgraduate courses was recommended by many respondents. An alternative could be

development of e-learning modules, since a study demonstrated that traditional learning versus e-learning did not differ in improvement of healthcare professionals behaviors, skills, or knowledge.[18]

The statement "Oral characteristics of the Peutz-Jeghers syndrome are distinct mucocutaneous pigmentations on the lips and oral mucosa" was answered correct by 93.3% of the gastroenterologists. This might be related to the fact that the mucocutaneous pigmentations occurs in over 95% of individuals with the Peutz–Jeghers syndrome and are only missing in rare cases.[19,20] Therefore, the mucocutaneous pigmentations are easily observed by gastroenterologists during every visit of the patient. In addition, this syndrome was first described in 1921 by the Dutch internist Jan Peutz, which might also explain why this disease is well known among gastroenterologists in the Netherlands.[21]

As far as we know, this is the first study that assessed the knowledge of gastroenterologists and dentists about gastrointestinal diseases with oral manifestations and the frequency, extend and content of their interdisciplinary communication. Although the response rate in this study was relatively low (20.5% for gastroenterologists and 20.6% for dentists), the respondents were representative for gastroenterologists and dentists in the Netherlands with regard to age and gender. The relatively low response rate could have introduced a bias in the results of our study since gastroenterologists and dentists that are interested in oral manifestations of gastrointestinal diseases and who have communicated in the past with each other might have been more motivated to complete the questionnaire. Another limitation is that the results reflect the situation in the Netherlands and may not apply to gastroenterologists and dentists in other countries.

## Conclusion

This study suggests that the knowledge of gastroenterologists and dentists about gastrointestinal diseases with oral manifestations is limited. Both gastroenterologists and dentists acknowledge this observation and feel that the communication between one another should be improved because both valuated interdisciplinary consultations as very useful for the treatment of their patients. Gastroenterologists and dentists suggest to improve the communication by aligning the medical and dental studies more closely and through postgraduate courses.

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# Chapter 9

## Summary, general discussion and future perspectives

# Summary, general discussion and future perspectives

Inflammatory bowel diseases (IBD) primarily involve the bowel but may also be associated with extra-intestinal manifestations such as the skin, eyes and oral mucosa. Oral lesions may precede gastrointestinal involvement and thereby act as an early sign of IBD. The studies presented in this thesis aimed to investigate various aspects of the oral manifestations of IBD in general and their relation to bowel surgery, salivary secretion rate and biochemical composition of saliva. In addition, the current knowledge and interdisciplinary communication of gastroenterologists and oral health care professionals about gastrointestinal diseases with oral manifestations was explored.

We started with two reviews about oral manifestations of Crohn's disease **(Chapter 2)** and ulcerative colitis **(Chapter 3)** summarizing the literature on this topic. Oral manifestations in IBD may precede, coincide or present after intestinal symptoms. Frequently observed oral lesions include aphthous ulcerations, oedema and granulomatous swelling known as "cobblestones". IBD patients may also be more susceptible for more common oral health problems, such as dental caries, periodontitis, and xerostomia (subjective feeling of dry mouth).

In **Chapter 4,** we investigated the salivary secretion rate and saliva composition of patients with Crohn's disease (CD) and found that patients with active intestinal disease (based upon the clinical complaints using the validated Harvey-Bradshaw index ≥5) have a significantly higher output of mucin 5B (units per minute) compared to patients without active intestinal disease (Harvey-Bradshaw index <5) indicating a different saliva composition in patients with active intestinal disease. This is in line with another study that compared inflammatory proteins in saliva samples from patients with IBD with saliva samples from controls and found that the proteins IL-6 and MMP-10 were significantly increased in stimulated saliva of patients with IBD.[1] We did not find a significant correlation between the salivary secretion rate and disease activity, which is in line with previous studies that investigated the correlation of salivary flow rate and disease activity in CD patients.[2,3] In **Chapter 5**, we investigated the salivary secretion rate and saliva composition in ulcerative colitis (UC) patients. We found that xerostomia is significantly related to disease activity (based upon the clinical complaints using the validated Simple Clinical Colitis Activity Index, active ≥5 and non-active <5), whereas the objective saliva secretion rate is not. Regarding the saliva composition, we found no significant difference in the amylase nor the mucin 5B concentration in active versus non-active intestinal disease activity. We anticipate that this might be related to

the fact that we only looked at two parameters (amylase and mucin 5B), and a more comprehensive set of biomarkers might be necessary for detection and monitoring of the intestinal disease activity rather than just one or two biomarkers. For example, in non-small cell lung carcinoma, the combination of five biomarkers in saliva differentiated lung cancer patients from controls with a sensitivity of 93,75% and a specificity of 82,81%.[4] The combination of three biomarkers in saliva had a sensitivity of 85% and a specificity of 80% in detecting gastric cancer.[5] Salivary metabolites in young children with type 1 diabetes mellitus (DM1) distinguish uncontrolled DM1 from healthy controls.[6] Another study found that the severity of the diabetes mellitus/HbA1c values in type 1 diabetes mellitus were significant correlated to both the salivary and serum oxidative stress markers.[7]
Future research should focus on the possibility of using saliva for detection and monitoring the activity of IBD, especially since saliva collection is easy, non-invasive and inexpensive.[8] Potential biomarkers in saliva could be identified by untargeted broad exploration after which a second study should confirm and validate the potential biomarkers in a new cohort. These studies should not be limited to proteins in saliva, but could also include other constituents of saliva like metabolites and the oral microbiome. A recent study in treatment naïve children diagnosed with IBD found a dysbiosis in the oral microbiome that was related to disease severity which resolves over time after successful IBD therapy.[9] Another study found that the salivary microbiome in children with type 1 diabetes mellitus differed from healthy controls and that several genera that were found in the saliva of children with type 1 diabetes mellitus were associated with the gut microbiome found in type 1 diabetes mellitus patients.[10]

In **Chapter 6**, we explored the prevalence of caries and periodontitis in 229 IBD patients compared to an age and gender-matched control group of patients without IBD from the Academic Centre for Dentistry Amsterdam (ACTA) by determining the DMFT index (Decayed, Missing, Filled Teeth) and DPSI (Dutch Periodontal Screening Index). CD patients had a significant higher DMFT index compared to the control group, but there was no significant difference in periodontal disease as determined by the DPSI between IBD patients and the control group. A recent study assessed the self-reported oral health and periodontitis in CD and UC patients, and found increased odds for worse oral health and periodontitis for both groups compared to controls and CD patients having 91% higher odds for having <20 teeth.[11] A systematic review and meta-analysis found that IBD patients have an increased risk of having periodontitis and stated that longitudinal studies are needed to establish a possible causal relationship between periodontal disease and IBD.[12] Another study hypothesizes that IBD outcomes can be

worsened by microbial and inflammatory changes originating from the gingival niche through saliva perpetuating a vicious circle.[13] DPSI may be more suitable for the assessment of the presence of periodontitis rather than the severity of periodontitis. Therefore, we recommend future researchers to perform full-mouth measurements of the periodontal situation of IBD-patients, including bleeding on probing, clinical attachment loss, pocket depth, plaque-index and smoking habits as these parameters have shown to be predictors for fast regression of periodontal disease.[14,15]

In a case report published in the patient magazine of the Stoma Federation of The Netherlands, a patient stated that she had fewer oral health problems after surgical removal of the inflamed part of her intestine.[16] This was the starting point of the study presented in **Chapter 7**, in which we investigated the oral and dental health in IBD patients after removal of (a part of) the inflamed intestine and compared the results with data on oral and dental health that were obtained from a previous study that had investigated the oral and dental health in the general population in The Netherlands (TNO-cohort).[17] The results showed that the increased risk of oral and dental health problems in IBD patients remained after surgical removal of (a part of) the inflamed intestine. However, the findings in this study need to be interpreted with caution because it is possible that some parts of the reduced oral health of patients with a stoma may be caused by more dental restorations that have been performed before intestinal resection surgery. Therefore, prospective studies are warranted to further investigate our observations.

In **Chapter 8,** we explored the knowledge and interdisciplinary communication of gastroenterologists and dentists with a questionnaire about gastrointestinal diseases with oral manifestations and found that the knowledge of both gastroenterologists and dentists was limited and could be improved. Both professional groups considered interdisciplinary communication valuable but this communication was currently considered insufficient. To improve the knowledge and the interdisciplinary communication, the gastroenterologists and dentists wanted more postgraduate courses and suggested to align the curricula of medical and dental studies more closely. A recent study assessed the ability of medical and dental students to recognize oral manifestations of selected systemic diseases and found that medical students lack knowledge, diagnostic ability and confidence to diagnose oral signs of systemic diseases. The study suggests pairing medical and dental students, rotations in dental clinics for medical students and engaging medical and dental students in collaborative research activities of common interest.[18]

As available time is often a limiting factor for health professionals to pursue postgraduate education, deployment of time-efficient teaching methods seems desirable. It can be considered to use e-learning modules for postgraduate education since a systematic review reported that e-learning makes little or no difference in health professionals' behaviors, skills or knowledge when compared to traditional learning.[19] In the flipped classroom model, students encounter information before classes start and the class time is focused on higher order thinking like case-based discussion or problem solving. This type of education has shown to be equally effective compared to traditional learning.[20] Another option would be blended learning, a combination of face-to-face learning and e-learnings, which have shown better effects on knowledge outcomes compared to traditional learning in health education.[21]

The studies presented in this thesis have a retrospective or cross-sectional design. A drawback of cross-sectional research is that they are not suited to establish a cause-and-effect relationship. Well-designed longitudinal studies may provide a clearer and better insight and understanding of various aspects responsible for oral involvement in IBD. Other limitations of the studies presented in this thesis are that many data are self-reported, relatively small sample sizes and that most data have been obtained in an academic or tertiary referral centre. Future clinical studies should take these limitations into consideration. In the following paragraphs, we would like to give some suggestions for future clinical research investigating the possible link between IBD and oral health.

Dental caries appears when tooth-adherend cariogenic bacteria (primarily *Streptococcus mutans*) metabolize sugars leading to production of acid which demineralizes the teeth. A study that investigated the habitual dietary intake of IBD patients showed that patients with active disease consumed significantly more portions of sugar-containing beverages compared to patients with IBD in remission.[22] Another study found an increased taste threshold for sweet and a higher intake of sugar in CD patients compared to non-CD controls.[23] Although the association of dietary patterns and the incidence of IBD is not completely elucidated[24], we recommend future clinical research to assess the dietary habits of IBD patients in a food diary as some dietary habits, especially in combination with altered saliva composition, may make IBD patients more susceptible for dental caries.

A study on the validity of self-reported oral health performed by 1275 participants has shown that the self-reported number of teeth were valid and reflected the clinical status.[25] Another study validated self-reported data on number of teeth and periodontal variables in 723 randomly selected subjects and confirmed that the self-

reported data about number of remaining teeth were valid, but that self-reported information about periodontal variables like gingival bleeding, pocket depth and tooth mobility were less reliable.[26] As oral manifestations of IBD involve soft tissue lesions, we suggest future researchers to include a standardized clinical oral examination by an oral health care professional to objectify all the different aspects of the oral and dental health. It would be interesting to perform a prospective clinical study where standardized clinical oral examinations are performed at different time points: immediately after IBD diagnosis, during flare-ups and remissions and after certain period of time after the start of medical treatment. When sufficient numbers of patients are followed, such a clinical cohort might ultimately discover a possible correlation between the degree and severity of IBD and changes in oral health.

Finally, it is of importance that not only gastroenterologists and oral health care professionals, but also IBD patients themselves are aware of the possible oral manifestations in IBD. Patient's federations and information on websites with general information about IBD could help to increase the awareness of patients. In this context it seems important to involve IBD patients in the design, development and set up of the clinical studies mentioned above. IBD patients can contribute by sharing their experiences, symptoms and changes during the disease process and how it reflects on their day-to-day life and quality of life. They also can estimate the burden of the study for the IBD patients, and their involvement in the design of a study hopefully lowers the threshold for IBD patients to participate in a study.

In conclusion, the studies presented in this thesis added further knowledge about oral manifestations in IBD. Secondary, it suggests that the knowledge and the interdisciplinary communication of gastroenterologists and oral healthcare professionals about gastrointestinal diseases with oral manifestations is limited and should be improved for optimal patient care.

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# Appendix

## Nederlandse samenvatting

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Inflammatoire darmziekten (IBD) komen primair voor in de darmen maar kunnen ook geassocieerd zijn met afwijkingen daarbuiten, bijvoorbeeld van de huid, de ogen en de orale mucosa. In sommige gevallen kunnen orale afwijkingen al aanwezig zijn voordat de ziekte zich in de darmen presenteert en kunnen daardoor dienen als een vroege aanwijzing voor IBD. Het doel van de studies in dit proefschrift is om de verschillende aspecten van orale afwijkingen bij IBD en de relatie daarvan met eventuele darmresectie, speekselsecretie en speekselsamenstelling te onderzoeken. Daarnaast werd de kennis van maag-, darm en leverartsen (MDL-artsen) en tandartsen over gastro-intestinale ziekten met mogelijke orale afwijkingen en de interdisciplinaire communicatie tussen MDL-artsen en tandartsen, mondhygiënisten en mond- kaak en aangezichtschirurgen onderzocht.

We begonnen met twee literatuurstudies over orale afwijkingen bij de ziekte van Crohn (CD) **(hoofdstuk 2)** en colitis ulcerosa (UC) **(hoofdstuk 3)** die dienen als overzicht van de literatuur over dit onderwerp. Orale afwijkingen bij IBD kunnen zich voorafgaand, tegelijk of na de symptomen in de darm presenteren. Veel voorkomende orale afwijkingen zijn aften, oedeem en granulomateuze zwellingen dat ook wel bekend staat als “cobblestones”. Daarnaast zijn IBD-patiënten mogelijk ook vatbaarder voor meer algemene mondgezondheidsproblemen, zoals cariës, parodontitis en xerostomie (subjectief gevoel van een droge mond).

In **hoofdstuk 4** onderzochten we de speekselsecretiesnelheid en speekselsamenstelling van patiënten met CD. Patiënten met een actief ziekteproces in de darmen (gebaseerd op de gevalideerde Harvey-Bradshaw index $\geq$ 5) bleken een significant hogere uitscheiding van Mucine 5B (eenheden per minuut) in het speeksel te hebben vergeleken met patiënten zonder actieve ziekte (Harvey-Bradshaw index < 5). Dit duidt op een andere speekselsamenstelling bij patiënten met IBD met actieve ziekte in de darmen. Dit is in overeenstemming met een andere studie die ontstekingseiwitten in speeksel van IBD patiënten vergeleek met speeksel van controle personen, en vond dat de eiwitten IL-6 en MMP-10 significant hoger waren in gestimuleerde speeksel van patiënten met IBD[1]. We vonden geen significante correlatie tussen de speekselsecretiesnelheid en ziekte activiteit, hetgeen in overeenstemming is met eerdere studies die speekselsecretiesnelheid en ziekte activiteit bij patiënten met CD onderzochten[2,3]. In **hoofdstuk 5** onderzochten we de speekselsecretiesnelheid en speekselsamenstelling van patiënten met UC. Xerostomie was significant gerelateerd aan de ziekteactiviteit in de darmen (gebaseerd op de gevalideerde Simple Clinical

Colitis Activity Index, actief ≥5 en niet actief <5). De objectieve speekselsecretiesnelheid bleek niet significant gerelateerd aan de ziekteactiviteit in de darmen. Daarnaast bleek er geen significant verschil in de speekselsamenstelling wat betreft amylase en Mucine 5B concentratie in UC-patiënten met actieve versus degenen met niet-actieve ziekte. We veronderstellen dat dit mogelijk gerelateerd is aan het feit dat er slechts twee parameters (amylase en Mucine 5B) onderzocht zijn. Mogelijk is er een meer uitgebreide set van speeksel-biomarkers nodig om de ziekteactiviteit te kunnen detecteren en te monitoren, zoals het geval is bij andere aandoeningen. Bij niet kleincellig longcarcinoom kan een combinatie van vijf speeksel-biomarkers onderscheid maken tussen longkanker patiënten van controle personen met een sensitiviteit van 93,75% en een specificiteit van 82,81%[4]. Een combinatie van drie biomarkers in het speeksel heeft een sensitiviteit van 85% en een specificiteit van 80% voor het detecteren van maagkanker[5]. Speeksel metabolieten van jonge kinderen met diabetes mellitus type 1 (DM1) kunnen ongecontroleerde DM1 onderscheiden van gezonde controle personen[6]. Een andere studie vond dat de ernst van de diabetes mellitus/HbA1c waarden in DM1 significant gecorreleerd waren aan zowel speeksel als de serum oxidatieve stress markers[7]. Toekomstig onderzoek bij IBD zou zich moeten toeleggen op de mogelijkheid om speeksel te gebruiken voor detectie/opsporing en monitoring van de ziekte activiteit van IBD, zeker omdat speeksel als diagnostische vloeistof eenvoudig, niet invasief en goedkoop kan worden afgenomen[8]. Potentiële biomarkers voor IBD in het speeksel kunnen worden geïdentificeerd door te starten met een brede, niet doelgerichte exploratie naar biomarkers waarna een tweede studie de potentiële biomarkers kan bevestigen en valideren in een nieuw cohort. Deze studies dienen niet alleen gericht te zijn op eiwitten in speeksel, maar ook op andere bestanddelen van speeksel zoals metabolieten en het orale microbioom. Een recente studie vond dysbiose in het orale microbioom van onbehandelde kinderen met IBD, hetgeen gerelateerd was aan de ernst van de ziekteactiviteit. Daarnaast vond dezelfde studie dat de dysbiose verdween na succesvolle IBD therapie[9]. Een andere studie vond dat de samenstelling van het orale microbioom bij kinderen met DM1 anders is dan die van gezonde controlepersonen en dat sommige typen bacteriën in het orale microbioom van kinderen met DM1 geassocieerd zijn met het microbioom in de darmen van patiënten met DM1[10].

In **hoofdstuk 6** exploreerden we de prevalentie van cariës en parodontitis onder 229 IBD patiënten en vergeleken dit met een leeftijd en geslacht gematchte controlegroep van patiënten zonder IBD van het Academisch Centrum voor Tandheelkunde Amsterdam (ACTA). Hiervoor werden de DMFT-index (Decayed, Missing, Filled Teeth) en DPSI (Dutch Periodontal Screening Index) toegepast. CD-patiënten bleken een

significant hogere DMFT-index te hebben vergeleken met de contolegroep, maar we vonden op basis van de DPSI geen significant verschil in parodontale ziekte tussen IBD-patiënten en de controlegroep. Een recente studie naar de zelf gerapporteerde orale gezondheid en parodontitis in CD en UC patiënten en vond een verhoogde kans op slechtere orale gezondheid en parodontitis in beide groepen vergeleken met de controle groep waarbij CD patiënten 91% hogere kans hebben om < 20 tanden te hebben[11]. Een systematisch literatuuronderzoek met meta-analyse vond dat IBD patiënten een verhoogde kans hebben op parodontitis en vermelde dat longitudinale studies nodig zijn om een mogelijke oorzaak-gevolg relatie tussen parodontitis en IBD aan te tonen[12]. Een andere studie veronderstelt dat het beloop van IBD slechter kan verlopen door microbiële en inflammatoire veranderingen afkomstig van de gingivale niche die via het speeksel een vicieuze cirkel in stand houdt[13]. DPSI is mogelijk meer geschikt om de aanwezigheid dan de ernst van de parodontitis te bepalen. We raden toekomstige onderzoekers daarom aan om een volledige pocketstatus inclusief bloeding bij sonderen, klinisch aanhechtingsverlies, pocketdiepte en plaque-index te gebruiken om de parodontale situatie bij IBD patiënten te beoordelen en te informeren naar leefstijlfactoren zoals roken, aangezien deze parameters belangrijke voorspellers lijken te zijn voor snelle progressie van parodontale ziekte[14,15].

In een artikel gepubliceerd in het tijdschrift van de Nederlandse stomavereniging werd een casus beschreven van een patiënte die minder orale klachten had nadat het ontstoken deel van haar darm chirurgisch was verwijderd[16]. Dit was de aanleiding voor de studie die wordt gepresenteerd in **hoofdstuk 7**, waarin we de orale en dentale gezondheid van IBD patiënten waarbij een (deel van) de ontstoken darm is verwijderd vergelijken met data over orale en dentale gezondheid uit een bevolkingsonderzoek onder de algemene populatie in Nederland (TNO-cohort)[17]. De resultaten laten zien dat het verhoogde risico op orale en dentale gezondheidsproblemen bij IBD blijft bestaan na chirurgische verwijdering van (een deel van) de ontstoken darm. De resultaten van deze studie dienen echter met enige voorzichtigheid te worden geïnterpreteerd omdat sommige delen van de verminderde orale en dentale gezondheid zouden kunnen worden veroorzaakt doordat er meer dentale restauraties zijn vervaardigd in de periode voorafgaande aan de darmresectie. Prospectieve studies zijn nodig om onze observaties verder te onderzoeken.

In **hoofdstuk 8** exploreerden we de kennis van MDL-artsen en tandartsen met vragenlijsten over gastro-intestinale ziekten met orale manifestaties en vonden dat de kennis van zowel MDL-artsen als tandartsen over dit onderwerp beperkt was. Beide groepen vonden interdisciplinaire communicatie waardevol maar vonden de mate

ervan op dit moment onvoldoende. Om de kennis en interdisciplinaire communicatie te verbeteren raden de MDL-artsen en tandartsen aan om meer nascholingscursussen te volgen en om de curricula van de studies geneeskunde en tandheelkunde beter op elkaar af te stemmen. Een recente studie beoordeelde het vermogen van geneeskunde en tandheelkunde studenten om orale manifestaties van bepaalde systemische ziekten te herkennen en vond dat geneeskunde studenten kennis, diagnostisch vermogen en vertrouwen missen om orale tekenen van systeemziekten te diagnosticeren. Deze studie raadt aan om geneeskunde en tandheelkunde studenten tijdens de studie aan elkaar te koppelen, geneeskunde studenten een stage te laten lopen bij de opleiding tandheelkunde, en geneeskunde en tandheelkunde studenten gezamenlijk onderzoek te laten doen op onderwerpen van gemeenschappelijk interesse[18]. Aangezien tijd vaak een limiterende factor is voor gezondheidsprofessionals om nascholingscursussen te volgen, lijkt inzet van tijd-efficiënte onderwijsmethoden hierbij gewenst. Het kan worden overwogen om e-learning modules te ontwikkelen aangezien een systematische literatuuroverzicht laat zien dat e-learning modules geen of weinig verschil hebben vergeleken met traditionele onderwijsvormen met betrekking tot effecten op gedrag, vaardigheden en kennis van gezondheidsprofessionals[19]. In de "flipped classroom" methode ontvangen studenten voorafgaand aan de klassikale les al informatie zodat de tijd in de klas kan worden besteed aan onderwijs waarbij een beroep wordt gedaan op denken van een hogere orde, zoals casusbesprekingen of oplossen van problemen. Dit type onderwijs blijkt even effectief als traditioneel leren[20]. Een andere optie is "blended learning", een combinatie van face-to-face leren en e-learning, wat in gezondheidsonderwijs betere resultaten heeft laten zien wat betreft kennis vergeleken met traditioneel leren[21].

De studies die worden gepresenteerd in dit proefschrift zijn retrospectief of cross-sectioneel van aard. Een nadeel van cross-sectioneel onderzoek is dat het niet geschikt is om een oorzaak-gevolg relatie aan te tonen. Goed ontworpen, longitudinale studies zullen waarschijnlijk duidelijkere en betere inzichten kunnen geven in het begrip van de verschillende aspecten die verantwoordelijk zijn voor orale betrokkenheid bij IBD. Andere beperkingen van de gepresenteerde studies zijn dat veel data zelf-gerapporteerd zijn, het relatief kleine studiegroepen betreffen, en dat de meeste data in een academisch ziekenhuis zijn verzameld waardoor de patiënten mogelijk niet representatief zijn voor de gemiddelde IBD-patiënt in Nederland. Toekomstig klinisch onderzoek dient met deze beperkingen rekening te houden. In de komende alinea's willen we enkele suggesties doen voor toekomstig klinisch onderzoek naar het mogelijke verband tussen IBD en orale gezondheid.

Cariës ontstaat wanneer op de gebitselementen aangehechte cariogene bacteriën (met name *Streptococcus mutans*) suikers metaboliseren, hetgeen leidt tot productie van zuren die de gebitselementen demineraliseren. Een studie die de voedingsgewoonten van IBD patiënten onderzocht, liet zien dat patiënten met actieve darmontsteking significant meer hoeveelheden van suiker-bevattende dranken consumeren vergeleken met IBD patiënten in remissie[22]. Een andere studie vond een verhoogde drempelwaarde voor de perceptie van zoet én een hogere intake van suiker bij CD patiënten vergeleken met controle patiënten[23]. Hoewel de associatie van voedingsgewoonten en de incidentie van IBD niet volledig is opgehelderd[24], raden we toekomstige klinische onderzoekers aan om IBD patiënten hun voedingsgewoonten te laten registreren in een voedingsdagboek aangezien sommige voedingsgewoonten, met name in combinatie met een veranderde speekselsamenstelling, ervoor kunnen zorgen dat IBD patiënten mogelijk meer vatbaar zijn voor cariës.

Een studie naar de validiteit van zelf-gerapporteerde mondgezondheid met 1275 deelnemers heeft laten zien dat zelf rapportage van het aantal gebitselementen valide is en de klinische status goed weergeeft[25]. Een andere studie naar de validiteit van zelf gerapporteerde data over het aantal gebitselementen en parodontale variabelen in 723 random geselecteerde personen bevestigde dat de zelf gerapporteerde data over aantal gebitselementen valide is, maar dat de zelf gerapporteerde informatie over de aanwezigheid van gingivale bloeding, pocket diepte en mobiliteit van gebitselementen minder betrouwbaar is[26]. Aangezien orale manifestaties van IBD vaak weke delen betreft, raden wij toekomstige onderzoekers aan om een gestandaardiseerd klinisch onderzoek te laten verrichten door een mondzorgprofessional (tandarts of MKA-chirurg) om de verschillende aspecten van orale en dentale gezondheid te objectiveren. Het zou interessant zijn om een prospectief klinische studie uit te voeren waarbij gestandaardiseerd klinisch onderzoek wordt uitgevoerd op verschillende meetmomenten: direct na de diagnose IBD, tijdens flare-ups en remissie, en na een bepaalde periode na de start van de IBD behandeling. Wanneer een voldoende aantal patiënten kan worden opgevolgd, zou een dergelijk klinisch cohort mogelijk nadere kennis kunnen opleveren over de relatie tussen de mate van ernst van de IBD en veranderingen in de orale gezondheid.

Tot slot is het belangrijk om niet alleen MDL-artsen en orale gezondheidsprofessionals, maar ook IBD-patiënten zelf bewust te maken van de mogelijke orale manifestaties bij IBD. Patiëntenverenigingen en informatie op websites over IBD zouden kunnen helpen met het meer bekend maken bij patiënten. In deze context lijkt het belangrijk om IBD-patiënten te betrekken bij het ontwerp, de ontwikkeling en het opzetten van de

eerdergenoemde klinische studies. IBD-patiënten kunnen daaraan bijdragen door het delen van hun ervaringen, symptomen en veranderingen gedurende het ziekteproces te delen met onderzoekers, en hoe deze veranderingen effect hebben op hun dagelijkse leven en hun kwaliteit van leven. Ook kunnen patiënten de belasting van een onderzoek inschatten en leidt hun betrokkenheid bij de opzet van een studie er mogelijk toe dat de drempel voor IBD-patiënten om deel te nemen aan de studie wordt verlaagd.

Concluderend voegen de studies, die worden gepresenteerd in dit proefschrift, meer kennis toe over orale manifestaties bij IBD. Daarnaast suggereert het beschreven onderzoek dat de kennis en interdisciplinaire communicatie tussen MDL-artsen en orale gezondheidsprofessionals over gastro-intestinale ziekten met orale manifestaties gelimiteerd is en verbeterd dient te worden voor een optimale patiëntenzorg.

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# Appendix

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# Appendix

## Chapter information

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# Appendix

## Curriculum Vitae

# Curriculum Vitae

Christopher Tan was born on March 28th, 1989, in Amstelveen, the Netherlands. He graduated from the St. Ignatiusgymnasium in Amsterdam and pursued Dentistry at KU Leuven in Belgium, where he graduated Cum Laude in 2012. After that, he started studying Medicine at the University of Amsterdam while working as a dentist in his own practice in Uithoorn. Simultaneously, he initiated a PhD project on oral manifestations in inflammatory bowel diseases. In 2018, he began his training in Oral and Maxillofacial surgery at Amsterdam University Medical Center. By 2022, he became a registered Oral and Maxillofacial surgeon and started as a consultant in the Northwest Hospital Group in Alkmaar and Den Helder, Dijklander Hospital in Hoorn, Marina Clinic in Volendam, and Missiehuis Clinic in Hoorn.

# Appendix

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# Dankwoord

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