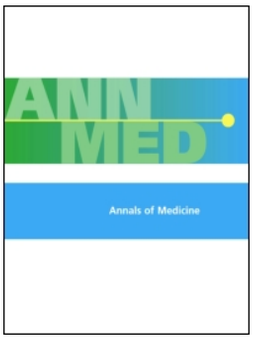

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ORIGINAL ARTICLE

# Proximal collagenous gastroenteritides: Clinical management. A systematic review

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***Aim.*** **While collagenous colitis represents the most common form of the collagenous gastroenteritides, the collagenous entities affecting the proximal part of the gastrointestinal tract are much less recognized and possibly overlooked. The aim was to summarize the latest information through a systematic review of collagenous gastritis, collagenous sprue, and a combination thereof.**
***Methods.*** **The search yielded 117 studies which were suitable for inclusion in the systematic review. Excluding repeated cases, 89 case reports and 28 case series were reported, whereas no prospective studies with or without control groups were identified. Further, no randomized, controlled trials were identified. The total number of patients with proximal collagenous gastroenteritides reported was 330.**
***Results.*** **An overview of clinical presentations, prognosis, pathophysiology and histopathology, as well as management of these disorders is presented. The prognosis of both collagenous gastritis and sprue seems not to be as dismal as considered previously. Data point to involvement of immune or autoimmune mechanisms potentially driven by luminal antigens initiating the fibroinflammatory condition.**
***Conclusions.*** **To reach the diagnosis it is recommended that biopsies are obtained during gastroduodenoscopies. Therapies with anti-secretory strategies, glucocorticoids, and in some cases iron supplementation are suggested, although rational treatment options from randomized, controlled trials do not exist for these rare or even overlooked disorders.**

**Key words:** Collagenous duodenitis, collagenous gastritis, collagenous sprue, diagnosis, histology, therapy

**Key messages**

- Collagenous gastritis and collagenous sprue, which both are more frequent among females, have clinical similarities with other diseases, e.g. irritable bowel syndrome and celiac disease.
- Knowledge of these diseases will enable clinicians and pathologists to reach the correct diagnosis at an early stage; thus, it is recommended that biopsies are obtained during upper endoscopies of the gastrointestinal tract in patients complaining of unspecific dyspeptic symptoms and diarrhea, even though there are no endoscopic signs or solely minor changes such as nodularity of gastric or duodenal mucosa.
- The prognosis of both collagenous gastritis and sprue seems not to be as dismal as earlier reported.
- Therapy and awareness of potential causes of drug-induced collagenous gastroenteritides might be a step toward preventing progression of fibrosis and thereby enhance quality of life.

## Introduction

The well-known clinicopathologic syndrome collagenous colitis is characterized by chronic diarrhea and microscopic colorectal inflammation (1), a condition that is frequent among elderly persons, especially women (female:male ratio 7.5:1) (2), with a prevalence matching that of ulcerative colitis (3). Collagenous colitis (4) together with lymphocytic colitis (5) constitutes microscopic colitis, an umbrella term for these two distinct diseases with unknown etiologies. Collagenous colitis presumably arises as a result of unknown luminal antigens as diversion of the fecal stream improves or resolves collagenous colitis, whereas re-establishment of gut continuity may cause relapse (6). Various factors are linked to the risk of developing microscopic colitis. These include smoking, coexisting autoimmune diseases (7), drugs, and malabsorption of bile acids (1,8), and, furthermore, familial occurrence of microscopic colitis has been reported (9–12). Randomized controlled trials for treatment of collagenous colitis have shown that budesonide at a dosage of 9 mg/day for 8 weeks followed by tapering over the next 4–8 weeks is effective (13). In case of a relapse soon after a successful course of budesonide treatment, reintroduction at a lower dosage may be considered for a prolonged period, and very rarely is surgery necessary (14).

However, other, rarer or maybe not realized disorders are the proximal collagenous gastroenteritides (i.e. affecting the gastrointestinal tract proximal of the colon). These disorders are usually divided based on their anatomic localization into

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collagenous gastritis and collagenous sprue (the latter also designated 'collagenous duodenitis/bulbitis/enteritis/ileitis'), both of which may affect the colon simultaneously. Nevertheless, it is yet unknown whether the collagenous gastroenteritides, including collagenous colitis, are variants of the same disease given the disparate clinical presentations. Further, the pathogenic mechanisms for the increased subepithelial collagen deposition in the gastrointestinal tract is still speculative and an area begging for well-funded basic research.

Inflammation seems an integral part of tissue fibrosis, and various conditions including celiac disease (15), collagenous colitis (1), lymphocytic colitis (1), inflammatory bowel disease (16), and a number of systemic autoimmune diseases (17) are all associated with collagen deposition. Furthermore, constant signs of immune activation, including epithelial overexpression of HLA-DR and the presence of $CD25^+$ cells in the lamina propria, have been described in gastric tissue from patients with collagenous gastritis (18,19), suggesting that inflammation is an integral component of the pathogenesis. Further, the finding that the collagenous band consists mainly of type III collagen, which is associated with repair processes, points toward a post-inflammatory reaction-associated collagen deposition (20,21).

Collagenous gastritis was described initially in 1989 (22), whereas collagenous sprue was described several years earlier in 1947 (23), but was formally introduced in 1970 (24). Thus, 116 cases have been reported of collagenous gastritis without colonic involvement and 17 cases with coexisting collagenous colitis; 16 cases have been reported of both collagenous gastritis and collagenous sprue without colon involvement, and 27 cases with coexisting collagenous colitis; and lastly, 115 cases have been reported of collagenous sprue without colonic involvement, and 39 cases with coexisting collagenous colitis up to February 2014 in the English literature.

We here present a systematic review of these rare forms of proximal collagenous gastroenteritides with an overview of clinical presentation, pathophysiology, histopathology, and prognosis, as well as management of these disorders.

## Materials and methods

A systematic review was performed based on the guidelines established by the PRISMA criteria (25).

### Eligibility criteria

We wanted to include all randomized, controlled trials, observational studies, case series, and case reports evaluating diagnosis and treatment outcomes among patients with collagenous gastritis, collagenous sprue, or the combination thereof, with or without simultaneous colonic involvement. Outcome assessment also included endoscopy, previous medications, other diseases, and histologic follow-up. Only literature published in English was included, and a histologic evaluation of the collagenous band was an inclusion criterion.

### Data sources and searches

A search was performed in Medline, Embase, and the Cochrane Library up to February 2014 using the combinations of Medical Subject Heading (MeSH) search terms and keywords: collagenous gastritis OR collagenous bulbitis OR collagenous duodenitis OR collagenous sprue OR collagenous enteritis OR collagenous ileitis. Figure 1 shows a flow chart of the study screening process. Further relevant congress abstracts were identified in Embase.

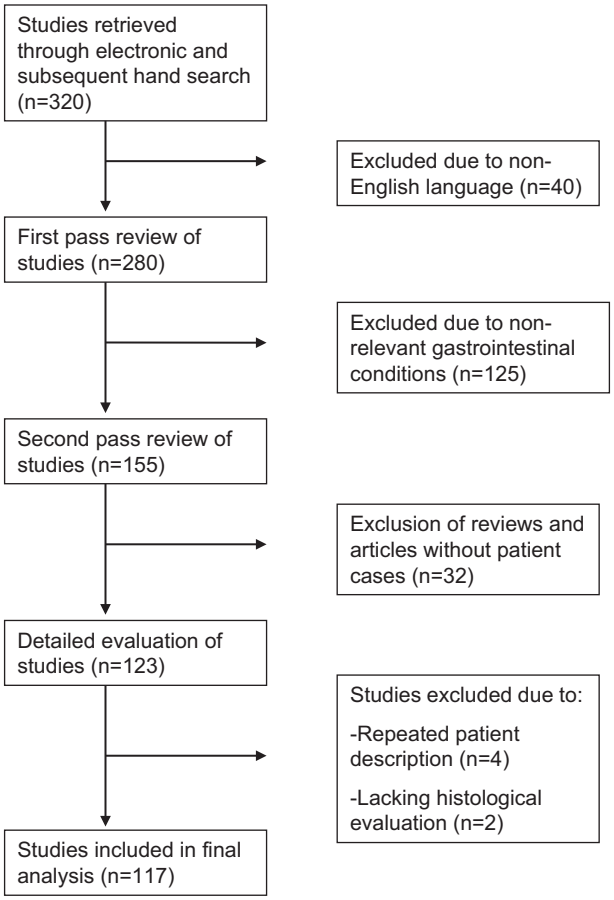


Figure 1. Flow chart of the study screening process.

### Study selection

Two authors independently identified candidate articles from the initial search. Subsequently, these two authors (O.H.N. and C.S.) independently reviewed the full texts of candidate articles to identify interventions and assess study quality. Any discrepancies between the independent searchers were resolved in consensus with the other authors.

### Data extraction and assessment of methodological quality

The search yielded a total of 119 studies that met the inclusion criteria. Of these reports, two included already described cases; thus, 117 studies (70 articles and 47 abstracts) were suitable for inclusion in the systematic review. Excluding the repeated cases, 89 case reports and 28 case series were reported, whereas no prospective studies were identified. The total number of patients with proximal collagenous gastroenteritides with or without coexisting collagenous colitis was 330. No randomized, controlled trials were identified. Given the considerable variation in study designs, differences in study focus areas, patient selection, and definition and selection of outcomes in the identified studies, a meta-analysis from this systematic review was not conducted.

## Results

### Clinical features, including presentation and prognosis

The natural history of collagenous gastritis and collagenous sprue is incompletely elucidated, particularly given the rarity of these disorders and a considerable variation in the reported assessments. Based on this systematic review of 117 studies, the

clinical presentation of proximal collagenous gastroenteritides (i.e. excluding colonic involvement) was divided in accordance with the anatomic region of the GI tract involved (Table I). As seen from Table I, these conditions are predominantly found among females.

### *Collagenous gastritis*

Collagenous gastritis seems to be a chronic persistent histologic condition characterized by a chronic intermittent clinical course (26). The thickness of the collagen plate has not been related to the severity of the disease (27). The collagen plate and its subepithelial distribution may decrease or increase with or without treatment (28–33). Although observations of endocrine cell hyperplasia and epithelial changes indefinite for dysplasia raise concerns about an increased risk for development of gastric neuroendocrine neoplasia and adenocarcinoma, no reports have so far shown any linkage of malignancy development in relation to collagenous gastritis (33).

Endoscopically, the involved mucosa may appear thickened with a nodular, diffuse appearance that predominantly involves the gastric body (34). Nodularity of the gastric mucosa often seems to be characteristic for collagenous gastritis especially in children and adolescents, but it is not seen in all cases. Other reported findings include gastric mucosal erythema, erosions, hemorrhages, ulcerations, and exudates. The reason why collagenous gastritis is frequently associated with the distinctive endoscopic nodular pattern remains unclear. Presumably, it does not derive from the thickness of the subepithelial collagen band as more deposited collagen has been identified in the depressions compared to the nodular lesions in one study (35).

From the extracted data (Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.899102) it can be seen that the onset of collagenous gastritis (median age of diagnosis 17 years for all patients, Table I) in children and adolescents is more isolated, often presenting with dyspepsia and anemia from upper GI bleeding together with epigastric pain including endoscopic signs of nodularity but without any other systemic symptoms. In contrast, adult onset presents more frequently with systemic symptoms including weight loss and diarrhea.

### *Collagenous sprue*

Collagenous sprue, which is also considered as a chronic disorder, usually presents with persistent watery diarrhea and weight loss due to malabsorption (Table I) (36). At endoscopy, collagenous sprue sometimes presents with rather non-specific lesions of the proximal part of the small intestine, including patchy distribution of pale mucosal appearances and slight mucosal scalloping.

Collagenous sprue shares some clinical and histologic features with celiac disease (37,38), including villous atrophy of the small bowel. In case the patient fails to respond to a gluten-free diet, this condition should be suspected among those with diet-refractory 'celiac disease' (39–41). Moreover, the celiac disease blood panel has never been reported to be 'positive' in isolated collagenous sprue.

Historically, collagenous sprue, in contrast to collagenous gastritis and collagenous colitis, has been considered to be a syndrome with poor prognosis (24,40,42–44) and has even been associated with malignancy (T-cell lymphoma) (40,45,46). However, a recent large, comprehensive study with up to 10 years of follow-up revealed the outcome of collagenous sprue not to be dismal (47). Even though the diagnosis is potentially fatal and some patients experience an initial progressive downhill course, the majority of patients have a favorable response to glucocorticoids and/or immunomodulators (Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.899102) (36). Recognition of an occult celiac

Table I. Subgroups of collagenous gastroenteritides showing common symptoms at presentation, gender and age distribution, usual treatment options, and prognosis.

| Anatomic subgroups of collagenous gastroenteritides (excluding solely collagenous colitis) | Common presentations | Sex distribution; median (mean) age of onset | Usual treatment options | Prognosis from evaluation of available literature |
|---|---|---|---|---|
| Collagenous gastritis | • Anemia (iron)<br>• Gastric pain<br>• Belching/nausea<br>• Vomiting<br>• Fatigue | F/M: 1.6<br>17 (28) y ($n = 50$) | • PPI<br>• Iron and folic acid supplementation<br>• (Glucocorticoids) | Equivalent to background population |
| Collagenous gastritis and colitis | • Diarrhea<br>• Anemia<br>• Bloating<br>• Vomiting<br>• Weight loss | F/M: 4.5<br>18 (31) y ($n = 11$) | • PPI<br>• Glucocorticoids<br>• (Iron supplementation) | Equivalent to background population |
| Collagenous gastritis and sprue | • Diarrhea/watery stools<br>• Bloating<br>• Weight loss | F/M: 9.0<br>68 (62) y ($n = 10$) | • PPI<br>• Glucocorticoids | Equivalent to background population |
| Collagenous gastritis, sprue, and colitis | • Bloating<br>• Diarrhea<br>• Weight loss<br>• Nausea<br>• Anemia | F/M: 1.1<br>57 (48) y ($n = 17$) | • Glucocorticoids | Equivalent to background population |
| Collagenous sprue | • Weight loss<br>• Hypoalbuminemia<br>• Diarrhea<br>• Bloating<br>• Anemia | F/M: 1.9<br>62 (59) y ($n = 99$) | • Glucocorticoids | Impaired prognoses with linkage to malignancy (especially T-cell lymphoma) and to complications following malnutrition |
| Collagenous sprue and colitis | • Nausea<br>• Diarrhea<br>• Abdominal pain<br>• Weight loss | F/M: 2.6<br>62 (54) y ($n = 29$) | • Glucocorticoids | Equivalent to collagenous sprue |

PPI = proton pump inhibitor; F = female; M = male.

disease in this setting is crucial from a therapeutic perspective because a gluten-free diet may suffice to resolve clinical symptoms and may even diminish changes on small-bowel biopsies as well (36,48).

Isolated collagenous sprue is, from scrutinizing the available literature, most often diagnosed in elderly persons (median age of 62 years for all patients described; Table I).

## Histopathology

The diagnosis of collagenous gastritis and collagenous duodenitis/sprue is made by histology, which shows distinctive findings, i.e. an increased deposition of collagen beneath the basement membrane. The collagen deposition is apparent on routine hematoxylin-eosin staining but can be enhanced with special stains (Figure 2). In the literature a wide range of collagen band thicknesses are associated with the collagenous gastroenteritides (49). Although still under discussion, a minimum width of 10 μm is usually stated as a diagnostic criterion, compared with 3–7 μm in controls. The collagen band tends to be irregular and focal with a ragged pattern on the lower edge and often entraps lamina propria cellular elements and small capillaries (41).

Additional frequent but non-specific histologic findings are mucosal thinning, intraepithelial lymphocytosis, and surface epithelial damage with flattening and detachment. In the lamina propria, the inflammatory cell response is predominantly a mononuclear infiltrate with few neutrophils and eosinophils. In this way there is no evidence for a link to another rare chronic disorder of the digestive tract, eosinophilic gastroenteritis (50).

The histologic pattern of subepithelial collagen deposits is similar to that observed in the colon of patients with collagenous colitis (4), but is very different from the diffuse mucosal fibrosis seen in patients with various chronic gastritides, including autoimmune gastritis, healing ulcers, post-radiation gastritis, and scleroderma. The finding of focal collagen deposits in biopsies from the duodenum is not a specific diagnostic tool for collagenous sprue, but it is unusual in typical celiac disease and should raise suspicion for a refractory course. Furthermore, the trend towards mucosal thinning and an atrophic appearance stands in contrast to the crypt hyperplasia of typical celiac disease (40).

Morphometric analyses of the subepithelial collagen from patients with diverse intestinal diseases including celiac disease have never been performed, hampering the determination of histologic criteria necessary for collagenous sprue. Hence, a lack of consensus on the diagnostic criteria exist, even though the presence of a $>$ 10-μm subepithelial band of collagen extending into the lamina propria is generally agreed on (30,39).

The hallmark histological feature of lymphocytic colitis is diffuse intraepithelial lymphocytosis (IEL) with intraepithelial $CD3^+/CD8^+$ T lymphocytes exceeding 20 per 100 surface epithelial cells (51). In collagenous colitis the increase in IELs is usually less pronounced, and the key histological feature is the thickened subepithelial collagenous band (1,52).

An increase in the number of IELs is common to several other diseases, including sprue, infectious colitis, autoimmune diseases, and drug-induced lymphocytosis. However, these differential diagnoses can often be distinguished by means of histopathological features, and the diagnosis of microscopic colitis should hence be based on clinical symptoms and histology.

## Therapy

Treatment of proximal collagenous gastroenteritides has not and will probably never be investigated in randomized, controlled trials, which poses a bias in the recommendation of treatment regimens. Multiple anti-inflammatory therapies have been reported, including glucocorticoids and immunomodulators (thiopurines), and symptom improvement has been achieved also with high-dose proton pump inhibitors (PPIs) (Table I and Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.899102). Further, the potential causes of drug-induced collagenous gastroenteritides and the use of agents that might exacerbate diarrhea (e.g. dairy products) should be considered, and perhaps eliminated for a while (8). Recently the tumor necrosis factor (TNF) inhibitor, infliximab, has been added as a beneficial option (53,54) which might be linked to a recent observation in experimental colitis that anti-TNF-α prevents intestinal fibrosis (55). Because anemia is frequently observed in proximal collagenous gastroenteritides (especially collagenous gastritis), iron supplementation may be required.

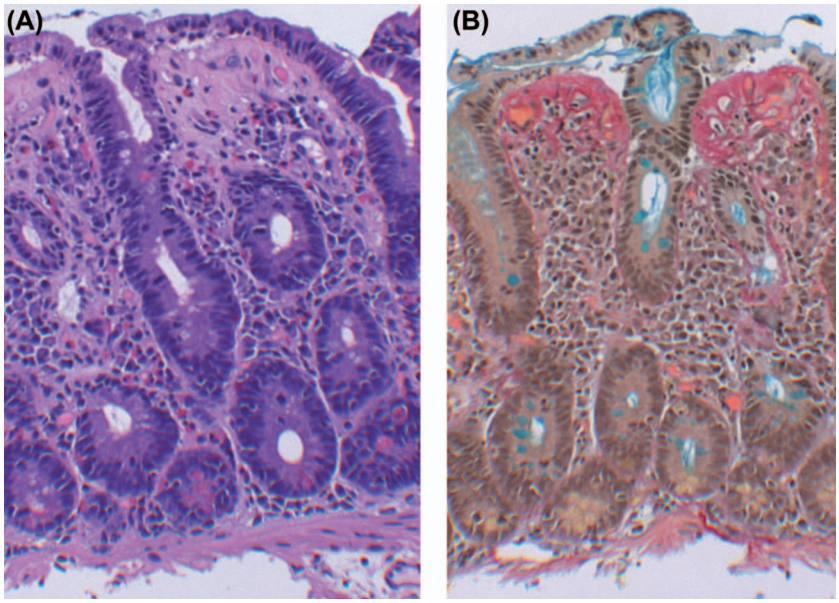


Figure 2. Collagen deposition in duodenal biopsies. A: hematoxylin-eosin. B: Alcian blue/Picro–Sirius red. A diffuse collagen deposition beneath the basement membrane is found. Cellular elements and small capillaries are entrapped in the collagen layer.

## Discussion

There is no doubt that proximal collagenous gastroenteritides belong to a category that has been and will remain quite underestimated because they are rare disorders. Gastroenterologists need to be aware of the collagenous gastroenteritides when evaluating a patient with epigastric pain, dyspepsia, anemia, upper gastrointestinal bleeding, progressive weight loss, and diarrhea, particularly when an upper gastrointestinal endoscopy shows nodularity of the gastric and/or duodenal mucosa. Biopsies should be obtained and evaluated in such cases.

Overall, from reviewing the literature systematically (Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.899102) proximal collagenous gastroenteritides are benign processes which with current treatment options do not have the poor prognosis as previously considered. Deaths are, however, still observed in a minority of patients with collagenous sprue, most often as a consequence of malnutrition (36,47). Further, collagenous gastritis should be considered in younger age groups, whereas collagenous sprue more often is diagnosed in elderly persons, as is collagenous colitis.

In relation to celiac disease the response to gluten as well as serology is tested in order to reach the diagnosis. Occasionally HLA-haplotyping is also performed to determine the celiac susceptibility genotypes HLA-DQ2 or DQ8 (56). There is speculation about a similar connection to collagenous sprue; however, such a connection does not seem to be clear. Several studies have shown association between DQ2/8 and collagenous sprue (47,57–60), whereas others have shown that collagenous sprue is not dependent on the DQ2/8 allele (61–63). Rubio-Tapia et al., however, showed an increased prevalence of DQ2 in 21 tested patients compared to the background population (56,62). Collectively the celiac disease-susceptible HLA alleles do not seem to be required for the development of collagenous sprue but may predispose patients to various autoimmune conditions. Thus, several patients are reported to suffer from concomitant immune-mediated conditions like autoimmune hypothyroidism, autoimmune hepatitis, lupus, or diabetes (Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.899102), and a study has reported 63% of the patients with collagenous sprue to suffer from autoimmune conditions (47). Due to a general lack of follow-up on the reported cases, including their subsequent development of autoimmune conditions, a collective overview is hard to make. Nevertheless, autoimmune conditions seem to be overrepresented in these patients.

The etiology of the collagenous gastroenteritides is unknown, but immune or autoimmune reactions must be suspected as part of the pathogenesis based on recent discoveries of general immune activation which seems to develop into a fibroinflammatory condition. A growing number of potential etiologic courses include luminal antigens, allergic reactions to environmental or dietary antigens, drug-related reactions, and recently the finding of increased numbers of $IgG4^+$ plasma cells in the intestinal lamina propria.

The mechanisms behind the collagen deposition remain a subject of debate. Fibrosis is believed to develop on the basis of an inflammatory process and may progress, once established, despite resolution of the inflammation. Specifically, the inflammatory response induces the activation and proliferation of the extracellular matrix (ECM)-producing myofibroblasts. Myofibroblasts derive from tissue fibroblasts, resident pericytes, myeloid progenitors, and through transdifferentiation from endothelial, epithelial, and smooth muscle cells. Their activation is orchestrated by the local environment including cytokines, chemokines, growth factors, and ECM, where pro-fibrotic factors like transforming growth factor (TGF)-β and connective tissue growth factor (CTGF) are major contributors (64,65).

Myofibroblasts from patients with collagenous sprue show elevated expression levels of both the main fibrogenic gene *procollagen I* and tissue inhibitor of metalloproteinase-1 (TIMP-1). TIMP-1 inhibits the collagen-degrading metalloproteinases (MMP)-1 and -3, thus a disturbance of the MMP/TIMP-system may lead to an excessive collagen deposition and decreased collagen degradation (57).

Initiating factors of fibrosis might be exposure of luminal antigens to the subepithelium, which explains why diversion of the fecal stream mitigates collagenous colitis (6). Besides inflammation-mediated cytokines, stimulation by pathogen-associated molecular patterns (PAMPs) leads to differentiation and activation of myofibroblasts which are key events in fibrosis (66,67). Another initiating factor could be viral induction in analogy with liver fibrosis in hepatitis B and C (68). Once the fibrotic process is established, anti-inflammatory treatments seem to have a diminished effect on the progressing fibrosis influenced by resident myofibroblasts and the complex mix of pro-fibrotic mediators in the subepithelial microenvironment (66,69,70).

Despite well-known pro-fibrotic cytokines including interleukin (IL)-1, IL-6, and TNF-α, components of the renin-angiotensin system (RAS) also influence fibrosis. Thus, angiotensin II is a strong inducer of TGF-β1, and local production of RAS-derived bioactive peptides in the intestine may lead to fibrosis by creating an imbalance of TIMP-1/MMP expression in favor of TIMP-1 (70).

Evidence for an autoimmune pathogenesis of collagenous enteritides has recently been proposed (71). Through screening of patients with collagenous sprue (some with coexisting collagenous gastritis or colitis), a significant increase in the average count of $IgG4^+$ plasma cells was discovered in the intestinal lamina propria in a subset of patients. Following glucocorticoid treatment and clinical response, the levels of $IgG4^+$ plasma cells dropped (71). However, two reports of tissue IgG4-levels in collagenous gastritis conclude that it is too infrequently observed to establish its involvement in the pathogenesis (72,73). IgG4 is unable to activate the complement cascade and only plays a limited role in immune activation. IgG4-related diseases constitute a range of conditions with infiltration of IgG4-positive plasma cells and elevated plasma IgG4, which is often associated with fibroinflammatory conditions (74,75). Due to the conflicting and sparse observations it is not possible to conclude on the relevance of IgG4 in the collagenous gastroenteritides, neither as related to pathogenesis, nor as consequence of the diseases which remains to be explored (74).

Taken together, these associations support the hypothesis that collagenous gastroenteritides have an immune or autoimmune basis coupled with a local shift into a collagenous phenotype of the fibroblast lineage within the subepithelium. An increased incidence of immune or autoimmune disorders seems to be associated with these patients. Furthermore, findings indicate an increased prevalence of the HLA-haplotypes DQ2/8 among patients with collagenous sprue, although the statistics require further analysis in larger patient cohorts.

Angiotensin II is, as mentioned above, of importance for collagen deposition, and the antihypertension angiotensin II receptor antagonist, olmesartan, has been linked to proximal collagenous gastroenteritides (62,76–78). However, it seems from examining the available literature that it is not olmesartan per se that causes the collagenous deposition, as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists, including olmesartan, may reduce fibrosis (79). This is underlined

by the delayed development of fibrosis following olmesartan intake and possibly points towards an immune-mediated damage (62). Thus, it is possible that drug-induced impairment of angiotensin II generation may modify the local TGF-β level. This, in combination with an ongoing inflammatory process, may interfere with the fibrogenic balance of the GI tract.

The anemia often observed in collagenous gastritis (34) may be associated with gastric bleeding resulting from damage of dilated capillaries entrapped in the subepithelial fibrous bands. Further, the edematous vascular congestion and inflammatory infiltrate of the mucosa and submucosa might contribute to the nodular appearance of the mucosa (27). The onset of collagenous gastritis in adults more frequently results in a systemic condition including weight loss and diarrhea often associated with autoimmune disorders, whereas endoscopic nodularity seen in youngsters is not a frequent feature. Whether pediatric and adult collagenous gastritis should be categorized as distinct disorders is premature at this point due to the few known cases.

### Limitations

Limitations of studies identified in this systematic review of rare forms of proximal collagenous gastroenteritides included small sample sizes and a paucity of studies with control groups. Further, it should be noticed that only limited follow-up intervals are stated in most case reports, which might affect the description of concomitant disorders occurring and diagnosed at a later stage.

## Conclusions

Gastroenterologists should always consider the diagnosis of collagenous gastroenteritides when evaluating a patient complaining from epigastric pain, dyspepsia, anemia, upper gastrointestinal bleeding, progressive weight loss, and diarrhea, especially if nodularity of the gastric and/or duodenal mucosa is observed endoscopically, and biopsies are a prerequisite in the diagnostic process. From scrutinizing the available literature iron supplementation in anemic patients, anti-secretory strategies with emphasis on proton pump inhibitors, which, however, might affect iron absorption (80), as well as anti-inflammatory drugs including glucocorticoids seem useful treatment options.

To improve our knowledge of prognosis and disease assessment, long-term follow-up of patients with proximal collagenous gastroenteritides will in time shed more light on this puzzling condition. Because the collagenous deposition may develop once established it is recommended to treat the underlying inflammation, whenever identifiable, at the earliest stage possible to limit the extent of the fibrotic development.

Rational treatment options for collagenous gastritis and/or collagenous duodenitis/sprue do not exist but need to be established in future randomized, controlled trials, a key issue that is rather difficult in a rare or even overlooked disorder.

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Ole Haagen Nielsen (O.H.N.) conceived the study. Christoffer Soendergaard (C.S.) and O.H.N. extracted the data, and Lene Buhl Riis (L.B.R.), Silvio Danese (S.D.), and Rasmus Dahlin Bojesen (R.D.B.) were guarantors. All authors analyzed the data and approved the final manuscript.

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## Supplementary material available online

Supplementary Table I.