Diploma Thesis

Evolving Patterns in the Histologic Diagnosis of Gastritis

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Graz, Mai 2013 Eva-Maria Wolf

Declaration of Authorship

I hereby declare that following diploma thesis has been written by myself without any assistance from third parties. I have not used other than the declared sources for the preparation of this thesis. The results of the study are currently under evaluation in a peer-reviewed journal.

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe. Die Ergebnisse der Studie werden in einem durch Fachleute geprüfte Zeitschrift publiziert werden (sind derzeit „under review“).

Graz, Mai 2013 Eva-Maria Wolf

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Abstract

Aims: The study aimed to assess the prevalence of different types of gastritis, to investigate histologic parameters arguing in favour of or against reactive gastropathy, and to correlate histologic findings with clinical symptoms and the endoscopic diagnosis of gastritis. **Methods**: A total of 1,123 individuals participated in a prospective multicentre study. Endoscopists classified individuals as positive or negative for gastritis and rendered the putative cause. Histologic diagnosis of *Helicobacter* gastritis was made according to the Updated Sydney System. Diagnosis of reactive gastropathy was based upon Dixon's parameters of foveolar hyperplasia, smooth muscle fibres in the lamina propria, and vasodilatation and congestion of superficial mucosal capillaries. Adding paucity of acute and chronic inflammatory cells to analysis, a new score with visual analogue scales for the diagnosis of reactive gastropathy was developed. **Results**: Histologic diagnosis of gastritis was made in 639 (56.9%) participants. In all, 210 (18.7%) individuals were diagnosed with *Helicobacter* gastritis, 215 (19.1%) with post *Helicobacter* gastritis, 234 (20.8%) with reactive gastropathy, 26 (2.3%) with autoimmune gastritis, and 6 (0.5%) with focally enhanced gastritis related to Crohn's disease, respectively. All three histologic parameters in favour of the diagnosis of reactive gastropathy were positively associated with the endoscopic diagnosis of gastritis, yet negatively associated with *Helicobacter* infection. In contrast, the presence of acute and chronic inflammatory cells in the lamina propria was positively associated with *Helicobacter* infection. No association between diagnosis of *Helicobacter* gastritis and endoscopic diagnosis of gastritis was observed. Integrating the histologic parameters in the proposed score (-6 to 18) demonstrated strong association between histologic and endoscopic diagnosis of gastritis. **Conclusions**: Reactive gastropathy was more common than active *Helicobacter* gastritis. Agreement between histologic and endoscopic diagnoses was better in reactive gastropathy than in *Helicobacter* gastritis**.** The proposed score with visual analogue scales may enhance diagnostic accuracy of the histologic diagnosis of gastritis. It should be validated in future studies.

Zusammenfassung

Ziel: Ziel war es die Prävalenzen der verschiedenen Formen der Gastritis zu eruieren, histologische Parameter, welche für und gegen reaktive Gastropathie sprechen, zu untersuchen und die Befunde mit klinischer Symptomatik und endoskopischer Diagnose der Gastritis zu korrelieren. **Methoden:** Es nahmen 1,123 Personen an der prospektiven multizentrischen Studie teil. Die EndoskopikerInnen mussten die TeilnehmerInnen als positiv oder negativ für Gastritis einordnen und die mutmaßliche Ursache angeben. Die histologische Diagnose einer *Helicobacter G*astritis erfolgte nach dem „Updated Sydney System“, die einer reaktiven Gastropathie nach den Kriterien von Dixon: foveoläre Hyperplasie, glatte Muskelfasern in der Lamina propria sowie Dilatation und Blutstauung oberflächlicher Kapillaren. Diese Parameter wurden zusammen mit der Entzündungszellinfiltration analysiert, um einen neuen Score mit visuellen analogen Skalen für die Diagnose reaktive Gastropathie zu entwickeln. **Ergebnisse:** Bei 639 (56.9%) TeilnehmerInnen bestand histologisch eine Gastritis. Bei 210 (18.7%) Personen wurde eine *Helicobacter* Gastritis diagnostiziert, bei 215 (19.1%) eine Post *Helicobacter* Gastritis, bei 234 (20.8%) eine reaktive Gastropathie, bei 26 (2.3%) eine Autoimmungastritis und bei 6 (0.5%) eine fokale Gastritis bei Morbus Crohn. Die histologischen Parameter welche für eine reaktive Gastropathie sprechen, waren positiv assoziiert mit der endoskopischen Diagnose einer Gastritis, negativ mit einer *Helicobacter* Infektion. Im Gegensatz dazu war das Vorhandensein von akuten und chronischen Entzündungszellen in der Lamina propria positiv mit einer *Helicobacter* Infektion assoziiert. Keine Assoziation bestand zwischen der Diagnose einer *Helicobacter* Gastritis und der endoskopischen Diagnose einer Gastritis. Die Parameter wurden in einen neuen Score einbezogen, der eine gute Assoziation zwischen der histologischen und der endoskopischen Diagnose zeigte. **Schlussfolgerung:** Die reaktive Gastropathie zeigte eine höhere Prävalenz als die aktive *Helicobacter* Gastritis. Die Übereinstimmung zwischen histologischen und endoskopischen Diagnosen war besser bei reaktiver Gastropathie als bei *Helicobacter* Gastritis**.** Der vorgeschlagene Score erhöht möglicherweise die Genauigkeit der Gastritisdiagnostik. Er sollte in zukünftigen Studien validiert werden.

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Abbreviations

PPI proton pump inhibitor

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Introduction

Background

Gastritis remains to be a major health problem around the globe, leading to considerable costs for the health care system because of its high prevalence and its chronic or recurrent nature prompting referral to gastroscopy. The disease may be caused by different agents and/or pathogens.

Helicobacter Gastritis

The advent of *Helicobacter pylori*, first identified as spiral organisms on the surface of gastric epithelial cells, substantially changed our view on the etiology of disease and subsequent histologic changes (1, 2). Since then, Helicobacter infection has emerged to be the most common chronic human bacterial infection and the most common cause of chronic gastritis. Its prevalence, however, is known to show considerable geographic variability mainly depending on the socio-economic status of the population. Thus, prevalence rates in Europe and the United States range from 7 to 40% (3-7) while prevalence rates are considerably higher in Asia and South America, accounting for up to 80% of the population (5, 8-12). In general, the most striking histologic feature of *Helicobacter* gastritis is the infiltration of neutrophils in the lamina propia, in the surface epithelium, and within the foveolar lumen (13). Moreover, bacterial organism can be observed in the foveolar lumen. An increase of chronic inflammatory cells (mononuclear cells) indicates *Helicobacter* infection as well (13).

Reactive Gastropathy

Historically, it was in 1983 when Dewar and co-workers (14) for the first time noted an association of the histologic features foveolar hyperplasia and vasodilatation and congestion with bile reflux. In 1986, Dixon and co-workers (15) coined the term “reflux gastritis” and proposed a score (“reflux score”) for its assessment. Later on, it was also described in patients taking nonsteroidal anti-inflammatory drugs (16-20). Subsequently, the designation of reflux gastritis was changed into “chemical gastritis”

indicating the pathogenic role of nonsteroidal anti-inflammatory drugs (19). The Updated Sydney System finally introduced the term “chemical gastritis” or “reactive gastritis” (13). The term “gastropathy” is favoured by authors who want to emphasise that the mucosal reaction is regenerative and not inflammatory (13, 21). Reactive gastropathy has been associated with increased exfoliation of mucosal surface cells leading to increased proliferation of crypt-lining cells (22). In their milestone publication, Dixon and co-workers (15) identified foveolar hyperplasia, prominence of smooth muscle fibres as well as vasodilatation and congestion, together with paucity of acute and chronic inflammatory cells, as the key histologic features of the disease. A recent study from the United Sates of more than half a million patients observed reactive gastropathy in 15.6 % individuals (6).

Post *Helicobacter* Gastritis

Post *Helicobacter* gastritis (syn. ex-*Helicobacter* gastritis) may be found after eradication of *Helicobacter* organisms. This type of gastritis is suspected when individuals histologically show a mild, non-active, chronic inflammation of the lamina propria, with or without lymphoid aggregates and intestinal metaplasia, and normal surface epithelium (23, 24).

Autoimmune Gastritis

This type of gastritis is believed to be rare compared to other types and was originally described in pernicious patients (25). It is assumed that *Helicobacter* infection plays a substantial role in initiating autoimmune gastritis and pernicious anaemia (25-28). Autoimmune gastritis is usually caused by auto-antibodies against parietal cells and against intrinsic factor. Histologically, autoimmune gastritis shows oxyntic cell injury (with pseudohypertrophy of residual parietal cells) and advanced glandular atrophy and intestinal metaplasia especially affecting the corpus mucosa. In end stage disease “pseudopyloric” mucus gland metaplasia and pancreatic acinar cell metaplasia are a common finding (23, 29).

Focally enhanced Gastritis related to Crohn's Disease

This type of gastritis occurs in association with Crohn's disease. However, it is more characterised by histologic changes such as patchy and acute inflammation with possible glandular abscesses, than by macroscopic changes typical for Crohn's disease such as aphthae and ulcers (24, 29).

Intestinal Metaplasia and Atrophy

Intestinal metaplasia is characterised by the change from a gastric epithelial phenotype to a small or large intestinal phenotype with goblet cells in order to be more resistant against harmful agents. Atrophy is observed after the destruction of the gastric glands due to the inflammatory process of gastritis (26). The presence of atrophic gastritis with intestinal metaplasia represents a well-recognised risk factor for the development of gastric cancer (30, 31).

Endoscopy and Histology of Gastritis

The correlation between endoscopic appearance of the gastric mucosa and histologic diagnosis of gastritis obtained from gastric biopsy specimens continues to be weak (23, 32-36). Approximately 30 years after the discovery of *Helicobacter* infection as major cause of gastritis, ultimately leading to widespread eradication therapy, we posed the question if there is a shift in the prevalence of the different types of gastritis in Central Europe and if the routine use of advanced imaging techniques, such as high-resolution endoscopy, may have improved the correlation between endoscopic and histologic findings.

Histologic examination of gastric biopsies is crucial for determining the cause of gastritis. Although the diagnosis of reactive gastropathy is nowadays rather common in gastric biopsies (6), the histologic features of the "reflux score", such as foveolar hyperplasia, hyperplasia of smooth muscle fibres, vasodilatation and congestion of superficial mucosal capillaries, acute and chronic inflammatory cells, proposed by Dixon and co-workers has so far not been associated prospectively with both clinical and endoscopic data.

Aim of the Study

Our prospective observational multicentre study aimed at assessing the actual prevalence of different types of gastritis (such as *Helicobacter* gastritis, post *Helicobacter* gastritis, reactive gastropathy, autoimmune gastritis, and focally enhanced gastritis related to Crohn's disease). In addition, our study systematically evaluated Dixon's histologic parameters of gastritis, and correlated histological findings with both clinical and endoscopic data. In a final step, a new scoring system with visual analogue scales for the diagnosis of reactive gastropathy is proposed.

Materials and Methods

We conducted a prospective observational study to assess the prevalence of different forms of gastritis and to evaluate different histologic parameters for the diagnosis of gastritis, correlating histologic findings with clinical and endoscopic data, with the aim of developing a new scoring system for the diagnosis of reactive gastropathy. Data will be presented following the STROBE Statement aimed at strengthening the reporting of observational studies (37).

Study Population

Participants were prospectively recruited in the multicentre Central European *histo*Gerd trial that aimed at systematically investigating clinical, particularly endoscopic data and histological findings in individuals, with and without symptoms of reflux disease who underwent endoscopic evaluation of their upper gastrointestinal tract.

In Austria three clinical departments (Department of Internal Medicine, Krankenhaus der Barmherzigen Brüder, St. Veit/Glan, Department of Surgery, Division of General Surgery, and Department of Internal Medicine, Division of Gastroenterology and Hepatology, Medical University of Graz, Graz, Austria) and in Germany two private practices (Dr. M. Geppert and Dr. B. Schmack, Bayreuth, and Dr. H. Bordel, Dr. R. Müller and Dr. B. Wigginghaus, Osnabrück) participated in the investigation.

During the study period, individuals (females and males) scheduled for elective endoscopic examination for various, unselected reasons were offered participation. Individuals with previous surgery leading to abnormal anatomy in the upper gastrointestinal tract, particularly at the gastroesophageal junction, were excluded. In Austria, participants were recruited between November 2011 and April 2012, in Germany between December 2011 and May 2012, respectively.

Ethics Board Approval

The investigation was carried out in accordance with the Declaration of Helsinki. Each participant provided written informed consent. The study was approved by the Institutional Review Boards of the Medical University of Graz (EK 24-052 ex 11/12) and the University of Erlangen (EK 4571 ex 11/12), respectively, and was registered at ClinicalTrials.gov (NCT01576289).

Endoscopy

Biopsy sites

The upper gastrointestinal tract of all participants was examined according to a standardised protocol devised for the study. Biopsies were systematically taken with a minimum of two antrum and two corpus biopsies, based upon the Updated Sydney System (13). Routine biopsies of the incisura angularis were not taken, as they are known to provide little additional information to that obtainable from antrum and corpus biopsies alone (38).

Patient's symptoms and medical indication for endoscopy

We used a standardised reporting system, including both clinical (basic demographic data, patient's symptoms and medical indication for the procedure, with multiple answers possible) and endoscopic data. Specifically, endoscopists were asked to classify symptoms as (i) heartburn, (ii) epigastric discomfort and/or pain, (iii) diarrhoea and/or other symptoms suggesting malabsorption, or (iv) other symptoms, such as bloatedness, nausea and vomiting (with multiple answers possible). Endoscopists were also asked to classify the medical indication for endoscopy as (i) disease of oesophagus, (ii) disease of stomach, (iii) disease of small bowel, or (iv) other indication, such as preoperative endoscopy (e.g. prior to cholecystectomy, bariatric surgery, or organ transplantation), evaluation of patients with inflammatory bowel disease for upper gastrointestinal tract involvement, and evaluation of patients with anaemia, weight loss, and metastatic disease with unknown primary. The reporting system for clinical data including sex, age, patient's symptoms, medical indication for the procedure and usage and dosage of PPI is shown in **Figure 1**.

Klinisches Protokoll

(Bitte nicht ausfüllen)
Code:
Zentrum / PatientIn
...../.....

Kenndaten

Name, Vorname(n):

Geschlecht ☐ männlich ☐ weiblich

Geburtsdatum:

Klinische Beschwerden / Indikation zur Endoskopie

Beschwerden		**Indikationen**	
O	Reflux	O	Endoskopie „wegen Ösophagus“
O	Epigastrische Symptome	O	Endoskopie „wegen Magen“
O	Diarrhö / Malabsorption	O	Endoskopie „wegen Duodenum“
O	Andere: …….....	O	Andere: …….

(z.B. andere Beschwerden / Indikationen: Pat. betreffend GIT beschwerdefrei / Indikation vor Herz-OP)

Klinisch-anamnestische Daten

Größe:

Gewicht:

Medikamenten- und Alkoholanamnese:

PPI	☐ ja ☐ nein			
Falls ja:	☐ regelmäßig	☐ unregelmäßig		
seit wann:	Substanz:		Dosierung:	mg/d
Andere Säureblocker	☐ ja ☐ nein			
Falls ja:	☐ regelmäßig	☐ unregelmäßig		
seit wann:	Substanz:		Dosierung:	mg/d
NSAR	☐ ja ☐ nein			
Falls ja:	☐ regelmäßig	☐ unregelmäßig		
seit wann:	Substanz:		Dosierung:	mg/d
Alkohol	☐ ja ☐ nein			
Falls ja:	☐ regelmäßig	☐ unregelmäßig		
Menge:	…… g/die			

1/2

Figure 1: Reporting system for clinical data (in German)

Endoscopic diagnosis of gastritis

Based upon standard criteria, such as mucosal redness and/or friability, the endoscopists had to classify participants as positive or negative for the diagnosis of gastritis. If participants were considered positive, the endoscopists were additionally asked to render the most probable aetiology, i.e. *Helicobacter* gastritis, reactive gastropathy, or autoimmune gastritis (**Figure 2**).

Specifically, the endoscopists rendered a diagnosis of putative *Helicobacter* gastritis when they observed patchy or diffuse erythema, accompanied, in varying extent, by enlargement of mucosal folds, haemorrhage as well as signs of mucosal atrophy, such as discoloration, thinning, and transparency of vessels (39).

Reactive gastropathy was considered when the inflammatory changes were accentuated in the pre-pyloric antrum showing oedema and redness, typically as reddish streaks within intact mucosa, sometimes also superficial flat or elevated erosive changes (40).

Endoscopy was considered suggestive of autoimmune gastritis when inflammatory and, particularly, atrophic changes prevailed in the corpus. If classification did not appear feasible, “unclassifiable gastritis” was recorded.

All endoscopists were very experienced in the field, the majority of them working in endoscopy units for at least one decade, performing more than 500 gastroscopies per year, respectively. Before the investigation, all endoscopists were trained in order to familiarise them with the biopsy protocol and, particularly, the reporting system. For endoscopy, four institutions used the OLYMPUS EVIS EXERA II series (Olympus Europe Holding GmbH, Hamburg, Germany) with video gastroscopes GIF-H180 and Q180, respectively. One institution (Osnabrück) used the FUJI EPX-4450HD Electronic Video Endoscopy System with EG-590WR video gastroscopes (Fujifilm Corporation, Tokyo, Japan). Computed virtual chromoendoscopy (e.g. narrow-band imaging) was not applied routinely to detect gastritis.

Endoskopische Daten

(Bitte nicht ausfüllen)
Code:
Zentrum / PatientIn
...../.....

Magen:

Gastritis ☐ **ja** ☐ **nein**

Falls ja: ☐ **Typ A Gastritis**
☐ **Typ B Gastritis**
☐ **Typ C Gastritis**
☐ **nicht zuzuordnen**

Intestinale Metaplasie ☐ ja ☐ nein

Ösophagus:

Hiatushernie ☐ ja ☐ nein

Los Angeles Klassifikation

Stadium

N	☐	Normal mucosa
M	☐	Minimal changes to the mucosa, such as erythema and/or whitish turbidity
A	☐	Non-confluent mucosal breaks ≤ 5 mm in length
B	☐	Non-confluent mucosal breaks ≥ 5 mm in length
C	☐	Confluent mucosal breaks ≤ 75% circumferential
D	☐	Confluent mucosal breaks ≥ 75% circumferential

Prag Klassifikation bei Barrett-Ösophagus
(bitte mit Pfeilen markieren)

C: zirkuläres Segment (in cm)

M: maximale Ausdehnung (in cm)

16
14
12
10
8
6
4
2
0

◄ True position of GEJ

Bemerkungen (spezielle Befunde, z.B. Erosionen, Ulzera, Polypen):

Arzt / Ärztin: Name …… Unterschrift ……..

2/2

Figure 2: Reporting system for endoscopic data (in German)

Histopathology

Biopsy specimens were fixed in 4% buffered formalin and embedded in paraffin, sectioned at 4-5 levels and stained with haematoxylin and eosin (H&E). In equivocal cases, *Helicobacter* infection was assessed using Warthin-Starry Silver stain. All biopsies were examined by two experienced gastrointestinal pathologists (Univ.Doz.Dr. Cord Langner and Dr. Micheal Vieth) who were blinded to clinical data including endoscopic findings. Basically, classification and grading of gastritis was based upon the Updated Sydney System (13) paying special attention to the aetiology of disease, e.g. *Helicobacter* infection, as well as its consequences, such as the development of mucosal defects and/or metaplasia. The protocol for the histologic reporting system is shown in **Figure 3**.

Histologic diagnosis of gastritis

In *Helicobacter* gastritis, the density of chronic, i.e. lymphocytes and plasma cells, and active, i.e. neutrophils, inflammation was graded according to the visual analogue scales presented in the Updated Sydney System (13).

Post *Helicobacter* gastritis (syn. ex-*Helicobacter* gastritis) was diagnosed in individuals with mild, non-active, chronic inflammation of the lamina propria, with or without lymphoid aggregates (and intestinal metaplasia), and normal surface epithelium (23, 24).

A diagnosis of reactive gastropathy was made following the criteria presented by Dixon and co-workers (15). Specifically, visual analogue scales from 0 (normal) to 3 (marked) were allotted for each of the following histologic features according to its severity (**Figure 4**): foveolar hyperplasia (with reactive epithelial changes, such as mucin depletion and nuclear enlargement and hyperchromasia), hyperplasia of ascending smooth muscle cells in the lamina propria (with or without oedema and apical fibrosis), and vasodilatation and congestion of superficial mucosal capillaries. Details are presented in **Table 1**.

A diagnosis of autoimmune gastritis was made in individuals presenting with oxyntic cell injury (with pseudohypertrophy of residual parietal cells, if present) and

advanced glandular atrophy and intestinal metaplasia affecting the corpus mucosa. In end stage disease “pseudopyloric” mucus gland metaplasia and pancreatic acinar cell metaplasia are a common finding. In contrast to the gastric corpus, the mucosa of the antrum may appear normal or may show minor inflammatory changes (23, 29).

In individuals with established diagnosis of Crohn’s disease, involvement of the stomach was diagnosed in the presence of focally enhanced gastritis, with or without non-caseating granulomas, aphthous erosions and/or fissures (29).

Intestinal metaplasia

The extent and severity of intestinal metaplasia was categorised in accordance with the OLGIM (operative link on gastric intestinal metaplasia assessment) staging system which represents a modification of the OLGA (operative link for gastritis assessment) proposal for staging gastritis by replacing gastric atrophy by intestinal metaplasia, thereby increasing interobserver agreement (41, 42).

Teil 2

(Bitte nicht ausfüllen)
Code:
Zentrum / PatientIn
...../.....

Biopsien aus Magen und Duodenum (2PE Antrum, 2PE Korpus und 4PE Duodenum)

Magen	**Antrum**	**Korpus**
Magenmukosa mit Antrumdrüsen	ja nein	ja nein
Magenmukosa mit Korpusdrüsen	ja nein	ja nein
Normaler Befund	ja nein	ja nein
HP-Gastritis	ja nein	ja nein
Anzahl HP	1 - 2 - 3	1 - 2 - 3
Aktivität (Sydney)	1 - 2 - 3	1 - 2 - 3
Chronizität (Sydney)	1 - 2 - 3	1 - 2 - 3
Post(Ex)HP-Gastritis	ja nein	ja nein
Autoimmungastritis	ja nein	
C-Gastritis	ja nein	

ANTRUM		Foveolar hyperplasia	Smooth muscle fibers	Vasodilatation and congestion	Acute inflammation	Chronic inflammation
	0					
	1					
	2					
	3					

Intestinale Metaplasie	ja nein	ja nein
Ausprägung:	1 - 2 - 3	1 - 2 - 3
Typ:	I - II - III	I - II - III
Atrophie	ja nein	ja nein
Ausprägung:	1 - 2 - 3	1 - 2 - 3
Nekrose (Erosion/Ulkus)	ja nein	ja nein
Parietalzellhyperplasie		ja nein
Ausprägung:		1 - 2 - 3
Drüsenkörperpolyp		ja nein
LG Dysplasie (IEN)	ja nein	ja nein
HG Dysplasie (IEN)	ja nein	ja nein
Karzinom	ja nein	ja nein

Duodenum

Aktive Entzündung	ja nein
Gastrale / Foveoläre Metaplasie	ja nein
Falls ja – HP-Besiedelung	ja nein
– Lokalisation	Bulbus tiefes Duodenum
Magenschleimhautheterotopie	ja nein
Sprue / Zöliakie	ja nein
Falls ja, Marsh-Typ:	

Bemerkungen:

Figure 3: Reporting system for histology (in German)

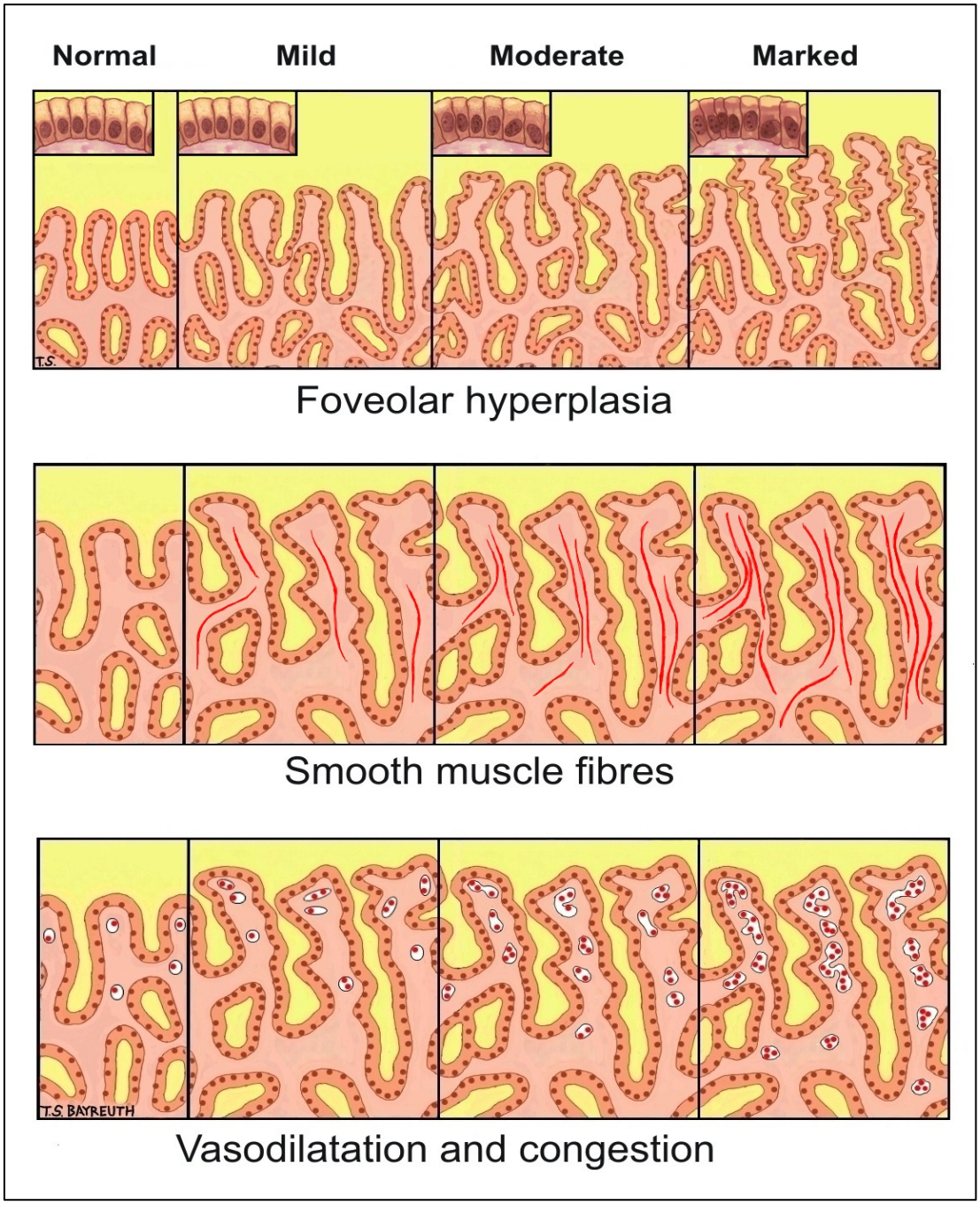

Figure 4: Visual analogue scales, provided by Dr.Tilman Schulz (coauthor of the multicentre study)

The scales refer to the following histologic features in favour of reactive gastropathy: foveolar hyperplasia (with reactive epithelial changes, inset), hyperplasia of ascending smooth muscle fibres in the lamina propria, and vasodilatation and congestion of superficial mucosal capillaries. Each visual analogue scale ranges from 0 (normal) to 3 (marked).

Parameter	Grade	Description
Foveolar hyperplasia	Grade 1	Mild elongation of the foveolae without depletion of apical mucin in surface epithelial cells, absence of nuclear atypia
	Grade 2	Moderate elongation of the foveolae with incomplete depletion of apical mucin in surface epithelial cells, mild nuclear atypia
	Grade 3	Marked elongation and tortuosity of the foveolae with depletion of apical mucin in surface epithelial cells, moderate nuclear atypia
Smooth muscle fibres	Grade 1	Mild hyperplasia of smooth muscles fibres (discernible at x40 objective lens)
	Grade 2	Moderate hyperplasia of smooth muscles fibres (discernible at x20 objective lens)
	Grade 3	Marked hyperplasia of smooth muscles fibres (discernible at x4 objective lens)
Vasodilatation and congestion	Grade 1	Mild vasodilatation and congestion of mucosal capillaries (discernible at x40 objective lens)
	Grade 2	Moderate vasodilatation and congestion of mucosal capillaries (discernible at x20 objective lens)
	Grade 3	Marked vasodilatation and congestion of mucosal capillaries (discernible at x4 objective lens)

Table 1: Histologic parameters of chronic gastritis in favour of a diagnosis of reactive gastropathy

Statistical Analysis

All data were included within a prospective joint database. The quality of this database was tested by random sample taking in 5% of the recruited individuals which revealed mis-reporting in 0.14%. Categorical variables are presented as absolute and relative frequencies, numerical variables as medians and ranges, as well as means. Differences in categorical variables were examined using the chi-square test or Fisher's exact test, as appropriate. Differences in continuous variables between groups were analysed using the Mann-Whitney U-Test. In addition, the associations of the histologic parameters (chronic inflammation, active inflammation, foveolar hyperplasia, smooth muscle fibres in the lamina propria, as well as vasodilatation and congestion) with *Helicobacter* infection and endoscopic diagnosis of gastritis, respectively, were examined by logistic regression (multivariable analysis) with the histologic parameters as independent numeric variables and *Helicobacter* infection and endoscopic diagnosis of gastritis as dependent dichotomous variables. The results are presented as odds ratios and 95% confidence intervals (CI) for the change of one unit (grade 0-3) of the independent variables. All statistical calculations were performed using NCSS: Hintze, J. (2007). NCSS, LLC. Kaysville, Utah, U.S.A. (www.ncss.com). Two-sided p-values <0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 1,123 individuals participated in the investigation (**Figure 5**). There were 600 (53.4%) females and 523 (46.6%) males (female:male ratio = 1.15:1). Median age was 53 years (mean 52.3, range 15 through 93).

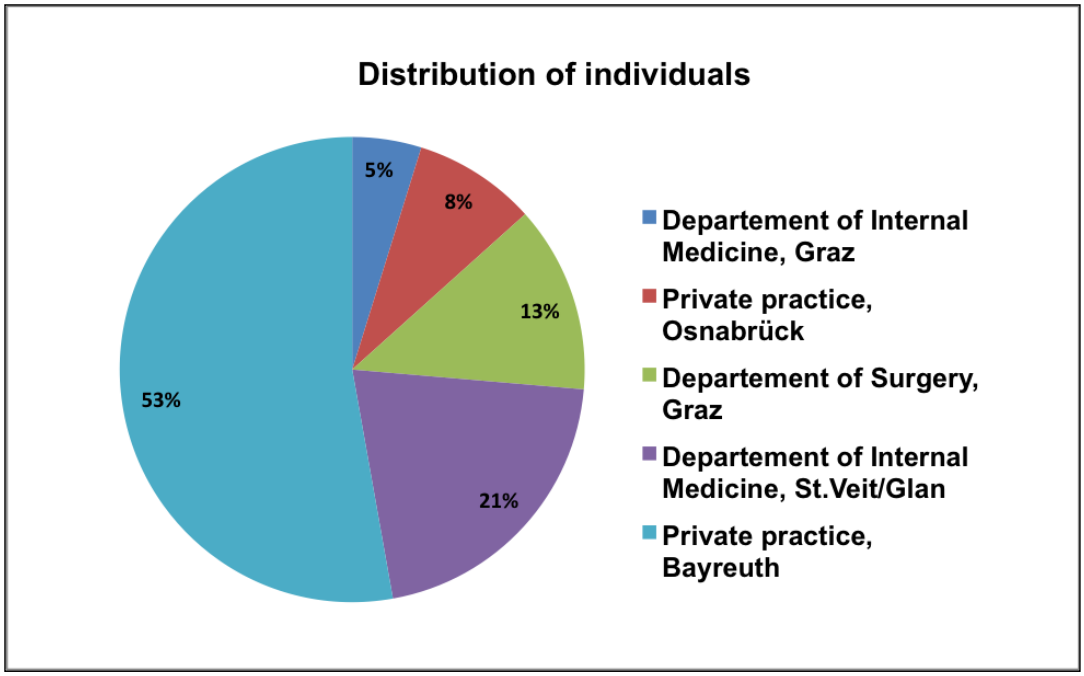

Figure 5: Distribution of the 1,123 individuals among the participating institutions

In all, 152 (13.5%) participants did not report on any symptoms or complaints. In this subgroup, anaemia and/or positive faecal occult blood test, preoperative endoscopy (e.g. prior to cholecystectomy, bariatric surgery, or organ transplantation), follow-up endoscopy (e.g. Barrett's oesophagus), and positive familial history of gastric cancer were the leading causes prompting referral to gastroscopy. The remaining 971 (86.5%) participants reported on different health problems: 543 (48.4%) reported on dyspepsia and/or epigastric pain, 445 (39.6%) reported on substernal heartburn and 90 (8.0%) on diarrhoea and/or symptoms suggesting malabsorption. Other symptoms were noted in 312 (27.8%) participants, with weight loss, nausea and vomiting,

abdominal distension with bloatedness, and fatigue being the most common (**Figure 6**).

In 147 (13.1%) participants, no medical indication for gastroscopy was provided. When the medical indications of the remaining participants were stratified, 477 (42.5%) individuals were evaluated for diseases of the oesophagus (e.g. reflux disease), 653 (58.1%) individuals were evaluated for diseases of the stomach (e.g. gastritis, peptic ulcer disease), and 162 (14.4%) individuals were evaluated for diseases of the small bowel (e.g. celiac disease). In 187 (16.7%) individuals the endoscopists referred to “other” indications, such as preoperative endoscopy (e.g. prior to cholecystectomy, bariatric surgery, or organ transplantation), evaluation of patients with inflammatory bowel disease for upper gastrointestinal tract involvement, and evaluation of patients with anaemia, weight loss, and metastatic disease with unknown primary (**Figure 7**).

At time of investigation, 534 (47.5%) participants were on PPIs, with 350 (65.5%) receiving PPIs on a regular basis. For 162 of these, data regarding the duration of PPI intake were available, with mean and median values accounting for 31.4 and 12 months, respectively.

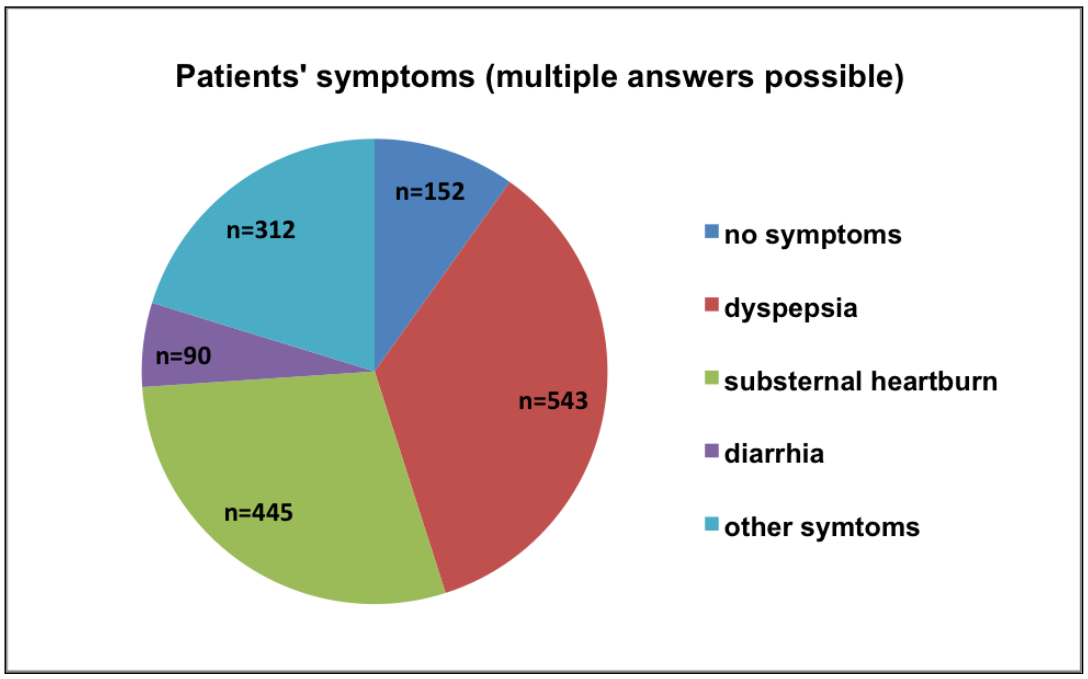

Figure 6: Distribution of patients’ symptoms and/or complaints

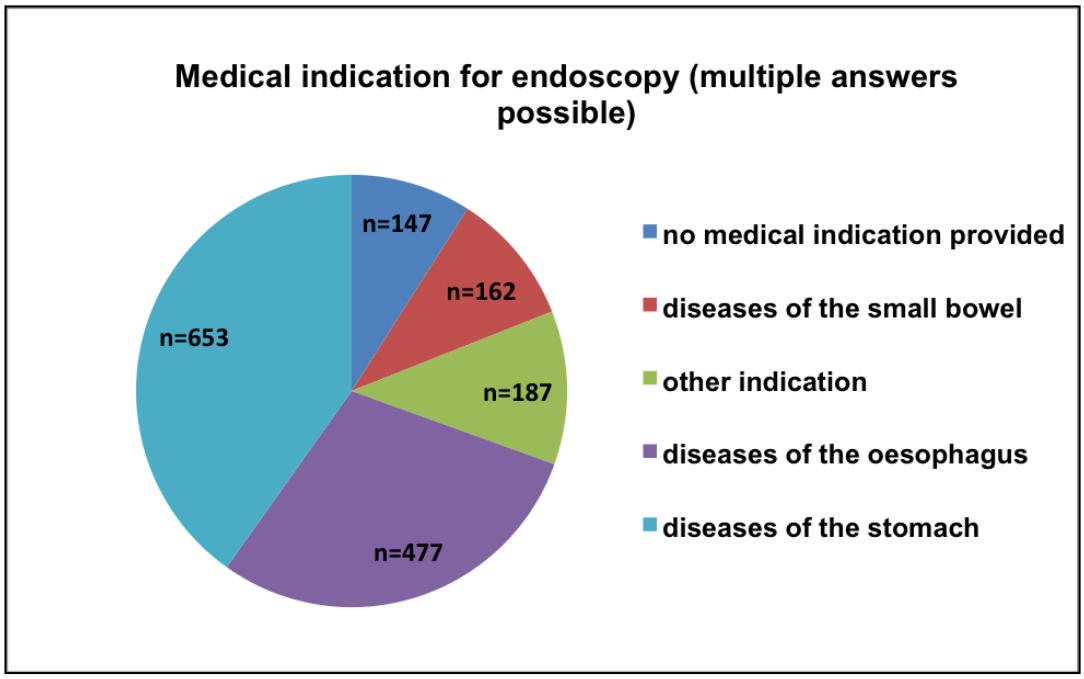

Figure 7: Distribution of medical indication for endoscopy

Endoscopic Diagnosis of Gastritis

An endoscopic diagnosis of gastritis was made in 534 (47.6%) individuals, while the mucosa of 589 (52.4%) individuals was normal on gross inspection. These two groups showed a significant difference in age: Participants with gastritis were older (median 56, mean 54.8 years) than those without gastritis (median 51, mean 49.9 years; $p<0.001$, Mann-Whitney U-Test). In addition, the subgroup with gastritis showed a higher percentage of males (48.9%), compared to the subgroup without gastritis (44.5%), but this difference was not statistically significant ($p=0.15$).

When the endoscopists were asked to classify endoscopic findings according to the putative aetiology, 13 out of 534 (2.4%) participants were considered to present with autoimmune gastritis, 32 (5.9%) with *Helicobacter* gastritis, and 172 (32.2%) with reactive gastropathy, respectively. Exemplifying endoscopic images are given in **Figure 8**,**9** and **10**. In 317 (59.4%) individuals, however, an etiological classification was not possible (“unclassifiable gastritis”).

Notably, there was no statistically significant association between the endoscopic diagnosis of gastritis and patients' symptoms and/or complaints. In the subgroup of participants with endoscopic diagnosis of gastritis, 269 (50.4%) reported on epigastric symptoms, in the subgroup with endoscopically normal mucosa 274 (46.5%) participants, respectively (p=0.21).

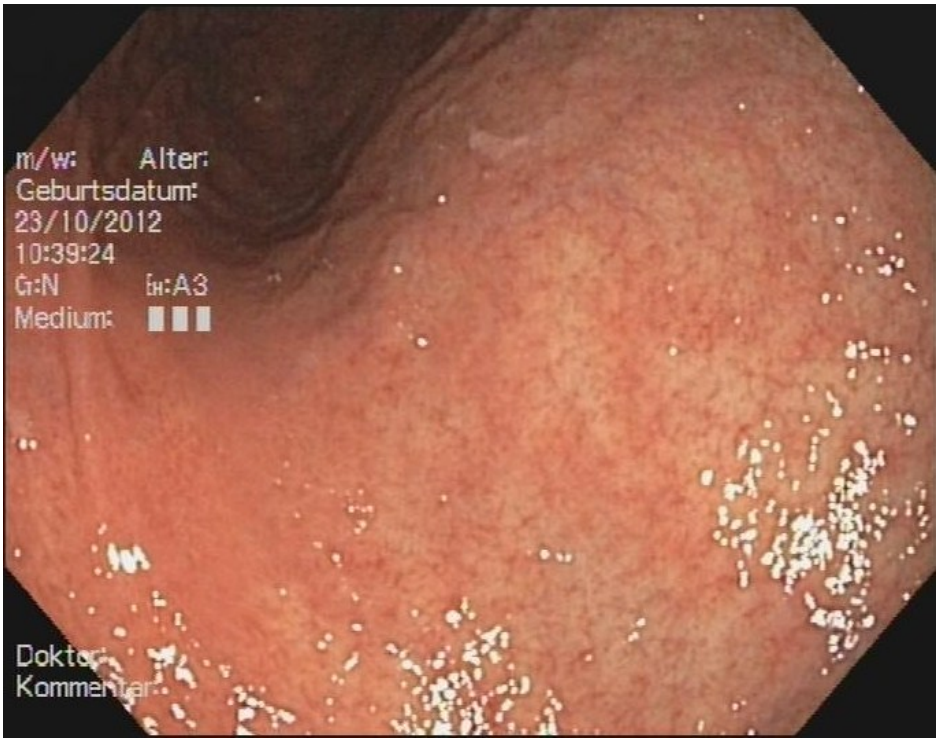

Figure 8: Example of an endoscopic diagnosis of autoimmune gastritis with atrophic changes

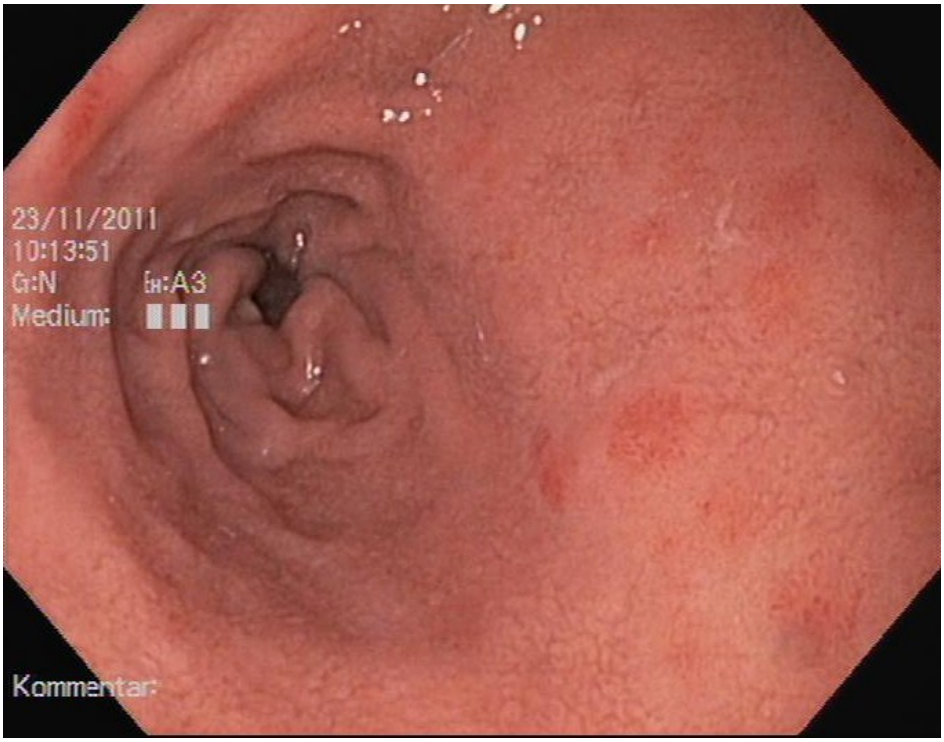

Figure 9: Example of an endoscopic diagnosis of *Helicobacter* gastritis with patchy and diffuse erythema

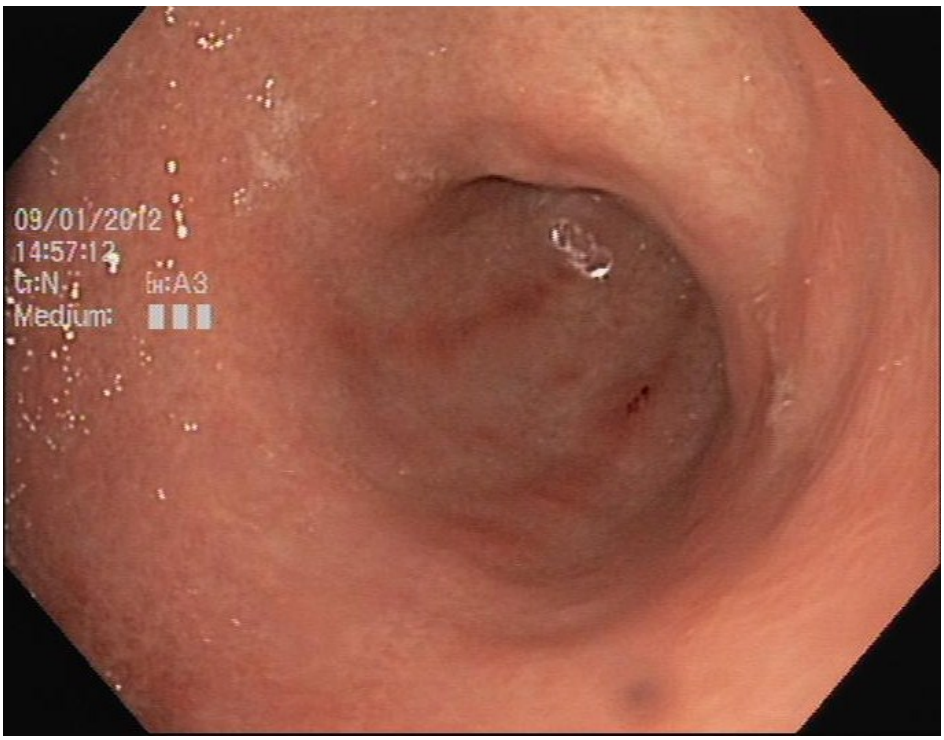

Figure 10: Example of an endoscopic diagnosis of reactive gastropathy with reddish streaks in the pre-pyloric antrum

Histologic Diagnosis of Gastritis

A histologic diagnosis of gastritis was made in 639 (56.9%) individuals, while the mucosa of 484 (43.1%) individuals was normal upon histology. These two groups showed a significant difference in age: Individuals with gastritis were older (median 56, mean 54.5 years) than those without gastritis (median 50, mean 49.2 years; $p<0.001$). In addition, the subgroup with gastritis showed a higher percentage of females (54.8%), compared to the subgroup without gastritis (51.7%), but this difference was not statistically significant ($p=0.31$)(**Table 2**).

In all, 210 out of 1,123 (18.7%) individuals were diagnosed with *Helicobacter* gastritis (**Figure 11** ,**12** and **13**), 215 (19.1%) with post *Helicobacter* gastritis (**Figure 14**), 234 (20.8%) with reactive gastropathy, 26 (2.3%) with autoimmune gastritis (**Figure 15**), and 6 (0.5%) with focally enhanced gastritis related to Crohn's disease, respectively. There were significant differences in age ($p<0.001$) and gender ($p<0.001$) distribution among the histologic subtypes (**Table 2**).

In 46 out of 639 (7.2%) individuals histologically diagnosed with gastritis, combinations of different histologic subtypes were noted, the most common being reactive gastropathy and post *Helicobacter* gastritis in 21 cases (**Table 3**). When individuals with autoimmune gastritis showed synchronous reactive gastropathy, post *Helicobacter* gastritis or both, these were diagnosed in antrum biopsies. Likewise, when reactive gastropathy was associated with post *Helicobacter* gastritis, the latter was diagnosed in biopsies obtained from the corpus.

		N	Female (F)	Male (M)	Ratio (F:M)	Median Age	Mean Age	Age Range
No Histologic Gastritis		484	250	234	1.07:1	50	49.2	15-93
Histologic Gastritis		639	350	289	1.2:1	56	54.5	17-91
	Helicobacter Gastritis	210	105	105	1:1	51	51.5	17-84
	Post *Helicobacter* Gastritis	215	84	131	1.56:1	61	58.7	18-91
	Reactive Gastropathy	234	122	112	1.09:1	56	55	17-91
	Autoimmune Gastritis	26	18	8	2.25:1	64.5	62.2	26-84
	Crohn's Disease	6	5	1	5:1	30	37.6	20-42

Table 2: Histologic diagnosis of gastritis related to patient age and gender

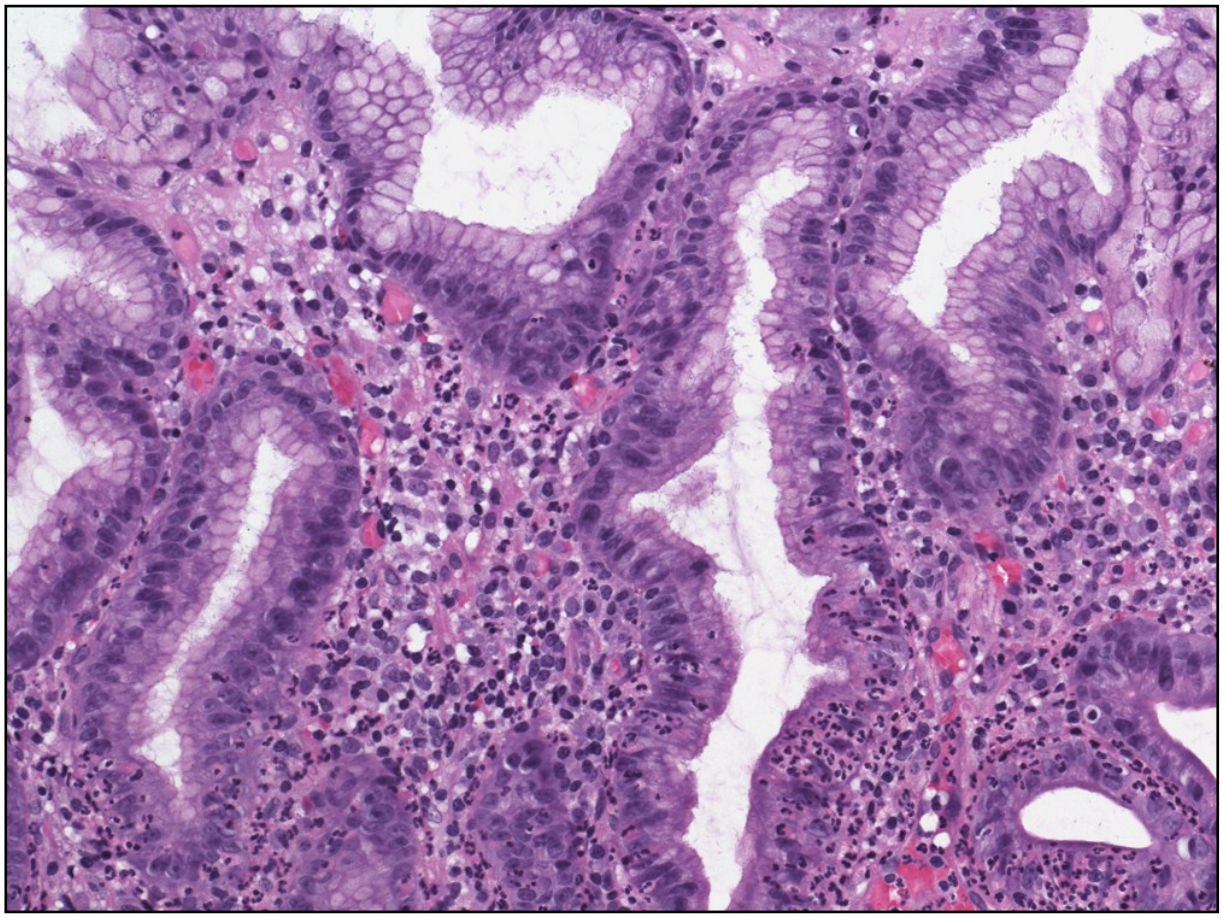

Figure 11: Example of a histologic diagnosis of *Helicobacter* gastritis (original x100)

Moderate infiltration of mononuclear cells and neutrophils within the stroma, graded according to the visual analogue scales presented in the Updated Sydney System (13). Note presence of *Helicobacter* organisms on the mucosal surface.

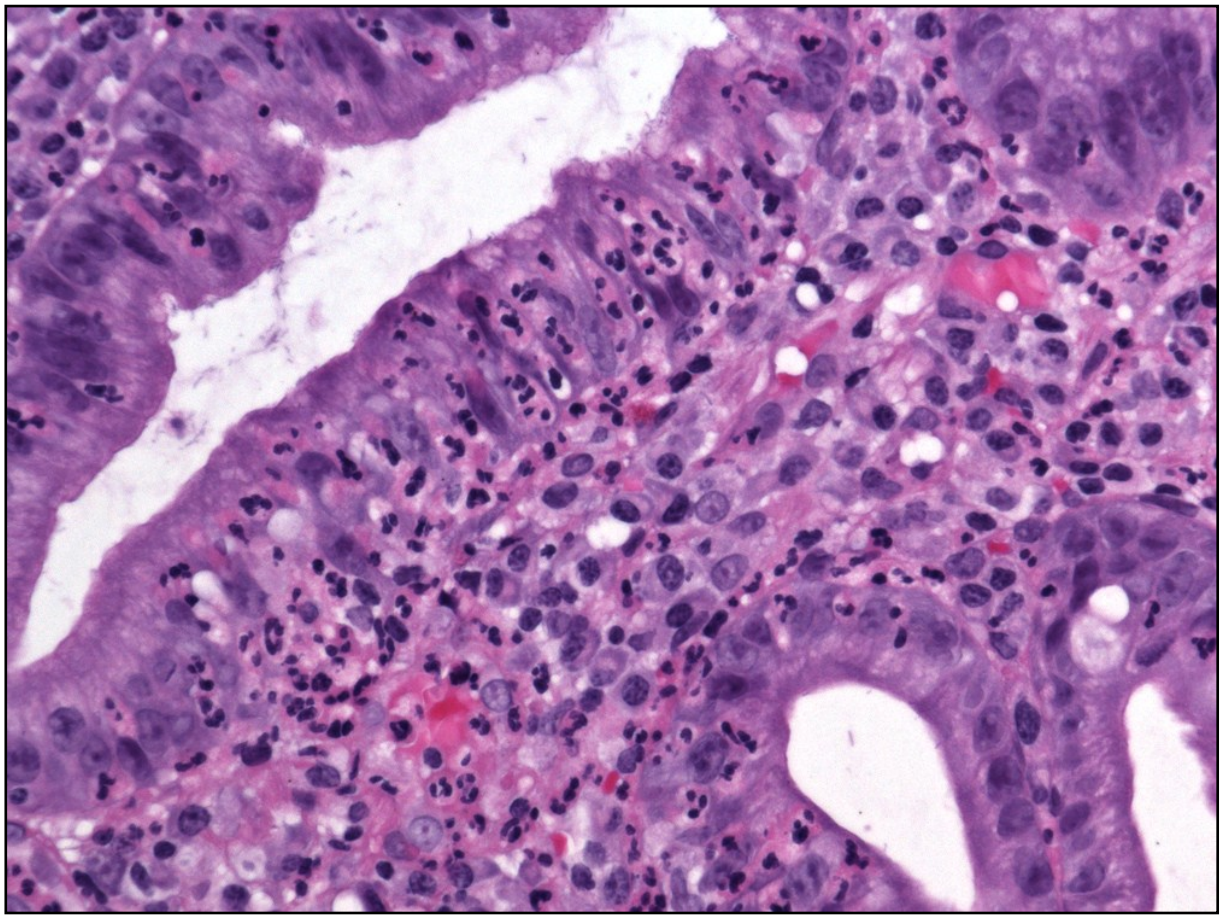

Figure 12: Example of a histologic diagnosis of active *Helicobacter* gastritis (original x200)

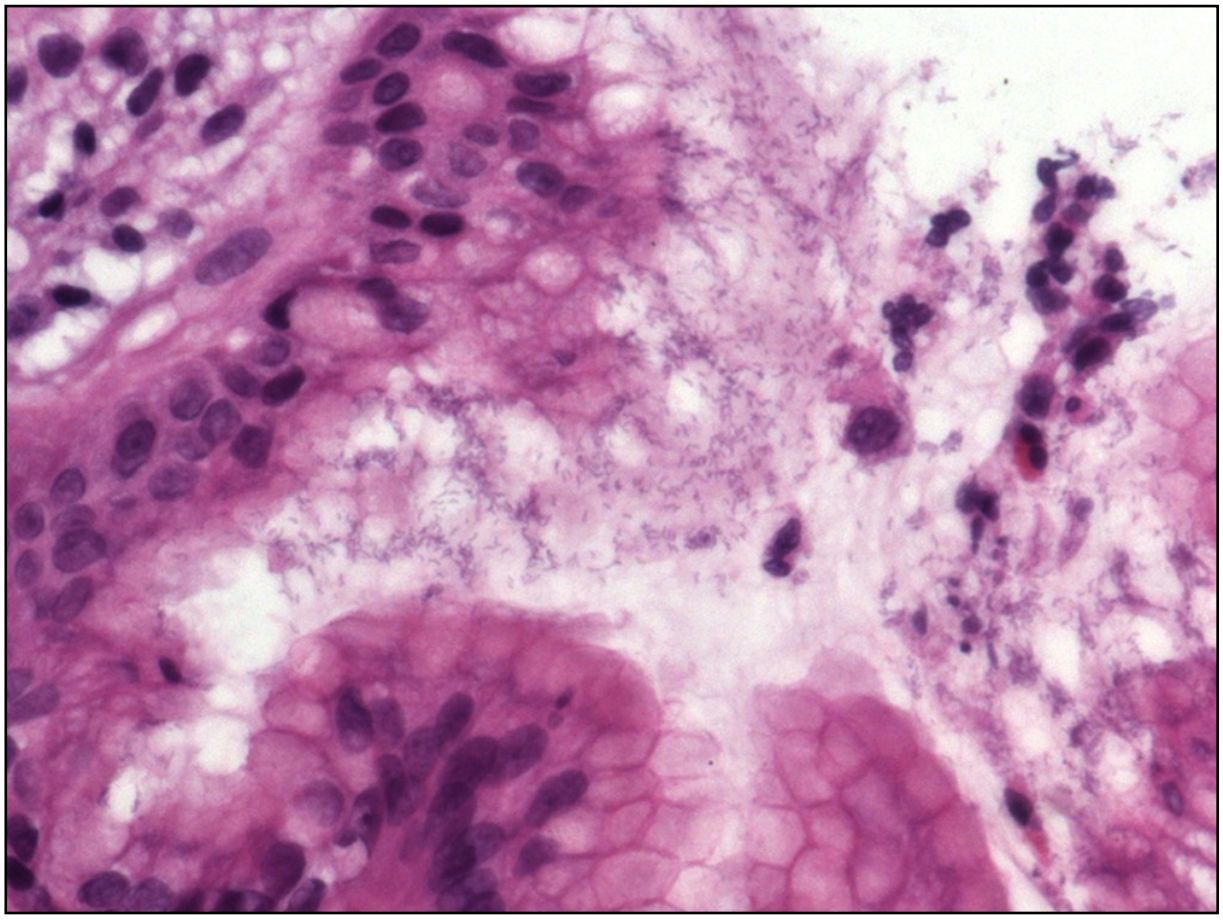

Figure 13: *Helicobacter* organisms within the mucus on the mucosal surface (original x400)

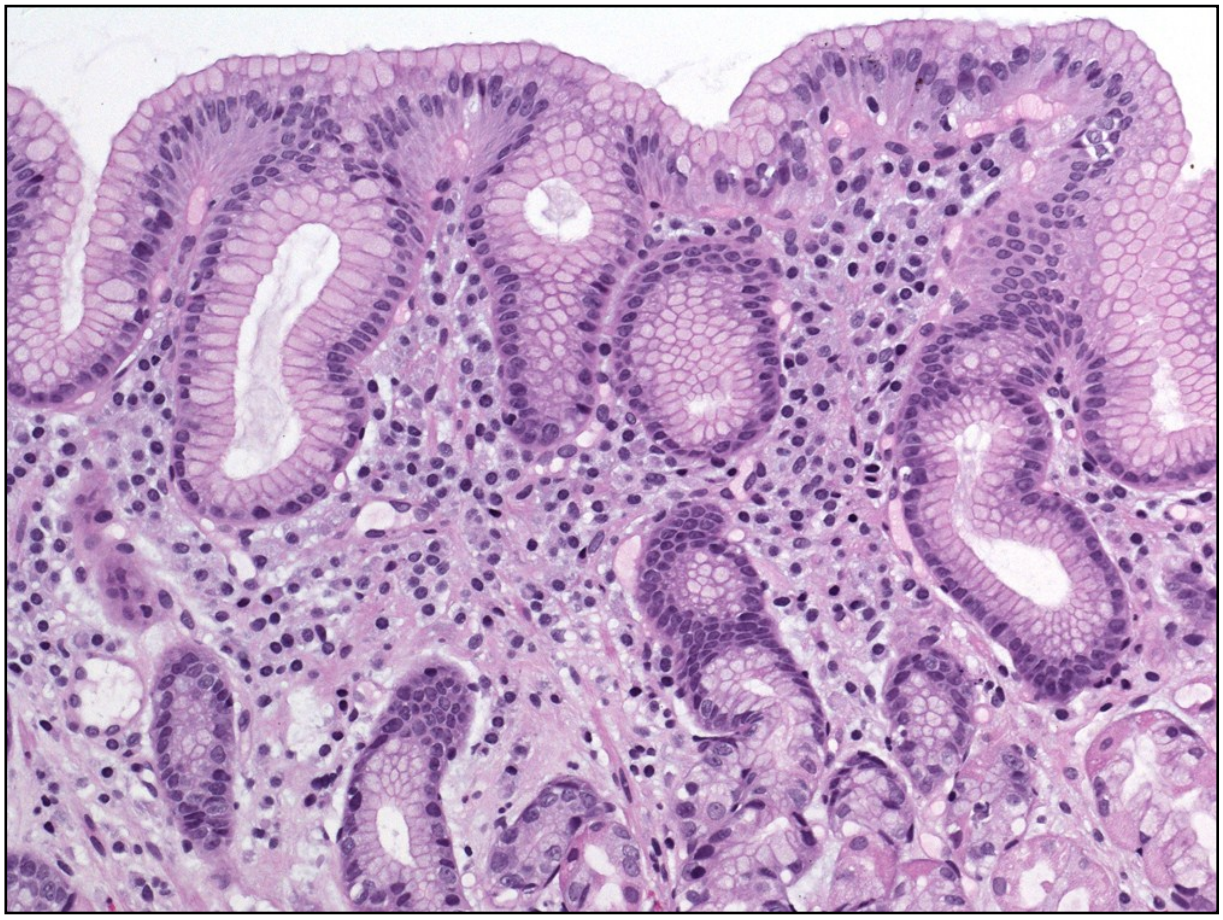

Figure 14: Example of a histologic diagnosis of post *Helicobacter* gastritis (original x100)

Mild chronic inflammation of the lamina propria and normal surface epithelium are seen.

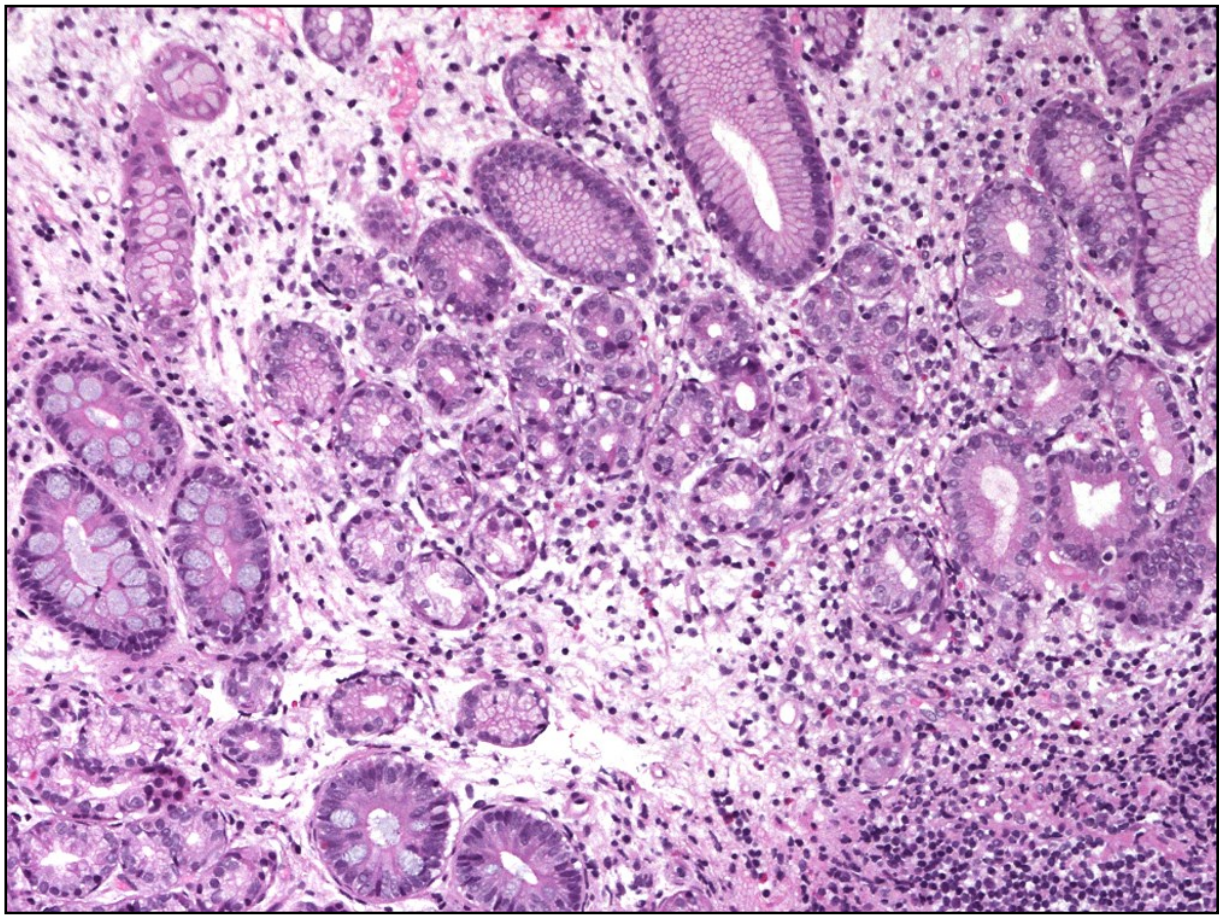

Figure 15: Example of a histologic diagnosis of autoimmune gastritis (original x40)

Corpus mucosa with mild to moderate chronic inflammation with advanced glandular atrophy and intestinal metaplasia is seen.

Histologic Type of Gastritis		**N**	**%**
***Helicobacter* Gastritis (HG)**		**210**	**18.7**
	HG only	208	18.5
	HG + Reactive Gastropathy	1	0.1
	HG + Crohn's Disease	1	0.1
Post *Helicobacter* Gastritis (PHG)		**215**	**19.1**
	PHG only	176	15.7
	PHG + Reactive Gastropathy	21	1.9
	PHG + Autoimmune Gastritis	11	1
	PHG + Reactive Gastropathy + Autoimmune Gastritis	6	0.5
	PHG + Crohn's Disease	1	0.1
Reactive Gastropathy (RG)		**234**	**20.8**
	RG only	201	17.1
	RG + post *Helicobacter* Gastritis	21	1.9
	RG + post *Helicobacter* Gastritis + Autoimmune Gastritis	6	0.5
	RG + Autoimmune Gastritis	5	0.4
	RG + *Helicobacter* gastritis	1	0.1
Autoimmune Gastritis (AG)		**26**	**2.3**
	AG only	4	0.4
	AG + post *Helicobacter* Gastritis	11	1
	AG + post *Helicobacter* Gastritis + Reactive Gastropathy	6	0.5
	AG + Reactive Gastropathy	5	0.4
Crohn's Disease (CD)		**6**	**0.5**
	CD only	4	0.4
	CD + *Helicobacter* Gastritis	1	0.1
	CD + post *Helicobacter* Gastritis	1	0.1

Table 3: Histologic diagnosis of gastritis and combinations of different histologic subtypes

Relation between Histologic and Endoscopic Diagnosis of Gastritis

The histologic diagnosis of gastritis was significantly associated with the endoscopic diagnosis of gastritis: 351 out of 639 (55%) individuals with histologically diagnosed gastritis were positive upon endoscopy compared to 183 out of 484 (37.8%) individuals without histologic abnormalities ($p<0.001$). This difference was due to individuals with reactive gastropathy, autoimmune gastritis, and Crohn's disease whereas for individuals with *Helicobacter* and particularly for individuals with post *Helicobacter* gastritis no significant differences were noted (**Table 4**).

		N	**No Endoscopic Gastritis (n=589)**	**Endoscopic Gastritis (n=534)**
No Histologic Gastritis		484	301 (62.2%)	183 (37.8%)
Histologic Gastritis		639	288 (45.1%)	351 (54.9%)
	Helicobacter Gastritis	210	103 (49%)	107 (51%)
	Post *Helicobacter* Gastritis	215	103 (47.9%)	112 (52.1%)
	Reactive Gastropathy	234	85 (36.3%)	149 (63.7%)
	Autoimmune Gastritis	26	9 (34.6%)	17 (65.4%)
	Crohn's Disease	6	1 (16.7%)	6 (83.3%)

Table 4: Correlation between histologic and endoscopic diagnoses of gastritis

Helicobacter Density and Gastritis Activity

Helicobacter gastritis was active in 209 out of 210 (99.5%) individuals, with 86 (41.1%) individuals showing antrum-predominant activity, 17 (8.1%) corpus-predominant activity, and 106 (50.7%) the same level of inflammatory activity in both locations, respectively. The inflammatory activity seemed to be dependent on the presence of intestinal metaplasia. Thus, in individuals with active *Helicobacter* gastritis and intestinal metaplasia (being present predominantly in the antrum) only 10 out of 37 (27%) showed antrum-dominant activity compared to 76 out of 172 (44.2%) cases of active *Helicobacter* gastritis lacking intestinal metaplasia ($p=0.07$). This

finding, although not significant, indicates that the development of intestinal metaplasia in the antrum caused a shift of inflammatory activity to the proximal parts of the stomach in our cohort. This shift, however, was not accompanied by a similar shift in *Helicobacter* density: In individuals with active *Helicobacter* gastritis with intestinal metaplasia 24 out of 37 (64.9%) showed greater or equal *Helicobacter* density in the corpus (compared to the antrum) compared to 101 out of 172 (58.7%) cases lacking intestinal metaplasia (p=0.58).

Histologic Diagnosis of Intestinal Metaplasia

Histologic diagnosis of intestinal metaplasia was made in 148 out of 1,123 (13.2%) individuals, reflecting 141 out of 639 (22.1%) individuals with histologic diagnosis of gastritis and 7 out of 484 (1.4%) individuals with otherwise normal mucosa (p<0.001). Intestinal metaplasia was diagnosed in the antrum in 135 (12%) and in the corpus in 24 (2.1%) individuals, with 11 individuals showing intestinal metaplasia in both locations. Ninety-three (62.8%) individuals were classified OLGIM stage I, 41 (27.7%) stage II, 9 (6.1%) stage III, and 5 (3.4%) stage IV, respectively. Of the 14 individuals with OLGIM stage III/IV, eight had *Helicobacter* gastritis, four post *Helicobacter* gastritis, and two reactive gastropathy.

Intestinal metaplasia was most common in individuals with autoimmune gastritis (76.9%), followed by post *Helicobacter* gastritis (32.1%), reactive gastropathy (19.7%), and *Helicobacter* gastritis (17.6%), respectively (p<0.001). Taking into account the different prevalence of the different types of gastritis, individuals diagnosed with intestinal metaplasia had post *Helicobacter* gastritis in 46.6%, reactive gastropathy in 31.1%, *Helicobacter* gastritis in 25%, and autoimmune gastritis in 13.5% of cases, respectively. Of note, in individuals with autoimmune gastritis, intestinal metaplasia was more common in the corpus (61.5% corpus vs. 26.9% antrum) compared to all other types of gastritis which showed intestinal metaplasia predominantly in the antrum. Even taking into account the different prevalence of the different types of gastritis, the comparably rare autoimmune gastritis was the most common cause of intestinal metaplasia diagnosed in corpus biopsies (**Figure 16**).

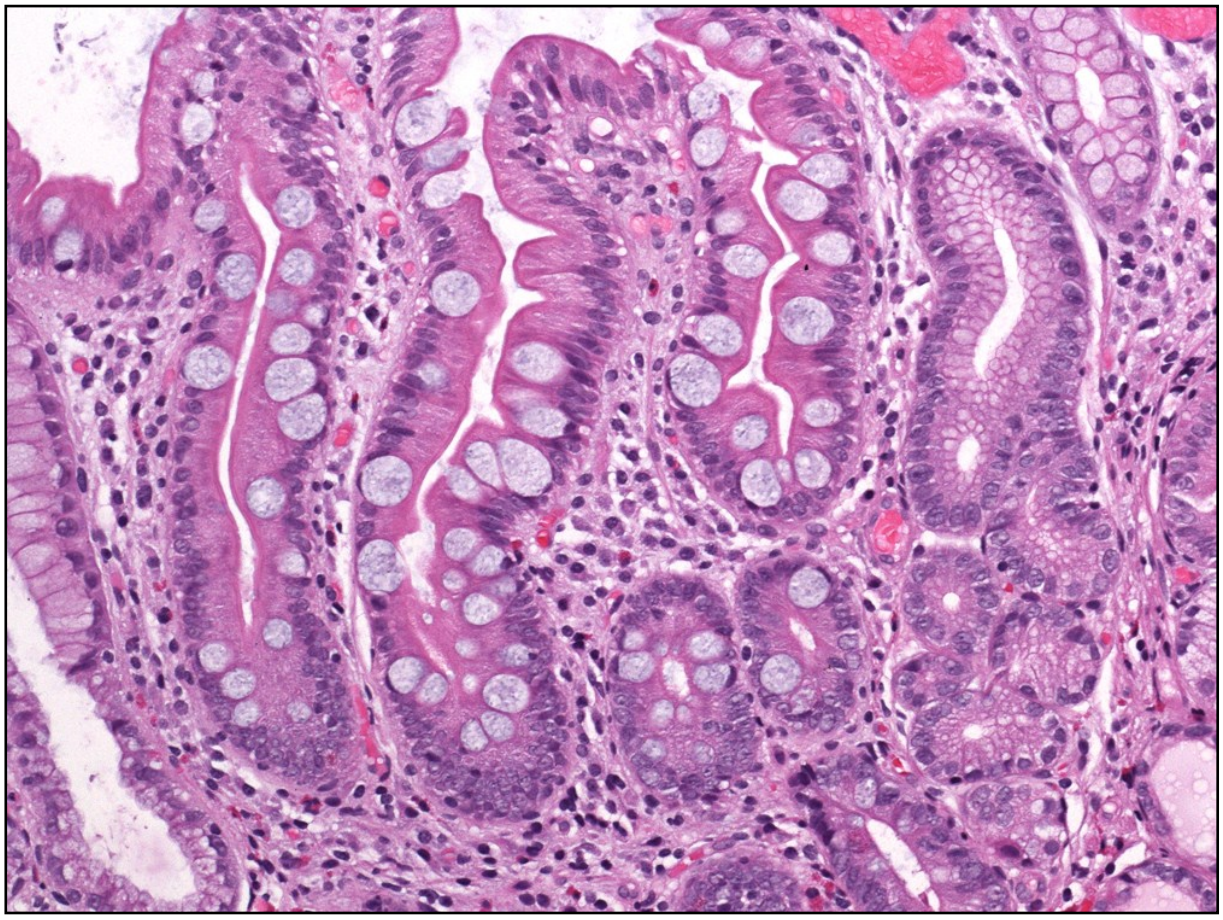

Figure 16: Example of intestinal metaplasia (original x100)

Presence of Mucosal Breaks

Mucosal breaks, i.e. erosions and/or ulcers were present in 37 (3.3%) individuals, with 30 individuals showing mucosal breaks only in the antrum, 6 only in the corpus, and 1 in both locations, respectively. In 36 of these individuals a histologic diagnosis of gastritis was made. The most common histologic association was reactive gastropathy (n=20), followed by post *Helicobacter* gastritis (n=11), *Helicobacter* gastritis (n=9), Crohn's disease (n=3), and autoimmune gastritis (n=1), with eight individuals showing a combination of different subtypes.

Relation between Histologic Parameters and *Helicobacter* infection

Regarding the different parameters indicative of chronic gastritis and/or chronic epithelial injury, foveolar hyperplasia, smooth muscle fibres in the lamina propria, vasodilatation and congestion of the lamina propria, chronic inflammation, and active inflammation were noted in 806 (71.8%), 381 (33.9%), 561 (50%), 584 (52%), and 206 (18.3%) individuals, respectively, albeit in varying quantities (**Table 5**). All parameters were significantly associated with the presence of *Helicobacter* infection: While foveolar hyperplasia, smooth muscle fibres in the lamina propria, vasodilatation and congestion of the lamina propria were more common in *Helicobacter* negative individuals, the presence of chronic and active inflammation argued for *Helicobacter* infection (**Table 5**). Of note, mild vasodilatation and congestion of the lamina propria was more common in *Helicobacter* positive individuals due to mild changes related to the inflammatory process as such (**Figure 17**). Moderate and marked changes, however, were clearly more common in *Helicobacter* negative individuals.

In multivariable analysis, both active and chronic inflammation showed a highly significant positive association with *Helicobacter* infection: odds ratio: 98; 95% CI: 41-235; $p<0.001$ (active inflammation); odds ratio: 4.9; 95% CI: 2.5-9.6; $p<0.001$ (chronic inflammation). Foveolar hyperplasia showed a moderate negative association (odds ratio: 0.44; 95% CI: 0.21-0.93; $p=0.30$) while for smooth muscle fibres in the lamina propria as well as for vasodilatation and congestion no independent association was noted.

Relation between Histologic Parameters and Patients' symptoms

When the five histologic parameters were related to patients' symptoms and/or complaints, however, no statistically significant association was observed (**Table 6**).

	***Helicobacter* negative (n=913)**	***Helicobacter* positive (n=210)**	**P-value**
Foveolar hyperplasia			
Absent	230 (25.2%)	87 (41.4%)	<0.001
Grade 1	491 (53.8%)	108 (51.4%)	
Grade 2	138 (15.1%)	15 (7.1%)	
Grade 3	54 (5.9%)	0 (0%)	
Smooth muscle fibres in lamina propria			
Absent	541(59.3%)	201(95.7%)	<0.001
Grade 1	244 (26.7%)	9 (4.3%)	
Grade 2	103 (11.3%)	0 (0%)	
Grade 3	25 (2.7%)	0 (0%)	
Vasodilatation and congestion of lamina propria			
Absent	471 (51.6%)	91 (43.3%)	<0.001
Grade 1	277 (30.3%)	113 (53.8%)	
Grade 2	104 (11.4%)	5 (2.4%)	
Grade 3	61 (6.7%)	1 (0.5%)	
Chronic inflammation			
Absent	535 (58.6%)	4 (1.9%)	<0.001
Grade 1	357 (39.1%)	44 (21%)	
Grade 2	21 (2.3%)	160 (76.2%)	
Grade 3	0 (0%)	2 (1%)	
Active inflammation			
Absent	904 (99%)	13 (6.2%)	<0.001
Grade 1	6 (0.7%)	108 (51.4%)	
Grade 2	2 (0.2%)	86 (41%)	
Grade 3	1 (0.1%)	3 (1.4%)	

Table 5: Histologic parameters of gastritis related to the presence of *Helicobacter* infection

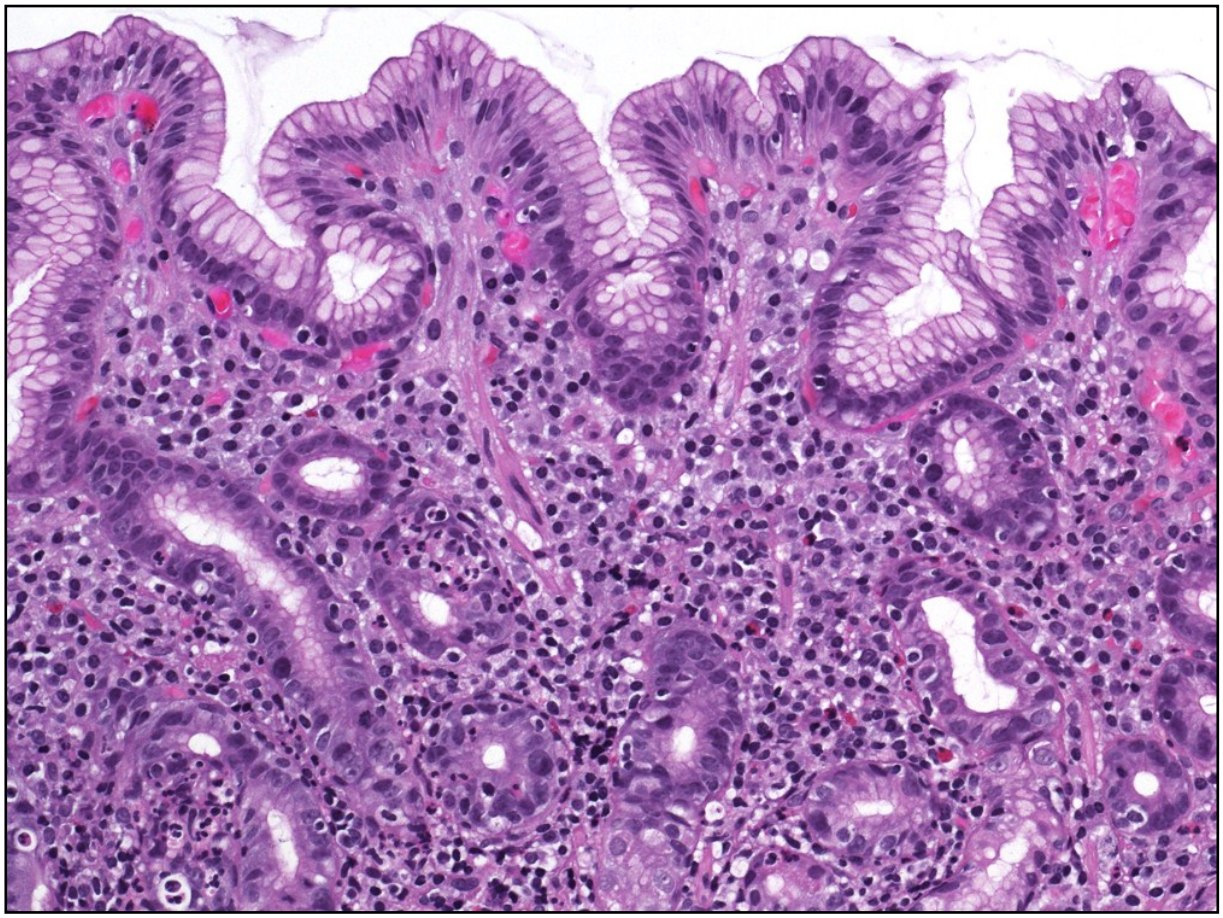

Figure 17: Mild vasodilatation and congestion of superficial mucosal capillaries in *Helicobacter* gastritis (original x100)

	No epigastric symptoms (n=580)	Epigastric symptoms (n=543)	P-value
Foveolar hyperplasia			
Absent	178 (30.7%)	139 (25.6%)	0.13
Grade 1	290 (50%)	309 (56.9%)	
Grade 2	83 (14.3%)	70 (12.9%)	
Grade 3	29 (5%)	25 (4.6%)	
Smooth muscle fibres in lamina propria			
Absent	372(64.1%)	370 (68.1%)	0.33
Grade 1	138 (23.8%)	115 (21.2%)	
Grade 2	59 (10.2%)	44 (8.1%)	
Grade 3	11 (1.9%)	14 (2.6%)	
Vasodilatation and congestion of lamina propria			
Absent	280 (48.3%)	282 (51.9%)	0.46
Grade 1	203 (35%)	187 (34.4%)	
Grade 2	61 (10.5%)	48 (8.8%)	
Grade 3	36 (6.2%)	26 (4.8%)	
Chronic inflammation			
Absent	270 (46.6%)	269 (49.5%)	0.13
Grade 1	205 (35.3%)	196 (36.1%)	
Grade 2	105 (18.1%)	76 (14%)	
Grade 3	0 (0%)	2 (0.4%)	
Active inflammation			
Absent	466 (80.3%)	451 (83.1%)	0.019
Grade 1	71 (12.2%)	43 (7.9%)	
Grade 2	43 (7.4%)	45 (8.3%)	
Grade 3	0 (0%)	4 (0.7%)	

Table 6: Histologic parameters of gastritis related to the presence of epigastric symptoms

Proposal of a New Histologic Scoring System for Reactive Gastropathy

Our data confirm the association of chronic and active inflammation with *Helicobacter* infection. In addition, they confirm Dixon's parameters characterizing reactive gastropathy, i.e. foveolar hyperplasia, smooth muscle fibres in the lamina propria, as well as vasodilatation and congestion of the lamina propria as most important histologic parameters for diagnosis.

We believe an ideal scoring system for the diagnosis of reactive gastropathy should add the three parameters in favour of the diagnosis (foveolar hyperplasia, smooth muscle fibres in the lamina propria, and vasodilatation and congestion of the lamina propria) and subtract the two that argue against it (chronic and active inflammation). As the parameters in favour of the diagnosis appear to be more important, their score was multiplied by a factor of two, leading to score values reaching from minus 6 to plus 18 (**Figure 18**). Expectedly, we observed a highly significant association of the proposed scoring system with *Helicobacter* status ($p<0.001$), with low values indicating *Helicobacter* infection and high values arguing strongly against it (**Table 7**). Exemplifying histologic images of different scores are provided in **Figure 19**,**20**,**21** and **22**.

As high scores not only argue against *Helicobacter* infection but argue also for the diagnosis of reactive gastropathy, we subsequently tried to define the best cut-off value for this diagnosis. Based upon the following two observations we considered score 7 to be the best cut-off value: *First*, mild, i.e. grade 1 foveolar hyperplasia is comparably common and may not be a significant finding. Likewise, mild, i.e. grade 1 vasodilatation and congestion shows similar percentages in *Helicobacter* positive and negative individuals, and only moderate/marked, i.e. grade 2/3 vasodilatation and congestion seems to be related to reactive gastropathy. Thus, scores based upon low grades, i.e. grade 1 evaluation in all parameters favouring the diagnosis of reactive gastropathy, thereby reaching a maximum score of 6, may only reflect normal variability. *Second*, 269 (24%) individuals were characterised by both epigastric symptoms and endoscopic diagnosis of gastritis. Applying the proposed cut-off value of 7, 74 out of 234 (31.6%) individuals considered positive for reactive gastropathy

showed both epigastric symptoms and endoscopic diagnosis of gastritis, compared to only 195 out of 889 (21.9%) individuals considered negative (p=0.003).

In all, applying score 7 as cut-off value, 234 (20.8%) individuals were considered positive for reactive gastropathy (scores seven through eighteen) and 889 (79.2%) participants negative (scores minus six through plus six), respectively.

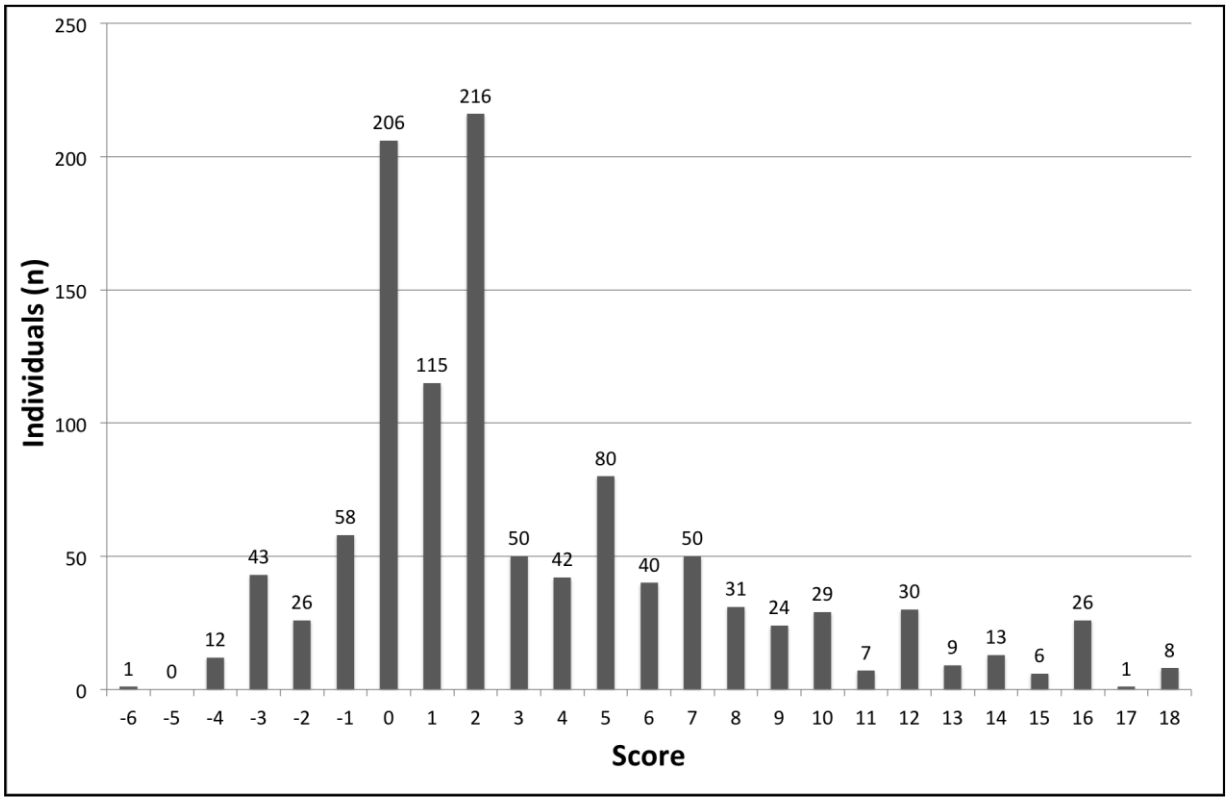

Figure 18: Distribution of individuals among the different scores

It shows the distribution of our study cohort of 1,123 individuals among the proposed new scoring system for the diagnosis of reactive gastropathy from minus 6 through plus 18.

Score	All individuals (n=1123)		*Helicobacter* negative (n=913)		*Helicobacter* positive (n=210)	
	n	%	n	%	n	%
- 6	1	0.1	0	0	1	100
- 5	0	0	0	-	0	-
- 4	12	1.1	1	8.3	11	91.6
- 3	43	3.8	0	0	43	100
- 2	26	2.3	5	19.2	21	80.8
- 1	58	5.2	43	74.1	15	25.9
0	206	18.3	148	71.8	58	28.2
1	115	10.2	89	77.4	26	22.6
2	216	19.2	190	88	26	12
3	50	4.5	49	98	1	2
4	42	3.7	38	90.5	4	9.5
5	80	7.1	78	97.5	2	2.5
6	40	3.6	39	97.5	1	2.5
7	50	4.5	50	100	0	0
8	31	2.8	31	100	0	0
9	24	2.1	24	100	0	0
10	29	2.6	28	96.6	1	3.4
11	7	0.6	7	100	0	0
12	30	2.7	30	100	0	0
13	9	0.8	9	100	0	0
14	13	1.2	13	100	0	0
15	6	0.5	6	100	0	0
16	26	2.3	26	100	0	0
17	1	0.1	1	100	0	0
18	8	0.7	8	100	0	0

Table 7: Proposed score for reactive gastropathy related to the presence of *Helicobacter* infection

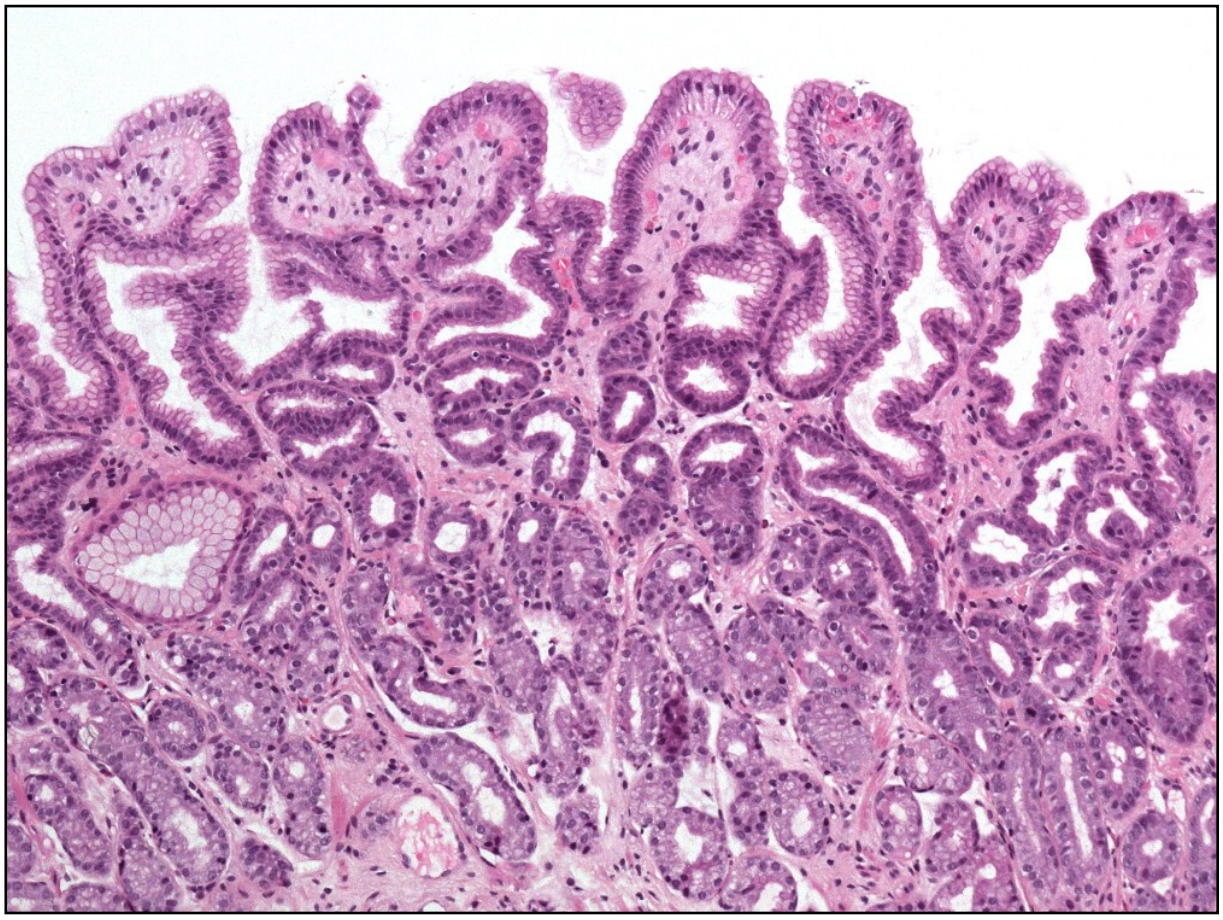

Figure 19: Example of reactive gastropathy (original x100)

Marked foveolar hyperplasia (grade 3, multiplied by 2), mild hyperplasia of smooth muscle fibres (grade 1, multiplied by 2), and mild vasodilatation and congestion (grade 1, multiplied by 2), without significant acute and chronic inflammation (grade 0, respectively) leading to a score of 10.

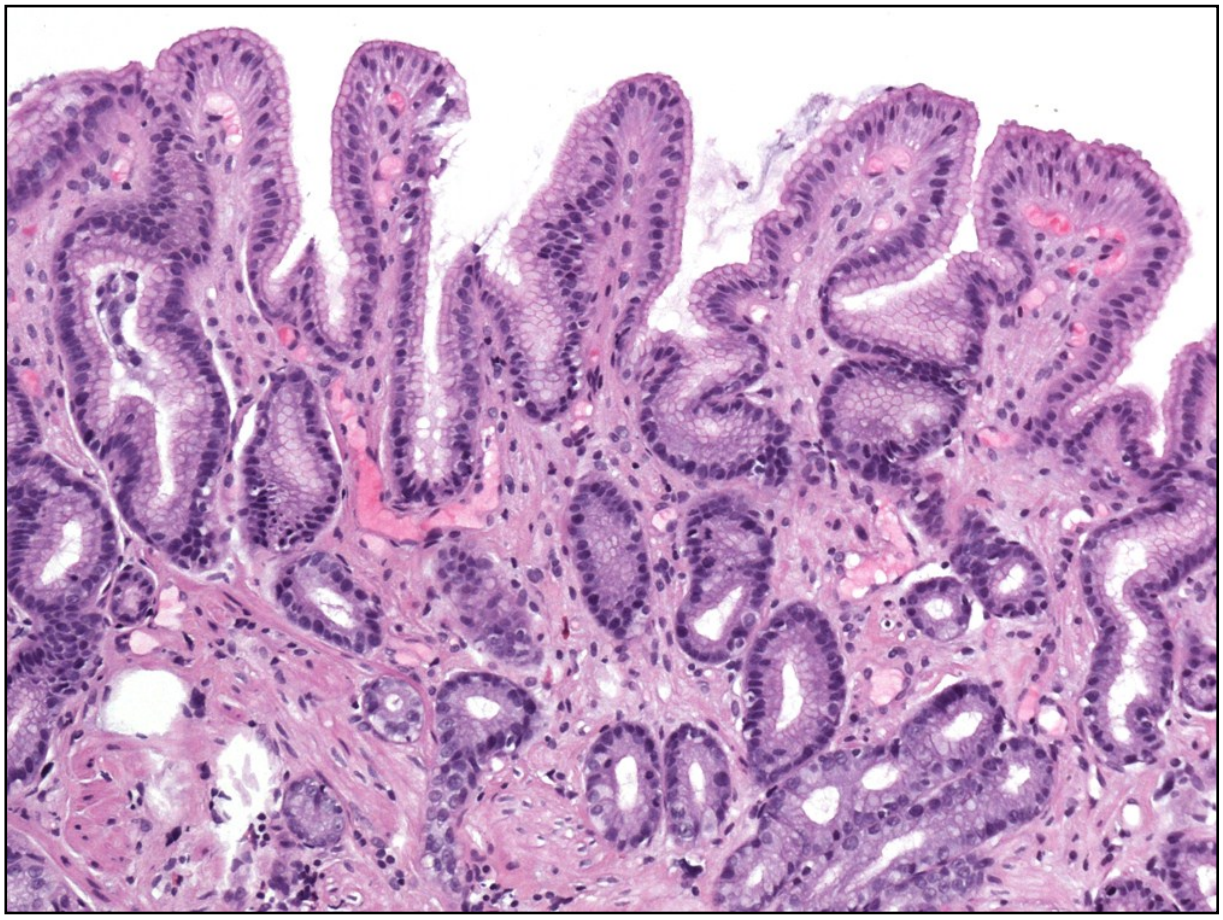

Figure 20: Example of reactive gastropathy (original x100)

Mild foveolar hyperplasia (grade 1, multiplied by 2), moderate hyperplasia of smooth muscle fibres (grade 2, multiplied by 2), and mild vasodilatation and congestion (grade 1, multiplied by 2), without significant acute and chronic inflammation (grade 0, respectively) leading to a total score of 8.

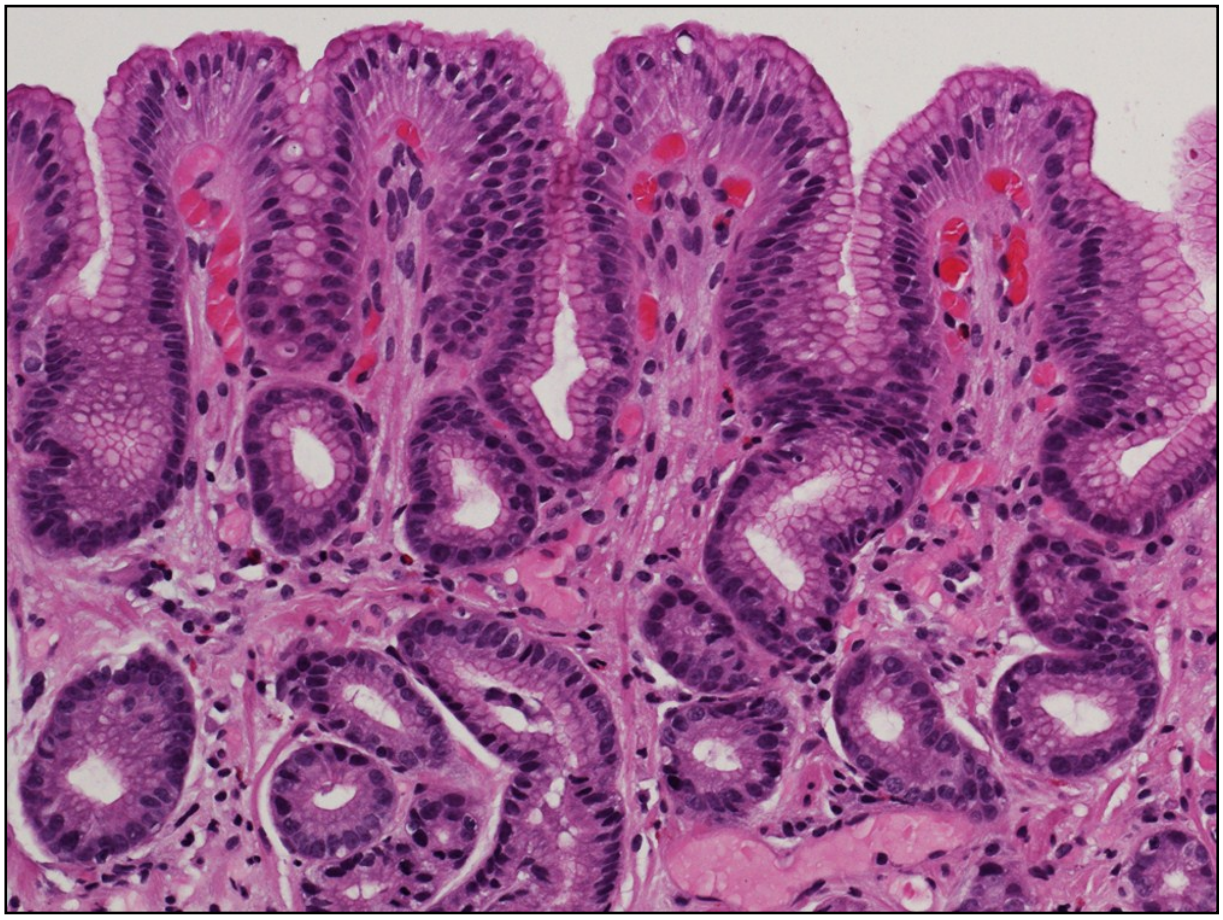

Figure 21: Example of reactive gastropathy (original x100)

Mild foveolar hyperplasia (grade 1, multiplied by 2), mild hyperplasia of smooth muscle fibres (grade 1, multiplied by 2), and moderate vasodilatation and congestion (grade 2, multiplied by 2), without significant acute and chronic inflammation (grade 0, respectively) leading to a total score of 8.

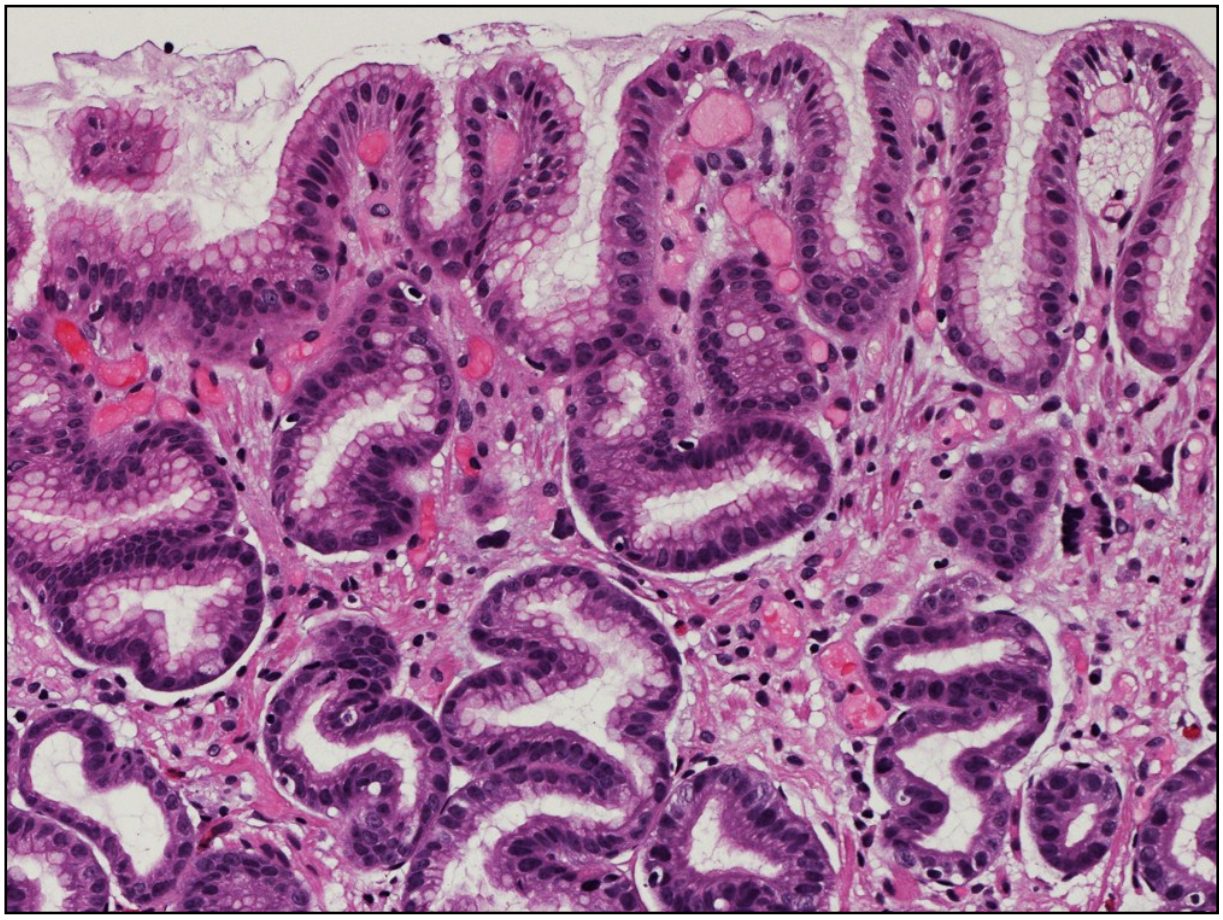

Figure 22: Example of reactive gastropathy (original x100)

Mild foveolar hyperplasia (grade 1, multiplied by 2), mild hyperplasia of smooth muscle fibres (grade 1, multiplied by 2), and marked vasodilatation and congestion (grade 3, multiplied by 2), without significant acute and chronic inflammation (grade 0, respectively) leading to a total score of 10.

Relation between Histologic Parameters and Endoscopic Findings

When the five histologic parameters evaluated for chronic gastritis and/or chronic epithelial injury were related to the endoscopic diagnosis of gastritis, remarkable differences were noted. Thus, all three parameters in favour of a diagnosis of reactive gastropathy, i.e. foveolar hyperplasia, smooth muscle fibres in the lamina propria, and vasodilatation and congestion were significantly associated with the diagnosis, whereas those related to *Helicobacter* infection were not (**Table 8**). In multivariable analysis, smooth muscle fibres in the lamina propria showed a significant association with the endoscopic diagnosis of gastritis (odds ratio: 1.35; 95% CI: 1.05-1.75; p=0.021). Foveolar hyperplasia showed a moderate association (odds ratio: 1.22; 95% CI: 0.97-1.52; p=0.08), while for vasodilatation and congestion no association was noted.

When the proposed score for reactive gastropathy was related to endoscopic findings, we observed a highly significant association between histology and endoscopy (p<0.001). Specifically, 149 out of 234 (63.7%) individuals with histologic diagnosis of reactive gastropathy (score 7 through score 18) were diagnosed with gastritis upon endoscopy, compared to 385 out of 889 (43.3%) participants not considered to have reactive gastropathy on histologic diagnosis (score -6 through score 6), respectively (p=0.002).

For scores 11 and higher, approximately 80% of individuals were also positive on endoscopy. For lower scores, however, no significant association was noted: 156 out of 346 (45.1%) individuals with score -6 through score 0, 229 out of 543 (42.2%) individuals with score 1 through score 6, and 64 out of 134 (47.8%) individuals with score 7 through score 10 were diagnosed with gastritis endoscopically (p=0.73), indicating higher sensitivity of histologic diagnosis (**Table 9**).

	No endoscopic gastritis (n=589)	Endoscopic gastritis (n=534)	P-value
Foveolar hyperplasia			
Absent	179 (30.3%)	138 (25.8%)	<0.001
Grade 1	340 (57.7%)	259 (48.5%)	
Grade 2	66 (11.2%)	87 (16.3%)	
Grade 3	4 (0.7%)	50 (9.4%)	
Smooth muscle fibres in lamina propria			
Absent	423(71.8%)	319 (59.7%)	<0.001
Grade 1	134 (22.8%)	119 (22.3%)	
Grade 2	29 (4.9%)	74 (13.9%)	
Grade 3	3 (0.5%)	22 (4.1%)	
Vasodilatation and congestion of lamina propria			
Absent	318 (54%)	244 (45.7%)	<0.001
Grade 1	216 (36.7%)	174 (32.6%)	
Grade 2	44 (7.5%)	65 (12.2%)	
Grade 3	11 (1.9%)	51 (9.6%)	
Chronic inflammation			
Absent	300 (50.9%)	239 (44.8%)	0.083
Grade 1	201 (34.1%)	200 (37.5%)	
Grade 2	86 (14.6%)	95 (17.8%)	
Grade 3	2 (0.3%)	0 (0%)	
Active inflammation			
Absent	488 (82.9%)	429 (80.3%)	0.37
Grade 1	52 (8.8%)	62 (11.6%)	
Grade 2	46 (7.8%)	42 (7.9%)	
Grade 3	3 (0.5%)	1 (0.2%)	

Table 8: Histologic parameters of gastritis related to the endoscopic diagnosis of gastritis

Score	All individuals (n=1123)		No endoscopic gastritis (n=589)		Endoscopic gastritis (n=534)	
	n	%	n	%	n	%
- 6	1	0.1	1	100	0	0
- 5	0	0	0	-	0	-
- 4	12	1.1	3	25	9	75
- 3	43	3.8	20	46.5	23	53.5
- 2	26	2.3	16	61.5	10	38.5
- 1	58	5.2	32	55.2	26	44.8
0	206	18.3	118	57.3	88	42.7
1	115	10.2	59	51.3	56	48.7
2	216	19.2	134	62	82	38
3	50	4.5	27	54	23	46
4	42	3.7	27	64.3	15	35.7
5	80	7.1	43	53.7	37	46.3
6	40	3.6	24	60	16	40
7	50	4.5	27	54	23	46
8	31	2.8	14	45.2	17	54.8
9	24	2.1	10	41.7	14	58.3
10	29	2.6	19	65.5	10	34.5
11	7	0.6	1	14.3	6	85.7
12	30	2.7	9	30	21	70
13	9	0.8	1	11.1	8	88.9
14	13	1.2	0	0	13	100
15	6	0.5	0	0	6	100
16	26	2.3	3	11.5	23	88.5
17	1	0.1	0	0	1	100
18	8	0.7	1	12.5	7	87.5

Table 9: Proposed score for reactive gastropathy related to the endoscopic diagnosis of gastritis

Relation between Intake of PPI and Diagnosis of Gastritis

Overall, the histologic diagnosis of gastritis was not significantly associated with PPI medication: 316 out of 533 (59.3%) individuals receiving PPI were histologically diagnosed with gastritis compared to 323 out of 590 (54.7%) individuals not receiving PPI (p=0.13). Notably, however, there was a significant association between the histologic type of gastritis and PPI therapy (p<0.001)(**Table 10**). An example of parietal cell hypertrophy and hyperplasia promoted by chronic usage of PPIs is shown in **Figure 23**.

In addition, similar to the effect of intestinal metaplasia, the inflammatory activity of *Helicobacter* gastritis seemed to be dependent on PPI medication. Thus, in individuals with active *Helicobacter* gastritis who received PPI only 25 out of 76 (32.9%) showed antrum-dominant activity compared to 61 out of 133 (45.9%) individuals not receiving PPI (p=0.08). This finding, although similarly not significant, indicates that treatment with PPI caused a shift of inflammatory activity to the proximal parts of the stomach in our cohort. Of note, in contrast to the situation in chronic gastritis with intestinal metaplasia, this shift was accompanied by a similar shift in *Helicobacter* density: In individuals with active *Helicobacter* gastritis who received PPI 56 out of 76 (73.7%) showed greater or equal *Helicobacter* density in the corpus (compared to the antrum) compared to 69 out of 133 (51.8%) individuals not receiving PPI (p=0.002).

		N	**No PPI (n=590)**	**PPI (n=533)**
No histologic Gastritis		484	267 (55.2%)	217 (44.8%)
Histologic Gastritis		639	323 (50.5%)	316 (49.5%)
	Helicobacter Gastritis	210	134 (63.8%)	76 (36.2%)
	Post *Helicobacter* Gastritis	215	100 (46.5%)	115 (53.5%)
	Reactive Gastropathy	234	97 (41.5%)	137 (58.5%)
	Autoimmune Gastritis	26	15 (57.7%)	11 (42.3%)
	Crohn’s Disease	6	2 (33.3%)	4 (66.7%)

Table 10: Correlation between histologic diagnosis of gastritis and intake of PPIs

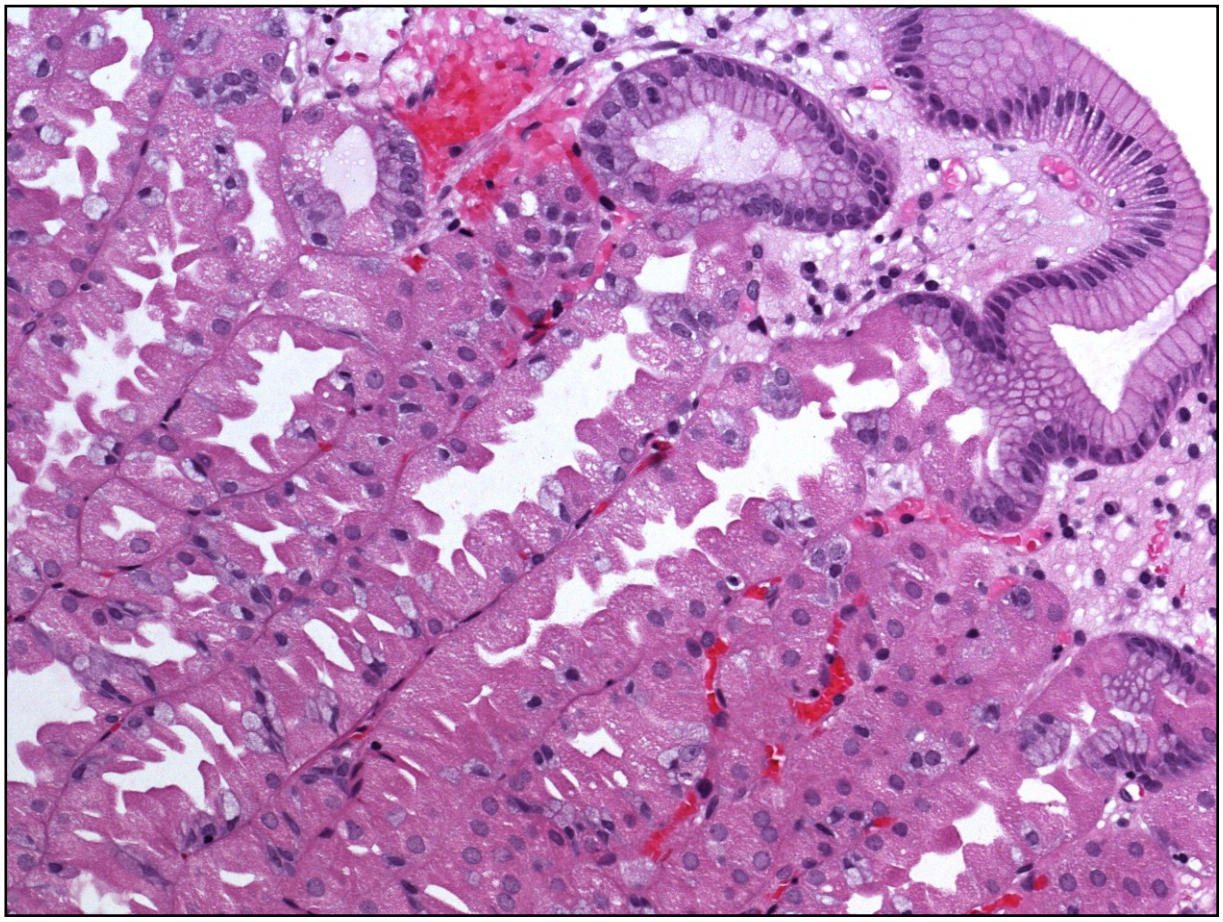

Figure 23: Example of parietal cell hypertrophy and hyperplasia induced by PPI therapy (original x100)

Discussion

Only shortly after the discovery of *Helicobacter* infection as the most common cause of chronic gastritis almost three decades ago (1, 2), first effective treatment strategies against the pathogen were introduced (43, 44). Owing to improved sanitary conditions, increasing knowledge about the infectious character of disease, and widespread use of antibiotics, the prevalence of *Helicobacter* infection is declining in emerging and, particularly, in industrialised countries (7, 45).

In our cohort, histologic diagnosis of gastritis was made in more than 50% of participants, with reactive gastropathy being more common than active or ongoing *Helicobacter* gastritis. Of note, and reported here for the first time, the majority of cases attributable to *Helicobacter* infection were no longer ongoing or active (post *Helicobacter* gastritis). We diagnosed a remarkably high number of individuals with post *Helicobacter* gastritis. This may be related to the fact that most previous studies did not consider post *Helicobacter* gastritis or ex-*Helicobacter* gastritis in their classification. We believe, however, that a histologic diagnosis of gastritis should always refer to the underlying cause of disease. Our data are well in the line with a recent retrospective study from outpatient endoscopy centres across the United States indicating that reactive gastropathy has emerged as the most common type of gastritis in Western countries (6).

In more than 5% of histologically diagnosed cases with gastritis, combinations of different histologic subtypes were noted. The most common was reactive gastropathy (in the antrum) in combination with post *Helicobacter* gastritis (in the corpus). In general, the morphologic criteria for diagnosis of different types of gastritis occurring synchronously within the same patient are not well established. Undoubtedly, however, these cases must exist, particularly facing the prevalence of the different types of gastritis. Already in 2001, Stolte and Meining (24) raised the question whether mixed “chemically induced/reactive and *Helicobacter* gastritis” does exist. Recently, Chen and co-workers (40) observed different parameters for reactive gastropathy, such as oedema and smooth muscle proliferation in the lamina propria

as well as vasodilatation and congestion in individuals tested positive or negative for *Helicobacter* infection. Their data indicate that a diagnosis of combined reactive gastropathy and *Helicobacter* gastritis is possible upon histology.

Interestingly, also autoimmune gastritis occurred considerably often in combination with post *Helicobacter* gastritis. This finding may be related to the putative role of *Helicobacter* infection in initiating autoimmune gastritis and pernicious anaemia (25-28). This view is supported by a study reporting on the healing of active, non-atrophic autoimmune gastritis by *Helicobacter* eradication (46).

In our study, intestinal metaplasia was diagnosed in 13.2% of individuals, reflecting 22.1% of individuals with gastritis diagnosed upon histology. The prevalence of intestinal metaplasia in the general population is known to vary around the globe, mostly depending on *Helicobacte*r infection status (47). In our cohort, intestinal metaplasia was most commonly observed in individuals with autoimmune gastritis, followed by post *Helicobacter* gastritis, reactive gastropathy, and finally *Helicobacter* gastritis. Intestinal metaplasia prevailed in the antrum, which is in line with literature data (47, 48). In individuals with autoimmune gastritis, however, intestinal metaplasia was almost exclusively found in the corpus.

The presence of atrophic gastritis with intestinal metaplasia represents a well-recognised risk factor for the development of gastric cancer (30, 31). These precancerous conditions are however often unevenly distributed throughout the stomach. For adequate staging and grading, at least four non-targeted biopsies of two topographic sites (at the lesser and greater curvature, from both the antrum and the corpus) have been recommended (30). The extent or severity of intestinal metaplasia has been linked to increased cancer risk. Applying the OLGIM criteria for staging of intestinal metaplasia, 9.5% of individuals with intestinal metaplasia or 2.2% with histological diagnosis of gastritis were classified into the high risk stages III and IV, the majority of whom suffering from *Helicobacter* or post *Helicobacter* gastritis. In the original presentation of the OLGIM system 23.2% of individuals had been classified stage III/IV (42). That cohort, however, had been selected based upon previous diagnosis of intestinal metaplasia and/or dysplasia and biopsy samplings were

obtained from twelve different topographic sites. In a recent large retrospective analysis from Italy, Rugge and coworkers (49) identified 229 (5.1%) stage III/IV patients in an unselected series including 4,552 patients.

A well-known axiom of chronic gastritis states that *Helicobacter* organisms adhere exclusively to native gastric epithelium and are not found on areas of intestinal metaplasia (45). Although some authors have pointed out some exceptions to this principle, this concept is generally correct, and a gastric biopsy specimen comprising primarily or exclusively metaplastic intestinal epithelium is inadequate to evaluate *Helicobacter* status (45, 50). In our study the development of intestinal metaplasia in the antrum was associated with a shift of inflammatory activity to the proximal parts of the stomach. Of note, these individuals with corpus-dominant gastritis and intestinal metaplasia in the antrum (and corpus) have been shown to be at particular risk for the development of cancer (51).

Dyspepsia is a common symptom in the general population. It shows marked geographic variability, with prevalence rates ranging from 10 to 45% (52, 53). In our cohort, nearly 50% reported on dyspepsia and/or epigastric pain. Remarkably, no association between reported symptoms and the endosopic diagnosis of gastritis was observed. Our data are in the line with other publications that also failed to identify an association between clinical symptoms and endoscopic findings (54-57). To the best of our knowledge, the study by Tahara and co-workers (58) is the only one that detected a statistically significant association between dyspepsia and endoscopy, particularly friability of the antrum mucosa as well as duodenal ulcer scarring, yet not regarding other endoscopic parameters. The fact that no association between histologic parameters and patients' symptoms and/or complaints was noted in our cohort is in the line with other studies (6, 58). Tahara and co-workers (58) did not identify an association between dyspeptic symptoms, *Helicobacter* status and histologic severity of gastritis. Likewise, in the recent study by Maguilnik and co-workers (6) none of the usual symptoms leading to gastroscopy, such as reflux, dysphagia, dyspepsia, or epigastric pain was associated with histologic diagnosis of reactive gastropathy.

PPI treatment has gained widespread acceptance as an effective and safe therapy for gastro-oesophageal reflux disease and the medication is also widely used for symptomatic treatment of dyspepsia (12, 59). In our cohort, the morphology of *Helicobacter* gastritis was dependent on PPI intake which caused a shift of inflammatory activity to the proximal parts of the stomach, comparable to the influence of intestinal metaplasia. Several investigators have noted a similar shift in inflammatory cell density from antrum to corpus in *Helicobacter* gastritis on PPI treatment (59-62). Logan and co-workers (63) reported that the density of *Helicobacter* in the antrum and corpus was reduced after PPI treatment while that in the fundus was increased with similar changes in the degree of inflammatory activity. These results are consistent with those obtained from other studies (62, 64). In contrast, Stolte and co-workers (65) only observed increased inflammatory cell density in the corpus mucosa, yet without any increase in *Helicobacter* colonisation.

Most investigators will agree that the diagnosis of gastritis should be based upon histologic examination of the gastric mucosa, since endoscopic features are of limited value and the correlation between histology and endoscopy remains to be unsatisfactory, particularly using conventional white light endoscopy (30, 33-36, 54, 66). The use of advanced imaging techniques, such as high-resolution magnifying endoscopy with narrow-band imaging or confocal laser endomicroscopy may, however, help to improve the accuracy of endoscopic diagnosis (67-69). These techniques take more time for examination and need more experience. Their application in daily routine examinations does therefore not seem to be practicable. In our study, applying high-resolution endoscopy without (computed virtual) chromoendoscopy, the agreement between endoscopic and histologic diagnoses was better in reactive gastropathy compared to the other types of gastritis. Thus, our data suggest that the endoscopic diagnosis of reactive gastropathy can be performed with higher accuracy than the endoscopic diagnosis of *Helicobacter* gastritis.

Traditionally, the histologic assessment of gastric biopsies is based upon the Updated Sydney System (13), evaluating the extent of chronic and active inflammation as well as potential consequences of chronic gastritis, such as intestinal

metaplasia and mucosal atrophy. This system is particularly suitable for the reporting of *Helicobacter* gastritis. Our study additionally assessed different parameters associated with chemical injury to the mucosa which were combined in visual analogue scales. Among them, foveolar hyperplasia with elongation and “corkscrew appearance” of gastric crypts is a key feature (15, 18). It has been associated with increased exfoliation of surface epithelial cells, related to cytokine stimulation or other inflammatory mediators (13). Depletion of apical mucin in surface epithelial cells and mild nuclear atypia usually coincide with foveolar hyperplasia. In fact, foveolar hyperplasia can be observed in all types of gastritis but it is particularly evident in reactive gastropathy (13, 15, 23). Interfoveolar smooth muscle fibres, emerging perpendicularly from the muscularis mucosae towards the surface epithelium, represent another important feature of reactive gastropathy. It still remains to be determined, whether it is only peristalsis that causes “pulling forces”, promoting the proliferation of smooth muscle fibres between the regenerating foveolae (18). The third main indicator of reactive gastropathy is vasodilatation and congestion of superficial mucosal capillaries, an eventually unspecific vascular response to epithelial damage and/or inflammation. These three parameters more or less define reactive gastropathy. Of note, the histological parameters may not be present in all patients, and concurrent *Helicobacter* infection may obscure the histologic changes (70). Mixed aetiology may in fact be the reason why Chen and co-workers (40) observed foveolar hyperplasia more often in *Helicobacter* positive individuals than in non-infected individuals. In our study, the presence of all three markers was negatively associated with *Helicobacter* infection. However, mild vasodilatation and congestion of the lamina propria was more common in *Helicobacter* positive individuals, most probably due to unspecific triggers related to the inflammatory process as such. Moderate and strong changes, however, were more common in *Helicobacter* negative individuals.

The other two parameters assessed in our investigation, i.e. chronic and active inflammation argue for a diagnosis other than reactive gastropathy, which was confirmed in our study. In fact, the presence of neutrophils strongly indicates *Helicobacter* infection (13, 40). The neutrophils disappear after cure, while chronic

inflammatory cells, such as lymphocytes and plasma cells can stay much longer after eradication therapy (71).

Although the three parameters foveolar hyperplasia, smooth muscle fibres in the lamina propria, and vasodilatation and congestion within the lamina propria represent the most important histologic parameters for the diagnosis of reactive gastropathy, no single histologic feature can be used to characterise or diagnose reactive gastropathy (70), and several attempts have been made to include these parameters in histologic scores to enhance diagnostic accuracy (15, 40, 72).

In contrast to Dixon's reflux score (15), we believe an ideal scoring system should add up the scores of the parameters in favour of the diagnosis of reactive gastropathy and subtract those arguing against it. In addition, we regard the fact that individuals with entirely normal mucosa already reach a score of six (for the "paucity" of chronic and active inflammatory cells) as problematic. Our proposed score (minimum = minus 6, maximum = plus 18) which is based on these assumptions showed a highly significant association with *Helicobacter* status, with low values indicating *Helicobacter* infection and high values arguing against it. The arguments why we considered 7 to be the ideal cut-off value for our scoring system have been presented in detail above. Applying this cut-off value, reactive gastropathy was diagnosed in more than 20% of individuals, thereby superseding *Helicobacter* infection as most common cause of gastritis. This finding is in accordance with a recent study from the United States that demonstrated reactive gastropathy to be the most common type of gastritis (15.6%), followed by *Helicobacter* gastritis (10.3%) (6).

The modification of Dixon's reflux score by Frezza and co-workers (72) appears rather simplistic, as the parameters foveolar hyperplasia and smooth muscle fibres were only graded as absent or present, because the authors believed a more extensive score "does not work". In addition, the authors did not consider vasodilatation and congestion in their scoring system, because they regarded this parameter to result from bioptic trauma and these features were also present in individuals from a control group (72). Our study, however, clearly shows that a three-tiered scoring system is feasible and particularly helpful in the evaluation of vascular changes, as pointed out above.

The scoring system proposed by Chen and co-workers (40) is similar to ours, as these authors also subtracted the scores for chronic and active inflammation. To avoid “negative” values in the final composite score, the authors “by definition” added a value of 6 to every score. Unfortunately, no cut-off value is provided for the diagnosis of reactive gastropathy, thereby limiting the principal use of that scoring system.

Remarkable differences were noted when the five histologic parameters of gastritis were related to the endoscopic diagnosis of gastritis. All three parameters in favour of a diagnosis of reactive gastropathy, i.e. foveolar hyperplasia, smooth muscle fibres in the lamina propria, and vasodilatation and congestion were significantly associated with the diagnosis, whereas those related to *Helicobacter* infection were not. Thus, our data suggest that the endoscopic diagnosis of reactive gastropathy can be performed with higher accuracy than the endoscopic diagnosis of *Helicobacter* gastritis.

In conclusion, reactive gastropathy was more common than *Helicobacter* gastritis in unselected individuals, participating in a large prospective Central European multicentre study. Combinations of different types of gastritis were observed in 7.2% of participants. Intestinal metaplasia was present in 22.1% of individuals with histologic diagnosis of gastritis. Of these 9.5% were categorised into OLGIM high risk stages III and IV. Agreement between histologic and endoscopic diagnosis was better in reactive gastropathy than in *Helicobacter* gastritis. Our data prove the association of chronic and active inflammation with *Helicobacter* infection and Dixon’s parameters of foveolar hyperplasia, smooth muscle fibres as well as vasodilatation and congestion as the key histologic parameters for the diagnosis of reactive gastropathy. Based upon these data, a new histologic score was developed which showed a significant association with the endoscopic diagnosis of gastritis, yet not with patients’ symptoms and/or complaints. The visual analogue scales and the proposed score may enhance diagnostic accuracy in routine assessment of gastric biopsies. They should be validated in future studies.

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