The interplay between *Helicobacter pylori*, gastro-oesophageal reflux disease, and intestinal metaplasia

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Helicobacter pylori infection and gastro-oesophageal reflux disease (GERD) account for most upper gastrointestinal pathologies with a wide spectrum of clinical manifestations. The interplay of both conditions is complex, in part intriguing, and has become a matter of debate because of conflicting results. The cardia is an area where both *H pylori* and abnormal GERD exert their damaging potential, inducing inflammation and its consequences, such as intestinal metaplasia. While the role of intestinal metaplasia within columnar lined epithelium (Barrett's oesophagus) in the context of GERD is well established as a risk for neoplasia development, the role of intestinal metaplasia at the cardia in the context of *H pylori* infection is unclear. A particular challenge is the distinction of intestinal metaplasia as a consequence of GERD or *H pylori* if both conditions are concomitant. Available data on this issue, including follow up of a small patient series, are presented, but more studies are required to shed light on this issue because they will help to identify those patients that need surveillance.

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Current epidemiological trends indicate an inverse relationship in the Western world between the rising incidence of gastro-oesophageal reflux disease (GERD) and the decreasing incidence of duodenal ulcer disease as the classical clinical expression of *Helicobacter pylori* infection as well as of *H pylori* infection in general.[1–3] There is still uncertainty whether epidemiological data reflect a real increase of the incidence and prevalence of GERD, or whether merely a higher awareness and more attention is paid by endoscopists in the detection of erosive oesophagitis.[4] There is no doubt, however, that the incidence of Barrett's carcinoma, which is the most serious consequence of GERD, has shown the steepest increase of all gastrointestinal tumours during past decades.[5]

A sum of additional aspects, including the lower prevalence of *H pylori* (around 10%) in patients with GERD, the increase of GERD following *H pylori* eradication, and the association that certain gastritis patterns (that is, atrophic corpus gastritis) would be rather inconceivable with GERD, have lead to the widespread opinion that *H pylori* exerts a protective effect on the oesophagus and may prevent the development of GERD as well as its complications.[1 6 7] However, the generation and sources of data, as well as their interpretation, are conflicting and contribute to keep the interplay of GERD and *H pylori* an intriguing one.[8–10]

There is an area, the cardia, where both the abnormal gastro-oesophageal reflux and *H pylori* may potentially exert their damage independently. However, they may be concomitant and interfere with each other. The result of *H pylori* infection and GERD at the cardia is an inflammatory reaction. In a subset of patients the inflammation may progress and lead to intestinal metaplasia.

In the following we will report on the complexity of the relationship between *H pylori* and GERD; the independent pathway of *H pylori* in the induction of inflammation and intestinal metaplasia, with special focus on the cardia; and the abnormalities of the oesophago–gastric junction (OGJ) in association with GERD. Further aspects are the characterisation of the intestinal metaplasia and the question of whether a distinction of intestinal metaplasia types will be attributed to either *H pylori* or GERD, and, finally, the fate of intestinal metaplasia during follow up.

THE *H PYLORI*–GERD RELATIONSHIP

The vast majority of pathologies in the oesophagus, stomach, and duodenum are related to either *H pylori* infection or GERD. Both conditions affect a large proportion of the population and they may occur either independently or concomitantly. The question of whether the two conditions are mutually exclusive, synergistic, or simply independent is an issue that was raised several years ago and is a matter of ongoing debate.[10 11] *H pylori* has a profound impact on the gastric mucosa and to a lesser extent on gastric physiology (gastrin, somatostatin, and acid secretion), whereas GERD is the result of an increased oesophageal exposure to gastric acid.[12–14] Gastric acid secretion, therefore, is the key factor in the relationship between *H pylori* and GERD. In patients who develop chronic atrophic gastritis as a consequence of *H pylori* infection, gastric acid is suppressed and so acid would no longer appear to be produced in a critical amount for the induction of GERD.[15 16] Retrospectively analysed data in a large patient group suggest that even a corpus predominant gastritis would exert a protective effect against GERD development.[17]

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Abbreviations: GERD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor; NERD, non-erosive reflux disease; ERD, erosive reflux disease; CLE, columnar lined oesophagus; SCJ, squamo–columnar junction; OGJ, oesophago–gastric junction; CK, cytokeratin

In most patients, especially in the Western world, *H pylori* induces an antrum predominant gastritis[18–20] and in this condition gastric acid secretion is rather increased,[12] which is also reflected in the different association of antrum predominant gastritis with duodenal ulcer and pangastritis with gastric ulcer.[21] Antrum predominant gastritis is also the usual phenotype in GERD patients infected with *H pylori*.[22 23]

Studies from Japan in patients with atrophic gastritis reported increased acid production following *H pylori* eradication and induction of GERD in a subset of patients.[24 25] These patients were, however, predisposed because of a pre-existing impaired anti-reflux barrier.[24 25] On the contrary, studies from Europe found that *H pylori* eradication did not lead to alterations in the duodenogastro-oesophageal reflux pattern[26] and the *H pylori* status in patients with GERD did not impact on the degree of oesophageal acid exposure.[22 27] From these pathophysiological considerations the risk for GERD development following eradication seems to be low and is, if at all, restricted to patients with atrophic gastritis in whom acid secretion recovers and meets with the premise of an abnormal gastro-oesophageal reflux barrier.

A strong argument for the protective role of *H pylori* against GERD came from epidemiological studies. A lower prevalence of *H pylori* infection in patients affected by GERD in the magnitude of 5–10% when compared with a control population has been reported by most authors.[6 8 10]

The protective potential of *H pylori* has further been emphasised in studies that discovered more virulent strains to be less prevalent or even absent in severe forms of GERD. Cag A carrying strains were suspected to protect from Barrett's adenocarcinoma.[28–30] These early observations, however, were not confirmed in a large US population.[31] By extending the analysis beyond Cag A to other *H pylori* virulence factors (vacAs1, iceA1), some authors report a decreased prevalence of these factors in patients with GERD or with more severe forms of GERD,[32 33] while others did not.[34]

The strongest argument for *H pylori* as a protective factor in GERD came from clinical trials. A higher incidence of erosive GERD following successful eradication in patients with duodenal ulcer disease had been reported[7 35] but was recently rebutted by the analysis of large clinical trials conducted in patients with duodenal ulcer and gastric ulcer, in whom no increase of GERD following eradication has been documented.[36 37]

The only advantage, with respect to the *H pylori* status, was the finding of a slightly (clinically irrelevant) increased healing of erosive oesophagitis with proton pump inhibitor (PPI) treatment. Healing of GERD with PPI treatment is marginally influenced by the *H pylori* status in severe forms due to a slightly increased efficacy of acid suppressants.[38]

In conclusion, we appreciate the clinical reality that there is a large population of patients with GERD and concomitant *H pylori* infection. There is inconclusive evidence that more severe forms of GERD have a lower prevalence of *H pylori* infection or are infected with less virulent strains. From all current debates concerning the clinical management of *H pylori* infection in patients with GERD, eradication treatment is recommended in those who require long term PPI.[39] In most recent studies relapses of GERD are not more frequent in those treated for *H pylori* infection.[40–42] However, in a further study, healing failure was more frequent in patients with *H pylori* eradication. Relapses in those patients with GERD on low dose PPI maintenance have also been reported to be more frequent following *H pylori* eradication.[23] Both PPI doses for initial healing (omeprazole 20 mg) and for maintenance (omeprazole 10 mg) do not correspond to current PPI standard dosing requirements.

H PYLORI CARDITIS AND INTESTINAL METAPLASIA

Early studies on *H pylori* have all concentrated on the pattern and degree of inflammation and mucosal damage in the gastric antrum, corpus, and fundus, but left out the cardia area. In 1994 Genta *et al*[43] in a careful investigation of the cardia drew attention to the fact that *H pylori* was present at this site in almost all patients in whom the infection was detected in the gastric antrum and body. Moreover, the degree of inflammation in the cardia was correlated with the degree of inflammation in the antrum and not with that in the corpus.[44 45]

Subsequent studies confirmed the presence of *H pylori* in the cardia in almost all patients carrying the infection in the distal stomach, but in contrast to the original observation with a lower colonisation density and lesser degree of inflammation compared with the gastric antrum.[44 46–49] In particular, patients with GERD had a reduced density of *H pylori* at the cardia.[42] This has been suggested to be a consequence of the down regulation of *H pylori* growth by the lower pH in this site compared with the pre-pyloric antrum. This hypothesis is supported by the observation that a high acidity pocket is created in the upper fundic zone following the ingestion of a meal.[50]

A progression of gastritis occurs over time in around 20% with development of intestinal metaplasia. The presence of intestinal metaplasia in the cardia occurs in parallel with the intestinal metaplasia in the antrum and is more prevalent than in the corpus.[51 52] The prevalence of intestinal metaplasia in the cardia in association with *H pylori* infection is reported from many studies to be highly variable and ranges 5–40%.[47 48 51–55]

Intestinal metaplasia as a consequence of *H pylori* positive gastritis appears usually after many years of persisting gastritis. Intestinal metaplasia is more frequent in older subjects (positive correlation with age) and is usually associated with atrophic gastritis.[56]

Currently the hypothesis favoured is that a genetic predisposition is more relevant to the development of intestinal metaplasia than specific strains of *H pylori*.[57] The presence of intestinal metaplasia in association with atrophic changes in the gastric mucosa constitutes an increased risk for the development of gastric cancer.[57 58] This is particularly true for the condition of a corpus predominant gastritis or pangastritis and relates to distal gastric cancer. It is presently not clear whether intestinal metaplasia at the cardia in association with *H pylori* represents a pre-neoplastic condition as well. A reversibility of intestinal metaplasia is unlikely to occur; however, data are conflicting. More important is the question of whether intestinal metaplasia, and what type, may progress to cancer.[57]

In summary, *H pylori* leads to chronic inflammation of various degrees that involves the gastric mucosa from the most distal gastric (pre-pyloric) region up to the cardia. The topographical pattern of chronic gastritis is variable and ranges from an antrum predominant gastritis to a corpus predominant gastritis or even atrophic pangastritis. The cardia is usually involved in all cases infected with *H pylori*. Around 20% of the *H pylori* infected subjects in Western populations develop intestinal metaplasia. It is noteworthy that the intestinal metaplasia develops at a much higher frequency in the antrum than in the corpus region, and the prevalence of intestinal metaplasia in the cardia parallels the prevalence in the antrum.[51]

Once intestinal metaplasia is established, *H pylori* is no longer capable of colonising this epithelium. However, because intestinal metaplasia is often a focal process, *H pylori* may survive on the gastric epithelium in the neighbourhood of intestinal metaplasia.

Table 1 Subjects with v those without intestinal metaplasia in the gastric cardia with regard to clinical and histological characteristics (patients with Barrett's oesophagus (CLE plus intestinal metaplasia) are excluded as far as presented data allowed for such adjustment)

Author	Patients	Definition of normal OGJ	Number and location of cardia biopsies	Total number of patients	Number of patients with normal OGJ	Number of patients with intestinal metaplasia	GERD symptoms	Erosive oesophagitis	Hernie	H pylori	Intestinal metaplasia antrum	Correlation with age
Spechler[77]	Patients for elective endoscopy	<2 cm of columnar epithelium in distal oesophagus	Two from columnar epithelium at SCJ	142	142	26 (18.0%)	no	yes†	nd	nd	nd	no
Johnston[69]	Consecutive patients for endoscopy	<2 cm of columnar epithelium in distal oesophagus	Two just distal to SCJ	170	?	16 (9.4%)	yes	no	nd	nd	nd	no
Öberg[54]	Consecutive patients	SCJ at the proximal extent of the gastric rugal folds; no evidence of columnar lined oesophagus	Minimum five form OGJ	334	246	29 (11.7%)	nd	yes	yes	no	no	nd
Nandurkar[73]	Consecutive patients, CLE <3 cm included	Short segment Barrett's included (<3 cm)	Two immediately distal to Z-line	158	?	46 (29.1%)	no	no	nd	no	nd	yes
Trudgill[78]	Randomly selected	By exclusion: Barrett's oesophagus defined as >3 cm between SCJ and proximal margin of gastric folds	Three immediately below the SCJ, and three at 2 cm from the gastric flare	120	120	21 (18.0%)	no	no	no	no	yes	yes
Hackelsberger[51]	Consecutive patients	Location of SCJ within 2 cm above OGJ with straight appearance of SCJ, no irregularity, no tongues or islands of columnar epithelium.	Two immediately below the SCJ	423	315	42 (13.0%)	no	no	nd	yes	yes	yes
El-Serag[80]	Consecutive patients	By exclusion of Barrett's oesophagus: defined as any length of columnar mucosa above the OGJ plus intestinal metaplasia	Two within 1–2 cm distal to the OGJ*	302	166	50 (30.0%)	no	no	nd	no	yes	yes
Voutilainen[52]	Consecutive dyspeptic patients	By exclusion: Barrett's oesophagus defined as incomplete intestinal metaplasia detected in the oesophagus	Two OGJ, that is proximal end of gastric folds	1058	1058	235 (22.0%)	no	yes	no	yes	yes	yes
Hirota[68]	Patients for endoscopy	Devoid of any tongues of pink columnar lined epithelium above the endoscopically defined OGJ	Two immediately distal to the Z-line	889	795	47 (5.9%)	no	no	no	yes	nd	yes
Peck-Radosavljevic[75]	Consecutive patients	OGJ without endoscopic lesion, no tongues of columnar epithelium	Two just below the SCJ, and two directly from the OGJ	200	186	22 (11.8%)	no	no	nd	no	yes	yes
Goldstein[48]	Consecutive patients	SCJ within 2 cm of mucosa proximal the uppermost gastric fold	One straddling the SCJ, one from within 1 cm below the SCJ	150	150	40 (37.3%)	nd	(yes)		yes	yes	
Carton[65]	Consecutive patients for endoscopy	Not given, n=63 had short segment columnar lining in oesophagus	Four immediately distal to the Z-line	200	126	34 (17%)‡	yes	yes	nd	no	no	no
El-Zimaity[67]	65 Selected patients, 71 controls	By exclusion: short segment Barrett's oesophagus	Two within 0.5 cm of the Z-line or OGJ	136	123	21 (15.4%)	no	no	nd	yes	yes	nd
Pieramico[76]	122 Consecutive GERD patients, 49 controls	By exclusion: any length of columnar appearing mucosa in tubular oesophagus lining with histological presence of intestinal metaplasia	Two within 1 cm below the SCJ*	171	171	32 (19.0%)	no	no	nd	yes	nd	nd
Ormsby[74]	Consecutive autopsies	SCJ located immediately distal to the proximal gastric folds, 18 cases with Barrett's excluded	Entire OGJ sectioned	223	205	22 (10.7%)	nd	nd	nd	**	yes	no
Wolf[79]	Consecutive patients	Group 1, columnar lining 0–1 cm	Two immediately distal to the SCJ, and two from 2 cm distal to the OGJ	658	511	77 (15.1%)	no§	no§	no§	yes§	yes§	yes§

Table 1 Continued

Author	Patients	Definition of normal OGJ	Number and location of cardia biopsies	Total number of patients	Number of patients with normal OGJ	Number of patients with intestinal metaplasia	GERD symptoms	Erosive oesophagitis	Hernie	H pylori	Intestinal metaplasia antrum	Correlation with age
Morini[72]	Consecutive patients with dyspeptic or reflux symptoms	Not given, nd on Barrett's cases	Two within 2 cm below a normal looking SCJ*	133		18 (13.5%)	no	no	no	yes	yes	nd
Dincer[66]	All patients undergoing upper endoscopy	No columnar epithelium proximal to the OGJ, EGJ proximal heads of gastric folds	One from columnar side of the SCJ, one from 2 cm distal to the OGJ*	60	59	6 (10.0%)	no	no	nd	inverse	no	yes
Goldblum[47]	108 GERD, 70 Barrett's, 60 controls	SCJ Same level as OGJ, 70 cases with Barrett's excluded	Two immediately below or a least within 5 mm of the OGJ	238	168	13 (7.7%)	inverse	nd	nd	yes	yes	nd
Law[70]	Consecutive patients	Most proximal margin of the gastric folds, only cases with cardia type mucosa were analysed (n=100)	Two antogradely at SCJ, two retrogradely immediately below the SCJ	145	136 (100)	34 (34%)	no	no	no	no	nd	yes
Oksanen[55]	Consecutive outpatients (<45 years)	No classic Barrett's oesophagus, SCJ normally located; but: n=4 tongues of columnar mucosa <5 mm, n=36 tiny tongues	One to two or more at the SCJ or within 5 mm from the SCJ	168	168	11 (6.5%)	no	no	no	no	no	?

*Studies with location of cardia biopsies that rather may be assigned to the gastric fundic mucosa. †Only for histological signs of oesophagitis. ‡15% Normal OGJ, 24% short segment. §Not differentiated with regard to length of columnar lining. ***"yes" for chronic gastritis.
CLE, columnar lined oesophagus; GERD, gastro-oesophageal reflux disease; OGJ oesophagogastric junction; SCJ squamocolumnar junction; IM intestinal metaplasia; nd no data.

GERD AND INTESTINAL METAPLASIA

GERD is associated with a wide spectrum of endoscopic and histopathological changes. From the endoscopic perspective, GERD presents as non-erosive reflux disease (NERD), erosive reflux disease (ERD), or as columnar lined oesophagus (CLE). A recent validated classification distinguishes between NERD and ERD of different severity degrees.[59] Histologically, CLE may contain three different types of mucosa: specialised intestinal metaplasia, cardiac type mucosa, or oxyntic mucosa.[60] Where the term Barrett's oesophagus has formerly been used for any CLE irrespective of histology, there is now general acceptance that Barrett's oesophagus designates CLE containing specialised intestinal metaplasia.[61] Although the determinants of the multifactorial aetiology of Barrett's oesophagus are not completely elucidated, gastro-oesophageal reflux is agreed upon as a necessary condition and as the most important causal factor. With the appropriate consideration of pitfalls such as hiatal hernia and erosive inflammatory lesions, the length of CLE segments is considered as short if <3 cm and long if >3 cm.

The importance of Barrett's oesophagus lies in its risk for adenocarcinoma of the oesophagus. This risk is increased from 10- to 30-fold. A recent meta-analysis calculated an incidence of 0.5% per patient–year.[62]

Barrett's oesophagus is detected in approximately 8% of patients with GERD and is more frequently associated with ERD of any degree than with NERD.[63] Of note, CLE is also accidentally detected in around 6% of patients who undergo upper gastrointestinal endoscopy for reasons other than GERD related symptoms.[64]

As CLE may contain gastric type epithelium, it is not surprising that CLE may be colonised by *H pylori*. The rate of colonisation in patients with an infected stomach varies considerably among different studies, ranging 0–90%.[6] When considering the different types of epithelium within CLE, it becomes clear that only gastric type metaplasia, not specialised intestinal metaplasia, can be colonised by the bacterium. It is unknown whether such colonisation may increase the risk of carcinoma within CLE.

H PYLORI AND/OR GERD AT THE ORIGIN OF INTESTINAL METAPLASIA AT THE CARDIA

In recent years several investigators have directed their attention to the detection of intestinal metaplasia at the gastro-oesophageal junction, in particular at the squamo–columnar junction (SCJ) in patients without any endoscopic abnormality such as long or short segment CLE. An important finding in these patients with an endoscopically normal cardia is that histological examinations of biopsies taken at or below the SCJ reveal a prevalence of intestinal metaplasia 6–37% with a mean of 15.9% (see table 1 and fig 1).[47 48 51 52 54 55 65–79]

The risk of intestinal metaplasia detected at the cardia with an endoscopically normal OGJ for adenocarcinoma is presently unknown. It may be close to the high risk of Barrett's oesophagus 10- to 30-fold,[62] or to the much lower risk of intestinal metaplasia in the stomach, which amounts to a factor of two to threefold.[58] As long as longitudinal data on this topic are scarce, the estimation of the risk is essentially based on extrapolations from clinical, endoscopic, and histological associations with intestinal metaplasia at the cardia.

All full paper publications with sufficient data on such associations, listed on Medline (search terms: intestinal metaplasia and cardia), are included in table 1. Some studies addressed such associations as a primary aim. In other papers, the analysis of subgroups allowed for an association, quasi as a secondary aim. Although not intending a formal meta-analysis, for the purpose of this table, we excluded as
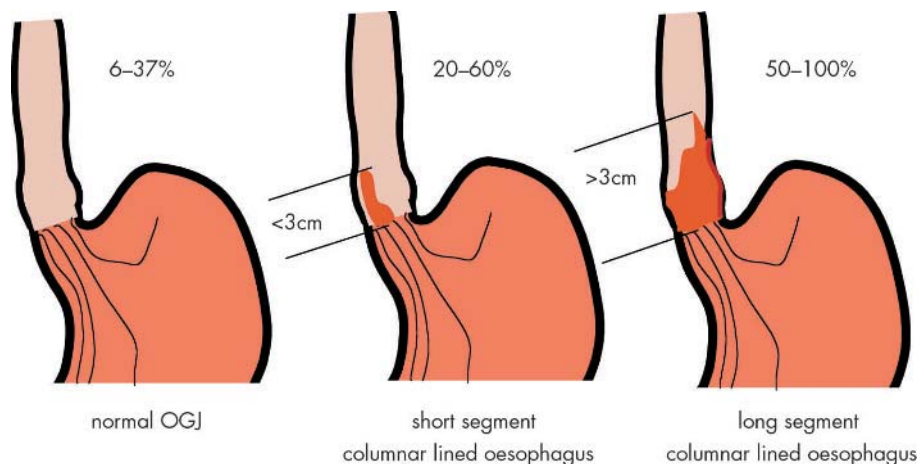
Figure 1 Prevalence of intestinal metaplasia dependent on endoscopic appearance of oesophagogastric junction.

far as possible those cases with Barrett's oesophagus, that is, CLE histologically exhibiting specialised intestinal metaplasia. In some publications, the study design excluded Barrett's oesophagus. In other studies, including patients with Barrett's oesophagus, we adjusted the prevalence of intestinal metaplasia by confining it to patients with a normal OGJ if the presentation of the data allowed for such data adjustment. This is the reason why the number of patients with a normal OGJ is smaller than the total number of patients in some of the studies. The prevalence of intestinal metaplasia in the general population is uncertain as all study samples represent patients with a clinical indication for endoscopy. One study investigated not endoscopies, but deceased patients selected for autopsy.[74]

The association of intestinal metaplasia is less frequent with GERD manifestations than the correlation to *H pylori* infection and intestinal metaplasia in the gastric antrum. Why this discrepancy? The main reason for it is the difference at the biopsy site. Almost all studies showing an association of intestinal metaplasia with GERD manifestations included cases with a maximum of 2 cm columnar lining in the lower oesophagus. Therefore, these studies in part investigated patients who would be classified nowadays as short segment Barrett's oesophagus rather than intestinal metaplasia at the normal OGJ.[69 73 77 81] The authors of all these studies report the patient characteristics independent of length of columnar lining and also independent of any endoscopic irregularities of the Z-line. In contrast, the vast majority of studies that excluded patients with any columnar lining in the lower oesophagus or patients with short segment Barrett's oesophagus did not confirm an association with GERD manifestations.

In some studies reporting associations of cardia intestinal metaplasia with intestinal metaplasia in the distal stomach and with *H pylori* infection, the so called cardia biopsies were taken at 1–2 cm below the OGJ or below the SCJ. As these studies do not report whether cardia intestinal metaplasia occurred on the grounds of cardiac type mucosa or fundic type mucosa, the biopsies have to be assigned to fundic mucosa rather than cardia mucosa.[66 72 76 81]

However, the majority of studies of an association of cardia intestinal metaplasia with intestinal metaplasia in the distal stomach and of *H pylori* infection targeted the biopsies precisely to the OGJ, defined as the proximal end of the gastric folds. Biopsies have been reported to contain squamous as well as columnar epithelium. Four studies even focused only on biopsies containing cardiac type mucosa.[54 67 70 81] Biopsies taken according to these criteria

	Complete type	Incomplete type	
Characteristic mucins	**Type 1, neutral mucins**	**Type 2, acid sialomucins**	**Type 3, acid sulphomucins**
Mucin histochemistry			
Alcian blue and periodic acid-Schiff (PAS)	magenta	Blue	Blue
Alcian blue and high iron diamine		Blue	Brown–black
Alcian blue and Gomori's Aldehyde Fuchsin		Blue	Purple

Table 2 Differentiation of intestinal metaplasia by mucin histochemistry

These staining characteristics regard the columnar cells, not the goblet cells, which stain blue with Alcian blue.

will more reliably stem from the gastric cardia than biopsies obtained from 1–2 cm below the OGJ, and allow a more precise allocation of intestinal metaplasia to the cardia.

The evidence from these studies is that intestinal metaplasia at the endoscopically normal OGJ is associated with intestinal metaplasia in the distal stomach and a consequence of *H pylori* infection, and less likely a consequence of an abnormal acid reflux (GERD).

Some of the studies in table 1 and further studies also address the comparison between patients with intestinal metaplasia at the cardia and patients with Barrett's oesophagus. These studies confirm that intestinal metaplasia at the cardia is more closely associated with intestinal metaplasia in the distal stomach and with *H pylori* infection than is intestinal metaplasia in Barrett segments. Reflux manifestation like symptoms, reflux oesophagitis, and abnormal reflux function tests (manometry and pH-metry) were found to be more frequent and/or more severe in patients with Barrett's oesophagus than in those with intestinal metaplasia at the cardia.[51 71 82–86]

Both types of comparisons, cardia intestinal metaplasia *v* histologically normal OGJ and cardia intestinal metaplasia *v* Barrett's oesophagus, support the association of intestinal metaplasia at the cardia with intestinal metaplasia in the distal stomach and with *H pylori* infection rather than with GERD. Notwithstanding this, unresolved issues continue to elude the origin and prognosis of intestinal metaplasia at the endoscopically normal OGJ. The association of cardia intestinal metaplasia with intestinal metaplasia in the distal

Table 3

Author	Patients	Therapeutic intervention	Median follow up (years)	Number of biopsies	Persistence of intestinal metaplasia (%)	Development of dysplasia
De Meester[100]	F	Fundoplication	2.1	6	5 (33%)	Regression of inital dysplasia in onese
Goldstein[48]	85	No data	2.4	2	6 (7%)	None
Morales[108]	28	No data	2.5	2–4*	19 (68%)	1 (1.4% /year)
Sharma[101]	34	No data	2	4	†	1 (1.5%/year)
Peitz‡	19	H pylori eradication, partly PPI	2.5	3	8 (42%)	None

*Targeted by methylene blue. †100% because intestinal metaplasia at follow up was inclusion criteria. ‡Unpublished.

stomach was often stronger than that with *H pylori* infection. Furthermore, age was frequently correlated with intestinal metaplasia. These observations show that the most important cause for intestinal metaplasia at the cardia is not only *H pylori* infection and a number of other aetiological factors are important, such as smoking, environmental and genetic factors, and duodenogastric reflux. Two studies have revealed a link between abnormal duodenal gastric (biliary) reflux and intestinal metaplasia at the cardia.[87 88]

The challenge in the individual case remains whether intestinal metaplasia at the cardia is the expression of an abnormal gastric reflux condition or is due to *H pylori* in those cases in which both conditions coexist.

Several histochemical and immunohistochemical methods have been proposed for the assignment of intestinal metaplasia at the cardia to either Barrett's oesophagus or gastric intestinal metaplasia. The most promising approaches are mucin staining and immunohistochemistry with antibodies against cytokeratin (CK) and colonic antigens.

The histochemical differentiation of mucins into three subtypes was first described in order to differentiate intestinal metaplasia in the stomach and to establish distinctive risk profiles of different types of intestinal metaplasia for gastric carcinoma.[89] The staining characteristic of the three subtypes are listed in table 2. In the stomach, intestinal metaplasia is mainly of type I. Type I is also designated complete type because it represents similar features as intestinal epithelium, including absorptive functions with a brush border. Type II and III lack such features and are therefore called incomplete. These types are more closely correlated with gastric adenocarcinoma than type I.[89] Such mucin typing of intestinal metaplasia has also been applied to intestinal metaplasia at the OGJ. Barrett's mucosa is to more than 90% the types II or III.[90–92] Intestinal metaplasia at the cardia, however, exhibits the incomplete type in only around 50%. Our own data support that mucin sub-typing may serve as an additional indicator for Barrett's oesophagus *v* gastric intestinal metaplasia.[92]

Regarding CKs, Ormsby *et al*[93] observed three distinct patterns of CK7 and CK20: Barrett type characterised by strong diffuse CK7 and superficial CK20 immmunostaining; gastric type with complete intestinal metaplasia characterised by absence of CK7 and strong diffuse CK20 staining; and gastric type with incomplete intestinal metaplasia showing weak patchy CK7 staining and moderate patchy CK20 staining. The reasonably good correlation with clinical and endoscopic characteristics of such systematic staining has been confirmed by Coulevard *et al*,[94] Wallner *et al*,[86] Jovanovic *et al*,[95] and Glickman *et al*,[96] whereas Mohammed *et al*[97] and El-Zimaitiy and Graham[98] did not find the CK pattern sufficiently helpful for differentiation. There are no data yet on the relevance of CK pattern for the prognosis regarding potential development towards neoplasia.

Another promising candidate for differentiation of intestinal metaplasia is Das1, an antibody shown to react specifically with colonic epithelial cells. In two studies, this antibody showed a significantly higher rate of positive immunohistochemistry in biopsies from Barrett's mucosa or cardia intestinal metaplasia than in biopsies from gastric antrum containing intestinal metaplasia.[96 99]

THE FATE OF INTESTINAL METAPLASIA AT THE CARDIA

The real nature of cardia intestinal metaplasia and its variant endoscopic and histological appearances will not be disclosed until sufficient longitudinal study data are available. The development of Barrett's oesophagus starts at or close to the OGJ. Hence, intestinal metaplasia at the cardia may represent the beginning of Barrett's oesophagus. It is well known that the extent of Barrett's oesophagus develops rapidly and then remains rather stable for many years.[100] Therefore, those cases with cardia intestinal metaplasia that represent the beginning of Barrett's oesophagus would be identified during follow up examinations.

The few currently available longitudinal studies[101–103] on the fate of cardia intestinal metaplasia describe a decreased prevalence of intestinal metaplasia at the cardia during follow up. The current data are listed in table 3. However, there are also data on intestinal metaplasia being only detected at a repeat endoscopy in cases with an endoscopically suspicious OGJ.[104]

Several explanations may account for such diverging results. One is therapeutic intervention. In one of the studies reporting a decreased prevalence of intestinal metaplasia at follow up, patients are examined after fundoplication. In our study, all patients with *H pylori* infection received eradication therapy and subsequently PPI treatment on demand. Other studies did not provide data on treatment during the interval until follow up.

Never the less, the rather low rate of persistence of intestinal metaplasia in the cardia, around 50%, is a surprising result. The available data, however, are too scarce to state that intestinal metaplasia at the cardia is really reversible. It still has to be excluded that disappearance of cardia intestinal metaplasia is not just a biopsy sampling error as intestinal metaplasia is known to be distributed in a patchy and mosaic pattern.[105 106] Such distribution is known for both gastric intestinal metaplasia as well as specialised intestinal metaplasia in the oesophagus.

The issue of sampling error also applies to studies reporting an increase in the prevalence of intestinal metaplasia. There are no follow up data in patients with an endoscopically as well as histologically normal OGJ. Jones *et al*[104] reported on cases with endoscopically suspected Barrett's oesophagus, but not confirmed by histology. Such a condition can also be defined as CLE without intestinal metaplasia. A repeat

endoscopy in these patients revealed intestinal metaplasia in 23% of the cases, which may be explained by sampling error rather than by the short term development of intestinal metaplasia. Furthermore, there is evidence that the experience of the endoscopist leads to a higher detection rate of intestinal metaplasia.[107][108]

The occurrence of dysplasia (nowadays designated as intraepithelial neoplasia) within cardia intestinal metaplasia has been reported only by one group in one patient after a median follow up interval of approximately 2 years.[102–109] Certainly, the number of patients observed as yet is too small to draw any conclusions. But by extrapolating data derived from cross sectional studies, we may conclude that the risk for neoplasia is lower than for Barrett's oesophagus.[68] Whether it is as low as the risk of gastric intestinal metaplasia to be associated with gastric cancer (two to threefold[58]) needs to be determined.

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