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Clinicopathological Findings of the Cardia and Gastroesophageal Junction in Adult Candidates for Endoscopy in Qazvin, Iran

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Abstract

Background: Chronic inflammation and intestinal metaplasia lead to gastric and esophageal adenocarcinoma. Past research has provided controversial findings about the etiology of inflammation and intestinal metaplasia in the cardia and the Z-line.
Objectives: The aim of this study was to evaluate clinicopathological findings of the cardia and gastroesophageal junction in adult candidates for endoscopy in Qazvin, Iran.
Methods: Biopsy was performed for 124 ambulatory adult patients without any evidence of cancer. Specimens were obtained from the antrum and the cardia of the stomach, the Z-line, and 2 cm above the Z-line. A comparison was made between the histological, clinical and endoscopic data obtained from the patients.
Results: *Helicobacter pylori* were significantly related to active inflammation in the antrum and the cardia, but not in the Z-line. Another finding was that active carditis was related to active antritis and active Z-line inflammation. A further observation was the positive correlation between cardiac and Z-line metaplasia. Finally, a relationship was observed between the type of cardiac mucosa and the presence of metaplasia in the cardia and the Z-line.
Conclusions: The study revealed that inflammation in the cardia and, to a lesser extent, the Z-line is related to *H. pylori* and antral gastritis and that the metaplasia of these areas is related to gastroesophageal reflux disease. Lastly, both *H. pylori* and gastroesophageal reflux disease are important in the pathology of these areas.

Keywords: Cardia, Z-Line, Gastroesophageal Reflux Disease, Histopathology, *Helicobacter pylori*

1. Background

Gastric and esophageal cancers are two of the most common human cancers. The most common type of gastric cancer is gastric adenocarcinoma and mostly follows chronic atrophic gastritis and intestinal metaplasia (IM), conditions which are most commonly caused by *Helicobacter pylori* (*H. pylori*) (1).

Esophageal adenocarcinoma, which has been shown to have increased in the recent years (2), is more commonly seen in the distal part of the esophagus adjacent to the gastric mucosa (1, 2) and follows chronic esophagitis and a form of esophageal IM called Barrett's Esophagus (BE) (1, 3, 4). The most common cause of BE is the Gastroesophageal Reflux Disease (GERD) (1). Gastroesophageal Reflux Disease itself is a common illness (5), which causes many problems and decreases quality of life (6).

A subcategory of adenocarcinoma is the adenocarcinoma of the gastroesophageal junction or the Z-line (1). Although gastric and esophageal adenocarcinomas look histologically similar, they have different clinical courses and prognoses (1, 7).

The treatment of *H. pylori* gastritis has been associated with a reduction in the case of gastric adenocarcinoma, yet no such reduction has been observed in the case of adenocarcinoma affecting the cardia, which is an area distal to the Z-line with an unclear origin and histology (8, 9); there has even been reports of an increase in the number of such cases of adenocarcinoma (1, 9, 10). Aside from that, it seems that *H. pylori* is protective of Z-line mucosa (1, 11).

Considering the inconclusive data from previous research about the etiology and pathogenesis of Z-line and cardiac adenocarcinoma, it is necessary to further study factors that contribute to cancer. Previous studies have shown that esophageal and gastric cancers are two common cancers in Iran (2, 12). *Helicobacter pylori* and GERD have been reported as predisposing factors of the esophageal and gastric cancers (12); but risk factors may vary by race and ethnicity in different populations. In addition, no previous study has been performed on this subject in Qazvin.

2. Objectives

The aim of this study was to evaluate clinicopathological findings of the cardia and gastroesophageal junction

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in adult candidates for endoscopy in Qazvin, Iran.

3. Methods

This cross sectional study was conducted on adult patients referred to the endoscopy ward of Booali Sina Hospital from October 2011 to October 2014. The study was confirmed by the medical ethics committee of Qazvin University of Medical Sciences. Written consent form was obtained from all patients.

Inclusion criteria were being an adult patient, and lack of any evidence of cancer or a critical condition such as varicose esophagus or history of gastrointestinal (GI) tract surgery. All eligible patients in the study period were entered using the census method. The exclusion criteria were systemic or skin disorders involving the GI tract, history of chemotherapy, radiotherapy, and ingestion of corrosive materials. In addition, patients who had received treatment for *H. pylori* not long before the experiment or those who had taken non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, steroid and anti-reflux drugs, and proton-pump inhibitors during the two weeks prior to the experiment were excluded from the study.

The demographic data were age, gender, body mass index (BMI), smoking habit, and coffee and alcohol consumption. Endoscopy was performed by a single gastroenterologist, using Olympus 260, Japan.

The patients were assigned to three groups depending on their complaints: (1) the GERD group, where the patients had the classic symptoms of the disease, including a heartburn sensation at least twice per week during the four weeks prior to the experiment; (2) the dyspepsia group, where the patients had other GI symptoms such as bloating, epigastric pain, early fullness during meals, nausea and vomiting; and (3) the "mixed or other" group, where the patients had non-classic symptoms of GERD or other indications for endoscopy.

The Los Angeles classification was used as follows for describing the esophagitis (13): the Z-line was defined as an area between the pale pink esophageal mucosa and the dark red gastric mucosa, hiatus hernia was defined as a situation in which proximal gastric folds were at least 2 cm away from diaphragmatic hiatus (14), and BE was defined as a situation in which there was salmon-colored mucosa in the tubular esophagus (1).

Any unusual findings in the endoscopy of the upper GI tract were reported, and biopsy was performed as follows: one specimen or two from the antrum, two specimens from the cardia in the retroflexion view, four specimens from the Z-line, two specimens from 2 cm above the Z-line, at least one specimen from any portions suspicious for BE, and one specimen from any abnormal or suspicious region.

The specimens were fixed using 10% formalin and were sent for blind histopathology examination. They were examined for *H. pylori* (using Hematoxylin and Eosin and Giemsa staining) and goblet cells (to determine IM). More specifically, BE was considered if goblet cells were seen in the specimens taken from the endoscopically suspicious regions of esophagus mucosa (1).

The specimens obtained from the cardia were examined for the type of the columnar mucosa: (a) mucous or mucous/oxyntic and (b) oxyntic (1).

The specimens from 2 cm above the Z-line were graded for esophagitis, including no inflammation, mild reactive esophagitis, mild active esophagitis, and active esophagitis (13).

The Sydney grading system was used for grading gastritis. This system specifies the following degrees of inflammation: 0 (none), 1 (mild), 2 (moderate) and 3 (severe).

Data analysis was performed using SPSS 18 (2010). Mean and standard deviation were used to describe frequency data. Chi-square test, t-test, and Spearman rank-order correlation coefficient were also used. P values of less than 0.05 were considered as statistically significant.

4. Results

The patients included 99 females (79.8%) and 25 males (20.2%) and ranged in age from 20 to 80, with the average age being 42.8 (SD = 15.04). No alcohol drinking or regular coffee consumption was detected, and only one male patient was a smoker.

Table 1 shows the relationship between the existence or lack of *H. pylori* and the three categories of clinical complaints of the patients. As can be seen, there was no relationship between *H. pylori* and clinical complaint ($P = 0.069$); however, the ratio of *H. pylori* negative to *H. pylori* positive was more significant in the GERD group (5:1) than in the other two groups.

Table 1 also demonstrates the relationship between *H. pylori* and histological findings. More specifically, *H. pylori* was more strongly associated with antral or cardiac chronic inflammation ($P < 0.001$) than with Z-line chronic inflammation ($P = 0.028$). Moreover, no relationship was observed between *H. pylori* and esophagitis ($P = 0.801$).

It can also be seen in Table 1 that *H. pylori* had a statistically significant relationship with active inflammation both in the antrum and the cardia ($P < 0.05$), but not in the Z-line.

In addition, *H. pylori* was not related to IM in any of the sites under study (i.e., antrum, cardia, and Z-line, with P values of 0.455, 0.466, and 0.711, respectively). It is worth not-

Table 1. A Comparison of Clinical and Histological Findings Considering *Helicobacter pylori* Infection State of the Patients[a]

Clinical and Histological Factors				H. P (-)[b]	H. P (+)[c]	Total	P Value
Clinical Complaints			GERD	10 (83.3)	2 (16.7)	12 (9.7)	0.069
			Dyspepsia	70 (74.5)	24 (25.5)	94 (75.8)	
			Mixed or other	9 (50.0)	9 (50.0)	18 (14.5)	
Histological parameters: Chronic or active inflammation	Degree of chronic inflammation	Antrum	None	14 (100.0)	0	14 (11.3)	< 0.001
			Mild	63 (87.5)	9 (12.5)	72 (58.1)	
			Moderate	11 (30.6)	25 (69.4)	36 (29.0)	
			Severe	1 (50.0)	1 (50.0)	2 (1.6)	
		Cardia	None	17 (100.0)	0	17 (13.7)	< 0.001
			Mild	59 (79.7)	15 (20.3)	74 (59.7)	
			Moderate	13 (40.6)	19 (59.4)	32 (25.8)	
			Severe	0	1 (100.0)	1 (0.8)	
		Z-line	None	9 (100.0)	0	9 (7.3)	0.028
			Mild	53 (75.7)	17 (24.3)	70 (56.4)	
			Moderate	27 (60.0)	18 (40.0)	45 (36.3)	
			Severe	0	0	0	
	Existence or non-existence of active inflammation	Antrum	Yes	5 (33.3)	10 (66.7)	15 (12.1)	< 0.001
			No	84 (77.1)	25 (22.9)	109 (87.9)	
		Cardia	Yes	6 (46.2)	7 (53.8)	13 (10.5)	0.047
			No	83 (74.8)	28 (25.2)	111 (89.5)	
		Z-line	Yes	4 (44.4)	5 (55.6)	9 (7.3)	0.116
			No	85 (73.9)	30 (26.1)	115 (92.7)	

[a] Values are expressed as No. (%).
[b] Cases where *H. pylori* does not exist.
[c] Cases where *H. pylori* exists.

ing that at this point we observed no relationship between GERD and severity of inflammation or IM in the cardia or the Z-line.

The relationship of degrees of esophagitis to clinical complaints, age, gender, BMI, and hiatus hernia is reported in Table 2. As is clear from the data, esophagitis only correlated with age (P = 0.013) and BMI (P = 0.038). Another observation was that BMI was inversely related to histological esophagitis.

It is worth noting at this point that the relationship of BE with the variables mentioned in the previous paragraph was among our concerns. However, since only five patients (4.03%) were diagnosed with BE, we decided not to report the details. Barrett's Esophagus was only found to correlate with clinical complaint (P = 0.001) and that it was more prevalent in GERD patients.

Table 3 presents the data obtained for the correlations among inflammations (both chronic and active) in the antrum, cardia, and Z-line. It can be seen that chronic inflammations in all the three sites were correlated with one another. In addition, active carditis was found to correlate with active antritis and active Z-line inflammation; however, no correlation was observed between active antritis and active Z-line inflammation. Furthermore, as for the correlation among chronic and active inflammations across the three sites under discussion, the following observations were made: chronic antritis correlated with active inflammation in the antrum and the cardia, but not in the Z-line; chronic carditis correlated with active inflammation in the cardia and the antrum, but not in the Z-line; and chronic Z-line inflammation was correlated with active inflammation in the Z-line and the antrum, but not in the cardia.

Table 4 summarizes the data for the correlations among antral, cardiac, and Z-line IM and BE. It is clear that there was a significant positive relationship between car-

Table 2. A Comparison of Clinical Complaints, Age, Gender, Body Mass Index, and the Existence or Lack of Existence of Hiatus Hernia Considering Degrees of Esophagitis[a]

Variable		No Inflammation	Mild Reactive Esophagitis	Mild Active Esophagitis	Active Esophagitis	Total	P Value
Age, y		41.4	41.5	56.4	60.5	42.8	0.013
Gender	Female	73 (73.7)	17 (17.2)	5 (5.1)	4 (4.0)	99 (79.8)	0.472
	Male	16 (64.0)	7 (28.0)	2 (8.0)	0	25 (20.2)	
BMI	< 25	33 (63.5)	12 (23.1)	5 (9.6)	2 (3.8)	52 (41.9)	0.038
	25 - 30	31 (67.4)	12 (26.1)	1 (2.2)	2 (4.3)	46 (37.1)	
	> 30	25 (96.2)	0	1 (3.8)	0	26 (21.0)	
Clinical complaints	GERD	8 (66.7)	3 (25.0)	0	1 (8.3)	12 (9.7)	0.425
	Dyspepsia	68 (72.3)	18 (19.2)	6 (6.4)	2 (2.1)	94 (75.8)	
	Mixed or other	13 (72.2)	3 (16.6)	1 (5.6)	1 (5.6)	18 (14.5)	
Hiatus hernia	Negative	65 (72.2)	15 (16.7)	7 (7.8)	3 (3.3)	90 (72.6)	0.389
	Positive	24 (70.6)	9 (26.5)	0	1 (2.9)	34 (27.4)	

[a]Values are expressed as mean or No. (%).

Table 3. Correlations Among Antral, Cardiac, and Z-Line Inflammations

Anatomic Site		Antrum		Cardia		Z-line	
		Chronic Antritis	Active Antritis	Chronic Carditis	Active Carditis	Chronic Inflammation	Active Inflammation
Antrum	Chronic antritis	-	0.324[a]	0.499[a]	0.230[b]	0.271[b]	0.011
	Active antritis	-	-	0.329[a]	0.438[a]	0.195[c]	0.087
Cardia	Chronic carditis	-	-	-	0.269[b]	0.229[c]	0.034
	Active carditis	-	-	-	-	0.045	0.209[c]
Z-line	Chronic inflammation	-	-	-	-	-	0.181[c]
	Active inflammation	-	-	-	-	-	-

[a]P < 0.001.
[b]P < 0.01.
[c]P < 0.05.

diac and Z-line IM (P = 0.004, r = 0.260), but there was no relationship between the other anatomic sites.

Table 5 shows how type of cardiac mucosa is related to cardiac and Z-line IM. The data indicate that the type of cardiac mucosa was correlated with both cases of IM, with cardiac IM having a stronger correlation (P = 0.001). More specifically, if the cardiac mucosa is of the mucous or mucus/oxyntic type, there is greater likelihood that the site under discussion will be afflicted with IM.

5. Discussion

A major finding of the study was that *H. pylori* did not bear a significant relationship with clinical complaint. However, the ratio of *H. pylori* negative to *H. pylori* positive was more significant in GERD patients. This latter finding supports the theory that *H. pylori* is protective against GERD (4, 15).

We also found a strong relationship between *H. pylori* and the severity of inflammation in the antrum and the cardia, and also between *H. pylori* and the presence of active inflammation in these sites despite the small number of cases and the low percentage of *H. pylori* positivity. The relationship between *H. pylori* and the cardia has also been reported elsewhere (4, 15-17), even when most patients were negative for *H. pylori* (18). The Z-line showed a different pattern: A less strong relationship between *H. pylori* and the severity of Z-line inflammation and no relationship be-

Table 4. The Correlations Among Antral, Cardiac, and Z-Line Intestinal Metaplasia

Anatomic Site		Intestinal Metaplasia			
		Antrum	Cardia	Z-Line	Esophagus (BE)
Intestinal metaplasia	Antrum	-	0.71	-0.63	0.145
	Cardia	-	-	0.260[a]	0.09
	Z-line	-	-	-	0.101
	Esophagus (BE)	-	-	-	-

Abbreviation: Barrett's esophagus.
[a] $P < 0.01$.

Table 5. The Relationship Between Type of Cardiac Mucosa With Intestinal Metaplasia (IM) in the Cardia and Z-Line[a]

	Intestinal Metaplasia		Types of Mucosa in the Cardia			P Value
			Mucous or Mucous/Oxyntic	Oxyntic	Total	
Anatomic site	Cardia	No	21 (18.4)	93 (81.6)	114 (91.9)	0.001
		Yes	7 (70.0)	3 (30.0)	10 (8.1)	
	Z-line	No	23 (20.0)	92 (80.0)	115 (92.7)	0.027
		Yes	5 (55.6)	4 (44.4)	9 (7.3)	

[a] Values are expressed as No. (%).

tween *H. pylori* and the presence of active Z-line inflammation.

Another point that deserves to be mentioned is that the relationship of *H. pylori* to cardiac and Z-line inflammation becomes less strong as we move from the distal to the proximal part of the stomach. Furthermore, when it comes to inflammation in the Z-line, some other factors may be important as well.

Furthermore, no relationship was seen between *H. pylori* on the one hand and antral, cardiac and Z-line IM on the other. Three reasons can be given to explain this finding: (1) we had a limited number of IM cases in our study, (2) *H. pylori* was loosely attached to the metaplastic mucosa, and considering that *H. pylori* tends to disappear in the case of chronic mucosal inflammation (1), (3) rather than excluding the patients, who had undergone treatment for *H. pylori* many years prior to the research, we only excluded those, who had been treated for *H. pylori* shortly before the research. Moreover, it has been shown that gastric mucosa may not return to normal despite *H. pylori* eradication (19).

A number of studies have not found a significant relationship between *H. pylori* and cardiac IM, but have reported a relationship between *H. pylori* and carditis (16). In contrast, some studies found that cardiac IM is related to *H. pylori* and antral IM (3).

Much research has focused on the relationship between cardiac IM and a few other factors. For instance, while cardiac IM has been found to be positively related to age (16), it has been shown to be negatively related to BMI (16), GERD, endoscopic esophagitis, and hiatus hernia (3).

Moreover, in our study, GERD had no correlation with cardiac or Z-line inflammation and IM, and perhaps this was because our study had the limitation of a small number of GERD cases.

Age was the only risk factor, which was histologically related to the degrees of esophagitis in our study. We also found a negative relationship between BMI and histological esophagitis, yet this finding may be accidental because most of our patients had a low BMI. We did not observe a relationship between esophagitis and hiatus hernia, which may be due to the limited number of GERD or esophagitis cases in our study. It should be noted that while some studies reported a relationship with hiatus hernia (14) and BMI (1), some other studies did not find such a relationship (12, 16). Other risk factors (i.e. alcohol and smoking) were nonexistent or minimal in our patients.

We were also interested in the relationship of BE with clinical complaints, age, gender, BMI, and hiatus hernia. Only 4.03% of the patients in our study were diagnosed with BE. The percentages reported in other studies for the prevalence of BE ranged between 1% (3) and 13% (16). Furthermore, a prevalence of 5.4% was reported for Iranian patients with dyspeptic problems (20). The prevalence of BE depends on issues such as the prevalence of etiological fac-

tors in the population under study, the type of clinical complaint, and indications for endoscopy. One study recommended to take biopsy specimens from the Z-line to rule out BE even though no endoscopic evidence of BE could be found (21).

We observed a correlation between BE and clinical complaints. Some other studies have also reported a correlation between BE and GERD symptoms (3, 16, 20). This has clinical implications, meaning that it is necessary to pay greater attention to BE in patients with GERD complaints.

The present research found no relationship between age and BE although BE patients were on average older than the other patients. In addition, although four out of five BE patients in our study were female, no relationship was seen between gender and BE, possibly because of the significantly larger number of female patients. As for female predominance in our study, it should be noted that patients could participate in our study regardless of gender if inclusion and exclusion criteria were satisfied and also if patients agreed to participate. Although gastric and esophageal cancer and perhaps the predisposing factors pertinent to them are more common among males (2), this cannot predict similar predominance in people, who refer to medical centers. A study from Iran reported female predominance (2 to 1) in patients with GERD symptoms (5).

It is worth noting that despite the predominance of BE (1, 16) and esophageal adenocarcinoma (2) among males, no relationship has been reported in the literature between BE and gender (3). Finally, unlike studies that have reported a relationship between BE and BMI, and hiatus hernia (3), we found no such relationship; an observation which may be attributed to the small number of our BE cases.

Another key observation of the study was the significant correlation between chronic inflammations in the antrum, cardia and Z-line. More specifically, while the correlation between chronic antritis and chronic carditis was the strongest, the relationship between chronic antritis and the chronic inflammation in the Z-line was the least strong. In addition, a relationship was found between active carditis and active antritis and also between active carditis and active Z-line inflammation, but no such correlation was observed between active antritis and active Z-line inflammation. Moreover, as for the correlations among chronic and active inflammations across the three sites at issue, chronic antritis was correlated with active antritis and active carditis. Similarly, chronic carditis correlated with active carditis and active antritis. Likewise, chronic inflammation in the Z-line was related to active inflammation in this area and also in the antrum.

We only found a relationship between cardiac and Z-line IM, but not between cardiac and antral IM or between Z-line and antral IM. It should also be noted that Z-line IM was observed in nine (equaling 7.3%) of our patients. In a study similar to ours, this figure was 15% (3). On the other hand, while we observed 10 cases of cardiac IM (8.1%), another study reported a much higher percentage (42%) (16).

Another significant outcome of the study was the correlation between the type of mucosa in the cardia and the presence of cardiac and Z-line IM. Since the specimens taken from these two sites were only a few millimeters away from each other, such a relationship seems logical. We also found that if the cardiac mucosa is of the mucous or mucus/oxyntic type, the site under discussion is more likely to be affected by IM. This observation implies the effect of the squamo-oxyntic gap on IM. This gap is a columnar epithelium between the squamous mucosa of the esophagus and the oxyntic mucosa of the stomach and it may be lined by mucous or mucous/oxyntic epithelium (22). In our study, cardiac and Z-line IM was more common in patients, who had this gap (i.e., the patients with a mucous or mucous/oxyntic type of mucosa in cardiac specimens). As this gap is equal to the microscopic sign of GERD (21, 22), we can suggest that microscopic GERD is related to cardiac and Z-line IM.

Overall, it can be concluded that both *H. pylori* and GERD probably have roles to play in the development of adenocarcinoma in the cardia and the Z-line, despite the fact that, as mentioned previously, some studies suggest that *H. pylori* is protective against GERD-induced injury (11). The reason may be a decrease in gastric acid secretions as inflammation and atrophy of the gastric corpus is secondary to *H. pylori* infection (1). Now, the question is why *H. pylori* and GERD cause inflammation in the cardia and the Z-line if atrophy has not happened yet. A study into the relationship of gastric pathology (including inflammation, *H. pylori* infection, and IM) to high-grade dysplasia and/or adenocarcinoma of the distal esophagus found that changes made by *H. pylori* infection to the composition of gastric acid in the patients with gastric pathology (despite a low prevalence of 17.8%) were statistically more significant than the control group ($P = 0.01$), suggesting that these changes may have a role in developing dysplasia and neoplasia (23). Given this, it could be suggested that *H. pylori* may reduce or intensify the adverse effect of GERD depending on the stage of gastritis. This hypothesis could be clarified by future studies.

This study had some limitations including its cross sectional design and the low number of participants. In addition, patients with dyspepsia were more frequent than patients with GERD. Conducting longitudinal studies with higher sample sizes will help better understanding of clinicopathological findings of these regions.

5.1. Conclusions

This study showed that the cardia and, to a lesser degree, the Z-line were affected by *H. pylori* and antral gastritis. Moreover, the relationship between microscopic GERD and the presence of IM both in the cardia and the Z-line supports the role of GERD in inducing inflammation and pathological changes in the two areas.

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Footnote

Conflict of Interest: None to declare.

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