



# May cardia mucosa histopathology aid in the diagnosis of gastroesophageal reflux disease in children?

Peiman Nasri<sup>1</sup>, Azar Naimi<sup>2</sup>, Zahra Salehi<sup>3</sup>, Hosein Saneian<sup>1</sup>, Majid Khademian<sup>1</sup>, Fatemeh Famoori<sup>1</sup>

<sup>1</sup>Metabolic Liver Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>2</sup>Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>3</sup>Pediatric Department, Isfahan University of Medical Sciences, Isfahan, Iran

## \*Correspondence to

Azar Naimi, Email: azar.naimi@med.mui.ac.ir

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## Abstract

**Introduction:** Gastroesophageal reflux disease (GERD) is a common diagnosis in children referred to pediatricians. This disease is diagnosed clinically based on the patient's signs and symptoms; however, there are endoscopic and pathological evaluations to diagnose this disease too. This study evaluated the relationship between GERD and cardia mucosa histopathology in children under six years old.

**Objectives:** Studies on adults with GERD had shown different cardia histopathology related to GERD, and this relationship in children was less evaluated. According to this and the high prevalence of GERD in children.

**Patients and Methods:** Children who were a candidate for endoscopy were selected. Endoscopy was conducted for each participant and biopsies from the cardia area were obtained. In the recovery room, Infant Gastroesophageal Reflux Disease Questionnaire-Revised (IGERQ-R) was completed by children's parents for identifying GERD in children. Then the relation between the presence of GERD and histopathology of the cardia area was assessed.

**Results:** In this study, 80 children with a mean age of  $33.8 \pm 20.7$  months were evaluated, while 53.8% of them were male. The histopathology finding in participants with GERD was 48.1% oxyntic mucosa and 51.9% oxyntocardiac mucosa with lymphoid aggregation. This histopathology in patients without GERD was 67.9% oxyntic mucosa and 32.1% oxyntocardiac mucosa with lymphoid accumulation. There was a significant relationship between GERD and cardia mucosa type ( $P=0.043$ ).

**Conclusion:** Children with GERD had different cardia histopathology compared with those without reflux disease.

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## Introduction

Gastroesophageal reflux disease (GERD) is a physiologic process in children, adolescents and adults and occurred in two-thirds of healthy children and is considered one of the most common chief complaints of children in pediatrician visits (1,2). GERD is caused by transient relaxation of the lower esophageal sphincter independent of swallowing that lets gastric contents pass to the esophagus (3). GERD manifests in children with different clinical symptoms. The common manifestations of GERD are regurgitation, vomiting, irritability, anorexia, feeding or eating refusal, dysphagia and odynophagia and also arching backward during milk feeding. Other manifestations sometimes accompany GERD including; wheezing or other symptoms of the upper respiratory tract (4). Upper gastrointestinal endoscopy is conducted for macroscopic evaluation of esophageal and cardiac mucosa and in GERD; this modality can show esophagitis, erosions, exudate, ulcers, strictures, metaplasia and polyps (5, 6). During endoscopy, biopsies are taken for microscopic evaluation and histological markers in GERD

## Key point

Gastric cardia histopathology can be helpful in GERD diagnosis in challenging cases

are papillary growth, basal cell hyperplasia and intercellular dilatation (7).

The gastric cardia is a very short zone of cardiac mucosa immediately distal to the typically located squamocolumnar junction (SCJ), also known as Z-line (8). Studies reported that cardia mucosa is presented in the junction of the esophagus and cardia in all biopsies of this site. Other studies showed that cardia mucosa extension to this site is due to gastroesophageal reflux (9,10). Some studies detected that the cardia comprises mucous glands at birth, whereas other studies suggest that mucous glands, when present, are a metaplastic response to GERD (11). A study on 150 patients with symptoms of GERD assessed the ability of endoscopy on diagnosing GERD and divided patients into two groups include normal and open cardia, according to the appearance of cardia at

endoscopy. This study revealed that endoscopic evaluation of cardia could identify patients with GERD (12). Studies reported that histological evaluation of biopsies during endoscopy in children showed simultaneous presence of columnar and squamous mucosa in cardia that expresses no relation between cardia inflammation and GERD. Indeed, more severe reflux symptoms were not associated with more severe inflammation in the cardia (8).

### Objectives

Studies on adults with GERD had shown different cardia histopathology related to GERD and this relationship in children was less evaluated. According to the high prevalence of GERD in children, this study aimed to assess the relationship between GERD and cardia mucosa histopathology in children under six years old.

### Patients and Methods

#### Study design

This study is an ante-grade observational study on children referred to the gastroenterology clinic of Imam Hossein hospital in Isfahan University of Medical Science (IUMS) during 2017-2018. Inclusion criteria were as followed; 1) Age less than six years, 2) Candidate for endoscopy, 3) Lack of coagulopathy or hematologic diseases, 4) Lack of the previous esophagus or cardiac surgery, 5) Lack of any congenital disorders, 6) Lack of any neurological or developmental disorders and 7) Parent's willingness to participate in this study. Children with any contraindication for taking biopsies during endoscopy were excluded from the study. Patients were selected based on the available sampling method. The study was wholly explained to children's parents and an informed consent letter was completed. Upper gastrointestinal tract endoscopy was conducted for all participants based on the standard protocol in the endoscopy ward of Imam Hossein hospital. During endoscopy, seven tissue biopsies were taken from each patient in the cardia site; two biopsies from under the Z-line area and five biopsies from the top of the Z-line area. All biopsies were floated in separate, labeled containers and sent to the pathology laboratory in Imam Hossein hospital. In the pathology laboratory, all specimens were evaluated by two pathologists and the type of mucosa in the cardia site was assessed and then reported.

After endoscopy in the recovery room, demographic data were extracted from the patient's profile, and children's parents completed infant gastroesophageal Reflux Disease Questionnaire-Revised (IGERQ-R) to evaluate the presence of GERD in each participant. This questionnaire is a 12-item questionnaire that assessed GERD symptoms during the last week. It includes three questions for regurgitation, three questions for crying, one question for arching back, two questions for feeding, one question for hiccups, two questions for apnea and color changes. Three pediatric gastroenterologists confirm the validity of this

questionnaire, and the Cronbach's alpha was 0.844 during this study (13). This questionnaire is scored between 0-42 and a score >16 is defined as GERD(12).

#### Statistical analysis

Data about endoscopy and histopathology findings and scores of the questionnaire were entered into Statistical Package for the Social Science (SPSS) version 26 (SPSS corp. Chicago, IL, USA) and then analyzed. The quantitative data were reported by mean and standard deviation and qualitative data were reported by number and percent. For evaluating the relation between variables, t-test and chi-square were applied. A two-sided  $\alpha$  level of 0.05 was used to assess statistical significance. The regional bioethics committee approved this study of the Isfahan university of medical science.

### Results

In this study, 80 children were evaluated. The mean age of participants was  $33.8 \pm 20.7$  months ranged from 2-72 months. About 53.8% (n=43) were male and 46.3% (n=37) were female.

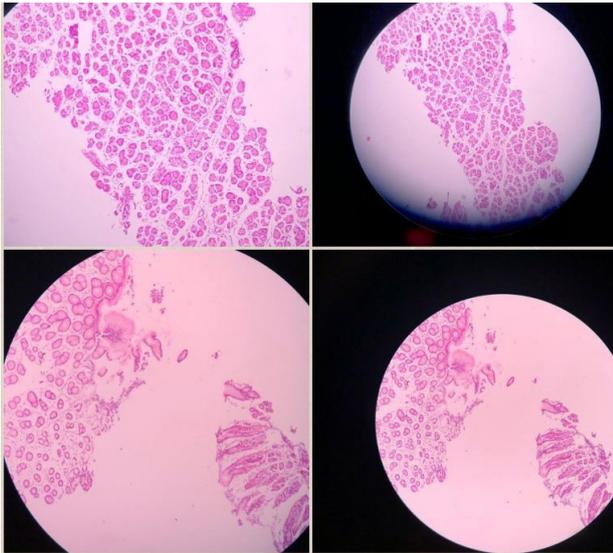
Based on IGERQ-R, the prevalence of GERD was 33.8% (n=27). Among those with GERD, 48.1% (n=13) had oxyntic mucosa in the cardia site and 51.9% (n=14) had oxyntic mucosa accompanied with other histopathology include cardiac mucosa (oxyntocardiac mucosa) and lymphoid aggregation. Among those without GERD, 67.9% (n=36) had pure oxyntic mucosa (Figure 1) and 32.1% (n=17) had oxyntic mucosa with cardiac mucosa (oxyntocardiac mucosa) or lymphoid aggregation (Figure 1b). According to the IGERQ-R, there was a significant relationship between the presence of GERD and the type of mucosa in children ( $P=0.043$ ) (Table 1).

According to the histopathology reports of the lower esophagus, the prevalence of GERD was 50% (n=40). Among those with GERD, 57.5% (n=23) had oxyntic mucosa in cardia site and 42.5% (n=17) had oxyntic mucosa and cardiac mucosa (oxyntocardiac mucosa). Histopathology report also showed, in those without GERD of the lower esophagus, 65% (n=26) had oxyntic mucosa and 35% (n=14) had oxyntic mucosa and cardiac mucosa (oxyntocardiac mucosa). There was no significant relationship between the presence of GERD of lower esophagus and cardia site histopathology findings ( $P=0.49$ ; Table 2).

### Discussion

This study evaluated the relation between the presence of GERD and histopathology of the cardia in children. It revealed that children with GERD had different cardia mucosa histopathology compared to those without GERD.

Cardia represented the distal 2 cm of the esophagus and is covered by cardiac mucosa (14). The average epithelial tissue in this site is squamous epithelial or pure oxyntic mucosa. The oxyntic mucosa can resist gastric acid while



**Figure 1.** Histology of cardia. (a and b): Pure oxyntic mucosa, Hematoxylin and Eosin staining  $\times 100$ , (c and d): oxyntocardiac mucosa, Hematoxylin and Eosin staining  $\times 100$

gastric acid can damage the squamous mucosa. The presence of cardiac mucosa and oxyntocardiac mucosa showed metaplasia of the squamous epithelium due to reflux. Oxyntocardiac mucosa is considered as a diagnostic histopathological criterion for GERD (15).

There are several studies on the histopathology of the cardia in adult patients with GERD. A study on 71 patients with GERD evaluated their biopsies during endoscopy and reported cardia mucosa in five categories; 1) Stratified squamous epithelium, 2) Pure oxyntic mucosa, 3) Pure cardia mucosa, 4) Oxyntocardiac mucosa and 5) Intestinal metaplasia mucosa. In this study, presence of combined cardiac mucosa and oxyntocardiac mucosa can predict the level of acid exposure in the lower esophagus (16). Another study on 114 patients with GERD reported that cardiac or oxyntocardiac mucosa is presented in the esophagogastric junction (17). A survey of patients with GERD or epigastric pain showed the mixture of cardiac

and oxyntocardiac mucosa at the normal-appearing squamocolumnar intersection. None of the biopsies contained gastric oxyntic mucosa (18). Likewise, a study on 334 patients with GERD showed that 74% of patients had cardiac mucosa or oxyntocardiac mucosa in their cardia biopsy during endoscopy and they were more likely to have abnormal 24-hours pH test and reported that the presence of cardiac or oxyntocardiac mucosa could show a significantly higher level of acid exposure (19).

According to another study, the presence of cardiac mucosa or oxyntocardiac mucosa is a sensitive histological indicator for reflux. According to previous investigations, the presence of inflammation can predict reflux or its severity (20).

The pathophysiologic studies of GERD reported that evaluating adult patients with GERD endoscopically and pathological, showed presence of three categorizations for GERD. They are including mild reflux defined as routine endoscopy and presence of cardiac mucosa or oxyntocardiac mucosa in specimens, moderate reflux defined as abnormal endoscopy and presence of cardiac mucosa or oxyntocardiac mucosa with a length of less than 2 cm and severe reflux defined as abnormal endoscopy and cardiac mucosa and oxyntocardiac mucosa with a length of more than 2 cm (20). This categorization was on adult patients and there is no category on children. According to this category, it is possible that endoscopic evaluation of children with GERD and histological assessment of cardia site by taking biopsies from cardia site can diagnose GERD in children in the lowest grade of this disease.

Our study has its strength and also suffers from limitations. One of the strengths of this study is evaluating the relation between cardia histopathology and the presence of GERD in children. Additionally, using a standard scale for diagnosing GERD in children that most previous population-based studies had used this scale in their studies, suggests. One of the limitations of this study is its small sample size that is too small for generating to the general population. In future studies, a more significant sample size should be considered. Another limitation of this study is no assessment of the length of cardiac mucosa in cardia during endoscopy in adult studies as a criterion for predicting the severity of reflux and degree of acid exposure. Further studies should be planned on children with GERD considering greater sample size; other variables include the length of cardiac or other mucosa and severity of the disease.

**Table 1.** The distribution of mucosal type of cardia in children with and without GERD based on IGERQ-R

Type of mucosa	With GERD	Without GERD	P value
	No. (%)	No. (%)	
Oxyntic	13 (48.1%)	36 (67.9%)	0.043
Oxyntic+ others (oxyntocardiac, lymphoid aggregation)	14 (51.9%)	17 (32.1%)	

There is a significant relation between GERD and type of mucosa in cardia

**Table 2.** The distribution of mucosal type of cardia in children with and without GERD based on lower esophagus histopathology reports

Esophagus	Cardia histopathology		P value
	Pure oxyntic No. (%)	Oxyntic + others No. (%)	
With GERD	23 (57.5%)	17 (42.5%)	0.49
Without GERD	26 (65%)	14 (35%)	

### Conclusion

In conclusion, children with GERD based on the IGERQ-R questionnaire had different cardia histopathology than those without GERD.

### Limitations of the study

All of the data of the present study were collected from Imam Hosein hospital, Isfahan, Iran. Hence, evaluating

the gastric mucosa of GERD patients employing a bigger statistical population is recommended.

#### Authors' contribution

MK and PN were the principal investigators of the study. HS, AN and ZS were involved in preparing the concept and design. FF revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

#### Conflicts of interests

The authors declare that they have no competing interests.

#### Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols (IR.MUI.REC.1396.3.481). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from the Pediatrics Residency thesis of Zahra Salehi at this university. Besides, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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