Serum Interleukin 5 as an Indicator of Eosinophilic Esophagitis in Patients with Chronic Upper GIT Symptoms

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Background and study aim: Eosinophilic esophagitis (EoE) is an immune-allergic mediated clinicopathologic condition characterized by symptoms of esophageal dysfunction with prominent eosinophilic infiltrate in the esophageal mucosa. Interleukin 5 (IL-5) play a role in eosinophil esophageal trafficking in EoE patients. This study aimed to assess serum interleukin 5 as an indicator of EoE in patients with chronic upper GIT symptoms.

Patients and Methods: This study included 80 adults with at least one of chronic upper GIT symptoms not responded to standard daily PPI therapy for 8 weeks, in whom upper GIT endoscopy was done with histopathological assessment of esophageal biopsies. EoE was diagnosed by detection of ≥15 eosinophils/high power field (HPF). Ten apparently healthy subjects were enrolled as a control group. Interleukin-5 (IL-5) in serum by ELISA was measured in all subjects.

Results: By histopathological examination, six patients (7.5%) were diagnosed to have EoE. Endoscopic esophageal furrows, fissures/wrinkles; white exudate/granularity and concentric rings (trachealization) were significantly more frequent in patients with EoE than non EoE. Median concentration of serum IL-5 in EoE patients was 222.2pg/ml with range 187.5-307pg/ml while, it was 32.1pg/ml with range 15.6-113.6pg/ml in non EoE patients and 11.8pg/ml with range 13.4-38.2pg/ml in controls with P value < 0.001. ROC curve analysis showed that serum IL-5 can significantly predict EoE at a cut-off value of ≥103.2pg/ml with sensitivity 100%, specificity 93.2%, PPV 54.5%, NPV 100%, Accuracy 93.8%, AUC = 0.989 and (95%CI) = 0.96-1.0.

Conclusion: Serum interleukin 5 could be used as an indicator for eosinophilic esophagitis diagnosis in patients with chronic upper GIT symptoms. However, histopathological diagnosis still necessary .

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus that had become widely recognized as a major cause of upper gastrointestinal morbidity **[1]**. EoE is well documented in children, while the adult type has recognized as a distinct entity and occurs in young males with dysphagia and allergic manifestations **[2]**. Disease pathogenesis involves the interplay of external and genetic factors, particularly food antigens and the eosinophil chemoattractant eotaxin-3, respectively **[3]**. EoE shares nonspecific symptoms with gastroesophageal reflux disease (GERD) like heartburn, dysphagia, chest pain and these symptoms can overlap with EoE symptoms **[4]**. It is important to differentiate between EoE and reflux esophagitis, not only because therapy differs but also because patients might suffer from needless therapeutic maneuvers exposure used for reflux esophagitis treatment such as long-term medical therapy with proton pump inhibitors (PPI) and surgical procedures like fundoplication **[5]**.

Endoscopic examination is required for diagnosis of EoE in which typical endoscopic findings include esophageal rings, narrowing or strictures, linear furrows, white plaques/exudates and mucosal fragility also termed crêpe-paper mucosa. However, in a small proportion of cases, esophageal mucosa may appear normal and the diagnosis would be missed if biopsies are not taken **[6]**. At least two to four biopsies should be taken from the proximal, mid and distal esophagus to maximize the sensitivity of EoE diagnosis **[7]**. The presence of more than 15 eosinophils/HPF with history of non-intake of PPI for 30 days before were used as prerequisite diagnostic criteria for eosinophilic esophagitis **[8]**. Central role for interleukin 5 (IL-5) in inducing eosinophil trafficking to the esophagus which, is necessary for the induction of eosinophilic esophagitis **[9]**. Usage of humanized monoclonal blocking anti-IL-5 antibody, that brought about significant decrease in symptoms of esophageal eosinophilia **[10]**. Serum indicators for diagnosis of EoE are required to be complement with histopathological assessment. This study aimed to determine the value of serum IL-5 as an indicator for EoE diagnosis.

PATIENTS AND METHODS

This case-control study was performed from January 2019 to November 2020 after ethical committee approval of the scientific research in Benha Faculty of Medicine and written medical consent included 80 consecutive adult patients attended to the endoscopy unit of Hepatology, Gastroenterology and Infectious disease Department-Benha University Hospitals for upper GIT endoscopy. Ten cross-matched age and sex apparently healthy subjects were enrolled as a control group.

Inclusion criteria:

-At least one or more of chronic symptoms suggestive of esophageal dysfunction as heartburn, dysphagia, odynophagia, chronic epigastric pain, recurrent vomiting, non-cardiac chest pain, regurgitation, belching, globus sensation, water brash and/or history of food impaction.

-Non response to standard daily PPI therapy for at least 8 weeks.

Exclusion criteria:

-History of upper GIT bleeding.

-Recent PPI intake for at least one month before endoscopic examination.

-Patients with organic lesions (mass or ulcer …etc.) detected during endoscopic examination.

-Infections (fungal or parasitic), drug reactions, graft-versus-host disease, patients with organ transplant, dermatological eczema, COPD and asthmatic patients.

-Achalasia, connective tissue disease, pemphigus, celiac disease, Crohn's disease and patients with rheumatologic diseases which are alternative etiologies of esophageal eosinophilia **[11]**.

Most of these morbidities can be excluded with a careful history taking, physical examination and conventional laboratory tests.

All patients were subjected to:

Clinical evaluation: Thorough history taken**.** General and local abdominal examination.

Laboratory investigation: after conventional laboratory investigation, measurement of serum interleukin-5 (IL-5) by ELISA (enzyme-linked immunosorbent assay) technique at Clinical and Chemical Pathology Department (Benha University Hospital) had been done. The human IL-5 kits included in this study were ELISA type and had size 48T/96T, range from 5.625-1000 pg./ml for application in quantitative detection of IL-5 in serum was done. Principle for detection based on sandwich ELISA technology. Anti-IL-5 antibody was precoated onto 80 well plates. The biotin conjugated anti-IL-5 antibody had been used as detection antibodies. Source of IL-5 kits was New Test Company.

Upper GI endoscopy: Midazolam or propofol were used in patients' sedation. Then upper GI endoscopy (Olympus system GIF-XQ 240) was done. Findings suggestive of EoE such as wrinkled oesophagus, whitish exudate and/or granularity, linear fissuring, vertical furrowing, fixed or transient concentric rings (trachealization), and proximal strictures were assessed **[12]**. The presence of GERD which was classified according to the Los Anglos (LA) classification system **[13]**, the presence of any other oesophageal abnormality and/or in the stomach or duodenum such as ulcers or masses …etc, were excluded. Tow biopsies were taken from each upper and mid- and lower esophagus for histopathological assessment.

Histopathological examination: Biopsies were preserved in 10% formalin and were cut by the Microtome apparatus and examined after

staining with Haematoxylin and Eosin. On histopathological examination, two blindly pathologists counted the eosinophils. The presence of more than 15 eosinophils/HPF without history of PPI intake for 30 days were used as prerequisite diagnostic criteria for eosinophilic esophagitis **[8]**.

Statistical analysis: Data were tabulated and analyzed by using SPSS version 16 software (Spss Inc, Chicago, ILL Company). The categorical data were presented as number and percentages. The quantitative data were expressed as mean ± standard deviation, median and range. Fisher's exact test had been used to analyze categorical variables, odds ratio (OR) and 95% CI were calculated when applicable. Quantitative data were tested for normality using Shapiro-Wilks's test, assuming normality at P >0.05. Student "t" test was used to analyze normally distributed variables among 2 independent groups. Categorical data were compared by using Chi-square test. ROC curve was constructed to detect cutoff values of IL-5 and blood eosinophils in prediction of EoE.

RESULTS:

Based on the EoE histological diagnostic criteria, EoE patients were six and non EoE patients were 74. Regarding demographic data, the mean age of EoE patients was 36.3±18.8years, which was ~ 2 years younger than non-EoE esophagitis patients (mean age 38.1±13.3 years) and 32.5±14.7 in controls. Female gender [4 (66.7%)] were more common in patients with EoE, 46 (62.2 %)] in non-EoE patients and 6 (60%) in controls] (table 1). As regard symptomatology of the studied patients, heartburn [6 (100%)], dysphagia [5 (83.3%)], chronic epigastric pain [6 (100%)], persistent vomiting [4 (66.4%)] and history of food impaction [4 (66.4%)] were more common in EoE patients (table 2). By laboratory assessment of the studied subjects (peripheral eosinophilic count), all six eosinophilic esophagitis patients had increased peripheral eosinophilic count (2.3-7.0%) than non-EoE patients and controls with statistically significant difference (table 3 and 6). Regarding endoscopic features, esophageal furrows, fissures and/or wrinkles; white exudate, plaques and/ or granularity and fixed or transient concentric rings (trachealization) were more common in EoE (50vs5.4%), (83.3vs6.8%) and (83.2vs 9.5%) and respectively. While hiatus hernia and GERD were not statistically significant between EoE and non-EoE patients (table 4). Regarding histopathological examination of the studied subjects, mucosal and sub mucosal edema, basal hyperplasia, papillae elongation, squamous cell layer thinning and infiltration lymphocytic or neutrophilic were more frequent in EoE compared with non-EoE patients (83.3, 83.3, 83.3, 66.7 and 83.3% vs 28.4, 28.4, 35.1, 23and 26%) with significant statistically difference. While, goblet Cell metaplasia was demonstrated only in 7 patients of non-EoE (table 5). Regarding serum IL-5 assay by ELISA, median concentration of serum IL-5 in EoE patients was 222.2pg/ml with range 187.5-307pg/ml while, it was 32.1pg/ml with range 15.6-113.6pg/ml in non EoE patients and 11.8pg/ml with range 13.4-38.2pg/ml in controls with P value < 0.001. ROC curve analysis showed that IL-5 can significantly predict EoE at a cutoff value of ≥103.2pg /ml with 100% sensitivity, 93.2% specificity, 54.5% PPV, 100% NPV, 93.8% Accuracy, AUC = 0.989 and (95%CI) = 0.96-1.0. ROC curve analysis showed that eosinophils can significantly predict EoE at a cutoff value of ≥3.5% with 83.3% sensitivity, 73% specificity, 20% PPV, 98.2% NPV, 73.8% Accuracy, AUC = 0.814 and (95%CI) =0.64-0.98.

Table (1): Demographic data in the studied subjects.

Variable		Non-Eosinophilic esophagitis (N=74)		Eosinophilic esophagitis (N=6)		Controls (N=10)		Test of significance	P value
Age (ys)	**Mean ±SD**	38.1±13.3		36.3±18.8		32.5±14.7		**Z_{MWU}= 0.48**	**0.59 (NS)**
	Range	18-73		18-60		**18-56**			
		No.	**%**	**No.**	**%**	**No.**	**%**	**OR (95%CI)**	**P**
Sex	**Male**	28	37.5	2	33.3	4	40	**1.4 (0.32-6.8)**	**1.0 (NS)**
	Female	46	62.2	4	66.7	6	60		
Residence	**Rural**	39	52.7	5	83.3	6	60	**0.31 (0.09-2.5)**	**0.21 (NS)**
	Urban	35	47.3	1	16.7	4	40		

Table (2): Clinical symptomatology in the studied patients.

Variable	Non-Eosinophilic esophagitis(N=74)		Eosinophilic esophagitis(N=6)		Test of significance OR (95%CI	P
	No.	%	No.	%		
Dysphagia	22	29.7	5	83.3	**11.8 (1.3-107.1)**	**0.015 (S)**
Heartburn	39	52.7	6	100.0	**13.5 (1.5-122.7)**	**0.033 (S)**
Recurrent vomiting	29	39.2	4	66.7	**3.1 (0.5-18)**	**0.22 (NS)**
Chronic epigastric pain	71	95.9	6	100.0	-------	**1.0 (NS)**
Non cardiac chest pain	1	1.4	0	0.0	-------	**1.0 (NS)**
Regurgitation	1	1.4	0	0.0	-------	**1.0 (NS)**
Belching	1	1.4	0	0.0	-------	**1.0 (NS)**
Odynophagia	1	1.4	0	0.0	-------	**1.0 (NS)**
Globus sensation	8	10.8	0	0.0	-------	**1.0 (NS)**
History of food impaction	9	12.2	4	66.7	**14.4 (2.3-90.5)**	**0.006 (S)**

Table (3): CBC in the studied subjects.

Variable	Non-Eosinophilic esophagitis (N=74)		Eosinophilic esophagitis (N=6)		Controls (N=10)		Test of significance Z_{MWU}	P value
	Median	Range	Median	Range	Median	Range		
Hb (gm/dl)	12.0	7.8-15.1	12.3	10.9-15.3	13.1	11.6-15.5	0.84	0.50 (NS)
WBCs (10^3x mm^3)	7.0	3.5-11.6	7.75	4-12	5.5	4-11	0.98	0.26 (NS)
PLTs (10^3x mm^3)	210	120-435	218.5	185-469	320	285-450	0.32	0.96 (NS)
Eosinophils (%)	3.0	0.5-6.0	5.0	2.3-7.0	1.5	0-3	2.53	0.09 (S)

Table (4): Endoscopic findings in the studied patients.

Variable		Non-Eosinophilic esophagitis) (N=74)		Eosinophilic esophagitis (N=6)		Test of significance OR (95%CI	P value
		No.	%	No.	%		
Esophageal furrows, fissures and/or wrinkles	**No**	70	94.6	3	50.0	**17.5 (2.6-115.9)**	**0.008 (S)**
	Yes	4	5.4	3	50.0		
White exudate and/ or granularity	**No**	69	93.2	1	16.7	**9.8 (1.09-88.4)**	**0.026 (S)**
	Yes	5	6.8	5	83.2		
Fixed or transient concentric rings (trachealization)	**No**	67	90.5	1	16.7	**16.7 (1.8-153.5)**	**0.005 (S)**
	Yes	7	9.5	5	83.3		
GERD	**No**	17	23.0	0	0.0	-----	**0.33 (NS)**
	Yes	57	77.0	6	100.0		
L.A grade (n=63)	**A**	22	38.6	2	33.3	------	**0.7 (NS)**
	B	29	50.9	3	50.0		
	C	5	8.8	1	16.7		
	D	1	1.8	0	0.0		
Hiatus hernia	**No**	58	78.4	4	66.7	**1.8 (0.3-10.8)**	**0.61 (NS)**
	Yes	16	21.6	2	33.3		

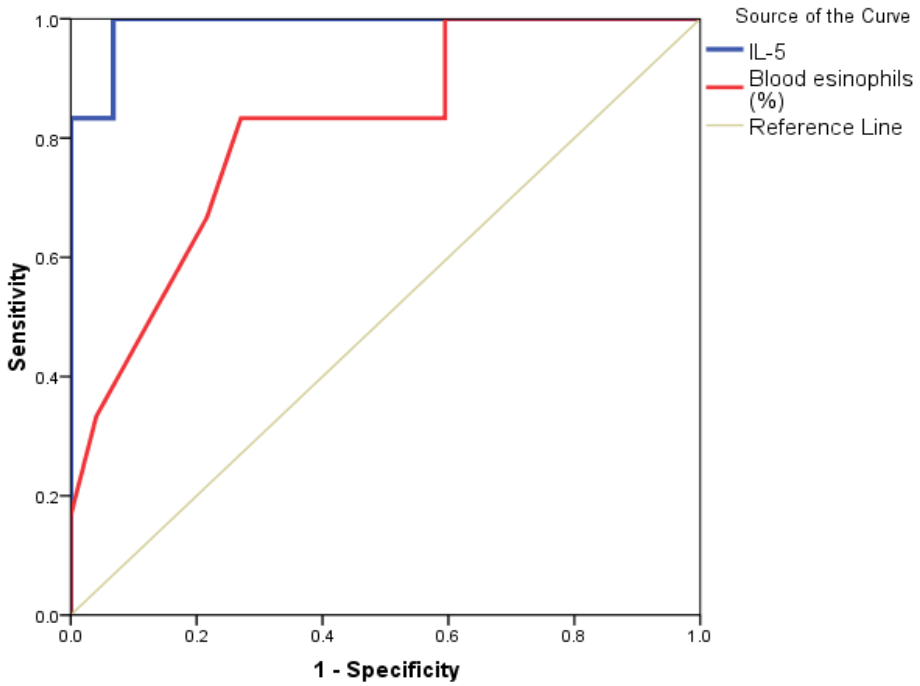
Table (5): Histopathological finding in the studied patients.

Variable		Non-Eosinophilic esophagitis (N=74)		Eosinophilic esophagitis (N=6)		Test of significance OR (95%CI	P value
		No.	%	No.	%		
Mucosal and sub mucosal edema	**No**	53	71.6	1	16.7	**12.6 (1.4-114.5)**	**0.013 (S)**
	Yes	21	28.4	5	83.3		
Basal hyperplasia	**No**	53	71.6	1	16.7	**12.6 (1.4-114.5)**	**0.013 (S)**
	Yes	21	28.4	5	83.3		
Elongation of the papillae	**No**	48	64.9	1	16.7	**9.2 (1.02-83.2)**	**0.03 (S)**
	Yes	26	35.1	5	83.3		
Thinning of the squamous Cell layer	**No**	57	77.0	2	33.3	**6.7 (1.1-39.8)**	**0.038 (S)**
	Yes	17	23.0	4	66.7		
Infiltration lymphocytic or neutrophilic	**No**	48	64.9	1	16.7	**9.2 (1.02-83.2)**	**0.03 (S)**
	Yes	26	35.1	5	83.3		
Goblet Cell metaplasia	**No**	67	90.5	6	100.0	------	**1.0 (NS)**
	Yes	7	9.5	0	0.0		

Table (6): Interleukin-5 (IL-5) in the studied groups.

Variable	Non-Eosinophilic esophagitis (N=74)		Eosinophilic esophagitis (N=6)		Controls (N=10)		Test of significance	P
	Median	Range	Median	Range	Median	Range	Z_{MWU}	
IL-5 (pg /ml)	32.1	15.6-113.6	222.2	187.5-307.1	11.8	13.4-38.2	3.45	<0.001 (HS)

ROC curve for the performance of IL-5 and blood eosinophils in prediction of EoE at cutoff 15 eosinophils / HPF



Score	Sens%	Spec%	PPV%	NPV%	Accuracy%	AUC	95%CI	P
IL-5 ≥103.2pg /ml	100%	93.2%	54.5%	100%	93.8%	0.989	0.96-1.0	<0.001 (HS)
Eosinophils ≥ 3.5%	83.3%	73%	20%	98.2%	73.8%	0.814	0.64-0.98	0.011 (S)

DISCUSSION

EoE is a chronic disorder characterized by symptoms of esophageal dysfunction and esophageal inflammation with intraepithelial eosinophils **[14]**. The common symptoms of EoE included dysphagia and food impaction but other symptoms such as heartburn, nausea, vomiting, chest or epigastric pain can also occur **[15]**. In this study, six cases of EoE (7.5%) out of 80 adult patients presenting with chronic upper GIT symptoms not responded to standard daily PPI therapy for 8 weeks, had been detected by histopathological examination of esophageal biopsies. This was in concordance with a study on 200 consecutive adult patients who underwent upper endoscopy and reported a 6.5% prevalence of EoE in the studied cases **[16]**. However, a national pathological data base to detect the prevalence of EoE had revealed 363 (~0.5%) cases from 74162 participants in the age ranged from 1 to 98 years **[17]**. In the current study EoE was revealed in females more than males with ratio 2 to 1 and mean age of EoE patients was 36.3±18.8years. This is in agreement with another study done by *Foroutan et al*, who stated that EoE patients were more to be in females younger than 52 years **[18]**. Unlike this study, another one by *Veerappan et al*, reported that EoE positive patients were more likely to be males younger than 50 years **[16]**. In this study, heartburn was present in all six patients with EoE (100%), dysphagia was present in five EoE patients (83.3%) and food impaction was present in four patients with EoE (66.7%). In the same track, *Brian et al* concluded that, dysphagia and heartburn were the primary presenting symptom of EoE then food impaction **[19]**. Other study by *Straumann et al* reported that, the most characteristic symptoms of EoE in adults were intermittent dysphagia, heartburn and may accompanied by food impaction **[20]**. In the same track, earlier study done by *Kapel et al* who stated that, the most common indication for endoscopy in EoE patients was dysphagia (70%) and heartburn was in (27.1%) **[17]**. While, another by *Rodrigues et al* reported that, the percentage of heartburn in EoE was 52% and food impaction was 48% **[21]**. The difference may be attributed to relatively small sample size of this study. In this study, the median of blood eosinophils was 5% with range 2.3-7% in EoE while, it was 3% with range 0.5-6% in non EoE patients and 1.5% with range 0-3% in controls (P value = 0.009). Blood eosinophils could significantly predict EoE at cutoff value of ≥3.5% with 83.3% sensitivity, 73% specificity, PPV%:20%, NPV%:98.2%, Accuracy:73.8%, AUC=0.814, 95%CI=0.64-0.98 and P value (0. 011). This was described in previous studies, which found EoE patients had higher numbers of eosinophils with 80% sensitivity also other one reported that the peripheral blood absolute eosinophil count (AEC) significantly correlated with esophageal eosinophil density ($P < 0.05$) **[22-23]**. Several lines of evidence support a role for allergic inflammation in the pathogenesis of EoE, and the most obvious evidence for such involvement is the central role of the eosinophil **[24]**. Despite the eosinophilia presence is common but not universal, that range from 30% to 100% in children and in an adult series mild eosinophilia occurred only in 50% of patients **[25]**. By upper endoscopic examination, three (50%) of the six positive cases of EoE showed esophageal furrows**,** fissures and/or wrinkles; five cases (83.3%) showed white exudate and/or granularity and five cases (83.3%) showed esophageal concentric rings (trachealization). Similar finding was reported by a prospective study done by *Dellon (2014),* in which endoscopic findings of EoE, such as esophageal fixed or transient concentric rings, furrows, fissures and/or wrinkles, and white exudate and/or granularity, are diagnostic but not specific **[26]**. However, *Kim et al* reported that, about 20% of EoE patients had normal endoscopic appearance of the esophagus **[6]**. Higher percentage had by *Mackenzie et al*. study who found that, about 42% of patients with EoE did not have the classic endoscopic picture of EoE **[27]**. In this study, 18 patients had hiatus hernia (22.5%) and 2 out of them had EoE. While, *Dellon et al (2015),* stated that younger age, male sex, presence of dysphagia, food allergies, presence of esophageal rings/furrows/plaques and lack a hiatal hernia had predicted EoE diagnosis with a very high degree of accuracy **[28]**. Also, *Jeremy and colleagues*, revealed that endoscopic esophageal ring was more in EoE and hiatus hernia was more in non-eosinophilic **[29]**. In this study, GERD in non- EoE patients was 78.8% mainly with Los Angeles grade B (50.9%) and GERD in cases of EoE was 100% which is in concordance with *Kirsch et al.*, who diagnosed GERD in 86% of their EoE cases **[30]**. Role of acid reflux in the pathogenesis of EoE is a debate matter and the clinical crossover between the two diseases in some patients would be explained as the esophageal

microenvironment becomes better recognized **[31]**. The difference of endoscopic finding may be attributed the small number of EoE cases in this study and lower prevalence rate of the disease. By histopathological examination of esophageal biopsies there was statistically significant difference between patients with EoE and non-eosinophilic regarding mucosal and sub mucosal edema with P value (0.013), basal hyperplasia with P value (0.013), elongation of the papillae with P value (0.03), thinning of the squamous cell layer with P value (0.038) and inflammatory cells lymphocytic or neutrophilic with P value (0.03). *Gunasekaran et al.*, compared esophageal histology in detail, apart from the eosinophil count, between EoE and in non-eosinophilic biopsies, the results were eosinophilic micro-abscesses, mucosal and sub mucosal edema, elongation of the papillae and epithelial desquamation were twice as common and significant in EoE group than non-eosinophilic **[32]**. In contrast *Sá et al.,* who reported that histopathological findings are nonspecific and cannot be used to distinguish between EoE and GERD **[33]**. In this study, serum IL-5 can significantly predict EoE at cutoff value of ≥103.2pg/ml with 100% sensitivity, 93.2% specificity, PPV% 54.5%, NPV% 100%, 93.8% Accuracy, AUC =0.989, 95%CI = 0.96-1.0 and P value (<0.001). In concordance with these reports, *Ishihara and colleagues*, reported IL-5 as possible biomarkers of eosinophilic esophagitis and adequately sensitive for clinical use **[34]**. Another prospective study considered IL-5 is a promising serum biomarker for diagnosing EoE with 89% sensitivity **[35]**. Unlike these results, another study in 2015 done by *Dellon and colleagues* who reported the difference in IL-5 between EoE cases and patients did not meet EoE criteria at baseline before and after therapy was non-significant **[36]**. Beside interleukin 5, other non-invasive biomarkers (eotaxin 3; interleukin 13; major basic protein and transforming growth factor beta 1) were assessed by *Sarbinowska et al* in EoE patients and concluded that, it is not possible to select one serum biomarker as efficient tool in prediction and prognosis of EoE. However, it is necessary to determine the markers several times and no parameter alone should be considered, but the whole group together, taken into consideration for the pathophysiological role and interdependencies **[37]**.

CONCLUSION

This study concluded that serum interleukin 5 and peripheral blood eosinophils count showed significant positive relation with eosinophilic esophagitis and could be helpful as indicators of the disease in patients with chronic upper GIT symptoms. Still, histopathological diagnosis of EoE continues to be necessary.

Limitations: Drawback of this study was the small number of EoE patients in studied subjects, which could be attributed to the disease is not common.

Recommendations: This study recommends studying of other biomarkers with emphasize on the serum concentration of individual marker in the diagnosis EoE and monitoring changes of these biomarkers from baseline after therapy. Also, EoE should be considered as an etiology in patients with long-standing upper GIT symptoms after standard PPI therapy with stress on of multiple, different level, esophageal biopsies taken during diagnostic upper GIT endoscopy.

Finding source: None.

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical approval: Approved.

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HIGHLIGHTS

- Eosinophilic esophagitis represents unusual cause of chronic esophageal dysfunction symptoms.
- Serum biomarker for its diagnosis is required to be as an indicator and complement of histological diagnosis.
- The current study aimed to assess serum interleukin 5 as an indicator of eosinophilic esophagitis (EoE) in patients with chronic upper GIT symptoms.
- The positive relationship between the increased level of serum interleukin 5 and possibility of eosinophilic esophagitis diagnosis was reported in this study.
- However, histological diagnosis remains to be necessary and further studies are required to investigate the usage of serum interleukin 5 in follow up of and monitoring disease therapy.

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