Review Article

Eosinophilic esophagitis: absolute eosinophilic count, peak eosinophilic count, and potential biomarkers of eosinophilic degranulation products—an in-depth systematic review

Segun Odetola[1], Joseph Feulefack[2], Consolato M. Sergi[2,3]^

[1]Department of Pathology, Dorset County Hospital, Dorchester, UK; [2]Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada; [3]Anatomic Pathology Division, Children's Hospital of Eastern Ontario (CHEO), University of Ottawa, Ottawa, ON, Canada

Contributions: (I) Conception and design: CM Sergi; (II) Administrative support: CM Sergi; (III) Provision of study materials or patients: S Odetola, CM Sergi; (IV) Collection and assembly of data: S Odetola, CM Sergi; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Consolato M. Sergi, MD, PhD, MPH, FRCPC, FCAP. Full Professor of Pathology & Pediatrics, University of Alberta & Ottawa; Chief, Pediatric Pathologist, Anatomic Pathology Division, Children's Hospital of Eastern Ontario (CHEO), University of Ottawa, 401 Smyth Road, Ottawa, ON K1H 8L1 Canada; Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada. Email: csergi@cheo.on.ca.

Background: Eosinophilic esophagitis is a chronic inflammatory disorder, often relapsing. There is an increasing need to develop new alternative diagnostic and monitoring methods on a critical basis, which will provide samples through none or minimally invasive procedures. This study aims to identify and document the types and roles of potential biomarkers in eosinophilic esophagitis released by eosinophils as well as the potential relationship to the peak eosinophilic count and the degree of degranulation of *in situ* eosinophils (DGE/DGE + NDGE: degranulated eosinophils/degranulated eosinophils and non-degranulated eosinophils).

Methods: This is the first in-depth systematic review study using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) parameters involving a literature search of academic databases (PubMed, Scopus, Medline, Google Scholar, and Cochrane Database, 2011–2022) targeting specifically the eosinophilic counts and ratio, and the eosinophilic degranulation products as potential biomarkers. Data were extracted from ten selected studies and presented on a spreadsheet.

Results: The studies show the ability to detect eosinophilic and non-eosinophilic degranulation products, and absolute eosinophilic count in samples, including blood and urine, thereby serving as potential surrogates in making the diagnosis or monitoring disease progression in the future. There is an obvious paucity of studies that correlate potential biomarkers to the degree of degranulation of *in situ* eosinophils.

Conclusions: A few minimally invasive methods and biomarkers may be suggested as alternative tools in diagnosing and monitoring eosinophilic esophagitis. While there is no consensus on the clinical usefulness of these biomarkers, our critical evaluation may suggest that the eosinophilic degranulation ratio (DGE/DGE + NDGE: degranulated eosinophils/degranulated eosinophils and non-degranulated eosinophils) in the esophagus may be critical for evaluating properly these biomarkers. An increasing trend may culminate in the potential clinical use of these biomarkers evaluated not only with the peak eosinophilic count, but also with the degranulation score upon regulatory bodies' approval to monitor eosinophilic esophagitis in the future. We strongly advocate for the necessity to score the esophageal biopsies with both a peak eosinophilic count and a score of the degranulated eosinophils.

Keywords: Review; esophagitis; eosinophilic; quality; control trials

^ ORCID: 0000-0002-2779-7879.

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Introduction

Eosinophilic esophagitis is a chronic inflammatory disorder, often relapsing. It is closely associated with excessive mucosal eosinophilic infiltration due to disturbance in immunological response involving eosinophils and other inflammatory blood cells and their secretory granules. A clinicopathological diagnosis recommends that a minimum of 15 eosinophils per high-power field, among other supporting histological features, are required for the diagnosis (1,2). Current recommendations require endoscopic biopsies from at least two sites and a minimum of five biopsy fragments because of the uneven distribution of eosinophils along the esophagus (1). Other histological features that support the diagnosis include surface layering of eosinophils, eosinophilic micro-abscesses, marked basal cell hyperplasia, and potential subepithelial fibrosis of the lamina propria, which is often a rare complication of eosinophilic esophagitis with poor response to treatment (*Figure 1*). It has been shown from a study that disease severity, as well as outcome, is directly proportional to the degree of mucosal infiltration by eosinophils, and this further affirms their critical roles in eosinophilic esophagitis (3). Etiological factors have been linked with an abnormal immune response to some diets or other environmental factors. For example, a study reported that 86% of their study population had food allergies while 65% had a background history of allergic conditions like asthma (4). Reports of a complex interplay of environmental and genetic factors may result in eosinophilic degranulation in the esophagus and subsequent immune-inflammatory response that culminates in esophageal mucosal damage (5). Consequently, a good understanding of the biology of eosinophil degranulation, its biological functions, and potential inhibitors is essential for new diagnostic methods, treatment options, and disease monitoring (6), particularly considering how rural health disparities may influence prevalence data in pediatric eosinophilic esophagitis (7). In *Figure 2*, the pathogenesis of degranulation is depicted.

Clinical symptoms and signs at diagnosis vary with age from different studies. Epigastric pain was found in a study as the most common symptom and, dysphagia as the least common, while an intermediate number of patients presented with heartburn (4). In another study, food impaction and choking were the most common symptoms among a study population reporting a significant rise in eosinophilic esophagitis in Korea from 2006 to 2017 (8). There was also a reported increase in the incidence of eosinophilic esophagitis in another study population (9). Indeed, some previous studies in searching histopathologic markers of progression have been fruitful, but clinical trials have not started properly yet (10-12). Essentially, the number of studies on symptoms and their variation is very large and involves several investigations across age groups and the readers may consider evaluate some recent references (9,11,13-19). Now, diagnosis and monitoring require invasive procedures like endoscopy. This poses a potential risk of complications and cost implications for these patients and the national government or healthcare providers. This is made worse due to the need for repeating endoscopic procedures for disease monitoring to assess the degree of response to treatment. Consequently, there is an increasing need to develop new alternative diagnostic and monitoring methods urgently. Samples may be obtainable through minimally-invasive procedures that include body fluids like blood, urine, and mucosal secretory fluids via processes that include esophageal string tests, cytosponge, trans-nasal endoscopy, and endoFLIP (20,21). It is important to emphasize that some procedures may be considered invasive in specific age groups. For this

Highlight box

Key findings

- Eosinophilic degranulation ratio in the esophagus may be critical for evaluating properly the biomarkers of eosinophilic esophagitis.

What is known and what is new?

- Eosinophilic esophagitis is a challenging relapsing disease.
- A few minimally invasive methods and biomarkers may be suggested as alternative tools in diagnosing and monitoring this esophagitis.

What is the implication, and what should change now?

- Potential biomarkers should be monitored using the proposed eosinophilic degranulation ratio.

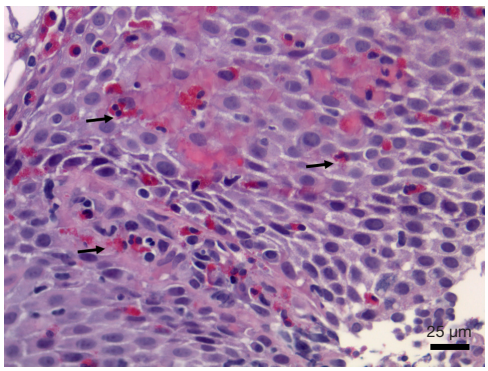

Figure 1 Microphotograph of a child with eosinophilic esophagitis showing a moderate degree of degranulation of eosinophilic granulocytes (arrows). Hematoxylin-eosin staining, ×400 original magnification; bar: 25 micrometers. Eosinophils have a diameter of 12–17 µm in fixed specimens (e.g., fixed smears). The cytoplasm of eosinophils is packed with rounded granules, which stain red on hematoxylin-eosin staining or re-orange with Romanowski stains. Eosinophil granules are of two types, including rounded granules and elongated or oval crystalloid-containing granules. Both types of granules contain an arginine- and zinc-rich basic protein, a peroxidase, and acid phosphatase. Moreover, β-glucuronidase, cathepsin, collagenase, histaminase, phospholipase B and D, and ribonuclease are also found. The ribonucleases include neurotoxin (Rnase2) and ECP. It has been found that eosinophilic granulocytes have a $T_{1/2}$ of about 4.5–8 hours in blood and they survive in the tissue for 8–12 days. ECP, eosinophilic cationic protein.

purpose, various biomarkers, including eosinophil and non-eosinophil degradation products like blood eosinophil-derived neurotoxin (EDN) and eotaxin-3, have been shown to potentially correlate with peak eosinophil counts (9). In another study, eosinophil peroxidase (EPO) sampled via esophageal brushing with subsequent assay showed sensitivity and specificity of close to 100% each when compared with peak eosinophil counts in tissue biopsies (22). These recent findings of potentially useful diagnostic and monitoring biomarkers, if replicated in other studies and approved, will hopefully help to bridge the knowledge gap in achieving non-invasive or minimally invasive methods and overcome some initial attempts or deadlocks (23-25).

This study uses a systematic approach to identify and document the types and roles of potential biomarkers in eosinophilic esophagitis, including eosinophil and non-eosinophil degranulation products, and the ratio of degranulated eosinophils over all eosinophils, including degranulated and granulated cells. Identifying and defining specific biomarkers could be a good premise to launch a search for potential inhibitors that may become useful in treating and managing eosinophilic esophagitis. These biomarkers will also be valuable tools for measuring disease activity (26). We present this article in accordance with the PRISMA reporting checklist (27) (available at https://tp.amegroups.com/article/view/10.21037/tp-23-478/rc).

Methods

This study aims to identify and discuss the potential roles of some newly described eosinophilic and non-eosinophilic degranulation products, which are primarily obtainable via non to minimally invasive methods, using a systematic review of recent studies.

Eligibility criteria and literature search

Systematic reviews are gold standards in public health, but they may not be qualified as PRISMA-based systematic reviews sometimes due to the heterogeneity of the retrieved studies. Despite the approach and the organic structure used are solid, some limitations are unavoidable and will be highlighted further below. Articles were included based on diagnostic criteria used in the study. Other inclusion criteria include new biomarkers, which can be sampled through non or minimally invasive procedures. Study designs range from cross-sectional studies to retrospective studies, and cohort studies. Studies that do not include eosinophil degranulation products or eosinophilic esophagitis were excluded. We systematically reviewed English-language articles using PubMed, Scopus, Medline, Google Scholar, and Cochrane Database with the assistance of an experienced statistician from January 2011 to December 2022. Search criteria include eosinophil*, esophagus*, degranulated, granulated, peripheral blood marker, biomarker, brush, string test, minimally invasive, semi-invasive, brush, and assay. Articles that fulfill the above inclusion criteria and contain all search elements were selected and duplicates were removed. All abstracts were retrieved and downloaded, and a further search was made to retrieve full articles that did not contain a PDF version in the initial search.

Study selection

The first author and the senior author reviewed all abstracts independently and included only articles that met all

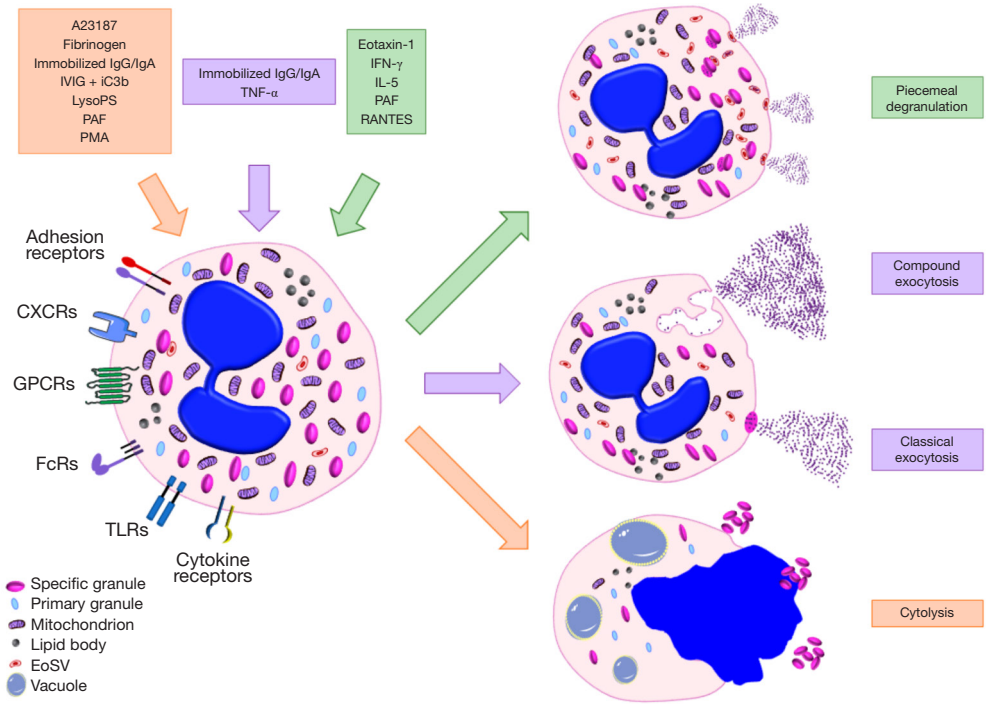

Figure 2 Schematic representation of the major mechanisms of eosinophil degranulation (reprinted from Fettrelet T, Gigon L, Karaulov A, *et al*. The Enigma of Eosinophil Degranulation. *Int J Mol Sci* 2021;22:7091). A23187, mobile ion-carrier that forms stable complexes with divalent cations, also known as calcimycin and calcium ionophore; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; iC3b, inactivated C3b, part of the complement system; LysoPS, lysophosphatidylserine; PAF, platelet-activating factor; PMA, phorbol-12-myristate-13-acetate; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma; IL-5, interleukin 5; RANTES, Regulated upon Activation, Normal T cell Expressed and Secreted (a chemokine secreted by platelets that has been activated mainly during flow conditions); CXCRs, CXC chemokine receptors; GPCRs, G protein-coupled receptors; FcRs, Fc receptors; TLRs, toll-like receptors; EoSV, eosinophilic secretory vacuoles.

inclusion criteria. All abstracts that contain non-desired items like reflux esophagitis or asthma were excluded from the study. The same authors retrieved and reviewed the full PDF copies of selected articles. All PDF copies of the articles were further examined and perused in detail. A consensus among all three authors was reached.

Data collection

We independently reviewed full PDF articles and extracted data on a Microsoft Excel spreadsheet. These data were subsequently examined, and a consensus was reached. Any discrepancy was resolved through agreement. The data spreadsheet includes names of lead authors, year of publication, age of study participants, sample size, use of control population or not, sample collection method, list of biomarkers, study design, biomarker detection method, and study outcome. Similar parameters were mostly included in other studies (28-30). *Table 1* provides the details of the studies investigated in this review.

Results

An initial search on Scopus and other online databases yielded 286 articles, out of which 20 were selected after abstract review, and these were further reviewed in full text. Consequently, ten articles were selected and included in this review.

All duplicates were removed from abstracts and full articles. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowsheet for data is presented in *Figure 3*.

Most of the articles were published in or after 2016, within the second half of our pre-approved study period.

Table 1 List of articles included in the in-depth review in alphabetical order according to the last name of the first author

Main author [year] (Ref)	Age (years), range or mean ± SD	N	Geo	Study	Ctrl.	Method	Biomarkers tested	Detection method	Statistically significant biomarkers	Outcomes
Avinashi [2020] (23)	4–17	43	Canada	CSPS	Yes	OPS, EB	EDN, EPO, MBP-1, IL-5, IL-8, IL-13	ELISA	EDN and EPO with PEC	Oropharyngeal swab assay not useful for diagnosis or monitoring
Carrasco [2017] (4)	1–14	14	Brazil	CSPS	No	EB	Eos granules	LM	Eos granules	Eos granules are present in up to 100% of EoE
Cengiz [2019] (30)	18–46	29	Turkey	CSPS	Yes	AEC, PEC	ECP	Immunoassay	ECP	ECP has high sensitivity and specificity for EoE and correlates with symptoms
Kim [2019] (8)	46.2±14.4	72	South Korean	RS	No	EB	EDN, eotaxin-3, tryptase	Immunoassay	EDN-eotaxin-3 with PEC, EDN-tryptase with EoE score	Tryptase, EDN, and eotaxin-3 levels in esophageal biopsy specimens could be promising biomarkers
Lu [2018] (31)	11.2±1.3	31	USA	CSPS	Yes	PB	HETE, AEC, cytokines	Immunoassay	HETE	Significant correlation between AEC and HETE
Peterson [2019] (29)	19–74	34	USA	Cohort	No	EB	MBP-1	IF	MBP-1	MBP-1 correlates with symptoms and may measure disease activity
Saffari [2016] (22)	n.a.	36	USA	CSPS	Yes	EB and OPS	EPO	SPA	EPO in brushings	EPO correlates with PEC; it can detect and monitor EoE activity
Schoepfer [2018] (32)	43.5±15.7	200	Switzerland	CSPS	Yes	EB	Eos granules	LM	Eos granules	Eos degranulation correlates with sub-epithelial Eos count and disease activity
Sridhara [2012] (33)	22–47	30	USA	RS	Yes	EB	EDN, MBP-1, tryptase	IF	Tryptase	Tryptase was higher in EoE than GERD and BE, unlike EDN/MBP-1
Wechsler [2021] (34)	8.8	41	USA	Cohort	Yes	Blood, urine	EDN, MBP-1, AEC	ELISA	AEC, CLC/GAL-10, ECP, EDN, OPN, MBP-1	AEC, CLC/GAL-10, ECP, EDN, OPN, and MBP-1 are superior to AEC alone in the diagnosis of EoE

SD, standard deviation; n.a., not available; Geo, geographical area; CSPS, cross-sectional prospective study; RS, retrospective study; Ctrl., controls; OPS, oropharyngeal swab; EB, endoscopic (esophageal) biopsy; AEC, absolute eosinophilic count; PEC, peak eosinophilic count; PB, peripheral blood; EDN, eosinophil derived neurotoxin; EPO, eosinophil peroxidase; MBP-1, major basic protein 1; IL-5, interleukin 5; IL-8, interleukin 8; IL-13, interleukin 13; ECP, eosinophilic cationic protein; HETE, 15(S)-hydroxyeicosatetraenoic acid; ELISA, enzyme-linked immunosorbent assay; LM, light microscopy; IF, immunofluorescence; SPA, spectrophotometric absorbance; EoE, eosinophilic esophagitis; Eos, eosinophilic; CLC/GAL-10, Charcot-Leyden crystal protein/galectin-10; OPN, osteopontin; GERD, gastro-esophageal reflux disease; BE, Barrett esophagitis.

Four of the studies were done in a pediatric population, five in the adult population, and one did not mention the age group of the study population in detail. Sample collection methods range from esophageal biopsies, combined esophageal biopsy and oropharyngeal swab, combined esophageal biopsy, and brushing, peripheral blood, a combination of esophageal biopsy, blood, and swab, and a combination of blood and urine (*Table 1*).

Most of the studies involved using controls (9 out of 10), while only one did not include the use of the control population. EDN and major basic protein 1 (MBP-1) were the most common biomarkers tested (4). EPO was tested in two studies, while other studies involved various combinations of multiple biomarkers, including absolute eosinophil count (AEC), eotaxin-3, eosinophilic cationic protein (ECP), and un-specified granule proteins. Immunoassay/immunofluorescence was the preferred method for biomarker measurement (4), two studies each used the ELISA method, and one was through spectrophotometry. *Figure 4* shows the frequency of

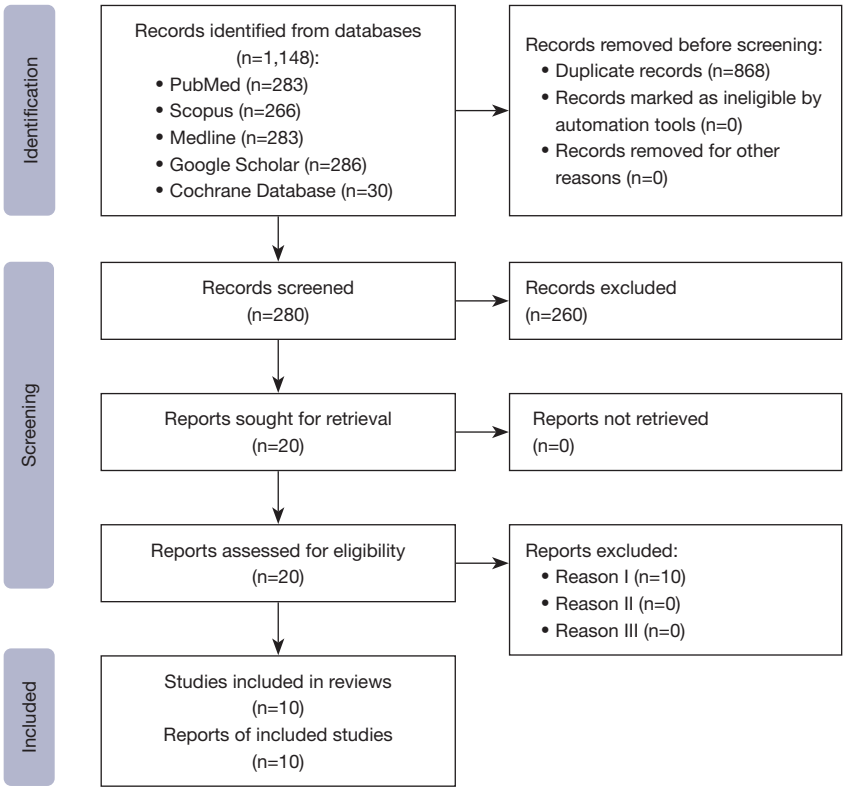

Figure 3 Flow diagram of the search process, including the outcomes from various data sources. The reasons for excluding articles were categorized into three groups. These are the reasons from most to least common: (I) being considered low or unsatisfactory quality; (II) being irrelevant to the main subject; (III) others, including the studies were not RCT, or the designed protocols were different from the traditional one, or the outcome evaluation methods were different, or there was loss of quantitative data, or occurrence of repetitive publications, or language limitations. RCT, randomized controlled trial.

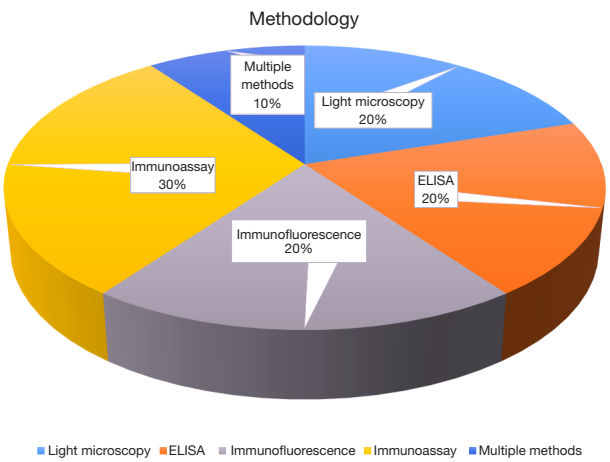

Figure 4 Frequency of detection methods by articles reviewed (see text for details). ELISA, enzyme-linked immunosorbent assay.

detection methods by articles reviewed.

Study outcome varies based on the type of biomarker tested for and if there was a test of association or significance and the interest in the literature is depicted (*Figures 5*,*6*). In one study, oropharyngeal swab biomarker testing for EPO, MBP-1, and EDN showed no significant correlation with peak eosinophil count, unlike when these biomarkers were assayed from samples that were obtained from esophageal mucosal biopsies. Some of the other studies showed their ability to detect eosinophil and non-eosinophil degranulation products, including blood/urine MBP-1, EDN, ECP, 15(S)-hydroxyeicosatetraenoic acid [15(S)-HETE], EPO, and absolute eosinophil count, thereby serving as potential surrogates in making a diagnosis or monitoring disease progression. In particular, 15(S)-HETE

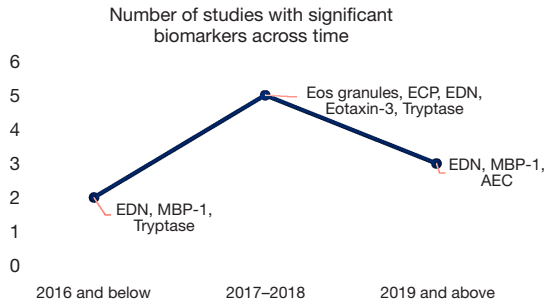

Figure 5 Number of studies with significant biomarkers over time (see text for details). AEC, absolute eosinophil count; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; MBP-1, major basic protein 1.

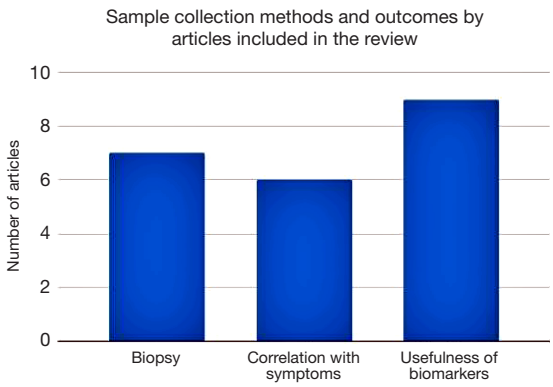

Figure 6 Interest in biomarkers identified in the examined databases over time (see text for details).

may participate in the dysregulated immune response which characterizes eosinophilic esophagitis. However, 15(S)-HETE alone is no better than AEC and Th2 cytokines as a noninvasive means to distinguish eosinophilic esophagitis from other gastrointestinal conditions. There may be some role for this novel marker in combination with other peripheral markers, such as EDN, eotaxin-3, and IL-13, in the diagnosis and management of eosinophilic esophagitis (31). The prediction of histologic changes with biomarkers and subepithelial remodelling may be quite challenging (32-34).

In another study, a random combination of any of these biomarkers with peripheral blood AEC was superior to only AEC (8). This combined method distinguishes successfully eosinophilic esophagitis from controls and correlates with histologic peak esophageal eosinophil counts (8). Similarly, MBP-1 shows a predictive role in diagnosis, unlike eotaxin-3, which was predictive of disease progression, and these findings further strengthen the need for a combination of biomarkers to be able to achieve positive multiplicative advantage (8,9). In a study, although the use of oropharyngeal swabs to collect samples for biomarker assay was easy and convenient, there was no evidence of a correlation between oral or oropharyngeal biomarkers and peak eosinophil count in the esophageal biopsy (23).

Quality assessment

Among different paper evaluation systems (JADAD, Delphi, CONSORT, and Cochrane Collaboration), we opted for the systematic review method with an "*ad hoc*" assessment. Differences in baseline features between groups, identification of allocation concealment, and dropout rates were used to evaluate the study quality. All included studies were considered harboring a satisfactory quality. All included studies were properly part of this systematic review.

Discussion

Eosinophilic esophagitis remains a puzzling disease that strongly needs further clarification on biomarkers and clinical standpoints (2,10-12,35-37). Although recently characterized as a distinct disease entity, eosinophilic esophagitis has held increasing incidence, especially in countries where it was previously described as a rarity. There is a disproportionately higher incidence in urban compared to rural areas. A study has suggested unequal distribution and easy accessibility of healthcare services as possible reasons (7). Kim *et al.* reported a significant rise in eosinophilic esophagitis in Korea from 2006 to 2017 (8). There was also a reported increase in the incidence of eosinophilic esophagitis in another study population (9). Our previous studies in searching histopathologic markers of progression have been fruitful, but clinical trials have not properly started yet (10-12). The utility to explore non-invasive diagnostic markers and monitoring tools for eosinophilic esophagitis has also been recently emphasized in a study on the age variation of eosinophilic esophagitis. The clinical presentation of this disease varies among different age groups, but the diagnostic criteria and therapeutic goals remain similar for both pediatric and adult groups (38). Ten studies were selected from an initial search of 286 based on the chosen criteria. The tested biomarkers include eosinophilic and non-eosinophilic granule proteins, AEC, and peak eosinophil count. Most

studies that tested for blood, serum, and urine biomarkers found a significant association with clinical status or peak eosinophil count. However, another study on oropharyngeal swab biomarkers showed no association with clinical level or peak eosinophil count. Following diagnosis, treatment methods vary, from dietary restriction to antibodies against eosinophil degranulation and inflammatory products. A study demonstrates significant disease control, clinically and histologically, by treating with steroid fluticasone propionate (24). Another study reported that an antibody to IL-5, mepolizumab, reduced intraepithelial eosinophils and improved endoscopic and histological findings among children with eosinophilic esophagitis (25).

Our study has identified preliminary findings through a systematic review of the most recent articles on using minimally invasive methods and biomarkers that may be useful as alternative tools in diagnosing and monitoring eosinophilic esophagitis. A few minimally invasive techniques and biomarkers may be helpful as alternative tools in diagnosing and monitoring eosinophilic esophagitis. While there is no consensus on the clinical usefulness of these biomarkers and sampling methods, our review has identified a paucity of *in situ* eosinophilic scores. We suggest that the degranulation ratio (DGE/DGE + NDGE) may be critical for evaluating these biomarkers. An increasing trend may culminate in the potential clinical use of clinical biomarkers upon approval by regulatory bodies in making future diagnoses. Our study affirms a recent surge in studies that seek to discover and characterize specific biomarkers and minimally invasive sample collection methods, as more than half of our reviewed articles were published in the most recent 6 years. Also, more of these studies were conducted in adults than children. The three most useful biomarkers have been shown to be EDN, MBP-1, and EPO, and these are more sensitive when combined with peripheral blood absolute eosinophil count. While there is no consensus on the clinical usefulness of these biomarkers and sampling methods, this study has identified an increasing trend that may culminate in their potential clinical use, upon approval by regulatory bodies, in making or monitoring eosinophilic esophagitis in the future.

This review may not reach the level of a PRISMA-based systematic review, because the studies taken into consideration are heterogenous, as displayed in our table with geographical areas and methodology used. Nevertheless, it is a solid review that may highlight the importance of biomarkers and, probably, the necessity to score the esophageal biopsies with both a peak eosinophilic count and a score of the degranulated eosinophils (degranulated eosinophils/degranulated eosinophils and granulated eosinophils). It is well known that there is a (I) risk of bias common to several studies, such as lack of blinding for subjective outcomes or unavailability of comprehensive data; (II) inconsistency of association or effect, as shown by high heterogeneity; (III) imprecision due to small sample size (the inclusion of such studies may be questionable, but there are numerous publications advocating to not eliminate studies only because the events under examination are few); (IV) indirectness of the clear-cut evidence, such as use of an intermediate or short-term outcome; and (V) likelihood of publication bias, as stated in Clarivate or Scopus guidelines. These limitations are paramount factors used to evaluate the level of evidence, but they may also be imperfect.

Conclusions

Overall, several identified clinically useful biomarkers and minimally invasive methods exist. Eosinophils and their products are more concentrated in tissues from esophageal biopsies than in body fluids and non-esophageal mucosal tissue, where they are often present in lower but assay-detectable concentrations. There is a need for more studies to improve our understanding of the proper monitoring of this disease. We confirm the clinical utilities of these biomarkers and minimally invasive methods in our quest to ease patients' discomfort and save costs. Currently, there is a necessity to advance research optimizing diagnostic strategies, tailoring therapeutical approaches, safely monitoring of patients no matter the age is, and improve long-term outcomes trying to avoid the rare postulated fibrosis of the submucosa with unavoidable chronicity of the disease. We strongly advocate for the necessity to score the esophageal biopsies with both a peak eosinophilic count and a score of the degranulated eosinophils (degranulated eosinophils/degranulated eosinophils and granulated eosinophils) and having an experienced gastrointestinal pathologist is probably crucial for further evaluation of potential biomarkers in blood.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-478/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-478/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-478/coif). C.M.S. serves as an unpaid editorial board member of *Translational Pediatrics* from March 2022 to February 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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