Eosinophilic esophagitis (EoE) is one of the most prevalent inflammatory disorders of the esophagus and is associated with dysregulated immune responses to ingested food products including milk, egg, and wheat. The esophagus of EoE shows several characteristic endoscopic features including linear furrows and mucosal rings, and extensive infiltration of eosinophils and epithelial hyperplasia are typically observed by pathologic examination. Patients with EoE experience dysphagia, food impaction, and disease anxiety, which significantly affect quality of life of patients and their families. The diagnosis of EoE is established by clinical symptoms of esophageal dysfunction and esophageal eosinophilia ≥ 15 eosinophils per high-power field (eos/hpf). Therefore, both initial diagnosis and histologic response to therapy can only be made through pathologic assessment of endoscopic biopsies. On the other hand, risks associated with esophagogastroduodenoscopy and requirements for procedural sedation/anesthesia result in increased health care costs and potential morbidity. Because eosinophilic inflammation in the esophagus is “patchy” in EoE, even multiple biopsies may not yield accurate results that reflect disease activity. The long-term requirement for invasive monitoring has spurred considerable efforts among clinicians and investigators in allergy/immunology and gastroenterology to identify alternative biomarkers to assess tissue infiltration of eosinophils.

The past effort to identify noninvasive biomarkers for EoE has resulted in limited success. One of the major obstacles is that the inflammatory response in EoE is largely confined to the esophagus. The peripheral blood absolute eosinophil count is the most widely investigated noninvasive biomarker of EoE; however, its diagnostic accuracy is relatively poor, in part because it is elevated in other allergic disorders such as asthma and atopic dermatitis. These diseases commonly occur as comorbidities in EoE. Similar investigations of the circulating levels of eosinophil granule proteins, including major basic protein (MBP), eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase (EPX), have yielded mixed results. Flow-cytometry-based assays assessing eosinophil cell surface markers or eosinophil progenitors in peripheral blood are promising but labor intensive. The minimally invasive approaches nearest to clinical implementation (eg, esophageal string test and Cytosponge [Medtronic, Dublin, Ireland]) sample the esophagus directly without endoscopy and analyze eosinophils and their granule proteins in the specimens histologically or by using immunoassays, which require specific reagents and tools.

To fill these major gaps in our knowledge, the study by Saffari et al in this issue of Mayo Clinic Proceedings describes a totally novel and interdisciplinary approach to diagnosis of EoE by combining expertise in nuclear medicine, biochemistry, gastroenterology, and allergy/immunology. MBP is the most abundant constituent of the eosinophil secondary granule and is implicated in the pathology of various eosinophilic disorders through its cytotoxic activities. MBP binds avidly to heparin by the charge and carbohydrate/lectin interactions. Indeed, Saffari et al previously showed binding of 99mTc-heparin to esophageal biopsy tissues obtained from patients with EoE ex vivo. They also demonstrated that eosinophilic inflammation can be quantified by single-photon emission computed tomography (SPECT) imaging of the biopsy specimens. The current study in this issue represents the first attempt to
apply this novel methodology in vivo in subjects with EoE.

A major benefit of nuclear imaging for EoE is the opportunity to assess the full length of the esophagus. As discussed, eosinophil infiltration in EoE is patchy, and multiple endoscopic biopsies are required to ensure adequate diagnostic sensitivity.\(^\text{15}\) Swallowing of \(^{99m}\text{Tc}\)-heparin circumvents this challenge and allows the operators to scan the entire esophagus for binding of the tracer to the tissues. Another major strength of the authors’ approach is that it accounts for eosinophil degranulation in addition to quantifying intact tissue eosinophils. Electron microscopy studies suggest that a majority of tissue eosinophils undergo cytolytic disruption in EoE,\(^\text{16}\) raising a concern that counting of intact eosinophils by histologic examination may underestimate the magnitude of eosinophilic inflammation. Indeed, assessment of eosinophil granule protein staining for EPX\(^\text{17}\) and MBP\(^\text{18}\) has been shown to correlate better with clinical symptoms than peak eosinophil counts. Some subjects may have granule protein deposition in the near absence of tissue eosinophilia.\(^\text{19}\) Here, the authors use a scoring system that evaluates immunofluorescent staining for MBP and its correlation with esophageal binding of \(^{99m}\text{Tc}\)-heparin. Despite a small sample size, they show strong correlations between MBP staining and radioactivity counts. Furthermore, \(^{99m}\text{Tc}\)-heparin binding was observed in the proximal region of the esophagus of an EoE subject (Subject 2 in the paper) in whom deposition of MBP was detected by immunostaining despite the lack of intact eosinophils by histology. These observations support the conclusion by the authors that the use of swallowed \(^{99m}\text{Tc}\)-heparin may aid in assessing eosinophil-related inflammation in the esophagus.

This study has certain limitations. As recognized by the authors, all subjects were male, and the sample size is small, limiting the range and distribution of eosinophil counts used to generate correlations. EoE symptoms were not assessed in order to determine the correlation between clinical severity and SPECT radiation counts. Moreover, the specificity of the heparin-MBP interaction requires some consideration, as heparin also binds to a number of other enzymes, cytokines, adhesion molecules, and proteases, including mast cell tryptase.\(^\text{20}\) Of note, nonspecific interactions with tryptase may present a unique advantage, as recent studies suggest that mast cells contribute to EoE disease pathology in the absence of prominent tissue eosinophilia.\(^\text{21}\)

One of disadvantages of any noninvasive biomarkers of EoE is that the assessment and medical intervention cannot be performed simultaneously. A number of patients with EoE may have esophageal narrowing/strictures or food impaction requiring dilation or endoscopic intervention. In addition, other causes of tissue eosinophilia (parasitic infection, celiac disease, connective tissue disorders) must be excluded to establish the diagnosis.\(^\text{4}\) As a result, most minimally invasive approaches are probably best suited for surveillance of disease and/or follow-up studies of clinical responses to dietary, pharmacologic, and biologic interventions. Another consideration is the added risk of radiation exposure. The average effective dose of radiation reported by the authors is 24.86 mSv. This is the equivalent of approximately 250 chest x-rays (0.1 mSv) or 3.5 chest CT scans (7 mSv). On average, a patient with EoE may undergo 3 endoscopies within a 4- to 6-month period at the time of initial diagnosis. As a result, substituting nuclear imaging for the current standard of care may increase the cumulative risk for radiation exposure.\(^\text{22}\) Similarly, application of nuclear imaging in pediatric patients with EoE needs some consideration.\(^\text{23}\) The authors are fully aware of these exposure issues, and, as discussed in their paper, use of a formulation with higher ratios of \(^{99m}\text{Tc}\)-labeled and unlabeled heparin may decrease overall \(^{99m}\text{Tc}\) dose substantially.

In summary, nuclear imaging is promising as a novel and useful clinical tool to obviate the need for surveillance endoscopy for EoE. Larger studies including more controls (eg, gastroesophageal reflux disease,
inactive EoE, and motility disorders) spanning a broad range of eosinophil counts and clinical severity are needed to validate this approach. These studies should also include assessment of validated patient-reported outcome measures for symptoms. Health care costs and the risks associated with exposure to radiation will likely be important considerations in identifying which patients are most likely to benefit from this mode of diagnosis.

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REFERENCES