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TRANSLATIONAL MEDICINE: BENCH TO BEDSIDE

Novel Tools, Biomarkers, and Disease Entities in Esophageal Disorders

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Esophageal Mucosal Impedance: A Biomarker of Eosinophilic Esophagitis Activity

Through-the-scope mucosal impedance (MI) testing to measure transepithelial resistance and permeability is gaining widespread interest among the esophageal community. Prior studies report lower MIs in gastroesophageal reflux disease (GERD); similarly, increased epithelial permeability is a postulated mechanism in eosinophilic esophagitis (EoE). Katzka, *et al.* examined MI's ability to predict EoE activity in a recent prospective study of 10 active EoE cases, defined as >15 eosinophils per high per field, 10 inactive EoE cases, and 10 control cases. Those with active EoE had lower overall and site-specific esophageal MI compared with inactive EoE and control cases. A cutoff impedance value of 2300 Ω yielded a 90% sensitivity and 91% specificity in determining disease activity. MI had a strong inverse relationship with both eosinophilia and dilated intracellular space score.[1]

These results support prior notions of abnormal esophageal epithelial permeability in active EoE and suggest that MI reliably distinguishes between disease activity. The question remains, is there a role for MI in EoE surveillance and management? Compared with the current standard of multiple esophageal biopsies, MI offers a time-efficient and seemingly cost-effective mechanism to gauge site-specific disease activity. We should consider using MI as an adjunctive tool in the surveillance of EoE activity; in time, MI may conceivably replace the role of histologic surveillance in guidelines. Still, MI's through-the-scope application does not obviate the need for endoscopy and a reliable office-based non-endoscopic tool to assess EoE activity is needed. In addition, the prognostic implications of MI results are unknown.

Functional Lumen Imaging Probe Topography: Not Just Another Colorful Tool

Currently, achalasia is defined by an elevated lower esophageal sphincter relaxation pressure and classified into three distinct subtypes (type I—100% failed peristalsis, type II—100% failed peristalsis with panesophageal pressurization, and type III —$\geq$20% swallows with premature contractions), with prognostic implications (type II having the best and type III having the worst therapeutic response).[2] Although esophageal manometry is the gold standard for diagnosis, its lack of catheter-contact pressure may limit detection of esophageal contractility. The functional lumen imaging probe (FLIP) utilizes impedance planimetry channels in a distensible bag to measure luminal cross-sectional areas and distensibility during controlled volumetric distension. In the esophagus, FLIP has been used to evaluate esophagogastric junction distensibility to guide treatment of achalasia and esophageal body distensibility as a prognostic marker in EoE.[4] The generation of color-coded FLIP topography plots with corresponding plots of volume distension and intrabag pressure over time has additionally enabled visualization of esophageal body contractility.[3]

Recently, Carlson *et al.* reported findings of FLIP topography of 51 achalasia patients, subtyped manometrically, and 10 normals. All normals manifested contractions. Unexpectedly, only 74% of type I cases had absent contractility and FLIP detected contractility in 26% of type I cases (13% occlusive and 13% non-occlusive). Contractile patterns were mixed for type II cases (31% non-occlusive, 35% occlusive, and 34% absent). All type III cases had contractility (70% occlusive) and frequently manifested repetitive retrograde contractions.[5] One type I patient who surprisingly demonstrated contractility with both repetitive antegrade and retrograde contractions on FLIP completely responded to pneumatic dilation. On the contrary, a type II patient with

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absent contractility on FLIP continues to experience dysphagia despite myotomy and pneumatic dilations. In both these examples FLIP outperformed manometry in detecting esophageal contractility. This study compellingly reports FLIP's ability to provide novel information about esophageal contractility, which may be a prognostic marker of post treatment peristaltic recovery. As our standard tools may incompletely characterize esophageal function, we should consider adding FLIP topography to our armamentarium of diagnostic tests in the pretreatment assessment of achalasia.

Dysmotility Associated Lymphocytic Esophagitis: A New Clinicopathologic Disorder

Lymphocytic esophagitis (LE) describes the histologic pattern of large number of esophageal intraepithelial lymphocytes (IEL) in a peripapillary distribution with no significant population of granulocytes, as opposed to reflux, infectious, or eosinophilic esophagitis. Although initially described a decade ago, the mechanism and clinical significance of LE remains elusive.[6] Generally, LE is considered a benign disorder and few studies have suggested an association between LE and autoimmune disorders. Dysphagia is reportedly the most common presenting symptom in LE; however, the causal relationship between these two is unknown.[6–9]

Xue *et al*. recently conducted a retrospective cohort study to characterize LE clinically, histologically, and immunophenotypically through a comparison of LE patients with no granulocytes ($n=21$), LE with few granulocytes, ($n=24$) and a "control" group of patients with reflux esophagitis and increased IEL (reflux esophagitis and increased IEL (REIL), $n=28$). The majority (76%) of LE patients demonstrated primary esophageal motility abnormalities on motility studies compared with only 54% of REIL patients. Across all three groups, CD4 as opposed to CD8 predominant IEL cases had a higher prevalence of esophageal dysmotility (nutcracker esophagus, diffuse esophageal spasm, hypercontractile esophagus, and ineffective motility).[10]

On the basis of these findings, the authors propose a new clinicopathologic entity, "dysmotility-associated LE", to describe the association between CD4 predominant IEL and primary motility disorders. This study suggests the pathogenesis of primary motility disorders to be CD4 T-cell mediated, offering potential for future investigation, and therapeutic intervention. Work is still needed to determine whether LE is an independent clinical entity or a non-specific response to esophageal injury. At present time, clinicians should consider dysmotility-associated LE and pursue motility testing in patients presenting with dysphagia and increased IEL without granulocyte predominance.

Pepsin: A Quick Office-based Test for the Detection of Gastroesophageal Reflux?

Pepsin is secreted as pepsinogen solely from gastric chief cells, and its presence in the esophagus or hypopharynx is considered to be a marker of gastroesophageal reflux. A lateral flow device to detect salivary pepsin has been developed as a quick non-invasive office-based tool to diagnose GERD. Small-scale studies report that salivary pepsin concentrations discriminate between controls and patients with esophageal and extra-esophageal symptoms of reflux; however, the optimal sampling protocol and normative thresholds remain unclear.[11] Currently, clinicians are reluctant to rely on salivary pepsin over the mainstay combination of diagnostic tools and empiric medical therapies to confirm or reject a diagnosis of GERD.

Hayat *et al*. recently assessed 24-h pH impedance and salivary pepsin samples (on waking, 1 h post lunch, and 1 h post dinner) in 87 controls and 111 subjects with heartburn. Overall, heartburn subjects were more likely to have at least one positive sample and a higher pepsin concentration compared with controls. Separated by pH monitoring, the majority with GERD and esophageal hypersensitivity had at least one positive sample compared with only a third of subjects with functional heartburn. Similarly, high pepsin concentrations were seen in GERD and esophageal hypersensitivity cases, whereas concentrations were low and similar to controls in functional heartburn cases. Thus, salivary pepsin uniquely discriminated between cases of GERD, esophageal hypersensitivity, and functional heartburn. In addition, postprandial pepsin concentrations were higher and more discriminatory compared with morning samples. The authors report a high specificity and positive predictive value ($>94.5\%$) when using a salivary pepsin concentration threshold of >210 ng/ml.[12] Although unlikely that salivary pepsin sampling will suffice as a stand-alone diagnostic tool, the prospect of an office-based quick inexpensive test to supplement other diagnostic data, such as response to therapy or results of pH-metry, is attractive and may help guide complex management decisions.

CONFLICT OF INTEREST

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