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DIAGNOSTIC DELAY IN EOSINOPHILIC ESOPHAGITIS: CAUSES, CLINICAL CONSEQUENCES AND OPPORTUNITIES FOR EARLIER RECOGNITION - A NARRATIVE REVIEW

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ABSTRACT

Background and Objective: Diagnostic delay in eosinophilic esophagitis (EoE) is a significant clinical problem associated with an increased risk of fibrostenotic changes in the esophagus. This review aimed to assess diagnostic delay, its associated factors, clinical consequences, and opportunities for earlier diagnosis of the disease.
Methods: A narrative review of PubMed/MEDLINE literature published between 2007 and 2026 was conducted. The analyzed studies addressed the time to diagnosis, patient- and healthcare-related factors, fibrostenotic progression, and diagnostic practices.
Results: Studies showed considerable variation in diagnostic delay, sometimes exceeding ten years. Associated factors included normalization of chronic symptoms, adaptive eating behaviors, delayed healthcare seeking, misdiagnoses, and insufficient esophageal biopsies. A longer time to diagnosis was associated with a higher incidence of fibrostenotic changes, particularly esophageal strictures. Potential strategies for earlier diagnosis included, among others, active assessment of dysphagia, appropriate evaluation of food impaction, adherence to biopsy protocols, and continuity of care.
Conclusions: The multifactorial nature of diagnostic delay in EoE requires consideration of both patient-related factors and abnormalities occurring at subsequent stages of the diagnostic process. A longer diagnostic delay is associated with a higher prevalence of fibrostenotic esophageal changes. However, available studies do not unequivocally confirm a cause-and-effect relationship. Prospective studies are needed to evaluate the effectiveness of strategies for earlier diagnosis and their impact on the risk of complications.

KEYWORDS

Eosinophilic Esophagitis, Diagnostic Delay, Delayed Diagnosis, Fibrostenotic Progression, Esophageal Strictures

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1. Introduction

1.1 Eosinophilic Esophagitis: Definition, Epidemiology and Clinical Significance

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease of the esophagus characterized by functional disturbances and the presence of an inflammatory infiltrate with a predominance of eosinophils in the mucosa. A key component of the disease's pathophysiology is a type 2 immune response, associated, among other factors, with exposure to allergens and impaired epithelial barrier integrity. The diagnosis of EoE is based on the coexistence of symptoms of esophageal dysfunction and the presence of at least 15 eosinophils per high-power field on histopathological examination, after ruling out other potential causes of esophageal eosinophilia [1]. In recent years, a steady increase in the incidence and prevalence of EoE has been observed, making this condition an increasingly significant clinical challenge. Epidemiological analyses demonstrate a rising number of diagnoses across various populations, although the rates vary geographically [2]. A European meta-analysis, which included 25 studies, showed that the increase in incidence exceeded the increase in the number of endoscopies performed. This suggests that the observed trends are not entirely due to improved access to diagnostic testing but may reflect a genuine increase in the prevalence of the disease [3]. EoE affects both adults and children, although the clinical presentation differs between these age groups. Younger patients are more likely to experience vomiting and abdominal pain, and feeding difficulties. In adolescents and adults, the most commonly reported symptoms are dysphagia and episodes of food impaction. The nonspecific nature of some of these symptoms can make early diagnosis of the disease difficult [1]. In clinical practice, the significance of EoE extends beyond swallowing difficulties. Chronic symptoms, the need to modify dietary habits, and social or emotional limitations all contribute to a significant reduction in patients' quality of life. Symptom severity and psychological factors are important determinants of health-related quality of life [4]. Persistent inflammation can lead to remodeling of the esophageal wall, fibrosis, and, consequently, the development of strictures, which increases the risk of long-term complications. The chronic and potentially progressive nature of this condition underscores the importance of early diagnosis and monitoring of its course [1,4].

1.2 Pathophysiology and Natural History of EoE

The pathogenesis of eosinophilic esophagitis (EoE) results from the coexistence of impaired epithelial barrier function and a chronic type 2 immune response, in which Th2 lymphocytes play a significant role. Disruption of epithelial integrity facilitates the penetration of antigens into deeper layers of the mucosa, leading to the activation of inflammatory mechanisms. The resulting inflammatory process, in turn, exacerbates damage to the epithelial barrier, contributing to the development of a mechanism that sustains and intensifies the course of the disease [5,6]. The cytokines IL-4, IL-5, and IL-13 play a significant role in the pathogenesis of EoE by regulating the inflammatory response. IL-4 helps maintain a Th2-type immune response, while IL-5 is responsible for controlling the maturation, survival, and function of eosinophils. IL-13 is of particular importance, as it stimulates the expression of eotaxin-3, which contributes to the influx of eosinophils into the esophageal mucosa and also influences the activity of epithelial cells. Molecular studies have demonstrated that IL-13 induces gene expression changes characteristic of EoE, indicating its significant role in both initiating and sustaining the inflammatory process [7,8]. Chronic eosinophilic infiltration leads to both local tissue damage and gradual tissue remodeling. Mediators released during the inflammatory process, including transforming growth factor β (TGF-β), stimulate the activity of fibroblasts and myofibroblasts, contributing to the excessive accumulation of extracellular matrix components. Consequently, subepithelial fibrosis develops, structural changes occur within the muscular layer, and the elasticity of the esophageal wall is gradually reduced. These changes can result in esophageal motility disorders, the formation of esophageal rings, and the development of strictures that impede the passage of food [6,9]. The clinical course of EoE consists of two main phenotypes: the inflammatory phenotype, in which an active inflammatory process of the mucosa predominates, and the fibrostenotic phenotype, associated primarily with established structural changes within the esophagus. The inflammatory phenotype is more common in children, whereas features of fibrosis and esophageal stenosis are more frequently observed in adults. These observations suggest that the disease may lead to progressive tissue remodeling over time; however, its course varies from person to person, and not every patient develops structural changes [10,11]. The course of EoE is significantly influenced by the duration of active inflammation that is not adequately controlled. Results from observational studies indicate that a prolonged period of untreated disease increases the risk of developing strictures and other changes resulting from esophageal tissue remodeling. This process can progress gradually over many years, even when the severity of symptoms remains relatively stable. Therefore, the duration of the disease is of significant importance in assessing its long-term outcomes and determining the possible consequences of delayed diagnosis [10,11,12].

1.3 Clinical Presentation and Diagnosis

The clinical presentation of EoE is highly variable, and the symptoms that occur depend largely on the patient's age. In infants and young children, nonspecific symptoms predominate, such as feeding difficulties, food refusal, vomiting, abdominal pain, and symptoms resembling those of gastroesophageal reflux disease. Abnormal weight gain is observed in some patients. In older children and adults, symptoms directly related to esophageal dysfunction are more common, primarily dysphagia when eating solid foods and episodes of food impaction [4,13]. Among adolescents and adults, dysphagia is one of the most common symptoms of eosinophilic esophagitis. However, the severity of this symptom does not always correspond to the actual stage of the inflammatory process or the presence of structural changes. Patients often develop strategies to make eating easier, such as chewing for a long time, drinking while eating, or avoiding foods with a hard texture. Adjusting eating habits can mask symptoms and lead to an underestimation of their severity. Diagnosis is also complicated by the fact that the clinical presentation of EoE may resemble other esophageal conditions, including gastroesophageal reflux disease [3,12]. The diagnosis of EoE is based on a combination of the clinical presentation and histopathological findings, as well as the exclusion of other conditions that may cause eosinophilic infiltration of the esophagus. The primary histological criterion is the detection of at least 15 eosinophils per high-power field (≥ 15 eos/HPF) in the tissue sample. According to current guidelines, the efficacy of proton pump inhibitor therapy is not a criterion for ruling out EoE. This also means that a trial of treatment with these medications is not necessary to confirm the disease [12,14]. An important part of the diagnostic process is gastroscopy, which allows for the evaluation of the esophageal mucosa for changes typical of EoE. The most commonly reported abnormalities include annular strictures, longitudinal furrows, whitish exudates, mucosal edema, and narrowing of the esophageal lumen. It should be noted that these changes do not occur in all patients, and the macroscopic appearance of the esophagus may not deviate from normal. For this reason, a normal endoscopic finding does not rule out EoE. Due to the heterogeneous

distribution of eosinophilic infiltration, it is recommended to obtain at least six biopsies from at least two different segments of the esophagus, regardless of the presence of visible lesions [15,16]. The diagnosis of EoE involves several consecutive steps: identifying symptoms that may indicate the disease, performing an endoscopic examination, obtaining an adequate number of biopsies, and conducting a histopathological evaluation of the collected tissue. Each of these steps can affect the time it takes to reach a correct diagnosis. Delays may result, among other things, from the nonspecific nature of the symptoms, failure to consider EoE in the differential diagnosis, or insufficient biopsy material obtained during gastroscopy [4,14,16].

1.4 Diagnostic Delay in EoE and Aim of the Review

The period between the onset of the first symptoms that may suggest the disease and the establishment of a definitive diagnosis of EoE is referred to as diagnostic delay. This delay remains a significant problem despite growing clinical awareness of EoE and advances in diagnostic guidelines. Observational studies suggest that a diagnosis may not be made until several, and sometimes more than a dozen, years after the onset of symptoms. In a Swiss cohort comprising 1,152 patients, the median delay was four years, and in 32% of patients, it exceeded ten years [17]. Factors contributing to diagnostic delay include patient-related determinants and healthcare-related determinants. The first group includes, among other things, downplaying symptoms, gradually adapting dietary habits, and delaying seeking medical care. The second group includes misdiagnoses, insufficient awareness of the disease, multiple consultations with specialists, and performing endoscopic examinations without taking esophageal biopsies [18]. Chronic, untreated inflammation may predispose patients to esophageal fibrosis, the development of strictures, and episodes of food impaction. Therefore, diagnostic delay has both organizational and clinical implications [17,19]. Data regarding changes in the time to diagnosis over the years remain inconclusive. A Swiss analysis found no evidence of a significant reduction in diagnostic delay over nearly three decades [17]. In contrast, the European EoE CONNECT registry showed a significant reduction in this delay, from 12.7 years in the earliest group analyzed to 0.7 years in the group with symptom onset after 2017 [19]. The discrepancies noted above suggest the need for a comprehensive assessment of the available evidence, taking into account differences among populations, diagnostic considerations, and clinical implications. The purpose of this narrative review is to summarize the current evidence regarding the prevalence and factors contributing to diagnostic delay in EoE, to assess its clinical consequences, and to identify opportunities for earlier diagnosis of the disease.

2. Methodology

2.1 Study design and scope

This paper presents a narrative review of the literature on diagnostic delay in eosinophilic esophagitis (EoE), its causes, clinical consequences, and possibilities for earlier diagnosis of the disease. The review includes data on the duration of diagnostic delay and its changes over the years, factors related to the patient and the healthcare system, and the relationship between time to diagnosis and the development of fibrostenotic changes in the esophagus. The analysis also includes studies on diagnostic gaps, endoscopic management, and strategies to improve the diagnosis of EoE. Findings from research on the pathophysiology of EoE were used to discuss potential relationships between chronic inflammation and structural remodeling of the esophagus.

2.2 Literature search strategy

The literature review was conducted using the PubMed/MEDLINE database from July through September 2026. The following search terms were used: “eosinophilic esophagitis” AND “diagnostic delay,” “eosinophilic esophagitis” AND “delayed diagnosis,” and “eosinophilic esophagitis” AND “diagnostic challenges.” To identify publications addressing specific aspects of the topic under analysis, the search was expanded to include the terms “patient delay,” “misdiagnosis,” “dysphagia,” “adaptive eating behaviors,” “food impaction,” “esophageal biopsies,” “fibrostenotic phenotype,” “esophageal remodeling,” “strictures,” and “natural history.” The publications included in the review were published between 2007 and 2026.

2.3 Eligibility criteria

This review included peer-reviewed English-language publications on diagnostic delay in EoE, its determinants, and clinical consequences, including observational studies, cohort studies, systematic reviews, meta-analyses, and relevant narrative reviews. Studies evaluating endoscopic management, biopsy practices, patient coping strategies, and opportunities to improve the diagnostic process were also included. Publications describing the pathophysiological mechanisms of EoE were selectively used to illustrate the mechanisms of fibrosis and esophageal remodeling. Studies not directly related to the scope of the review, duplicates, and non-peer-reviewed materials were excluded.

2.4 Study selection and data synthesis

The eligible publications were analyzed in terms of study design, population characteristics, methods for defining and measuring diagnostic delay, identified risk factors, and assessed clinical outcomes. Particular attention was paid to distinguishing between delays resulting from patient behavior and those resulting from the functioning of the healthcare system, methods for determining the onset of the first symptoms, and potential confounding factors. Data on fibrostenotic changes, food impaction, and the need for esophageal dilation were also analyzed, as were opportunities to improve diagnosis. Given the methodological and clinical heterogeneity of the available studies, the results were synthesized narratively, without conducting a meta-analysis or a formal assessment of the risk of statistical error.

3. Results

3.1 Extent and Trends of Diagnostic Delay in EoE

Despite progress in the diagnosis of the disease, diagnostic delay in eosinophilic esophagitis (EoE) remains a significant clinical problem. Cohort studies highlight significant variation in the time between the onset of the first symptoms and the establishment of a diagnosis, although in some sections of the population the delay still amounts to several years. These differences relate to both mean and median values, as well as to the proportion of patients who remain undiagnosed for over a decade [17,18,19]. In the study by Murray et al., which involved 1,152 patients, the median diagnostic delay was 4 years (IQR: 1–11), and the maximum delay was 56 years. In 32 per cent of study participants, the diagnosis was not established until at least ten years after the onset of symptoms. The results also showed a correlation between age and the duration of the delay, whilst an earlier onset of symptoms was associated with a longer period of undiagnosed illness [17]. A similar phenomenon was described in a multicenter study involving 261 patients. The median total delay was 36 months (IQR: 12–88). In 57.8% of patients, the delay exceeded two years. In 41.0%, it exceeded four years, whilst in 14.9%, the delay was at least ten years. The median patient-related delay was 18 months, whilst the delay attributable to medical management was 6 months. The difference was statistically significant ($p<0.001$) [18]. In a cohort study involving 721 patients, of whom 613 had time to diagnosis that could be estimated, the mean delay was 6.6 ± 7.8 years. Significant differences were observed between adults and children, at 7.2 ± 8.3 and 3.6 ± 4.0 years respectively ($p < 0.001$). A longer delay was also observed in men than in women. Differences between age groups also concerned the clinical presentation, with vomiting and abdominal pain being observed more frequently in children, whilst dysphagia and episodes of food impaction were mainly reported in adults [20]. Contradictory findings regarding temporal trends were reported in the European EoE CONNECT registry. In an analysis involving 1,132 patients, the median delay was 2.1 years (IQR: 0.7–6.2). In the subsequent groups categorized by the date of symptom onset, a systematic shortening of this period was observed, from 12.7 years prior to 2008 to 5.0 years between 2008 and 2011, 2.8 years between 2012 and 2013, 1.2 years between 2014 and 2017, and 0.7 years after 2017 ($p < 0.001$). These changes were accompanied by a lower number of previous endoscopies that did not lead to a diagnosis [19]. A more recent analysis of the same register, which included 3,298 patients, confirmed this positive trend. Among the 2,810 individuals for whom data were available, the median delay was two years (IQR: 0–6), and regression analysis showed that the delay decreased by approximately 8.5 months for each subsequent calendar year following the onset of symptoms ($p < 0.001$). At the same time, compliance of endoscopic practice with guidelines increased, including the frequency of taking biopsies from at least two sections of the esophagus and the use of the EREFS classification [21]. However, the results of the study covering the period 1989 - 2021 did not show a significant reduction in diagnostic delay, either in the annual analysis or in relation to the publication of the landmark guidelines of 2007 and 2011. The proportion of patients with a delay of at least ten years remained relatively stable [17]. Differences between studies may be due to variations in population characteristics, the organization of healthcare, recruitment methods and the methods used to analyze trends. The grouping of patients according

to the onset of symptoms or the time of diagnosis is also significant. Although the publication of successive guidelines and increased awareness of EoE have coincided with improvements in diagnostic practice in some European centers, the available findings do not unequivocally confirm that this progress has been uniform across all populations [17,19,21].

3.2 Patient-Related Determinants of Diagnostic Delay

In eosinophilic esophagitis (EoE), patient-related factors play a significant role in diagnostic delay. The gradual onset of symptoms, their varying severity and the ability to adapt eating habits may delay the diagnosis of the condition. As a result of these factors, patients may delay seeking medical advice, despite the continued presence of symptoms of esophageal dysfunction. This mechanism and its significance are confirmed by the results of a multicenter study involving 261 patients, in which the median patient-related delay- defined as the time from symptom onset to the first medical consultation- was 18 months (IQR: 5–49) [18]. The nature of the initial symptoms plays a key role. The symptoms of EoE do not always manifest as overt dysphagia, and their clinical presentation changes with age. In a study by Warners et al., which involved 721 patients, dysphagia and episodes of food impaction were reported more frequently in adults. However, in children, the main symptoms were vomiting, regurgitation and abdominal pain ($p < 0.001$). Identifying the link between these symptoms and esophageal disease can be complicated by such non-specific manifestations, particularly in younger patients who may not necessarily be able to describe their difficulties with eating in detail [20]. In the study by Pokrzywinski et al., the importance of the patients' and carers' perspectives was highlighted. The study involved 31 people with EoE, including children, adolescents and adults, as well as 11 carers. Participants described a lengthy and often complex diagnostic journey, which was associated with difficulties with eating, limitations in daily functioning and emotional distress. In pediatric groups, the main symptoms observed were abdominal pain, refusal to eat, vomiting and reflux-like symptoms. The analysis shows that feeding problems may initially suggest behavioral issues or non-specific gastrointestinal complaints [22]. One of the typical mechanisms by which EoE is masked is the development of compensatory behaviors whilst eating. Patients may gradually lengthen the duration of their meals, chew their food more thoroughly, break it down into smaller pieces, wash down each mouthful with liquid, and avoid foods whose consistency makes them difficult to swallow. These mechanisms reduce the perception of troublesome symptoms, may help to normalize chronic dysphagia and reduce the likelihood of reporting symptoms during medical consultations [23,24]. Evidence of such behavior was provided by a study by Alexander et al., which compared 10 adult patients with active EoE, 10 patients with inactive disease and 10 individuals from the control group. Patients with active EoE took an average of 18.3 minutes to eat a standard meal, compared with 12.4 and 13.0 minutes in the other groups respectively. These patients also made more chewing movements per mouthful (32.5 compared with 26.1 and 20.8, respectively) and consumed greater quantities of fluids. They were also more likely to take sips between mouthfuls, which indicates the use of fluids as a mechanism to facilitate swallowing. Such behaviors were associated with disease activity, which was assessed endoscopically [23]. Discrepancies between the actual severity of the disease and the subjective perception of symptoms may be due to long-term adaptation. Cases in which food impaction is the first event leading to diagnosis are particularly significant. In a study by Dilaghi et al., which involved 57 adult patients, EoE was diagnosed in 19 individuals (33.3%) following such an episode. In this group, 47.4% of patients had not previously reported esophageal symptoms, compared with 2.6% of patients diagnosed without food impaction ($p = 0.0001$). The median diagnostic delay was 12 and 4 years, respectively ($p = 0.009$), despite greater endoscopic activity in the group with food impaction [24]. Demographic data show that gender and age are also significant factors. In a cohort study by Warners et al., the mean delay was longer in men than in women (7.2 versus 5.3 years; $p < 0.001$) [20]. However, in a study involving 1,092 patients, the duration of symptoms prior to diagnosis averaged 9.4 years in adults and 3.0 years in children. The longest delays were observed in individuals whose symptoms began during adolescence or early adulthood. Although differences between racial groups were observed in the unadjusted analysis, this association did not persist after adjusting for age. The results indicate the importance of age as a factor associated with the duration of the undiagnosed period [25].

3.3 Healthcare-Related Determinants of Diagnostic Delay

3.3.1 Misdiagnosis and Delayed Referral

A delay in the diagnosis of eosinophilic esophagitis (EoE) may result from an incorrect initial diagnosis, misinterpretation of symptoms, or postponement of specialist assessment. The similarity between the clinical presentation of EoE and that of gastro-esophageal reflux disease (GERD) is of significant importance. Symptoms such as heartburn, regurgitation and chest pain can make it difficult to distinguish between these conditions, as they may occur in both. Furthermore, these conditions may co-occur, meaning that a diagnosis of reflux does not rule out the presence of eosinophilic esophagitis [18,26]. The scale of the problem was demonstrated in a multicenter study involving 261 patients. Previous misdiagnoses were recorded in 109 individuals (41.8 per cent). The most common diagnoses were GERD (67 patients; 25.7 per cent) and dyspnea (12 patients; 4.6 per cent). The median physician-related delay, defined as the time from the first consultation to the establishment of the correct diagnosis, was 6 months (IQR: 1–24). At the same time, assessment by at least two doctors was significantly associated with a longer overall diagnostic delay [18]. Another important factor may be prolonged empirical treatment with proton pump inhibitors (PPIs) without subsequent assessment of the cause of persistent symptoms. In a study by Kanakala et al., which involved 37 patients, 20 individuals (54 per cent) were receiving PPIs because they were suspected of having GERD, for an average of 7.5 years. In some patients, the response to treatment was only partial, whilst others showed no improvement. In the same study, there was a delay in referral for endoscopy in 18 cases (49%) of patients with dysphagia [27]. The importance of clinical awareness is also confirmed by data on gastroenterological practice. In an American survey involving 240 doctors, only 24 per cent reported a very good knowledge of the guidelines on EoE, and only 12 per cent applied all the diagnostic criteria in force at the time. These results highlight the discrepancy between recommendations and clinical practice, which may contribute to difficulties in making an accurate diagnosis of the disease [28]. A delay in referring a patient to a gastroenterologist or for an initial endoscopy may therefore significantly prolong the diagnostic process. Particular attention should be paid to patients with chronic dysphagia, recurrent food impaction or symptoms that persist despite treatment. In such cases, reassessment of the diagnosis and timely referral for endoscopic investigation may reduce the risk of further delay [26,27].

3.3.2 Endoscopic and Biopsy-Related Diagnostic Gaps

Errors during endoscopy and when collecting samples for histopathological examination are a major cause of diagnostic delay in eosinophilic esophagitis (EoE). Performing a gastroscopy without taking a biopsy may lead to the disease being overlooked, particularly if the esophageal mucosa does not show characteristic changes. A meta-analysis involving 4,678 patients with EoE showed a normal endoscopic appearance in 17% of patients. However, in prospective studies, this proportion was 7%. Macroscopic assessment alone is not sufficient to rule out EoE, as indicated by the limited sensitivity of various endoscopic features, which ranged from 15–48% [29]. Another problem is the insufficient number of biopsies and the fact that they are taken from only one section of the esophagus. Limited tissue sampling increases the risk of false-negative results, due to the focal nature of eosinophilic infiltration. In a study by Nielsen et al., which involved 102 patients and 1,342 biopsy specimens, the probability of detecting a diagnostic eosinophilic infiltrate increased from 63 per cent with a single specimen to 98 per cent with four, and to over 99 per cent with six. These results highlight the importance of taking into account different levels of the esophagus and the number of samples. Endoscopic guidelines emphasize the need to take multiple biopsies from at least two sites, even in the absence of visible abnormalities [30,31]. An episode of food bolus impaction represents a particularly significant missed diagnostic opportunity, as it often prompts the patient to seek urgent consultation with a gastroenterologist. In practice, however, endoscopic management is often limited to the removal of the impacted food bolus, without simultaneously investigating the cause of the event. In an American retrospective study involving 91 patients, biopsies were taken during the first endoscopy in only 29 per cent of those examined, even though the endoscopic findings suggested the possibility of EoE in 41 per cent of cases. Among the 30 patients in whom EoE was ultimately confirmed, the diagnosis was not established until subsequent endoscopic examinations in 14 of them [32]. Similar findings were observed in European studies. In a cohort study involving 180 cases of food impaction, a biopsy was performed in 18 per cent of patients. However, this proportion did not increase between 2013 and 2023. Another multicenter study showed that histopathological samples were obtained during urgent endoscopy in 52% of patients, and a new diagnosis of EoE was established in 68.9% of those who underwent a biopsy [33,34]. Diagnostic gaps may persist even after treatment has been completed. In a study by Lee et al., repeat endoscopy was recommended for 63 per cent of patients with EoE confirmed at the

initial examination. However, only half of these patients underwent the procedure within 90 days. Poorly planned follow-up, particularly after an endoscopy performed without a biopsy, can delay diagnosis. Taken together, the findings indicate that adherence to biopsy protocols and ensuring continuity of care following endoscopic intervention are important factors in reducing diagnostic delays in EoE [32,34,35].

3.4 Clinical Consequences of Diagnostic Delay

3.4.1 Esophageal Remodeling and Fibrostenotic Progression

One of the most significant consequences of delayed diagnosis of eosinophilic esophagitis (EoE) is the progressive remodeling of the esophageal wall, leading to the development of fibrotic and stenotic changes. Persistent, uncontrolled inflammation contributes to the activation of reparative processes which, with prolonged stimulation, can lead to excessive deposition of extracellular matrix components and subepithelial fibrosis. These changes also occur in the deeper layers of the esophageal wall, resulting in increased stiffness and reduced elasticity. Consequently, even before a marked stricture becomes visible on endoscopy, the esophagus's ability to dilate properly during swallowing is gradually impaired [6,9]. A study by Schoepfer et al., which involved 200 patients with EoE, demonstrated a link between the duration of undiagnosed disease and the severity of structural changes. The prevalence of esophageal strictures increased from 17.2% in those with a diagnostic delay of 0-2 years to 70.8% in those with a delay of more than twenty years. At the same time, the proportion of patients with fibrotic changes increased from 46.5% to 87.5%, respectively. In the analysis of risk factors, the duration of the diagnostic delay was a significant predictor of the presence of strictures at the time of diagnosis (OR = 1.08; 95% CI: 1.040-1.122) [36]. Similar findings were reported by Dellon et al. in a retrospective analysis of 379 patients. Patients with the inflammatory phenotype were younger and had a shorter duration of symptoms than those with the mixed or fibrosing-stenotic phenotype. Each additional ten years of age was associated with more than double the likelihood of the fibrosing-stenotic phenotype (OR = 2.14; 95% CI: 1.70-2.70). These findings support the concept of a gradual progression of EoE from predominant inflammation to established structural changes [37]. A multicenter study by Singli et al. provides further evidence. In this study, patients with the fibrosing-stenotic phenotype reported a longer duration of symptoms before diagnosis than patients with the inflammatory phenotype (8.1 versus 5.3 years). During treatment, regression of fibrosing-stenotic changes was observed in some patients, associated with a reduction in esophageal eosinophilia. This suggests that tissue remodeling is not always completely irreversible [38]. Pediatric observations also confirm the importance of controlling inflammation. In a cohort study involving 166 children, the histological response at the second follow-up endoscopy correlated with a lower risk of developing fibrosing-stricturing lesions in the unadjusted analysis (HR = 0.37; 95% CI: 0.14-0.99) . However, after adjusting for confounding factors, the association did not reach statistical significance. Overall, the study findings suggest that a prolonged period of undiagnosed inflammation increases the likelihood of esophageal remodeling. However, earlier diagnosis and effective control of disease activity may limit its progression [20,39].

3.4.2 Strictures, Food Impaction and Other Clinical Outcomes

A longer interval between the onset of the first symptoms of eosinophilic esophagitis (EoE) and diagnosis is associated with an increased incidence of structural complications, primarily esophageal strictures. In a retrospective study by Schoepfer et al., which included 200 patients, the incidence of strictures increased from 17.2 per cent with a diagnostic delay of 0-2 years to 70.8 per cent with a delay exceeding 20 years ($p<0.001$). The correlation was temporal in nature, and the duration of the delay was a significant factor associated with the presence of strictures at the time of diagnosis (OR = 1.08; 95% CI: 1.040-1.122). The results show that the risk of complications increases with the duration of undiagnosed disease [36]. A similar trend was observed in a cohort study comprising 721 patients. The proportion of patients with signs of fibrosis increased from 56 per cent when the delay was no more than two years to 92 per cent when the delay was at least 21 years ($p<0.001$). At the same time, the prevalence of predominant inflammatory features decreased from 62% to 20%, respectively. The presence of strictures was associated with a higher likelihood of food impaction (OR = 1.92; 95% CI: 1.37-2.67; $p< 0.001$). Patients with recurrent episodes of food impaction were also more likely to have more severe strictures [20]. The series of six cases described by Koutlas and Dellon provides direct observations of disease progression. Among patients who initially presented with an inflammatory phenotype, after a mean of 7.8 ± 2.0 years without treatment, strictures were found in five patients (83 per cent), whilst a reduced esophageal calibre was observed in four (67 per cent). Most patients required endoscopic esophageal dilation. Owing to the small number of cases, the generalizability of the results

is limited. However, the observations document the development of clinically significant complications in previously diagnosed but untreated patients [40]. A study by LaFata et al., involving 814 patients with EoE and symptoms of food impaction, discussed the significance of food impaction. In the groups requiring consultation at the A&E department, with or without endoscopy, strictures were present in 44% and 41% of patients respectively, compared with 35% of those with spontaneously resolving symptoms (p=0.04). Esophageal rings were found in 70%, 67% and 57% of patients, respectively (p< 0.001). Following treatment with topical corticosteroids, patients with a milder course of the disease were less likely to require esophageal dilation [41]. A meta-analysis of 14 studies involving 3,116 patients with food impaction confirms the risk of recurrence. The presence of EoE was associated with a more than threefold increased likelihood of a recurrent episode (OR = 3.28; 95% CI: 2.09-5.14; p<0.001). However, no significant association was found between the timing of endoscopy during an acute episode and the occurrence of adverse events. These results do not directly concern the length of the delay, but rather recurrences of food impaction [42]. Further data are provided by the observation of 166 children with EoE. The prevalence of fibrosing-stricturing lesions was 9 per cent, 15 per cent and 16 per cent during successive endoscopic assessments. Histological response and normalization of the endoscopic findings were associated with a lower risk of such lesions in unadjusted analyses. However, these associations ceased to be statistically significant after adjusting for confounding factors [39]. Overall, the findings of the studies point to a consistent association between long-standing undiagnosed EoE and esophageal strictures. Data on episodes of food impaction and the need for dilation further emphasize the clinical significance of structural changes. However, not all studies directly assessed the impact of the time to diagnosis [20,36,41].

3.5 Opportunities for Earlier Recognition

Early diagnosis of eosinophilic esophagitis (EoE) requires the identification of symptoms indicative of esophageal dysfunction and the ruling out of other conditions at each stage of the diagnostic process. A particularly important symptom is dysphagia with solid foods, which is considered one of the most characteristic manifestations of the disease in adults. Recurrent difficulty in swallowing, even if mild or sporadic, should prompt consideration of EoE in the differential diagnosis. It is also important to determine the duration of symptoms, as patients may perceive difficulty in swallowing as a harmless complaint for many years, one that does not require medical consultation [4,17]. A targeted interview regarding swallowing disorders may help to identify symptoms that patients do not report spontaneously. Questions concerning the need to drink fluids whilst eating, prolonged mealtimes, thorough chewing, dividing food into smaller portions, and avoiding foods of a particular consistency are of particular importance. Adaptive behaviors may reduce the perceived severity of swallowing difficulties, whilst masking underlying esophageal dysfunction. The American College of Gastroenterology guidelines highlight the need for a systematic assessment of such strategies, including the use of the IMPACT questionnaire. In children, particular attention should be paid to refusal to eat, difficulties in transitioning to a diet including solid foods, and prolonged mealtimes, as these symptoms may indirectly indicate dysphagia [4,21,23]. Another key element in the early diagnosis of EoE is the re-evaluation of patients whose symptoms suggestive of gastro-esophageal reflux disease persist. The presence of heartburn and regurgitation does not rule out EoE, particularly if these symptoms are accompanied by dysphagia or the avoidance of certain foods. If symptoms persist despite anti-reflux treatment, further diagnostic investigation should be considered, rather than repeatedly continuing empirical therapy without re-evaluating the diagnosis. A survey of 228 doctors revealed that only 38.2% of respondents reported taking biopsies from patients with refractory reflux symptoms and a normal endoscopic finding, who did not experience dysphagia or episodes of food impaction. This finding indicates heterogeneity in diagnostic practice. However, it does not allow for a direct assessment of the extent to which this approach affects the time to diagnosis [4,43]. An episode of food bolus impaction presents a significant opportunity for the diagnosis of EoE. Endoscopic management should involve not only the removal of the obstruction, but also an assessment of its possible cause. In a study by Lee et al., biopsies were taken during the first endoscopy in only 29 per cent of 91 patients, even though the endoscopic findings suggested a possibility of EoE in 41 per cent of them. Of the 30 patients who were ultimately diagnosed with the condition, the diagnosis was not established until subsequent examinations in 14 cases. Similar observations were made in a cohort comprising 180 cases of food impaction, in which biopsies were taken from only 18% of patients, and this percentage did not change significantly between 2013 and 2023. These findings indicate that the diagnostic potential offered by urgent endoscopy is not being fully utilized [32,33]. Improving diagnostic accuracy requires the consistent application of appropriate biopsy protocols. Current guidelines indicate the need to obtain at least six samples from at least

two levels of the esophagus, even in the absence of characteristic changes on endoscopic examination. Standardization of the biopsy procedure may reduce the risk of missing focal eosinophilic infiltration. If a biopsy was not taken during an urgent procedure, further diagnostic management should be planned and appropriate clinical follow-up ensured. In a study by Lee et al., follow-up endoscopy was recommended for 63 per cent of patients in whom EoE was confirmed during the initial examination. However, only half of them underwent repeat endoscopy within 90 days [4,32]. The level of knowledge among doctors and adherence to diagnostic guidelines are also significant factors. Voulgaris et al. demonstrated that biopsies were taken in 47.2 per cent of 163 patients with dysphagia or food impaction. Independent factors associated with the decision to take biopsies were the patients' age and the presence of characteristic changes on endoscopic examination. Meanwhile, the results of a European survey indicate that doctors with experience in diagnosing EoE were more likely to follow current guidelines. These findings support the development of training programmes and the implementation of standardized management pathways, taking into account the assessment of alarm symptoms, indications for biopsy and the organization of further patient care [43,44]. The data presented indicate that the greatest potential for reducing diagnostic delays lies in the active identification of dysphagia and adaptive behaviors, adherence to biopsy guidelines, and ensuring further diagnostic investigation following an episode of food impaction. However, there is still a lack of prospective studies enabling a direct assessment of the extent to which specific educational and organizational interventions contribute to reducing the time to diagnosis of EoE. In the ensuing discussion, a distinction should be made between clinically justified opportunities to improve diagnosis and interventions whose effectiveness has been confirmed in studies [4,32,43].

4. Discussion

4.1 Interpretation of the Main Findings

Data from the available literature indicate that diagnostic delays in eosinophilic esophagitis result from a combination of patient-related factors and factors related to the functioning of the healthcare system, rather than from a single diagnostic error. The individual stages leading to a diagnosis are interconnected. For this reason, difficulties at one stage can exacerbate problems at subsequent stages. These interrelationships may explain why even repeated interactions with the healthcare system do not always lead to a sufficiently early diagnosis of the disease [18,22]. The patient's normalization of symptoms plays a significant role in diagnostic delay. Chronic or mild dysphagia may lead patients to perceive difficulty swallowing as an individual characteristic of their eating habits rather than a symptom requiring diagnosis. Furthermore, patients simultaneously develop adaptive behaviors, such as chewing food thoroughly, prolonging meals, or avoiding certain foods, which can further reduce the perceived discomfort without eliminating its cause. As a result, the adaptive mechanisms that facilitate patients' daily functioning may simultaneously delay the decision to seek medical help. Furthermore, ingrained habits may mask typical symptoms of the disease, making it difficult to identify them correctly during a medical consultation [19,22,45]. The actions of medical staff may contribute to further prolonging the diagnostic process. Symptoms with low specificity - resembling, among other conditions, gastroesophageal reflux disease - may lead to a diagnosis of other conditions and delay further diagnostic testing. If a patient describes symptoms as infrequent or well-controlled through dietary changes, the likelihood of including EoE in the differential diagnosis may be lower. Misdiagnoses and the omission of key diagnostic steps - including the failure to perform a biopsy during endoscopy - should therefore be viewed as interconnected stages of a single process. As a result, the time to a correct diagnosis may be prolonged, even if the patient undergoes further testing [18,21]. Interpreting changes in the duration of the diagnostic delay over the years requires taking into account the heterogeneity of the available results. A Swiss study observed a persistent significant delay, while data from the European EoE CONNECT registry indicated a marked reduction in the delay. Subsequent analyses of this registry also noted an improvement in the alignment of endoscopic practice with current guidelines. However, results obtained at specific centers should not be automatically extrapolated to the entire population of patients with EoE, as they may not reflect the situation at all healthcare facilities [17,19,21]. Discrepancies between study results may stem from differences in patient inclusion criteria, center characteristics, duration of follow-up, and the age distribution of the groups analyzed. An additional source of uncertainty is the need to retrospectively determine the onset of symptoms, which can be particularly difficult in individuals who, for a long time, considered difficulty swallowing to be a natural part of daily life. The comparability of results may also be affected by differences in access to specialized tests and the degree of adherence to diagnostic recommendations. Furthermore, one should avoid unequivocally

attributing a reduction in delay to the publication of guidelines, as the observational nature of the available data does not allow for the confirmation of a direct cause-and-effect relationship [17,19,21]. The data presented as a whole indicate that delays in the diagnosis of EoE result from the coexistence of multiple factors, including patient behavior, how physicians interpret reported symptoms, and the accuracy of the successive stages of the diagnostic process. Effectively reducing this phenomenon therefore requires a comprehensive approach that takes into account all stages leading to a diagnosis, rather than focusing solely on improving individual medical procedures [18,22,45].

4.2 Diagnostic Delay and Fibrostenotic Disease Progression

One of the best-documented aspects of the natural course of eosinophilic esophagitis is the relationship between the time to diagnosis and the presence of fibrostenotic changes. Results from studies conducted in various patient groups indicate that a prolonged period between the onset of the first symptoms and diagnosis of the disease is associated with a higher incidence of esophageal rings and strictures. These observations suggest the possibility of a gradual progression of the disease, from a form dominated by inflammatory changes to a phenotype characterized by fibrotic remodeling. It should be emphasized, however, that this process does not occur in the same way in all patients and does not necessarily occur in every case of EoE [20,36,37]. Also noteworthy is the relationship between the duration of the diagnostic delay and the prevalence of strictures. This suggests that the duration of the disease may play a significant role in the development of structural changes within the esophagus. However, one should not assume that the fibrotic process proceeds in a linear fashion, with each additional year of the disease leading to a comparable increase in lesions. Risk data reflect correlations observed in specific populations and do not allow for precise prediction of the rate of progression in an individual patient [20,36]. A potential biological explanation for this relationship involves chronic type 2 inflammation, damage to the epithelial barrier, and the activation of tissue repair processes. A prolonged inflammatory response may stimulate fibroblasts and myofibroblasts, increase the accumulation of extracellular matrix components, and lead to a gradual decrease in the elasticity of the esophageal wall. Among other factors, signaling pathways associated with transforming growth factor beta (TGF-β) are considered significant in these processes. These mechanisms provide a biologically sound basis for the link between chronic inflammation and fibrosis. However, they do not establish a direct causal relationship between diagnostic delay and the development of structural changes [6,9]. An analysis of the course of EoE must also take into account the results of prospective studies and longitudinal observations. The low rate of progression from the inflammatory phenotype to the fibrostenotic phenotype during a relatively short follow-up period in treated patients need not contradict the results of retrospective analyses, which took into account the many years preceding diagnosis. This discrepancy may reflect the importance of effective control of the inflammatory process and the differing course of the disease before and after the initiation of therapy. However, there is still insufficient evidence to unequivocally determine the extent to which treatment prevents the development or progression of fibrostenotic lesions [10,38]. When interpreting the available results, one must take into account the limitations arising from the observational nature of most studies. The observed associations may be influenced by, among other factors, the patients' age and sex, the severity of the disease, prior treatment, and the criteria used to refer patients to specialized centers. Another significant source of uncertainty is the retrospective determination of when the first symptoms appeared, which carries a risk of memory bias. This problem may be particularly significant in individuals who have long adapted their eating habits to accommodate swallowing difficulties. Consequently, the time when the first symptoms were noticed may not coincide with the onset of the inflammatory process [20, 37]. When evaluating the presented relationships, it is particularly important to distinguish between diagnostic delay and the actual duration of untreated, active disease. The former refers to the time between the reported onset of symptoms and the establishment of a diagnosis, while the latter would require objective confirmation of inflammatory activity throughout the entire period under analysis. Treating these indicators as equivalent may lead to drawing overly broad conclusions regarding causality. For this reason, a long diagnostic delay should be viewed as a significant risk factor for the development of fibrostenotic changes, while acknowledging that its direct causal effect on the development of these changes has not been unequivocally confirmed [9,10, 36].

4.3 Clinical Implications and Strategies for Earlier Recognition

Reducing the time required to diagnose eosinophilic esophagitis (EoE) requires a comprehensive approach that takes into account both patients' awareness of their symptoms and the efficiency of the diagnostic system. A thorough medical history plays a crucial role and should go beyond typical upper gastrointestinal symptoms. Particular attention should be paid to the presence of dysphagia, especially in patients with chronic reflux-like symptoms, a lack of improvement following previous treatment, or coexisting atopic conditions [18,46]. When taking a medical history, it is also important to determine whether the patient uses specific strategies to make eating easier. Such behaviors may make swallowing difficulties seem less severe than they actually are. It is therefore advisable to include questions regarding the duration of meals, the thoroughness of chewing, the need to drink with each bite, the avoidance of foods with a certain consistency, and any past episodes of food impaction in the esophagus. Observational studies indicate that similar behaviors occur in patients with active EoE. Including these questions in the routine medical history may facilitate the identification of patients requiring further diagnostic evaluation, although the impact of this strategy on actually reducing the time to diagnosis should be confirmed in prospective studies [17,23]. Particular attention should be given to individuals experiencing recurrent episodes of dysphagia or food impaction. The occurrence of the latter should prompt not only appropriate intervention to remove the obstruction but also an investigation into the cause of the event. The low rates of biopsy performance during the initial endoscopy observed in clinical practice indicate a discrepancy between diagnostic recommendations and their implementation. Obtaining an adequate number of biopsies from different levels of the esophagus, if the patient's condition and clinical situation permit, can increase the likelihood of making an accurate diagnosis. If it is not possible to perform a biopsy during the initial examination, it is also important to plan further diagnostic procedures [32,33]. Effective diagnosis should also include ensuring continuity of patient care. Completing the diagnostic process requires communicating the results of the histopathological examination, determining the next steps, and ensuring that the patient can attend the recommended follow-up consultation. Reports of noncompliance with recommendations regarding further diagnostic testing indicate that performing an endoscopy alone does not always lead to a definitive explanation of the cause of the symptoms. It is therefore necessary to incorporate subsequent stages of management within an organized care pathway [32]. Another important measure is to increase awareness of EoE among primary care physicians, allergists, and medical staff working in emergency departments. The introduction of standardized management guidelines - covering the recognition of warning signs, indications for biopsy, and criteria for referring patients to a gastroenterologist - could reduce delays resulting from the organization of healthcare. At the same time, educational initiatives targeting patients could raise awareness of the disease and encourage them to seek medical help sooner [18,46]. Tools that enable the estimation of the likelihood of EoE based on clinical and endoscopic data also offer potential support for the diagnostic process. Available research findings indicate that predictive models may be useful in making decisions regarding further management. However, they do not replace histopathological examination, which remains the cornerstone of confirming the diagnosis. Furthermore, the European registry observed a correlation between improvements in biopsy practices and a reduction in the time to diagnosis. However, due to the observational nature of these data, it cannot be conclusively stated that the observed improvement resulted from a specific intervention. For this reason, the effectiveness of comprehensive diagnostic models should be verified in appropriately designed prospective studies [21,47].

4.4 Limitations of Current Evidence and Future Research Directions

Findings to date regarding diagnostic delay in eosinophilic esophagitis (EoE) are derived primarily from observational studies, including retrospective analyses. The nature of the available data makes it difficult to unequivocally establish cause-and-effect relationships. Reconstructing a patient's medical history based on medical records and information obtained from patients can lead to inaccuracies, especially when symptoms have persisted for many years. The reliability of the results may also be limited by the specific nature of referral centers, which more often admit patients with a more severe course of the disease or a more complex clinical presentation. Consequently, the study populations may not fully reflect the characteristics of all patients with EoE [12,18]. One of the problems that makes it difficult to compare the results of individual studies is the lack of a universally accepted, uniform definition of diagnostic delay. Although this term generally refers to the time between the onset of the first symptoms and the establishment of a diagnosis, the methods for determining the onset of symptoms vary depending on the methodology used. Particular difficulties arise with nonspecific symptoms and dysphagia, which can develop gradually. Additionally, some publications do not distinguish between the period preceding the first medical visit and the time spent on further diagnostic testing. The

absence of such a distinction makes it difficult to determine at which stage of the process delays most frequently occur and where corrective measures should be implemented [17,18]. Comparing study results is also complicated by differences in the length of follow-up periods and changes in the diagnosis of EoE over the years. Changes in diagnostic criteria, increasing knowledge about the disease, and the evolution of endoscopic practices may have influenced the likelihood of its detection. An analysis of the European EoE registry CONNECT showed a reduction in diagnostic delay over successive periods. However, it cannot be unequivocally concluded on this basis that the observed change was a direct consequence of the introduction or publication of guidelines. An additional source of uncertainty when comparing historical and contemporary cohorts is the variation in the available duration of patient follow-up [45]. Another challenge is the significant variation among the studied populations in terms of age, clinical presentation, geographic region, and access to specialized medical care. The concentration of studies in specific countries and clinical centers limits the ability to generalize the findings to populations with different characteristics. Furthermore, the underrepresentation of certain social groups and the limited availability of data on patients' socioeconomic status make it difficult to assess the impact of social inequalities on the diagnosis of EoE [48]. In future studies, particular emphasis should be placed on prospective, multicenter cohort analyses conducted according to a common definition of diagnostic delay and standardized guidelines for documenting the onset of symptoms. It is also important to distinguish between delays resulting from patient behavior and those related to the functioning of the healthcare system. Analyses should account for factors that may influence the duration of both periods. The effectiveness of standardized diagnostic pathways and the impact of educational interventions on the time to diagnosis also require further evaluation. It will be particularly important to determine whether shortening this period translates into a lower risk of subsequent complications, such as esophageal strictures, food impaction, or the need for dilation, regardless of the treatment used [18,45,48]. The limitations of this narrative review should also be taken into account. The selection of publications was based on the topic and objectives of this study, without conducting a systematic literature search in accordance with a pre-established and registered protocol. No formal assessment of the risk of bias was performed for each included publication, nor was a quantitative analysis in the form of a meta-analysis conducted. For this reason, the presented results constitute a qualitative summary of the available data. Differences in the methodologies of individual studies make it difficult to directly compare the duration of diagnostic delay and the strength of its association with the development of complications. Furthermore, the predominance of publications from specific healthcare systems limits the ability to generalize the findings to other populations. The proposed solutions therefore represent potential directions for further research, and their effectiveness requires confirmation in appropriately designed analyses.

5. Conclusions

This narrative review indicates that delays in the diagnosis of eosinophilic esophagitis (EoE) continue to pose a significant clinical challenge, despite increased awareness of the condition and the development of diagnostic standards. The available data indicate considerable variation in the time taken to diagnose EoE, and the improvement observed in some populations is not unequivocally confirmed across all the cohorts analyzed. Diagnostic delay is a multifactorial phenomenon, influenced by factors relating to both the patient and the organization and functioning of the healthcare system. The most significant factors contributing to diagnostic delay include the downplaying of chronic symptoms, the adoption of adaptive dietary strategies, delayed seeking of medical help, misdiagnoses and incomplete implementation of recommended diagnostic procedures. The insufficient use of endoscopy in the diagnosis of EoE remains a significant problem, particularly in patients with dysphagia or a history of food impaction. The available evidence points to a consistently observed association between a longer diagnostic delay and a higher prevalence of fibrosing-stenotic lesions in the esophagus. The observed relationship between disease duration and the severity of lesions, together with the biological mechanisms underlying chronic inflammation, suggests progressive tissue remodeling in the natural course of EoE. However, the predominantly observational nature of the available studies does not allow for a definitive establishment of a cause-and-effect relationship, nor does it permit the time to diagnosis to be equated with the actual duration of active, untreated disease. The greatest potential for reducing the time to diagnosis of EoE lies in the active recognition of dysphagia and adaptive behaviors, appropriate diagnostic management following an episode of food impaction, adherence to biopsy protocols, and ensuring continuity of patient care. The education of doctors and patients, as well as the standardization of diagnostic pathways, may also play a significant role. However, the effectiveness of these measures in reducing diagnostic delays

requires confirmation in further studies. Prospective, multicenter studies based on standardized definitions of diagnostic delay are needed to assess the effectiveness of the proposed interventions and to determine whether earlier diagnosis of EoE is associated with a lower risk of subsequent fibrostenotic complications.

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