

Eosinophilic esophagitis: Escalating epidemiology?

To the Editor:

Eosinophilic esophagitis (EE) is a chronic, inflammatory disorder of the esophagus.¹ The leading symptom in adults is dysphagia for solids with the imminent risk of food impaction.² The diagnostic criterion is a dense eosinophilic infiltration of the esophageal epithelium.¹ The inflammation may induce esophageal tissue damage and subsequent fibrosis with ensuing narrowing and stricture.^{1,3,4} Some demographic data exist for pediatric patients,⁵ but none for adults, the primary target population of this study.

We report on 23 adult cases selected from a continuing database begun in 1989 that enrolled EE patients prospectively. All patients presented here lived in Olten County, Switzerland, an area that had 1 gastroenterology and pathology center serving approximately 100,000 inhabitants and that had undergone no relevant demographic changes within recent decades. Database inclusion criteria were typical history, consistent endoscopic abnormalities, and histologic infiltration of the esophageal epithelium with ≥ 24 eosinophils per high-power field. Gastroesophageal reflux disease was excluded clinically and endoscopically.

The dominant symptom was dysphagia. Other symptoms were food impaction with the necessity of endoscopic intervention, heartburn, and retrosternal discomfort. Twenty-one of 23 patients (91.3%) were male. The average age at diagnosis was 34.3 years (range, 13-55 years). At diagnosis, patients had experienced dysphagia

for an average of 4.8 years (range, 0-22 years; Table I). Strikingly, 1 patient was completely asymptomatic and diagnosed only during a work-up for chronic diarrhea. Typical EE signs (scalelike white exudates) were endoscopically noted and histologically confirmed.

There was a strong association with atopic disease among patients and their families. In 3 patients, the father had confirmed EE, and we identified 1 family in which the father and both his children (boy and girl) had EE but, interestingly, only the boy suffered from atopy. These data suggest a familial form of EE not necessarily associated with atopy. That atopy-independent genes may predispose to EE is further supported by EE's high male:female ratio (Table I).

Throughout an almost 16-year observation period, an average annual incidence of 1.438 cases per 100,000 inhabitants was noted (range, 0-6) with a marked increase in newly diagnosed cases during the last years. On the basis of the documented chronicity of EE,⁴ the steady incidence resulted in a constantly increasing prevalence (Table I). Given the stability of the demographic and recording conditions, it is very likely that this remarkable trend reflects a real increase in EE and not just enhanced awareness. Furthermore, that our frequency calculations should be considered at minimum the tip of the iceberg has been recognized; many oligosymptomatic or asymptomatic cases may remain undiagnosed. Our data indicate that in adults, EE, once believed to be an extremely rare anomaly, occurs at a considerable frequency and may soon reach that of chronic inflammatory bowel diseases.

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TABLE I. Characterization and prevalence of adult EE

	Frequency (%) [*]															
Symptom																
Dysphagia	21 (91.3)															
Food impaction	7 (30.5)															
Heartburn	4 (17.4)															
Retrosternal discomfort	1 (4.3)															
Patient and family history																
History of rhinoconjunctivitis	12 (52.2)															
History of wheezing	7 (30.4)															
History of possible food allergy [†]	2 (8.7)															
Family history of atopic disease [‡]	8 (34.8)															
Family history of EE [‡]	3 (13.0)															
Incidence and prevalence	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04§
Incidence	2	0	1	1	2	1	1	0	2	0	1	2	0	3	1	6
Prevalence	2	2	3	4	6	7	8	8	10	10	11	13	13	16	17	23

^{*}Presenting symptoms as well as patient and family history of 23 adult EE patients. The frequency is indicated by both absolute and relative numbers. Cases may have had more than 1 symptom.

[†]History of positive SPT result, RAST, or anaphylaxis to specific dietary antigens.

[‡]First-degree relative.

[§]Prevalence of adult EE in Olten County between 1989 and September 2004.

^{||}Frequency estimates per 100,000 total population.

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Exhaled nitric oxide: The missing link between asthma and obesity?

To the Editor:

Asthma and obesity affect millions of persons worldwide. Both cross-sectional and longitudinal cohort studies have shown a positive association between both entities in children¹ and adults.² However, a pathophysiologic explanation for this association has not yet been established. We hypothesized that obesity might result in upregulation of pulmonary inflammatory mechanisms and studied the relationship between body mass index (BMI) and nitric oxide in exhaled air (eNO), which is an important inflammatory marker in patients with atopic asthma.³

We studied 24 (10 male and 14 female) healthy nonsmoking subjects. Subjects with a history of allergic rhinitis or lower respiratory complaints more severe than common colds were not included. After informed consent, eNO was measured during a 10-second expiration at 50 mL/s according to the American Thoracic Society guidelines (Niox; Aerocrine AB, Solna, Sweden).³ eNO values are reported as the mean value of 6 repeated measurements. None of the subjects took medications or nitrate-rich foods before the eNO measurements. The following lung function tests were performed (Masterlab, Viasys Healthcare, Hochberg, Germany): forced vital capacity, FEV₁, maximal expiratory volumes at 50% and 25% of total lung capacity, total lung capacity, residual volume, and carbon monoxide diffusion capacity corrected for alveolar volume and hemoglobin levels.

Mean (SD) age of the subjects was 27.9 (5.4) years, mean (SD) BMI was 23.0 (2.6) kg/m², and mean (SD) eNO level was 18.1 (7.4) ppb. Lung function parameters of all subjects were within the normal range. None of the

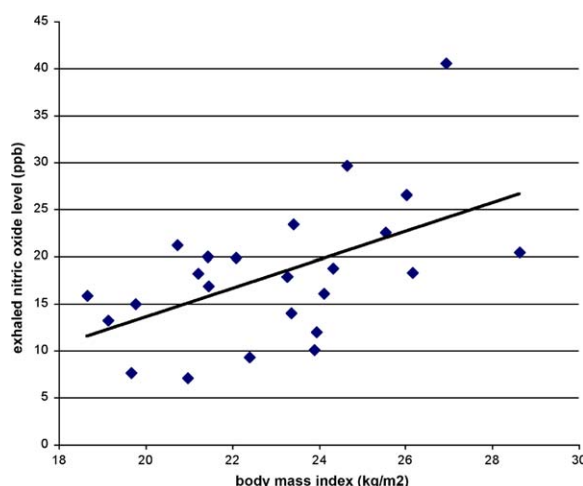


FIG 1. Association between BMI and eNO level in 24 healthy volunteers.

subjects had airflow obstruction, and mean (SD) FEV₁/forced vital capacity was 85.0% (6.2%). BMI was positively associated with mean eNO (linear regression coefficient, 1.5 ppb/kg/m²; 95% CI, 0.5-2.6; *P* = .007; Fig 1). This association did not change after adjustment for sex and age (1.5 ppb/kg/m²; 95% CI, 0.2-2.7; *P* = .02). No significant relationships between BMI or eNO and any of the lung function parameters were observed. The association between BMI and eNO was not influenced by adjustment for FEV₁ (1.8 ppb/kg/m²; 95% CI, 0.6-3.0; *P* = .005). Exclusion of the subject with the highest eNO value (Fig 1) did not materially influence the results.

Recent studies have shown that obesity leads to an increased release of proinflammatory molecules that contribute to obesity-associated complications. In obese subjects macrophage numbers in adipose tissue increase, producing significant amounts of TNF- α , inducible nitric oxide synthase, and IL-6.⁴ These data are supported by the finding that leptin, the protein of the putative obesity gene, upregulates the inflammatory immune response.⁵ Until now, no data on enhancement of inflammatory responses in the airways of obese subjects were available.

eNO has been established as a specific inflammatory marker in children and adults with atopic asthma. This marker in patients with asthma is strongly increased in comparison with healthy control subjects.³

Our findings show a significant increase in eNO levels in subjects with a high BMI. None of the subjects had a history or current symptoms of asthma or atopic disease. Lung function parameters were not negatively affected by increasing BMI. These data suggest direct or indirect upregulation of inflammatory processes outside the adipose tissue and suggest a contribution of obesity-related inflammatory activity to the pathophysiology of asthma. Linkage between obesity genes and nitric oxide synthase genes might be another explanation. Although our data from healthy subjects do not justify conclusions about pathophysiologic processes in disease states, our findings