






## SUPPLEMENT ARTICLE

# Nutritional status in eosinophilic gastrointestinal disorders: A pediatric case-control study

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## Abstract

Eosinophilic gastrointestinal disorders (EGIDs) represent an emerging group of heterogeneous diseases associated with failure to thrive, weight loss, protein-losing enteropathy, and malnutrition. To date, no studies have assessed the nutritional status, vitamin D, and other vitamin levels in patients with non-esophageal EGIDs. We aim to evaluate the nutritional profile of a cohort of children and adolescents with EGIDs. We performed a case-control study, enrolling a total of 98 patients, 38 (39%) patients with EoE, 22 (22%) patients with non-esophageal EGIDs, and 38 (39%) patients with non-allergic controls. Children with EGIDs had both mean ferritin and mean hemoglobin levels, together with other values such as folates and vitamin B12, within normal range and therefore did not have anemia. Albumin and prealbumin levels were within normal limits. Patients with EGIDs have mean vitamin D values slightly higher than non-allergic controls. Although this study is retrospective and referred to only one pediatric center, we found that Italian children and adolescents with EGIDs are neither malnourished nor deficient in vitamin D compared with controls.

## KEYWORDS

adolescents, children, eosinophilic esophagitis, Eosinophilic gastrointestinal disorders, nutritional status, vitamin D

## 1 | INTRODUCTION

Primary eosinophilic gastrointestinal disorders (EGIDs) are emerging inflammatory diseases of unknown etiology which may involve any part of the gastrointestinal (GI) tract and lead to a pathological eosinophilic mucosal infiltration.<sup>1,2</sup> Although their pathogenic mechanisms are mostly unknown, EGIDs seem to be commonly associated with atopy.<sup>3</sup> Based on the GI tract involved, EGIDs are classified in eosinophilic esophagitis (EoE) and non-esophageal EGIDs. EoE is currently considered one of the major causes of upper

gastrointestinal morbidity, with a significant burden on patients, caregivers, and the healthcare system.<sup>4</sup> Children with non-esophageal EGIDs may present non-specific GI symptoms, mainly depending on depth (mucosal, muscular, and serosal forms) and the extension of the inflammatory process.<sup>1</sup> On the contrary, patients with EoE generally develop symptoms due to esophageal dysfunction and inflammation. Although the prevalence is still unknown, several studies reported that EGIDs may be associated with malnutrition, including undernutrition, inadequate intake of vitamins and/or minerals, and overweight/obesity.<sup>4</sup> Vitamin D deficiency has also been reported in

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children with EoE with conflicting results.<sup>5</sup> To date, no studies have assessed the vitamin D and other vitamin levels in patients with non-esophageal EGIDs.

This study aims to evaluate the nutritional status of a cohort of children and adolescents with EGIDs, comparing to non-allergic controls and primarily focusing on BMI values and vitamin D levels.

## 2 | MATERIAL AND METHODS

We performed a case-control study, enrolling patients with EGIDs followed at the Center for Pediatric Eosinophilic gastrointestinal Disorders (CPED) in Pavia. The diagnosis of EoE was made according to current guidelines.<sup>6</sup> As there are no consensus guidelines for the diagnosis of non-esophageal EGIDs, we reviewed pathology reports based on the pathological cutoffs proposed by Collins et al (stomach  $\geq 30$  eos/HPF, small intestine  $\geq 50$  eos/HPF;  $\geq 54$  eos/HPF at ileum, right colon  $\geq 100$  eos/HPF, transverse and left colon  $\geq 84$  eos/HPF, rectosigmoid colon  $\geq 64$  eos/HPF).<sup>1</sup> Controls were non-allergic children and adolescents diagnosed with functional GI disorders (irritable bowel syndrome, functional constipation/diarrhea/dyspepsia) made according to the Rome IV criteria.<sup>7</sup> Patients  $< 19$  years were enrolled. All patients with a secondary cause of pathological eosinophilic inflammation of the GI tract, inflammatory bowel diseases, or coeliac disease were excluded. Data collected from enrolled patients included demographics (age at diagnosis, gender, ethnicity) and nutritional profiles. For each enrolled individual, we evaluated serum 25-hydroxy-vitamin D levels and body mass index (BMI). We also investigated the nutritional status of patients with EGIDs determining serum levels of folates, vitamin B12, albumin, prealbumin, hemoglobin, and ferritin. All data were extracted from electronic medical records (Ormaweb™ and Fenix™, Software) and entered into a spreadsheet. We replaced every patient identifier (patient name) with a specific numeric code. Informed consent was obtained from all participants.

Continuous variables were expressed as means and standard deviation (SD), while categorical variables were reported as numbers and percentages. Frequencies were tabulated for categorical variables. Bivariate analysis of categorical variables was conducted with the chi-square test or Fisher's exact test. Student's t test and Kruskal-Wallis test were used to compare continuous variables. A p-value less than .05 was considered significant. All analyses were performed using GraphPad Prism 8 for Mac, version 8.4.3 (GraphPad Software, San Diego, CA, USA).

### Key Messages

Vitamin D deficiency has been reported in children with eosinophilic gastrointestinal disorders (EGIDs) with conflicting results. To date, a few studies and no Italian articles assessed the vitamin D and other vitamin levels in patients with EGIDs.

Italian children and adolescents with EGIDs are neither malnourished nor deficient in vitamin D when compared to controls.

Further, more extensive and multicentric studies should be realized to investigate the nutritional status and vitamin profile of children with EGIDs.

## 3 | RESULTS

We enrolled a total of 98 patients, 38 (39%) with EoE, 22 (22%) patients with non-esophageal EGIDs, and 38 (39%) patients as non-allergic controls (Table 1). Male sex was prevalent in patients with EGIDs compared to controls. In children with EGIDs, there is no statistical difference in BMI values and prevalence of obese patients (p .52 and p .70, respectively) (Table 2). The mean vitamin D levels were a bit below the normal limit in children with non-esophageal EGIDs compared to those with EoE (27.1 ng/mL and 32.2 ng/mL, respectively). Children with EGIDs had both mean ferritin and mean hemoglobin levels, together with other values such as folates and vitamin B12, within normal range and therefore did not have anemia. Albumin and prealbumin levels were within normal limits.

The mean value of vitamin D was higher in patients with EGIDs (32.2 ng/ml in the EoE group and 27.1 ng/ml in the non-esophageal EGIDs group) than non-allergic controls (20.0 ng/ml), despite there was no statistically significant difference (p .05) (Table 3, Figure 1(A)). The BMI of children with EGIDs (19.0 kg/m<sup>2</sup> in the EoE and 18.1 kg/m<sup>2</sup> in the non-esophageal EGIDs group) is similar to that of the control group (19.4 kg/m<sup>2</sup>), with no statistical difference (Figure 1(B)).

## 4 | DISCUSSION

To date, a few retrospective studies and no articles in Italy assessed the nutritional status of patients with EGIDs. Despite several limitations (Table 4), these preliminary data showed that

	EoE (n = 38)	Non-esophageal EGIDs (n = 22)	Controls (n = 38)
Age, mean $\pm$ SD	9.9 $\pm$ 5.1	9.0 $\pm$ 4.1	9.2 $\pm$ 4.4
Males, n (%)	29 (76.3)	15 (68.2)	18 (47.3)
Caucasians, n (%)	29 (76.3)	21 (95.5)	34 (89.5)

TABLE 1 Demographic features of enrolled patients

Abbreviations: EGIDs, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; SD, standard deviation.

**TABLE 2** Nutritional status of patients with EGIDs

Nutritional status	EoE	Non-esophageal EGIDs	p-value
BMI (kg/m <sup>2</sup> ), mean ± SD	18.9 ± 5.0	18.1 ± 3.6	.52
Obese patients, n (%)	4 (10.5)	3 (13.6)	.70
Vitamin D (ng/mL), mean ± SD	32.2 ± 20.0	27.1 ± 10.1	.50
Folates (ng/mL), mean ± SD	7.5 ± 3.7	10.2 ± 6.5	.17
Vitamin B12 (µg/mL), mean ± SD	564.1 ± 332.5	598.0 ± 288.7	.80
Albumin (mg/dL), mean ± SD	4263.0 ± 330.4	4188.0 ± 413.4	.60
Prealbumin (mg/dL), mean ± SD	19.4 ± 4.6	20.7 ± 4.0	.50
Hemoglobin, mean ± SD	13.1 ± 1.1	13.5 ± 1.0	.13
Ferritin, mean ± SD	33.4 ± 19.7	29.7 ± 10.3	.5

Note: Normal values: albumin 3500–5200 mg/dL; folates 2–19.9 ng/mL; hemoglobin 12–17 g/dL; ferritin ng/mL (18–440) F (8–120); prealbumin 20–40 mg/dL; vitamin B12 243–894 µg/mL; vitamin D 30–100 ng/mL.

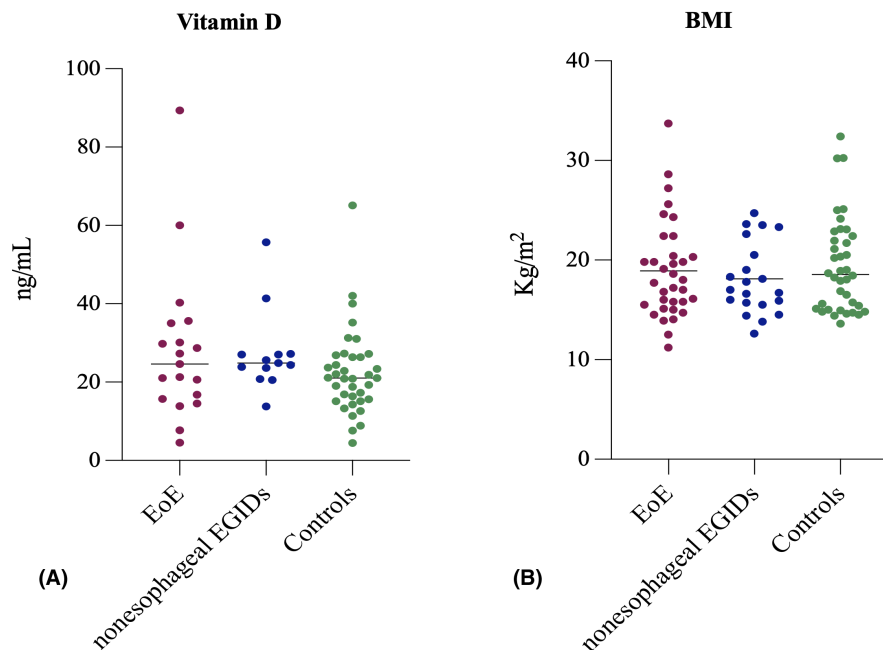
Abbreviations: BMI, body mass index; EGIDs, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; SD, standard deviation.

**TABLE 3** BMI values and vitamin D levels of enrolled patients

	EoE	Non-esophageal EGIDs	Controls	p-value*
BMI (kg/m <sup>2</sup> ), mean ± SD	18.9 ± 5.0	18.1 ± 3.6	19.4 ± 5.0	.63
Vitamin D (ng/mL), mean ± SD	32.2 ± 20.0	27.1 ± 10.1	20.0 ± 6.0	.05

Abbreviations: BMI, body mass index; EGIDs, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; SD, standard deviation.

\*Kruskal-Wallis test.



**FIGURE 1** (A) Vitamin D levels of enrolled patients. (B) BMI values of enrolled patients

Italian children and adolescents with EGIDs are neither malnourished nor deficient in vitamin D, compared with non-allergic controls. Almost all values concerning the nutritional profile were

within normal limits, and none of the children with EGIDs showed signs of anemia or protein-losing enteropathy. There is still limited published literature on vitamin deficiencies associated with EGIDs

TABLE 4 Limitations and strengths of the study

Limitations	Strengths
<ul style="list-style-type: none"> <li>Retrospective and monocentric pediatric study with a small sample size.</li> <li>Lack of consensus criteria for the diagnosis and therapy of non-esophageal EGIDs.</li> <li>Vitamin D levels and BMI values were assessed at diagnosis. These values may be influenced by treatment, and the absence of follow-up data did not allow to evaluate their modification over time.</li> <li>Controls are non-allergic children with functional gastrointestinal (GI) disorders. It is still unclear whether BMI and vitamin D may be related to the development or the worsening of functional GI diseases.</li> </ul>	<ul style="list-style-type: none"> <li>First Italian pediatric study that assessed the nutritional status of children and adolescents with eosinophilic gastrointestinal disorders (EGIDs), mainly focusing on vitamin D.</li> <li>Although retrospective, we realized a case-control study.</li> <li>Italian children and adolescents with EGID are neither malnourished nor deficient in vitamin D compared with non-allergic controls.</li> <li>EGIDs-related malnutrition is a clinical field that requires further effort to strengthen the efficacy of therapies and ensure a good patient's quality of life.</li> <li>A multidisciplinary approach (allergist, gastroenterologist, nutritionist, psychologist) is a winner key of EGIDs management.</li> </ul>

both pre-intervention and post-intervention.<sup>5</sup> Statistically, there was no difference in BMI values and prevalence of obese patients. Obesity is a global health problem associated with many chronic diseases. The pediatric obesity epidemic and obesity-related inflammation could be responsible for the increased prevalence of allergic disorders, including EGIDs.<sup>5</sup> To date, no study has investigated the possible role of obesity in EGIDs development. New insights about obesity as a possible EoE risk factor that may impair esophageal inflammation and symptoms are uncovered, but a tangible link between obesity and other allergic disorders, including EGIDs, is yet to be established.<sup>5</sup>

The mean vitamin D levels of children with EGIDs were slightly higher than those found in healthy controls. However, when considering the standard deviation of the mean vitamin D level of children with EGIDs, it can be inferred that lower levels of vitamin D were present among them. Vitamin D deficiency is mainly due to the quality of diet and the lack of sun exposure. Vitamin D has been shown to have a direct influence on immune function, inhibiting human dendritic cells and inducing T regulatory cells. Moreover, there is growing evidence on the influence of vitamin D on the pathogenesis of allergic diseases, such as asthma, atopic dermatitis, and food allergies.<sup>8,9</sup> Possibly, vitamin D deficiency could be somehow related to the pathogenesis of EGIDs, giving the fact that the prevalence of EoE is higher in Western countries and cold climate zones.<sup>5</sup> Vitamin D appears to play a role in maintaining the intestinal mucosal barrier and altering gene expression in smooth muscle cells, affecting pathways for cell recruitment, growth, and survival, which could contribute to tissue remodeling.<sup>8</sup> Low levels of vitamin D were reported in 42% of adults and 50% of children with EoE, clinically characterized by symptoms of food impaction.<sup>5</sup> Such data on non-esophageal EGID are yet to be reported. In our study, we could not demonstrate a possible link between vitamin D deficiency and EGIDs, possibly because of the small sample size and the retrospective study design. More research is needed on the causal relationship of vitamin D when it comes to EGIDs and if supplementation would aid remission. Further, more extensive studies should be carried out to investigate whether vitamin D deficiency in children with EGIDs is just a circumstantial coincidence as a side effect of personal lifestyle or medical restriction of sources due to other comorbidities such as allergies.

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## CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

## AUTHOR CONTRIBUTIONS

**Martina Votto:** Conceptualization (equal), methodology (equal), and writing—original draft (equal). **Giacomo Bonitatibus:** Writing—review & editing (equal). **Maria De Filippo:** Writing—review & editing (equal). **Serena Anjali Pitigalage Kurera:** Writing—review & editing (equal). **Ilaria Brambilla:** Methodology (equal) and writing—review & editing (equal). **Carmen Guarracino:** Methodology (equal) and writing—review & editing (equal). **Mara De Amici:** Methodology (equal). **Gian Luigi Marseglia:** Supervision (lead) and writing—review & editing (equal). **Amelia Licari:** Conceptualization (equal), supervision (lead), and Writing—review & editing (equal).

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