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Frequent report of vitamin deficiencies and use of supplements and complementary/alternative treatment approaches in patients with eosinophilic gastrointestinal diseases

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Abstract

Background: Eosinophilic gastrointestinal diseases (EGIDs) impact nutrition.
Objectives: To assess the frequency of vitamin deficiencies, supplement use, and complementary/alternative-medication (CAM) use in EoE and non-EoE EGID patients.
Design: Cross-sectional study.
Methods: We surveyed members of EGID Partners (egidpartners.org), a patient-centered research network, to assess physician-diagnosed vitamin deficiencies, supplement use, and use of CAM in patients with EoE versus non-EoE EGIDs.
Results: Of 81 EGID patients (58 EoE and 23 non-EoE EGID), self-reported frequency of vitamin deficiencies were higher in non-EoE EGIDs compared to EoE (61% vs 50%; $p = 0.38$; Table 1). Most patients (77%) indicated taking vitamins or supplements, with higher frequency in non-EoE EGID cases (87% vs 72%; $p = 0.16$). Use of >30 different supplements was reported. For CAM, herbal approaches were more frequent in non-EoE EGIDs compared to EoE (26% vs 5%; $p = 0.008$).
Conclusion: Vitamin deficiencies and supplement/CAM use are frequent in EGIDs, highlighting the need for additional EGID treatment.

Plain language summary

Complementary medicine and EGIDs

Eosinophilic gastrointestinal diseases (EGIDs) are due to eosinophilic inflammation in different parts of the GI tract and can have a number of symptoms including poor nutrition. This study aimed to describe the proportion of patients with EGIDs that had a vitamin deficiency and used supplements and complementary/alternative medications (CAMs). We found more than half of patients had been diagnosed with a vitamin deficiency and more than three-quarters used supplements or CAMs. This implies that vitamin deficiencies and CAMs should be better studied in EGIDs to potentially improve health outcomes.

Keywords: complementary and alternative medications, eosinophilic colitis vitamin deficiency, eosinophilic enteritis, eosinophilic esophagitis, eosinophilic gastritis

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Introduction

Eosinophilic gastrointestinal diseases (EGIDs) are defined by abnormal infiltration of eosinophils in various segments of the GI tract without an identifiable secondary cause of eosinophilia. EGIDs include eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), eosinophilic colitis (EoC) and most commonly, eosinophilic esophagitis (EoE).[1] Though they are generally rare diseases, EGIDs have various clinical presentations that can be associated with significant morbidity impacting young children and adults.[2,3] Patients with EGIDs most frequently report nausea and upper abdominal pain and have extra-intestinal and psychosocial concerns.[4,5]

It is also known that EGIDs negatively affect food and nutrient intake. For instance, pediatric patients with EoE experience feeding difficulty and adverse feeding that contributes to poor nutrition and failure to thrive.[6,7] This is potentially worsened by the use of elimination diets to treat EGIDs.[8] Typical six food elimination diets (SFED) remove cow's milk, egg, nuts, soy, wheat, and shellfish from the diet which removes key nutrient sources. Recent studies have begun investigating the tolerability of more restrictive diets such as the rainbow elimination diet that eliminates more than 10 additional foods than SFED, but the overall extent of nutritional deficiencies remains understudied in EGIDs.[9] However, it is known that nutritional deficiencies are commonly seen in atopic conditions. One study reports that 49.7% of patients with non-EoE EGIDs have been diagnosed by a physician with a vitamin deficiency.[4] This is highly relevant considering vitamins like vitamin D have immunomodulatory functions and newly diagnosed EoE patients have lower vitamin D levels than non-EoE counterparts.[10] The frequency of vitamin deficiency and supplement use in EGIDs has not been well studied. Similarly, little is known about complementary/alternative medicine (CAM) use in EGIDs, and if there is a need for more effective treatment of EGIDs. While the U.S Food and Drug Administration approved the first biologic, dupilumab, and an oral budesonide suspension for EoE, the real-word efficacy of these therapies is still being determined. Meanwhile, the use of proton pump inhibitors, food elimination diets, and esophageal dilation have limited response rates.[11]

In this study, we aimed to assess the frequency of vitamin deficiency, supplement use, and CAM use in EoE and non-EoE EGID patients. We hypothesized that vitamin deficiencies would be more common in non-EoE EGIDs, given the more diffuse involvement of the GI tract, than in EoE, but that supplement and CAM use would be similar.

Methods

We performed a study based in EGID Partners (egidpartners.org), an online patient-centered research network designed and implemented by patient advocacy groups and EGID researchers. Subjects were recruited to join the cohort using informational emails, social media, webinars, medical record patient portals, and contact with physicians. Adults ($\geq$18 years) and caregivers of children $<$18 years of age could join. Once on the platform, participants provided online written informed consent by agreeing to join and proceed with the surveys. Since EGID Partners are a patient-powered research network, cases self-reported their EGID diagnoses based on local clinical protocols. The reliability of self-reporting EGID diseases online has been documented, similar to self-reporting of other GI conditions.[3,12] Participants 18 years and older completed surveys to determine their demographics, disease, and medical history; caregivers completed the surveys for participants younger than 18 years. Of note, EGID Partners were implemented prior to the new EGID nomenclature, so non-EoE EGID patients were classified as EoG, eosinophilic gastroenteritis (EGE), and EoC.[1]

To begin, we surveyed EGID Partners participants on what research topics most interested them. Participants identified vitamin and supplement use as an area of interest; therefore, we subsequently developed and implemented a survey to document physician-diagnosed vitamin deficiencies, vitamin and supplement use, and use of CAM (see Supplemental Appendix). The survey also included behavioral questions to evaluate additional factors that are known to impact nutrient levels. We compared patients with EoE to those with non-EoE EGIDs by evaluating baseline characteristics, vitamin deficiencies, and supplement/CAM use. For analysis, summary statistics were used to describe the demographics of EoE and non-EoE EGID patients. We

performed bivariate analyses to compare the two groups, with two-sample *t*-tests for means and Fisher's exact test for proportions. As this was a survey study in an existing cohort, we did not have a formal sample size calculation. The UNC Institutional Review Board approved this study and patients provided consent for participation. This is a brief report prepared using the STROBE guidelines for observational studies.[13]

Results

We analyzed 81 respondents with EGIDs, 58 of whom had EoE alone, and 23 had a non-EoE EGID (13 had EoG, 14 had EGE, 7 had EC, and 14 had overlapping disease locations). The mean (SD) age of all respondents was 35.1 (19.0) years; 64% were female, and 95% were White (Table 1). Adults represented 82% of respondents, and 18% were the caregivers of minors.

Vitamin deficiencies and supplements

The proportion of patients reporting vitamin deficiencies was numerically higher in non-EoE EGIDs compared to EoE (61% vs 50%, respectively; $p = 0.38$; Table 1). Across EGIDs, frequencies of deficiencies were numerically highest for vitamin D, iron, and B12 (86%, 60%, and 33%, respectively). The majority of patients (77%) reported taking vitamins or supplements at least once a week, with a numerically higher proportion in non-EoE EGID cases (87% vs 72%; $p = 0.16$). Use of more than 30 different supplements or vitamins were reported. The most used supplements were vitamin D (68%) and multivitamins (59%). Vitamin B12, C, iron, calcium, and probiotics were also widely used (Table 1).

Given that diet and alcohol use can both impact vitamin deficiencies, dietary and lifestyle behaviors were also assessed.[14] Though vitamin D and iron deficiencies were frequently reported, there was no significant difference in how often participants consumed cow's milk products ($p = 0.36$) or consumed at least 1 serving of green leafy vegetables ($p = 0.09$; Table 1) which are known sources of these vitamins. A total of 46% of respondents reported never drinking alcohol. Of those who drink alcohol, 100% of non-EoE EGID patients consumed 1–2 drinks at a time, compared to 87% of EoE EGID patients drinking 1–2 drinks and 10% drinking 3–4 drinks (Table 1).

CAM utilization

For CAM, herbal approaches were significantly more frequent in non-EoE EGIDs than EoE (26% vs 5%; $p = 0.008$). Notably, yoga and massage therapies were the most used CAM therapies, each used by 18% of participants. Chiropractic treatments and cognitive behavioral therapy (CBT) were used by 15% of EGID patients (Table 2). Acupuncture, cupping, and hypnosis were used by $\leqslant$5% of patients. No participants reported using nambudripad allergy elimination techniques or nutraceuticals for EGID treatment (Table 2).

Discussion

EGIDs can disrupt food intake and ultimately impact nutrient levels but the extent of vitamin deficiency has not been widely examined. In the setting of vitamin deficiencies in these patients, more information is also needed about the type of vitamins and supplements they take, as well as CAM use. In this study, we first assessed vitamin deficiencies that EGID patients have been diagnosed with and the vitamins and supplements they report taking. We found that nearly two-thirds of non-EoE EGID patients reported a diagnosis of vitamin deficiencies compared to half of EoE patients. The highest proportion of reported deficiencies were vitamin D, iron, and B12, and more than three-quarters of patients take vitamins and supplements. Vitamin deficiency can contribute to multiple health issues, including anemia, vision problems, neuropathy, poor bone health, and, in some cases, worsening of atopic diseases.[10,15] Therefore, frequent use of vitamins and supplements emphasizes a prevalent health issue in this population that requires further study.

For CAMs, we found that herbal medicines were frequently used in non-EoE EGID patients and that yoga, massage therapy, chiropractic, and CBT were used by $\geqslant$15% of participants. These findings are similar to the results of a different survey that found high CAM use in patients with EoE. This study investigated how factors such as the caregiver of the child's personal beliefs, perceptions, and own use of CAM influence their child's use of CAM.[16] In their data gathered from respondents who were mostly White (93%), male (72%), and had a median age of 9.5 years, they found 91% of caregivers used CAMs themselves,

Table 1. Comparison of vitamin and supplement use between EoE and non-EoE EGID patients in the EGID Partners cohort.

	Overall (*n* = 81)	**EoE (*n* = 58)**	**Non-EoE EGID (*n* = 23)**	***p***
Age at survey completion (mean years ± SD)	35.1 ± 19.0	36.8 ± 18.6	31.1 ± 19.9	0.27
Adults with EGIDs respondents (*n*, %)	65 (80)	50 (86)	15 (65)	0.03
Gender (*n*, %)				0.34
Female	46 (57)	32 (55)	14 (61)	
Male	35 (43)	26 (45)	9 (39)	
Any vitamin deficiency diagnosed (*n*, %)	43 (53)	29 (50)	14 (61)	0.38
Which vitamin (*n*, %)[a]				
A (retinol)	0 (0)	0 (0)	0 (0)	—
B1 (thiamine)	1 (1)	1 (4)	0 (0)	0.48
B2 (riboflavin)	2 (5)	1 (4)	1 (8)	0.59
B6 (pyridoxine)	3 (7)	3 (7)	1 (7)	0.98
B7 (biotin)	1 (3)	1 (4)	0 (0)	0.48
B9 (folate)	4 (10)	2 (8)	2 (15)	0.53
B12 (cobalamin)	14 (33)	7 (25)	7 (50)	0.11
C (ascorbic acid)	3 (7)	1 (4)	2 (15)	0.19
D	36 (86)	23 (82)	13 (93)	0.35
E (tocopherol)	1 (3)	1 (4)	0 (0)	0.48
K	2(5)	2 (7)	0 (0)	0.31
Iron	25 (60)	16 (55)	9 (69)	0.39
Zinc	6 (15)	2 (7)	4 (31)	0.05
Selenium	1 (3)	1 (4)	0 (0)	0.48
Manganese	3 (7)	1 (4)	2 (15)	0.19
Take vitamins or dietary supplements >1 day/week (*n*, %)	62 (77)	42 (72)	20 (87)	0.16
Multivitamin[b]	35 (59)	25 (63)	10 (53)	0.47
A (retinol)	2 (3)	2 (5)	0 (0)	0.32
Vitamin B complex	7 (12)	6 (15)	1 (5)	0.26
B1 (thiamine)	2 (3)	1 (3)	1 (5)	0.58
B2 (riboflavin)	5 (8)	4 (10)	1 (5)	0.54

(Continued)

Table 1. (Continued)

	Overall (*n* = 81)	EoE (*n* = 58)	Non-EoE EGID (*n* = 23)	*p*
B6 (pyridoxine)	2 (3)	2 (5)	0 (0)	0.32
B7 (biotin)	4 (7)	4 (10)	0 (0)	0.15
B9 (folate)	6 (10)	4 (10)	2 (11)	0.95
B12 (cobalamin)	14 (23)	9 (22)	5 (25)	0.79
C (ascorbic acid)	15 (25)	11 (28)	4 (21)	0.60
D	41 (68)	27 (66)	14 (74)	0.54
E (tocopherol)	7 (12)	5 (13)	2 (11)	0.83
K	3 (5)	2 (5)	1 (5)	0.97
Iron	17 (28)	10 (24)	7 (37)	0.29
Zinc	12 (20)	8 (20)	4 (21)	0.93
Selenium	3 (5)	2 (5)	1 (5)	0.97
Manganese	1 (2)	1 (3)	0 (0)	0.49
Calcium	14 (24)	8 (20)	6 (32)	0.33
Melatonin	8 (14)	4 (10)	4 (21)	0.25
Saw Palmetto	0 (0)	0 (0)	0 (0)	—
Magnesium	13 (22)	9 (23)	4 (21)	0.90
Curcumin	5 (8)	4 (10)	1 (5)	0.54
Turmeric	9 (15)	6 (15)	3 (16)	0.94
CBD	8 (14)	6 (15)	2(11)	0.64
Fish oil	12 (20)	9 (23)	3 (16)	0.55
CoQ10	9 (15)	7 (18)	2 (11)	0.49
Collagen	8 (14)	5 (13)	3 (16)	0.73
Other[c]	8 (14)	8 (20)	0 (0)	0.04
Probiotics >1 day/week	16 (20)	9 (16)	7 (30)	0.13
How often are cow's milk products consumed (*n*, %)				0.36
Never	29 (36)	20 (34)	9 (39)	
Once a week	15 (19)	8 (14)	7 (30)	
2–5 times a week	17 (21)	14 (24)	3 (13)	
Once a day	13 (16)	10 (17)	3 (13)	
Multiple times each day	7 (9)	6 (10)	1 (4)	

(Continued)

Table 1. (Continued)

	Overall (*n* = 81)	EoE (*n* = 58)	Non-EoE EGID (*n* = 23)	*p*
How often is at least 1 serving of green leafy vegetables consumed (*n*, %)				0.09
Never	5 (6)	2 (3)	3 (13)	
Less than once per month	1 (1)	1 (2)	0 (0)	
1–2 times per month	14 (17)	9 (16)	5 (22)	
1–2 times per week	22 (27)	13 (22)	9 (39)	
3 or more times per week	39 (48)	33 (57)	6 (26)	
How often are mammalian/animal meats or seafood consumed (*n*, %)				0.005
Never	7 (9)	3 (5)	4 (17)	
Less than once per month	2 (2)	0 (0)	2 (9)	
1–2 times per month	4 (5)	3 (5)	1 (4)	
1–2 times per week	11 (14)	5 (9)	6 (26)	
3 or more times per week	57 (70)	47 (81)	10 (43)	
Frequency of alcohol use (*n*, %)				0.006
Never	37 (46)	19 (33)	18 (78)	
Monthly or less	13 (16)	11 (19)	2 (9)	
2–4 times per month	12 (15)	10 (17)	2 (9)	
2–3 times per week	10 (12)	9 (16)	1 (4)	
4 or more times per week	9 (11)	9 (16)	0 (0)	
For those drinking alcohol, how many standard drinks are typically consumed (*n*, %)				0.67
1–2	39 (89)	34 (87)	5 (100)	
3–4	4 (9)	4 (10)	0 (0)	
5–6	1 (2)	1 (3)	0 (0)	
7–9	0 (0)	0 (0)	0 (0)	
10 or more	0 (0)	0 (0)	0 (0)	

[a]Data available for *n* = 27 and *n* = 13 for EoE and non-EoE EGID, respectively.
[b]Data available for *n* = 40 and *n* = 19 for EoE and non-EoE EGID, respectively.
[c]Includes Mucuna pruriens; algae-based omega-3, milk thistle, SAMe, gingko, and glucosamine products.
EGID, eosinophilic gastrointestinal diseases; EoE, eosinophilic esophagitis.

which correlated to higher use of CAMs in the caregiver's children and in patients, the most commonly used CAMs were probiotics (53%) and other nutritional supplements (64%).[16] In comparison, we found probiotic use to be much lower at 20%, suggesting that unique factors may influence the choice of CAM use for EGIDs. Their findings suggest that the use of CAM by caregivers of children with EoE is a strong indicator that the child will trial CAMs as well. Other

Table 2. Comparison of complemental and alternative medicine use between EoE and non-EoE EGID patients in the EGID Partners cohort.

	Overall (*n* = 81)	EoE (*n* = 58)	Non-EoE EGID (*n* = 23)	*p*
Complementary alternative treatments in the last year (*n*, %)*				
Acupuncture	4 (5)	3 (5)	1 (4)	0.85
Acupressure	3 (4)	2 (4)	1 (4)	0.87
Chiropractice/Chiropractor	12 (15)	6 (11)	6 (26)	0.08
Cognitive Behavioral Therapy (CBT)	12 (15)	9 (16)	3 (13)	0.73
Cupping	3 (4)	3 (5)	0 (0)	0.26
Herbal medicines	9 (11)	3 (5)	6 (26)	0.008
Homeopathy	1 (1)	1 (2)	0 (0)	0.52
Hypnosis	3 (4)	1 (2)	2 (9)	0.14
Integrative medicine	2 (3)	1 (2)	1 (4)	0.51
Kinesiology	1 (1)	1 (2)	0 (0)	0.52
Massage therapy	14 (18)	10 (18)	4 (17)	0.96
Nambudripad (NAET)	0 (0)	0 (0)	0 (0)	—
Nutraceuticals	0 (0)	0 (0)	0 (0)	—
Yoga	14 (18)	12 (21)	2 (9)	0.19

*Data available for *n* = 56 and *n* = 23 for EoE and non-EoE EGID, respectively.

reasons for choosing CAM include a perceived lack of improvement on conventional medicine alone and worsening symptoms. Therefore, providers caring for EGID patients should understand that CAM therapies are frequently used, even without an evidence base, and should ask patients about CAM use and attempt to understand patient's reasoning for usage.

There is a strong need for additional treatments for EGIDs, considering the varied patient responses to traditional therapies, and complementary/alternative medicine remains an intriguing option. In one case report, an 11-year-old with severe EoE and a history of atopic disease achieved complete remission with Traditional Chinese Medicine (TCM). Before using CAM, he trialed elimination diets and swallowed corticosteroids but continued to have severe emesis and subsequent failure to thrive. After starting TCM, he had prolonged asymptomatic periods even after reintroducing previously eliminated foods, he gained healthy weight, and his repeat endoscopy with biopsy found 0–7 eosinophils/hpf. [17] Such novel treatment approaches may alleviate the burden of disease for patients and address psychosocial factors during the treatment course. [5]

Our study fills an important knowledge gap regarding EGIDs, although it has its limitations. We did not assess the types of multivitamins respondents reported, though these supplements are not standardized by the FDA and may vary in composition and ingredients. The dosage and frequency of vitamin use was not evaluated, nor was the time at which participants received their formal diagnosis of a vitamin deficiency. We do not have data on which respondents were on an elimination diet at the time of survey completion, as this may impact nutrient levels or supplement use. We also acknowledge that this is a relatively

small sample size and relies on patient self-reporting, and we could not make comparisons to a normal or healthy population. Still, there were strengths to our study. The data findings directly addressed a topic that EGID patients reported wanting to have researched. By using a survey to ascertain this information from the EGID Partners cohort, we analyzed responses from a variety of people over a larger geographical area, and likely with larger numbers, than if surveys were limited to a single site assessment.

In conclusion, this study demonstrates that vitamin deficiencies are reported by >50% of EGID patients and may be more common in non-EoE EGIDs. Vitamin and supplement use was very common, with frequent CAM utilization as well. The frequent use of vitamins, supplements, and CAM highlights a potential unmet need in the role for CAMs in improving disease management with supplemental therapies. As a result, this study initiates important discussion regarding vitamin and CAM use, warranting further exploration to address the limitations above. Such work should evaluate whether these findings differ among patients undergoing elimination diet therapies and those with varying patterns of vitamin use since this information was inaccessible in our study. Future research should also consider how traditional treatment options impact vitamin levels and if EGIDs are clinically, endoscopically, and histologically improved by the use of CAM.

Declarations

Ethics approval and consent to participate

The UNC Institutional Review Board approved this study (approval # 20-0141) and all participants written provided informed consent to join this study and complete the surveys when they joined EGID Partners and by agreeing to proceed with the surveys. Participants were required to be at least 18 years old to provide informed consent. Therefore, in the case of a minor patient, consent was obtained from the parent/guardian/caretaker who completed the survey on behalf of the minor.

Consent for publication

The consent provided by participants describes their understanding and agreement that their study responses and data may be published in the aggregate and in de-identified format.

Author contributions

Brenderia A. Cameron: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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Girish Hiremath: Investigation; Methodology; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data and materials may be made available upon request if proper approvals are in place and at the

discretion of the research team and EGID Partners steering committee.

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Supplemental material

Supplemental material for this article is available online.

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