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Research Paper:
Serum Levels of Interleukin-10 and Tumor Growth Factor-β1 in Children With Eosinophilic Gastrointestinal Disorders Compared to Control Groups

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ABSTRACT

Background: Eosinophilic Gastrointestinal Disorders (EGID) are a heterogeneous group of gastrointestinal disorders, associated with an increase of the eosinophils in the gastrointestinal mucosal tissue. Regulatory T cells (Tregs), as a subset of T cells, have a proven prominent role in immunopathology and protection against allergic diseases. Also, they appear to play a role in EGID pathogenesis. In the present study, serum levels of Tumor Growth Factor (TGF)-β and interleukin (IL)-10 were measured in patients with EGID compared to patients with Gastroesophageal Reflux Disease (GERD) and healthy subjects.

Materials and Methods: A total of 34 patients with EGID, 23 with GERD, and 25 healthy controls were included in the study. The diagnoses of EGID and GERD were made based on the patients' clinical symptoms, endoscopic findings, and biopsy confirmation. A questionnaire of demographic information, allergy history, as well as endoscopic-pathological and skin prick test results were completed and performed. The serum levels of TGF-β and IL-10 were measured using the ELISA method.

Results: Family history of allergic disorders in patients with EGID or GERD was significantly high compared to healthy controls (P=0.010, P=0.005, respectively). There was a statistically significant increase in serum levels of TGF-β1 (P=0.025), but no significant difference was observed in serum level of IL-10 among three groups. However, the serum level of IL-10 was significantly high in a subgroup of patients with upper gastrointestinal eosinophilic involvement compared to the healthy controls (P=0.018).

Conclusion: Significant increase in the serum level of IL-10 and TGF- β might be due to the Tregs dysfunction in EGID patients. Further studies should determine the role of Tregs in the pathogenesis of EGID.

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Introduction

Eosinophilic Gastrointestinal Disorders (EGIDs) are a heterogeneous group of GI disorders associated with a high number of eosinophils in the gastrointestinal mucosal tissue and specific symptoms depending on the affected area [1]. Regarding this category, most studies have been conducted on Eosinophilic Esophagitis (EOE), which is characterized by eosinophilic infiltration (≥15 eosinophils per High Power Field "HPF") in the esophagus [2, 3]. It can be detected at any age by symptoms of abdominal pain, regurgitation, dysphagia, nausea, and poor weight gain, refractive Gastroesophageal Reflux Disease (GERD) in children, and food impaction in adult [4]. EGID is considered as a polygenic allergic disorder associated with IgE-dependent reactions and delayed reactions related to Th2 profiles [5]. In this regard, various studies have confirmed the association between the atopy, food allergies, and other allergic diseases that can be revealed by positive skin tests (prick) for aero-allergens and or food allergens in patients with EOE [6]. The mechanism involved in GERD is very different since the immune system does not play a central role.

Regulatory T Cells (Treg Cells), a subset of T cells with a proven prominent role in immunoregulation and protection against allergic diseases, appear to play a role in EGID pathogenesis [7]. In a previous study in the United States in 2010, Fuentubella et al. showed no significant difference in the number of peripheral blood Treg in EOE subjects compared to those with GERD and healthy subjects. In contrast, immunohistochemical assessments showed a significant increase in the number of Tregs compared to GERD patients and healthy control. These results were confirmed by Foxp3 gene expression using Real-Time PCR [8]. Our previous study showed the increased number of Tregs in esophageal tissue and peripheral blood of patients with EOE (unpublished data). In this study, we compared serum levels of Tumor growth factor (TGF)-β and interleukin (IL)-10, as two anti-inflammatory cytokines secreted by Treg cells in children with EGID, GERD, and healthy controls.

Materials and Methods

Study population and ethical considerations

Eighty-two children (34 with EGID, 23 with GERD, and 25 healthy controls) were included in this study. Of 34 patients with EGID, 19 showed upper GI involvement (EOE and eosinophilic gastroduodenitis) and 15 had lower GI involvement. The patients with the history of autoimmune disorders, use of immunosuppressive drugs, steroids, and Nonsteroidal Anti-inflammatory Drugs (NSAIDs) were excluded.

The diagnosis of EGID was made based on the patients' clinical symptoms, endoscopic findings, and biopsy confirmation. The infiltrated eosinophil levels in lamina propria have to be more than the normal pediatric endoscopy biopsies for each region of GI [9]. Diagnosis of GERD was made based on the patients' clinical symptoms, endoscopic findings, (<15 eosinophils per HPF of esophageal biopsy). The healthy control individuals were selected from age- and sex-matched healthy children referred to the hospital for minor surgeries or check-up.

Collection of the samples and demographic data

Demographic data, including age, sex, and family history of allergy, present or histories of allergies like asthma, allergic rhinitis or atopic dermatitis, clinical manifestations of GERD, or other GI symptoms were collected using a standard questionnaire.

Skin Prick Test (SPT) for food and aeroallergens (extracts from Greer, USA) was performed for all included patients. The number of eosinophils per HPF in endoscopy or colonoscopy biopsies were reported and compared to the regional threshold. About 5 mL of venous blood samples were obtained from each patient. Their serum was isolated after centrifugation and stored at -70°C until the time of measurement.

Measurement of serum TGF-β and IL-10

Serum levels of Interleukin 10 (IL-10) and Transforming growth factor β (TGF-β) were measured using the ELISA method according to the manufacturers' instructions (R&D Systems, USA).

Statistical analysis

SPSS was used for statistical analyses and data with normal distribution were presented as Mean±SD and compared using One-way Analysis of Variance (ANOVA). Median (Min-Max) index was used where data were not normally distributed. The study variables were compared using Chi-Square and the Independent samples ttests (non-parametric tests). The level of significance was regarded as (≤0.05).

Results

Demographic data and clinical presentations

The study subjects were (62.2%) male and 37.8% female with a Mean±SD age of 8.43 (4.92) years. Male gender proportions in the EGID, GERD, and healthy control groups were (61.8%), (39.1%), and (84%), re-

spectively. There was no statistically significant difference in gender proportion among EGID with GERD or healthy groups (P=0.093 and P=0.062, respectively). But male gender was significantly frequent in the healthy group when compared to the GERD group (P=0.004). The Mean±SD age of EGID, GERD, and healthy control groups were 8.24±4.98, 8.52±4.91, and 6.56±4.11 years, respectively which were not statistically different between groups (P=0.283).

The allergic manifestation was significantly higher in patients with EGID and GERD in comparison with the healthy controls (P=0.0001) (Table 1), but there was no significant difference in allergic manifestation or family history of allergic disease between EGID and GERD groups (P =0.824) and (P=0.724), respectively (Table 2).

The results of skin prick tests showed no significant difference between the two groups of patients (P=0.375) (Table 3). Skin prick test results were positive in 24 (70.6%) patients with EGID and 13 (59.1%) patients with GERD. In the EGID group, (60%) were positive for air allergens and (58%) for food allergens. Animal dander and pollen were the most found positive air allergens. Also, wheat and egg were the most found positive food allergen sensitizations. In patients with GERD, (54%) had positive SPT for air allergens and 40% for food allergens. Animal dander and pollen, wheat and egg were the most positive air allergens and food allergens, respectively. We found no statistical difference in air allergen and food allergen sensitizations between these groups (P=0.927) and (P=0.249), respectively.

The cytokine pattern in subjects with EGID and GERD and healthy subjects

The Mean±SD serum level of TGF-β1 in patients with EGID was 868.9±68.6 pg/mL, and 690±64.3 pg/mL in patients with GERD compared to healthy controls as 641.4±47.7 pg/mL. The results of the parametric analysis showed a statistically significant difference in serum level of TGF-β1 in patients with EGID and GERD compared to the healthy controls (P=0.025) (Figure 1 A). This difference was almost significant between the four groups (upper-GI involved EGID, lower-GI involved EGID, GERD, and healthy individuals) (P=0.054) (Figure 1 B).

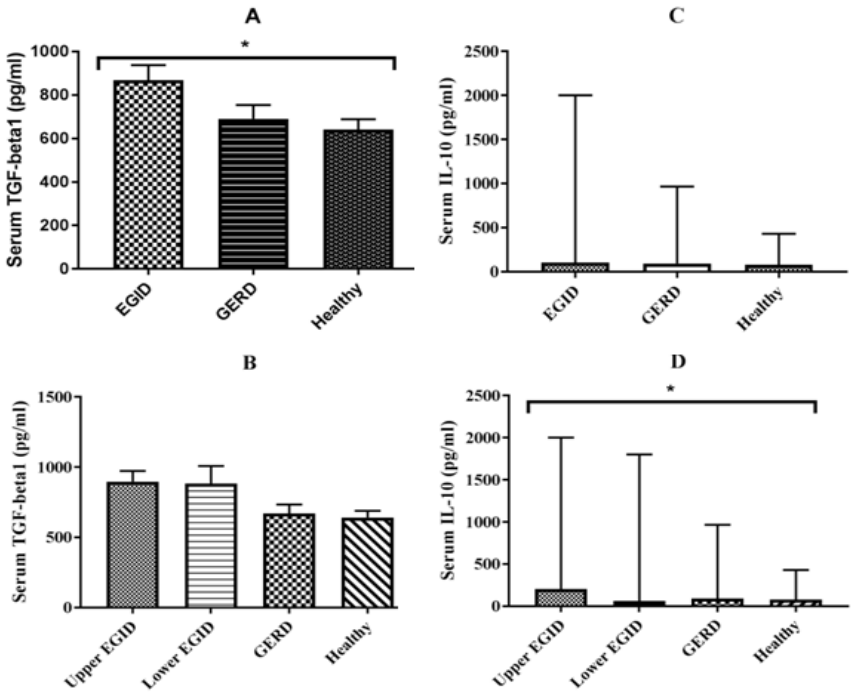

Figure 1. Comparison of serum TGF-β1 and IL-10 levels in the studied groups

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A: The serum TGF-beta1 levels in studied groups; B: The same as A when patients with EGID are divided into two distinct groups based on the involved area of the GI tract; C: The serum IL-10 levels in studied groups; D: The same as C when patients with EGID are divided into two groups based on the involved area of the GI tract.

Statistically significant differences were tested with 1-way ANOVA and the Tukey's multiple comparison test.

*P<0.05

Table 1. Comparing the prevalence of allergic manifestations history between the EGID, GERD, and control groups

Allergic manifestations	%			P		
	Subjects With EGID	Subjects With GERD	Healthy Subjects	Subjects With EGID Compared to Healthy	Subjects With GERD Compared to Healthy	Subjects with EGID compared to those with GERD
Allergy	69.7	65.2	12.5	<0.0001*	<0.0001*	0.724
Asthma	3	4.3	0.0	1.000	0.489	1.000
Atopic Dermatitis	6.1	13	0.0	0.504	0.109	0.392
Allergic Rhinitis	6.1	13	8.3	1.000	0.666	0.392
Blood in Stool	18.2	13	0.0	0.034*	0.004*	0.082
Food Allergy	48.5	38.9	4.2	0.0001*	0.004*	0.488

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GERD: Gastroesophageal reflux disease; EGID: Eosinophilic gastrointestinal disorder

* P≤0.05

Table 2. Comparing the prevalence of the family history of allergy between the EGID, GERD and control groups

Allergic Manifestations	%			P		
	Subjects With EGID	Subjects With GERD	Healthy Subjects	Subjects With EGID Compared to Healthy	Subjects With GERD Compared to Healthy	Subjects with EGID compared to those with GERD
Allergy	54.5	60.9	20.8	0.010*	0.005*	0.638
Asthma	21.2	26.1	4.2	0.121	0.048*	0.671
Atopic Dermatitis	6.1	13.0	0.0	0.504	0.109	0.367
Allergic Rhinitis	33.3	21.7	12.5	0.071	0.461	0.345
Food Allergy	12.1	21.7	0.0	0.130	0.022*	0.464

GERD: Gastroesophageal reflux disease; EGID: Eosinophilic gastrointestinal disorder

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* P≤0.05

Table 3. Positive skin test results in the subjects with EGID compared to those with GERD

Skin Test Against	(%)		Subjects With EGID Compared to Those With GERD (P)
	EGID Subjects	GERD Subjects	
Airborne allergens	55.9	54.5	0.927
Food allergens	58.8	40.9	0.249
Animal allergens	38.2	50.0	0.304
Pollen allergens	29.4	31.8	0.760
Fungal airborne allergens	14.7	18.2	0.719
Milk allergens	2.9	9.1	0.551
Egg allergens	23.5	18.2	0.750
Cereal allergens	26.5	18.2	0.745
Nut allergens	17.6	9.1	0.696
Seafood allergens	5.9	9.1	0.632
Allergens of other foods	38.2	22.7	0.268

GERD: Gastroesophageal reflux disease; EGID: Eosinophilic gastrointestinal disorder

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* P≤0.05

The median serum level of IL-10 in subjects with EGID was (103.3) pg/mL (0.0-2001.0), and (92.39) pg/mL (0.0-966.48) in GERD patients compared to (78.8) pg/mL (0.0-429.6) in the healthy controls. The results of the non-parametric analysis found no significant difference between these groups and healthy controls (P=0.520) (Figure 1 C and E). However, when patients with EGID are divided into two categories based on the involved area (upper and lower GI involved EGID), there is a statistically significant difference between the groups in serum level of IL-10 (P=0.018) (Figure 1 C and D).

Discussion

Eosinophilic Gastrointestinal Diseases (EGIDs) affect the GI tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia. The immunopathology of EGID is not fully revealed, but several studies have shown the association between EGID and atopy and food allergy. Also, some reports have highlighted the probable role of Tregs in the development of EGID [10]. Here, we studied serum levels of IL-10 and TGF-β1 as regulatory T-cell cytokines in patients with EGID, GERD, and healthy controls.

Food allergens are known as common pathogenic triggers of EGID [1]. The applicability of SPT was approved in a study conducted in 2012 on patients with EOE in the USA, which was mostly positive for cow's milk. Kagal Walla et al. showed remarkable improvement in clinical signs and histopathologic manifestations only by removing cow's milk from the patients' diet [11]. Various studies also suggest a high prevalence of positive skin test in EGID subjects for milk- and wheat-derived allergens [12, 13]. Food elimination is an effective treatment, but the finding of the culprit food allergen is a challenging issue. In one study, Four Food Group Elimination in (54%) of adult patients with EOE. A third of FFGED non-responders in the study mentioned above responded to Six Food Group Elimination Diet (SFGED), resulting in a combined efficacy of (72%) of both strategies [10]. Although medical and family history of allergy was predominantly positive in patients with EGID, we found no significant difference in the pattern of sensitivity to food allergens between patients with EGID and GERD.

Diet (FFGED) achieved clinicopathological remissionEsophageal epithelial cells of EOE patients produce thymic stromal lymphopoietin, which induces Th2 differentiation [14, 15]. Recent studies suggest a different role of regulatory T cells in pediatric and adult EOE [16]. TGF-β controls cell growth, proliferation, differentiation, and apoptosis as well as stimulation of ex-tracellular matrix proteins resulting in the development of tissue fibrosis[17]. Some studies have shown that polymorphisms in the promoter of TGF-β are associated with susceptibility to EOE [18-22]. The de-crease in the level of peripheral Tregs has been reported in patients with chronic urticaria [23]. In this re-gard, in our previous study, we showed a significant increase in Treg cell population as the main producer of TGF-β and IL-10 in the biopsy of patients with EOE using immunohistochemistry compared to the healthy and GERD subjects (unpublished data).

At the same time in another study, we showed a significant increase in circulating Treg cells in the blood of the patients with EOE compared to the healthy and GERD subjects using flow cytometry (unpublished data). The level of serum cytokines in allergic disorders has been reported differently; in patients with chronic urticaria, proinflammatory cytokines like Il-6 were significantly higher than healthy controls [24]. In this study, we found statistically significant differences between the serum levels of IL-10 and TGF-β in subjects with EGID compared to those with the GERD and healthy subjects. As the serum level of TGF-β in subjects with EGID is much higher (Figure 1 A & B) than that in the GERD patients and healthy subjects, the serum levels of these cytokines could be used as differential markers. On the other hand, we found a significant increase in serum IL-10 level in EGID patients with upper GI tract involvement in comparison with other groups (Figure 1 D).

It seems that Treg cells in these patients do not have sufficient suppressive power, which might be due to FOXP3 polymorphisms resulting in a compensatory increase in Treg cells number [25]. It has also been argued that Treg cells prevented the response of Th2 cells in non-atopic individuals, but the function of these cells was considered to be defective in allergic patients [26]. In this study, the levels of TGF-β and IL-10 in patients with EGID showed a significant increase compared to those with the GERD and healthy controls. Considering the finding of increased Treg cells in the biopsy and blood samples of EOE patients in our previous study and the results of the present study, further studies should evaluate the function of Tregs in situ to clarify the reason of the inability of these cells in controlling the inflammation.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences and

written informed consent was obtained from the parents of all participants.

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Authors' contributions

Design of the work: Delara Babaie, Sara Jafarian, Mahboubeh Mansouri, Mehrnaz Mesdaghi; Acquisition and interpretation of data: Delara Babaie, Zahra Daneshmandi, Sara Jafarian, Zahra Chavoshzadeh, Mahboubeh Mansouri, Aliakbar Sayyari, Farid Imanzadeh, Naghi Dara, Pejman Rohani, Katayoon Khatami, Maryam Kazemiaghdam, Yalda Nilipour, Maliheh Khoddami, Reza Gholami, Mehrnaz Mesdaghi, Reihane Motaghinezhad, Shima Rasouli; Revising the Manuscript: Delara Babaie, Mehrnaz Mesdaghi; Drafting of manuscript: Shima Rasouli.

Conflicts of interest

The authors declared no conflict of interest.

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