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Original Article

Gastrointestinal Challenges in Patients with Epidermolysis Bullosa: Insights from a Cross-Sectional Analysis in Iran

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ABSTRACT

Background:
In light of the relatively low prevalence of epidermolysis bullosa and the absence of research focused on gastrointestinal complications in Iran, our study sought to address this gap. Given the limited body of knowledge in this particular area, there is a crucial need to explore and identify gastrointestinal complications in patients with epidermolysis bullosa and understand the associated factors.

Materials and Methods:
The present study was conducted cross-sectionally. 67 patients with epidermolysis bullosa were selected by census and included in the study. Demographic information of patients, including age and sex, was recorded. The patients were fully examined by a gastroenterology specialist, and a history was taken for gastrointestinal diseases. The data were statistically analyzed using the SPSS software, version 28.

Results:
67 individuals with epidermolysis bullosa were evaluated for this investigation. The patients had simplex (23.9%), dystrophic (29.9%), junctional (4.5%), and unknown (41.8%) varieties of epidermolysis bullosa. Halitosis (64.2%), constipation (59.7%), food stuck in the throat (56.7%), mouth ulcers (52.2%), flatulence (50.7%), stomach discomfort and unpleasant taste in the mouth (47.8%), difficult swallowing (44.8%), and reflux (37.3%) were the most frequent gastrointestinal problems among these individuals.

Conclusion:
The current study found that gastrointestinal issues are widespread in individuals with epidermolysis bullosa; hence, it is advised that suitable preventative and therapeutic measures be implemented, as well as multispecialty therapy.

Keywords: Epidermolysis bullosa, Gastrointestinal complications, EB, Dermatology

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INTRODUCTION

Epidermolysis bullosa (EB) is a rare genetic dermatosis. A genetic condition with 30 distinct genotypes and manifestations. It is either an autosomal dominant or recessive genetic disease. At present, 20 distinct genes have been discovered for EB. The fragility of the mucosal skin and blister development distinguishes EB. Blisters are produced by a reduction in the number of proteins responsible for the integrity and cohesiveness of the skin's epidermis. In many situations, the epidermal connection ruptures, resulting in cancer on the surface of squamous cells (1-7). Based on the most recent expert categorization, EBs fall into four major types. These classifications—EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB)—reflect molecular abnormalities and are mostly dependent on the degree of cleavage in the skin. Additionally, there is a subclassification for EB that is based on extracutaneous tissue involvement, clinical phenotypic features, and the genetic path and genes found in this path. Globally, EB affects both sexes and affects one to three out of every 100,000 children annually; however, data from the United States suggest that the condition is more severe (8-10).

The disease's symptoms often start to show at birth, but in certain cases, they can not show up until later in adolescence. This can make the proper diagnosis take till maturity.

Various mutations lead to various structures in EB genetic diseases, and the severity of the disease and its clinical symptoms vary depending on which section of the gene is mutated (11, 12).

Certain disease phenotypes exhibit a wide spectrum of extracutaneous consequences that lead to mortality, along with more severe symptoms. Issues may arise at the epithelial tissue level in areas such as the heart and blood vessels, mouth, dental tissues, eyes, reproductive and urinary tract, and digestive tract. Although there is currently no proven cure for EB, early discovery helps manage extracutaneous problems, stop blistering, heal wounds that have been caused, and reduce discomfort. Significant advances in our understanding of the biology of the skin have been gained via research on EB disease. Gene editing, together with the replacement of relevant proteins and genes, has advanced clinical-cellular therapies and raised patient and physician optimism globally (13).

The current study sought to detect digestive difficulties in individuals with epidermolysis bullosa to develop preventative and therapy strategies.

MATERIALS AND METHODS

This study was carried out using a cross-sectional approach. Patients diagnosed with EB who were referred to medical training facilities associated with Shiraz University of Medical Sciences comprised the research sample. 67 individuals with EB were chosen for the research based on a census. Patients were searched using hospital and clinic records, and relevant tests were conducted, given the low occurrence of patients with EB. Patients' age and sex, among other demographic data, were noted. A gastrointestinal specialist made a thorough examination of the patients, recorded their medical history of digestive disorders, and, if required, carried out the appropriate experimental and diagnostic procedures.

Statistical analysis was performed on the data using IBM SPSS software version 28. Quantitative data in subgroups were tested for normality using the Shapiro-Wilk and Kolmograph-Sminrov tests.

Comparing quantitative data based on the normal distribution of data was done using the Mann-Whitney or independent t tests, whereas subgroup comparisons of qualitative data were done using Fisher's exact test. In every analysis, a P value of less than 0.05 was deemed significant.

Ethics consideration:

The study design and protocol were approved and monitored by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1400.355).

RESULTS:

In the present study, 67 patients were examined. The demographic information of the patients is shown in table 1.

Table 1. Demographic information of the patients

Age (years), mean (standard deviation)	15.84 (9.25)
Sex, number (percentage)	
Boy	38 (56.7%)
Girl	29 (43.3%)
Functional disorder in the family, number (percentage)	
No	61 (91%)
Yes	6 (9%)
Organic disorder in the family, number (percentage)	
No	64 (95.5%)
Yes	3 (4.5%)
Type of epidermolysis bullosa, number (percentage)	
Simplex	16 (23.9%)
Dystrophic	20 (29.9%)
Junctional	3 (4.5%)
Unknown	28 (41.8%)
History of surgery, number (percentage)	
No	65 (97%)
Yes	2 (3%)

Table 1. Demographic information of the patients

Need to consume laxatives, Number (percentage) No Yes	 34 (50.7%) 33 (49.3%)
Balloon history, number (percentage) No Yes	 51 (76.1%) 16 (23.9%)
Number of balloons, mean (standard deviation)	0.55 (1.19)
Total number of patients (percentage)	67 (100%)

The frequency of digestive problems of patients was compared according to the type of EB, but no significant difference was seen among different types of EB (P>0.05). This comparison is shown in table 2.

Table 2. Comparison of patients' digestive problems frequency according to the type of epidermolysis bullosa

Type	**Simplex**		**Dystrophic**		**Junctional**		**Unspecified**		**P value**
Digestive problems	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Constipation	7	43.8%	12	60.0%	3	100.0%	18	64.3%	0.317
Nausea	3	18.8%	3	15.0%	0	0.0%	6	21.4%	0.956
Vomit	4	25.0%	3	15.0%	0	0.0%	3	10.7%	0.612
Painful swallowing	6	37.5%	12	60.0%	0	0.0%	12	42.9%	0.237
Food stuck in the throat	7	43.8%	14	70.0%	2	66.7%	15	53.6%	0.438
Stinging sensation in the throat	2	12.5%	9	45.0%	1	33.3%	6	21.4%	0.128
The presence of blood in vomit	0	0.0%	2	10.0%	0	0.0%	1	3.6%	0.529
Indigestion	1	6.3%	2	10.0%	0	0.0%	0	0.0%	0.279
Burp	5	31.3%	2	10.0%	0	0.0%	10	35.7%	0.146
Diarrhea	1	6.3%	4	20.0%	0	0.0%	1	3.6%	0.295
Stomach ache	9	56.3%	9	45.0%	1	33.3%	13	46.4%	0.873
Fecal incontinence	0	0.0%	1	5.0%	0	0.0%	2	7.1%	0.813
The presence of bright blood in the stool	1	6.3%	0	0.0%	0	0.0%	1	3.6%	0.747
The presence of dark blood in the stool	0	0.0%	0	0.0%	0	0.0%	0	0.0%	-
Foamy diarrhea	1	6.3%	2	10.0%	0	0.0%	0	0.0%	0.279
Flatulence	8	50.0%	8	40.0%	2	66.7%	16	57.1%	0.635
Reflux	4	25.0%	5	25.0%	1	33.3%	15	53.6%	0.141
Bad breath	9	56.3%	13	65.0%	1	33.3%	20	71.4%	0.497
Bad taste in the mouth	7	43.8%	8	40.0%	1	33.3%	16	57.1%	0.623
Ulcers in the mouth	7	43.8%	12	60.0%	2	66.7%	14	50.0%	0.728
Steatorrhea	1	6.3%	1	5.0%	0	0.0%	0	0.0%	

*Fisher's exact test.

Also, the frequency of digestive problems in patients is shown in table 3.

Table 3. Frequency of digestive disorders in the patients

Digestive problems	Number	Percentage	Total
Constipation	40	59.7%	67 (100%)
Nausea	12	17.9%	67 (100%)
Vomit	10	14.9%	67 (100%)
Painful swallowing	30	44.8%	67 (100%)
Food stuck in the throat	38	56.7%	67 (100%)
Stinging sensation in the throat	18	26.9%	67 (100%)
The presence of blood in vomit	3	4.5%	67 (100%)
Indigestion	3	4.5%	67 (100%)
Burp	17	25.4%	67 (100%)
Diarrhea	6	9.0%	67 (100%)
Stomach ache	32	47.8%	67 (100%)
Fecal incontinence	3	4.5%	67 (100%)
The presence of bright blood in the stool	2	3.0%	67 (100%)
The presence of dark blood in the stool	0	0.0%	67 (100%)
Foamy diarrhea	3	4.5%	67 (100%)
Flatulence	34	50.7%	67 (100%)
Reflux	25	37.3%	67 (100%)
Bad breath	43	64.2%	67 (100%)
Bad taste in the mouth	32	47.8%	67 (100%)
Ulcers in the mouth	35	52.2%	67 (100%)
Steatorrhea	2	3.0%	67 (100%)

The average age of the patients was compared according to the presence of gastrointestinal problems, as shown in table 4.

The average age of patients with painful swallowing was significantly lower than that of patients without this problem (P<0.05).

The average age of patients with wind throat was significantly lower than that of patients without this problem (P<0.05).

The average age of patients with foamy diarrhea was significantly lower than that of patients without this problem (P<0.05).

However, in comparison of the frequency and severity of digestive problems according to the age group of patients, no significant difference was seen in any of the cases.

Table 4. Comparison of the average age of patients according to the presence of digestive problems

Digestive problems	No		Yes			
Age	Average	Sd	Average	Sd	Statistical test	P value*
Constipation	16.44	8.99	15.44	9.52	Mann-Whitney	0.547
Nausea	15.59	8.76	17.00	11.65	Mann-Whitney	0.883
Vomit	15.66	8.57	16.90	13.02	Mann-Whitney	0.826
Painful swallowing	13.12	6.92	19.20	10.70	Mann-Whitney	0.022

Table 4. Comparison of the average age of patients according to the presence of digestive problems

Digestive problems	No		Yes			
Age	Average	Sd	Average	Sd	Statistical test	P value*
Food stuck in the throat	14.48	7.50	16.88	10.38	Mann-Whitney	0.531
Stinging sensation in the throat	15.07	8.54	17.94	10.96	Mann-Whitney	0.428
The presence of blood in vomit	16.13	9.36	9.67	2.31	Mann-Whitney	0.202
Indigestion	15.29	8.50	27.67	18.15	Mann-Whitney	0.172
Burp	14.11	7.75	20.94	11.52	Mann-Whitney	0.022
Diarrhea	16.12	9.44	13.00	7.13	Mann-Whitney	0.489
Stomach ache	16.07	9.42	15.59	9.21	Mann-Whitney	0.855
Fecal incontinence	15.71	9.23	18.67	11.50	Mann-Whitney	0.554
The presence of bright blood in the stool	15.81	9.19	17.00	15.56	Mann-Whitney	0.985
The presence of dark blood in the stool	15.84	9.25	-	-	-	-
Foamy diarrhea	16.27	9.25	6.67	.58	Mann-Whitney	0.031
Flatulence	15.17	8.14	16.50	10.30	Mann-Whitney	0.797
Reflux	15.75	8.81	16.00	10.14	Mann-Whitney	0.907
Bad breath	15.15	9.33	16.23	9.30	Mann-Whitney	0.605
Bad taste in the mouth	15.01	9.17	16.75	9.41	Mann-Whitney	0.425
Ulcers in the mouth	15.83	11.57	15.86	6.65	Mann-Whitney	0.315
Steatorrhea	15.90	9.29	14.00	11.31	Mann-Whitney	0.740

Also, the frequency of digestive problems was compared according to the sex of the patients, but it was shown that there was no significant difference in any of the cases (P>0.05).

In this study, the frequency of the severity of digestive problems was compared according to the sex of the patients, and the results were obtained as follows: the frequency of moderate severity of bad taste in girls was significantly higher than that of boys, and the frequency of low severity of bad taste in girls was significantly higher. It was less than boys (P<0.05).

The frequency of moderate and severe wind in girls was significantly higher than in boys (P<0.05).

In the remaining cases, no significant difference was seen according to sex (P>0.05).

Also, at the end, the frequency of patients according to the severity of digestive problems is shown in table 5.

Table 5. Frequency of the patients according to the severity of digestive problems

Type	Simplex				Dystrophic				Junctional		
Digestive problems	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number(Percent)
Constipation	27	40.3%	15	22.4%	16	23.9%	8	11.9%	1	1.5%	67 (100%)
Nausea	55	82.1%	10	14.9%	2	3.0%	0	0.0%	0	0.0%	67 (100%)
Vomit	57	85.1%	7	10.4%	3	4.5%	0	0.0%	0	0.0%	67 (100%)
Painful swallowing	37	55.2%	15	22.4%	12	17.9%	2	3.0%	1	1.5%	67 (100%)
Food stuck in the throat	29	43.3%	15	22.4%	16	23.9%	6	9.0%	1	1.5%	67 (100%)
Stinging sensation in the throat	49	73.1%	12	17.9%	5	7.5%	1	1.5%	0	0.0%	67 (100%)
The presence of blood in vomit	64	95.5%	3	4.5%	0	0.0%	0	0.0%	0	0.0%	67 (100%)
Indigestion	64	95.5%	2	3.0%	1	1.5%	0	0.0%	0	0.0%	67 (100%)
Burp	50	74.6%	15	22.4%	1	1.5%	1	1.5%	0	0.0%	67 (100%)
Diarrhea	61	91.0%	4	6.0%	2	3.0%	0	0.0%	0	0.0%	67 (100%)
Stomach ache	35	52.2%	21	31.3%	9	13.4%	2	3.0%	0	0.0%	67 (100%)
Fecal incontinence	64	95.5%	3	4.5%	0	0.0%	0	0.0%	0	0.0%	67 (100%)
The presence of bright blood in the stool	65	97.0%	1	1.5%	1	1.5%	0	0.0%	0	0.0%	67 (100%)
The presence of dark blood in the stool	67	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	67 (100%)
Foamy diarrhea	64	95.5%	1	1.5%	1	1.5%	1	1.5%	0	0.0%	67 (100%)
Flatulence	33	49.3%	9	13.4%	13	19.4%	10	14.9%	2	3.0%	67 (100%)
Reflux	42	62.7%	12	17.9%	10	14.9%	3	4.5%	0	0.0%	67 (100%)
Bad breath	24	35.8%	18	26.9%	21	31.3%	4	6.0%	0	0.0%	67 (100%)
Bad taste in the mouth	35	52.2%	17	25.4%	15	22.4%	0	0.0%	0	0.0%	67 (100%)
Ulcers in the mouth	32	47.8%	21	31.3%	12	17.9%	2	3.0%	0	0.0%	67 (100%)
Steatorrhea	65	97.0%	1	1.5%	0	0.0%	1	1.5%	0	0.0%	67 (100%)

DISCUSSION

In the present study, digestive problems were determined in patients suffering from EB referring to medical training centers affiliated with Shiraz University of Medical Sciences. The types of EB in the 67 people studied were as follows: simplex (23.9%), dystrophic (29.9%), junctional (4.5%), and indeterminate (41.8%). The most common digestive problems in these patients include bad breath (64.2%), constipation (59.7%), food stuck in the throat (56.7%), ulcers in the mouth (52.2%), flatulence (50.7%), abdominal pain and bad taste in the mouth (47.8%), painful swallowing (44.8%) and reflux (37.3%).

The most common digestive problems in the simplex type included bad breath, abdominal pain, bloating, food stuck in the throat, and constipation. The most common digestive problems in the dystrophic type included food getting stuck in the throat, bad breath, painful swallowing, constipation, and ulcers in the mouth. The most common digestive problems in the junctional type included constipation, food stuck in the throat, and flatulence.

In this context, Freeman et al. found in a study of 224 patients that 80 (31%) had EB simplex, 119 (53%) dystrophic, and 19 (8%) junctional. Gastrointestinal problems were present in 139 patients (62%). Dysphagia caused by esophageal stricture was seen primarily in the dystrophic group (53%), and constipation was the most common digestive problem, which is in line with the findings of the present study (14). In Ergun et al.'s study, the

results showed that gastrointestinal tract involvement is a well-known extracutaneous manifestation of dytrophic EB, but it also occurs in more than half and a third of subjects with junctional and simplex EB, respectively. Lower gastrointestinal tract complaints, especially constipation and blisters around the anus, were common (15), which is in line with the findings of the present study. In the study of Freeman et al., gastrointestinal complications were present in (58%) of all patients. In EB simplex, constipation and gastroesophageal reflux (GOR) were frequently observed. Constipation was common in patients with dystrophic EB who required laxatives and, in some cases, fiber supplements (16). In the analysis of subgroups in the present study, it was shown that the average age of patients with painful swallowing, wind in the throat, and foamy diarrhea was significantly lower than that of patients without this problem.

Gastrointestinal complications in people with EB have a complex pathophysiology that varies depending on the subtype and severity of the disease. These complications are primarily attributed to the inherent fragility of the mucosal lining in the gastrointestinal tract, similar to the skin fragility characteristic of EB. This mucosal fragility can lead to the formation of blisters and erosions in various parts of the gastrointestinal tract, including the mouth, esophagus, stomach, and intestines, often caused by routine mechanical trauma such as eating or digestion. In addition, dysphagia, a common manifestation of EB, is caused by blisters in the mouth and esophagus that make swallowing painful and challenging, which, in severe cases, can lead to malnutrition and dehydration (17,18). Chronic blisters in the lower esophagus can also lead to gastroesophageal reflux disease (GERD), causing further damage to the esophagus and discomfort when eating. Repeated inflammation and scarring of the esophagus may lead to esophageal stricture, narrowing of the esophagus, and impaired passage of food. In severe cases, gastrointestinal obstructions may be caused by ulcers and blisters in the stomach or intestines, which sometimes require surgical intervention. Inadequate dietary intake, attributed to dysphagia, pain, and feeding difficulties, can lead to nutritional deficiencies, particularly in children with EB, often leading to developmental delays. Impaired wound healing characteristic of EB can also exacerbate gastrointestinal complications by preventing proper healing of mucosal injuries (3,19).

CONCLUSION

The current study's findings demonstrated that patients with EB frequently experience digestive issues. The disease's complex pathophysiological mechanisms highlight the value of a multidisciplinary approach involving dermatologists, gastroenterologists, and nutritionists to provide patients with EB with comprehensive care and support catered to their individual needs and severity. Consequently, it is advised that these patients get multispecialty care as well as the proper preventative and treatment measures.

Limitations

The most important limitation of the present study was the small number of patients, which the researchers were able to overcome to a large extent by using the patients' medical records and examining all the medical training centers covered by Shiraz University of Medical Sciences.

HUMAN ETHICS:

The study adheres to the Helsinki Declaration for medical research in humans.

CONSENT FOR PUBLICATION:

The authors agreed to have their work published in this journal.

AVAILABILITY OF SUPPORTING DATA:

The data are available upon reasonable request.

CONFLICT OF INTEREST:

The authors declare no conflict of interest related to this work.

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