Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Enhancing Growth in Epidermolysis Bullosa: Nutritional Supplements and Dietary Interventions for Children and Adolescents

Pegah Rahbarinejad (MD)[1,2], Fatemeh Sadat Hashemi Javaheri (MD)[1,2], Mostafa Shahraki Jazinaki (MD)[1,2], Hamid Reza Kianifar (MD)[3,4], Saeedeh Talebi (MD)[3,4*]

[1] *Department of Nutrition, school of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
[2] *Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran.*
[3] *Department of Pediatric, Faculty of Medicine, Mashhad University of Medical sciences, Mashhad, Iran.*
[4] *Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*

ARTICLE INFO

Article type
Original article

Article history
Received: 04 November 2023
Revised: 03 December 2023
Accepted: 08 December 2023

Keywords
Adolescents
Children
Epidermolysis bullosa (EB)
Nutritional Support

ABSTRACT

Introduction: Epidermolysis bullosa (EB) represents a diverse set of disorders that affect the skin and mucous membranes. Ensuring proper nutrition for children and adolescents with Epidermolysis Bullosa is a vital aspect of their treatment plan. The objective of this study is to demonstrate how nutritional intervention in a specialized nutrition clinic can enhance their well-being.

Methods: This longitudinal study was conducted over a 3-year period at Akbar Children Hospital, a tertiary facility affiliated with Mashhad University of Medical Sciences in Iran. The study included all patients diagnosed with EB based on clinical symptoms and genetic studies.

Results: In the present study, the median (25-75 IQR) age of the participants was 81.0 (36.0-156.0) months, and 19% of the participants were girls. The median (25-75 IQR) weight was 17.5 (10.8-24.5) kg, and the mean ± SD of height was 109.9 ± 31.1 cm. Among all types of malnutrition, there was only a significant association between gastrointestinal complications and BMI-for-age z-score (OR: 0.08, P-value=0.039) in the crude model. After adjustment, there was no significant association between gastrointestinal complications and malnutrition. The mean values of weight at the baseline, the first, and the second appointment of the study were 21.3, 21.2, and 24.8 kg, respectively. Moreover, the mean height at the baseline, the first, and the second appointment of the study were 109.4, 121.0, and 123.4 cm, respectively.

Conclusion: Regular clinic visits and tailored nutritional interventions positively impact EB patients, emphasizing the importance of managing anemia and deficiencies for their well-being.

Please cite this paper as:
Rahbarinejad P, Hashemi Javaheri FS, Shahraki Jazinaki M, Kianifar HR, Talebi S. Enhancing Growth in Epidermolysis Bullosa: Nutritional Supplements and Dietary Interventions for Children and Adolescents. Rev Clin Med. 2023;10(3): 32-40

Introduction

Epidermolysis bullosa (EB) represents a diverse set of disorders that affect the skin and mucous membranes. In certain cases, it can lead to complications in organs such as the gastrointestinal tract, eyes, and genitourinary system (1). The classification of EB has been recently updated and now comprises four main categories: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and over 35 distinct subtypes of EB. Additionally, there's an exceedingly rare form called Kindler EB (KEB) (2, 3).

***Corresponding author:** Saeedeh Talebi,*
Department of Pediatric, Faculty of Medicine, Mashhad University of Medical sciences, Mashhad, Iran.
Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
***E-mail:**talebis@mums.ac.ir*

The prevalence of EB varies across different countries. Globally, approximately 50 out of every 1 million live births are diagnosed with EB, affecting 9 out of every 1 million individuals. Among these cases, about 92% are categorized as EBS, 5% as DEB, 1% as JEB, and 2% remain unclassified (4). In India, the estimated incidence is around 54 per million live births, according to data from the National Epidermolysis Bullosa Registry. In Iran, due to the absence of a dedicated registry system, the prevalence is unknown, but our center sees around 60 patients. (5). Only one EB registry study publishing in 2021 demonstrated that in Iran, a total of 538 individuals with Epidermolysis Bullosa (EB) were recorded, which translates to approximately 6.72 patients per 100,000 persons. The distribution of these cases was nearly equal among males and females. Among the 103 patients for whom the disease type was determined by a pathologist, 78 patients (75.7%) were diagnosed with the dystrophic type, 13 (12.6%) with the junctional type, 9 (8.7%) with the simplex type, and 3 (2.9%) with the kindler type. The most frequently reported complaints among these patients were related to dysphagia, followed by issues with tooth damage (6).

Ensuring proper nutrition for children and adolescents with Epidermolysis Bullosa is a vital aspect of their treatment plan (7, 8). This is crucial because the condition increases their metabolic demands, placing added stress on their immune system and the healing process. Furthermore, the symptoms of the disease can hinder the intake and absorption of essential nutrients, potentially leading to inadequate growth and developmental challenges (7-10). Furthermore, malnutrition in individuals with EB is often a consequence of a combination of reduced food intake and heightened nutrient requirements. This condition can manifest as failure to thrive, delayed puberty, anemia, and a series of clinical and biological complications. These factors collectively contribute to the impediment or slowing down of the wound healing process (11). Additionally, nutritional depletion and protein-energy malnutrition can lead to changes in immunocompetence, potentially increasing the susceptibility of EB patients to secondary bacterial infections, as documented in various reports (12).

As a result, nutritional status is greatly impacted by various complications like malnutrition, anemia, infections, dental issues, and ultimately, growth problems. Therefore, nutritional support plays a pivotal role in managing these patients (7). The objective of this study is to demonstrate how nutritional intervention in a specialized nutrition clinic can enhance their well-being.

Materials and Method

Participants: This longitudinal study was conducted over a 3-year period at Akbar Children Hospital, a tertiary facility affiliated with Mashhad University of Medical Sciences in Iran. The study included all patients diagnosed with EB based on clinical symptoms and genetic studies. Patients were categorized into two major subtypes based on clinical manifestations and genetic assessments conducted by dermatologists: EBS, JEB, or DEB.

Data Collection

Medical History: A comprehensive medical history of the disease was collected using a checklist specifically designed for assessing the nutritional status of EB patients. In present study we follow up EB patients every month for one year. Additionally, we monitored the changes in weight and height at four-month intervals. This allowed us to calculate the mean weight and height every four months, and in the end, we analyzed the trends in these measurements over the course of one year of the study.

Dietary Requirements: Subsequently, the energy and protein requirements were estimated for each patient based on their assigned subtype.

Nutritional Support: The method of food administration and the need for nutritional support were determined, taking into account the patient's clinical subtype.

Micronutrient Supplementation: Micronutrient supplements, including iron (Fe), zinc (Zn), calcium (Ca), and vitamin D3, were prescribed and administered as needed. In EB patients with minimal blistering and no gastrointestinal involvement, their nutritional needs are similar to those of healthy children of the same age and sex. Here, we provide a complete algorithm outlining the nutritional management protocol for EB patients (Figure 1) (13).

Infection Control: Addressing skin infections is crucial in EB patients, as inflammation is a major factor contributing to growth retardation and the risk of skin cancer. We conducted wound exudate cultures and administered appropriate antibiotics in cases of active infection, based on antibiogram results.

Anemia: Iron deficiency anemia (IDA) is a common micronutrient deficiency in EB patients (14). In our center, we followed a specific treatment algorithm for patients with IDA (Figure 2).

Nutritional Assessment and Management: We conducted a thorough dietary history

assessment using a dedicated checklist for EB patients. This included information about food consistency, gastrointestinal complications, time taken for meals, method of food delivery, and vitamin or nutritional supplement intake.

In the next step, a 24-hour dietary recall was used to determine the typical meal pattern and median total energy consumption.

Energy Calculation: Energy needs in EB patients depend on three factors: actual weight, skin involvement, and the presence of sepsis. We calculated their energy requirements using an equation to obtain the target Energy intake. We then gradually increased their calorie intake based on their average intake from the 24-hour recall to achieve the target. The calculation for the energy needed for catch up growth is as follows:

Energy requirements (kcal) = (current weight × appropriate age for height (kcal/kg)) × ([percentage of body involved in sepsis + sepsis severity + energy requirements for catch up growth] + 1)

Here's a breakdown of the components in the formula:

- *Current weight:* The current weight which was measured in every appointment by scale.
- *Appropriate age for height:* Determine the appropriate age for the patient's current height and find the corresponding kcal/kg value from the below table.
- *Percentage of body involved in sepsis:* The percentage of body involved in sepsis were divided to three categories including; 1- body surface area (BSA) 20% = 0.19, 2- BSA 40% = 0., and 3- BSA 100% = 0.95.
- *Sepsis severity:* The sepsis severity was categorized to mild, moderate, and severe which were equal to 0.2, 0.4, and 0.8; respectively.
- *Energy Needed for catch up growth:* This represents the additional energy required for growth which equal to 0.1-0.2.

Protein Calculation: Protein intake was estimated at about 115-120% of the recommended dietary allowance (RDA) for their age and gender. In fact, 20% of the total energy needs were allocated to protein.

Figure 1. Developing a structured nutritional management algorithm for individuals with Epidermolysis Bullosa (EB)

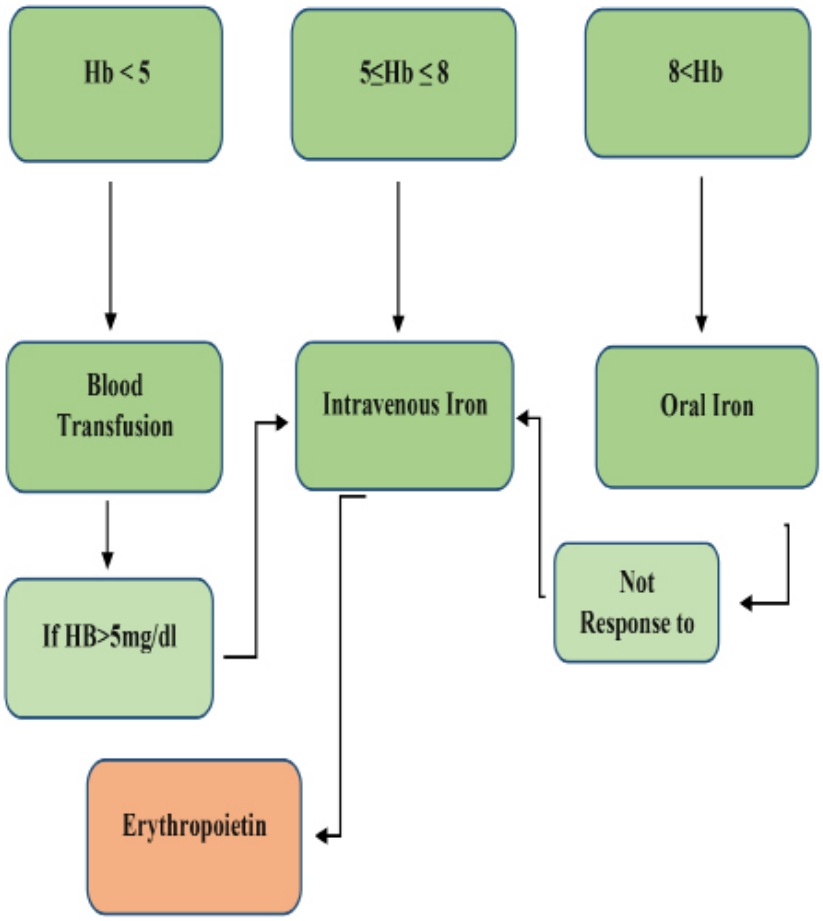

Figure 2. The treatment protocol for individuals with Epidermolysis Bullosa with Iron Deficiency Anemia (IDA)

Carbohydrates Calculation: Given that carbohydrates can increase inflammation, we restricted simple carbohydrates to less than 10% of the total energy needs. However, complex carbohydrates were increased. Specifically, complex carbohydrates with insoluble fiber were provided to patients with constipation but without dysphagia.

Fat Calculation: Around 30% of total calories were allocated from fat. To mitigate inflammation, foods enriched with omega-3 fatty acids were prescribed.

Anti-Inflammatory Diet: All these macronutrients were incorporated into anti-inflammatory diet menus tailored to each patient. The anti-inflammatory diet was designed based on the Dietary Inflammatory Index (DII).

The protocol of the present study was approved by the Institute's Ethics Committee of Mashhad University of Medical sciences (IR.MUMS.MEDICAL.REC.1401.288). The written informed was conducted the children or parents of patients (aged less than 18 years).

Results

In the present study, the median (25-75 IQR) age of the participants was 81.0 (36.0-156.0) months, and 19% of the participants were girls. Demographic, anthropometric, dietary, and clinical characteristics of the participants were presented in Table 1. The median (25-75 IQR) weight was 17.5 (10.8-24.5) kg, and the mean ± SD of height was 109.9 ± 31.1 cm.

Table 2 & 3 displays the association between the prevalence of malnutrition (by type) and sex. No significant associations were found between sex and all types of malnutrition. Furthermore, the prevalence of malnutrition based on type and severity was demonstrated in Table 4.

The comparison between energy requirement and energy intake based on the type of EB is shown in Figure 3.

Table 5 presents the association between gastrointestinal complications and malnutrition. Among all types of malnutrition, there was only a significant association between gastrointestinal complications and BMI-for-age z-score (OR: 0.08, 95% CI (0.01-0.87), P-value=0.039) in the

Table 1. Demographic, anthropometrics, dietary, and clinical characteristics of participants

variables		N (%) or Mean ± SD/ Median (25-75 IQR)
Age (month)		81.0 (36.0-156.0)
Sex	Boys	19 (40.4)
	Girls	28 (59.6)
Weight, (kg)		17.5 (10.8-24.5)
Hight, (cm)		109.9 ± 31.1
BMI		
Energy intake (kcl)		
Type of disease	Simplex	1 (2.2)
	Junctional	3 (6.5)
	Dystrophic	42 (91.3)
Mouth blister	Yes	32 (68.1)
No	15 (31.9)	
Small mouth	Yes	11 (23.4)
No	36 (76.6)	
Fixed tongue	Yes	4 (8.5)
No	43 (91.5)	
Denature tooth	Yes	28 (59.6)
No	19 (40.4)	
Reflux	Yes	15 (31.9)
No	32 (68.1)	
Dysphagia	Yes	16 (34.0)
No	31 (66.0)	
Stricture of esophagus	Yes	(14.9) 7
No	(85.1) 40	
Excess mucus excretion	Yes	(23.4) 11
No	(76.6) 36	
Regurgitation	Yes	(8.5) 4
No	(91.5) 43	
Painful defecation	Yes	(21.3) 10
No	(78.7) 37	
Bleeding with defecation	Yes	(12.8) 6
No	(87.2) 41	

crude model. After adjustment, there was no significant association between gastrointestinal complications and malnutrition (based on BMI-for-age z-score).

The mean values of weight at the baseline, the first, and the second appointment of the study were 21.3, 21.2, and 24.8 kg, respectively. Moreover, the mean height at the baseline, the first, and the second appointment of the study were 109.4, 121.0, and 123.4 cm, respectively. The trend of height changes from baseline to the second appointment of the study significantly increased based on repeated measurements of ANOVA (P-trend value were less than 0.001), while the trend of weight increased but had no significant changes (P-trend value = 0.429) (Figure 4 and Figure 5).

Among participants, the mean±SD levels of hemoglobin (Hb), RBC, MCHC, MCH, iron, and ferritin were 10.14±2.70 (g/L), 14.09±40.09 (10^{12}/L), 32.73±9.24, 23.91±11.71, 68.40±12.18

Table 2. The association between prevalence of malnutrition (by type) and sex.

Variables	Boys	Girls	P-value
WHZ, n (%)	5 (45.5)	4 (26.7)	0.476
WAZ, n (%)	3 (15.8)	5 (19.2)	0.762
HAZ, n (%)	6 (31.6)	8 (28.6)	0.636
BMIZ, n (%)	5 (31.3)	4 (20.0)	0.785

Table 3. The prevalence of malnutrition by type and severity

variables	Type of malnutrition			
	WHZ	WAZ	HAZ	BMIZ
Mild, n (%)	0	0	0	0
Moderate, n (%)	7 (14.9)	24 (51.1)	16 (34.0)	18 (38.3)
Severe, n (%)	19 (40.4)	21 (44.7)	28 (59.6)	18 (38.3)
All severity, n (%)	26 (55.3)	45 (95.7)	44 (93.6)	36 (76.6)

Table 4. The association between gastrointestinal complications and malnutrition

Variable	OR (95 % CI)	P-value
WHZ		
Model[1]	0.27 (0.03-2.02)	0.201
Model[2]	0.01 (0.01-1.48)	0.094
Model[3]	0.07 (0.003-2.02)	0.123
WAZ		
Model[1]	1.09 (0.11-10.88)	0.939
Model[2]	0.98 (0.08-11.48)	0.991
Model[3]	0.64 (0.05-8.82)	0.740
HAZ		
Model[1]	2.60 (0.27-24.65)	0.405
Model[2]	2.88 (0.26-32.11)	0.391
Model[3]	1.97 (0.15-25.44)	0.602
BMI for age z-score		
Model[1]	0.08 (0.01-0.87)	0.039
Model[2]	0.11 (0.01-2.14)	0.146
Model[3]	0.21 (0.01-6.84)	0.384

Regression logistic.
Model[1]: Crude.
Model[2]: adjusted for type.
Model[3]: Model[2] + additionally adjusted for energy intake.

Table 5. The levels of biochemical markers in EB patients.

Lab marker	Mean±SD	Minimum	Maximum
Hb (g/L)	10.14±2.70	4.30	13.60
RBC x (10^{12}/L)	14.09±40.09	3.40	208.0
MCHC	32.73±9.24	23.40	78.70
MCH	23.91±11.71	10.30	79.20
Iron (µg/dl)	68.40±12.18	38.20	96.90
Ferritin (ng/mL)	35.19±27.0	1.70	112.00

(µg/dl), and 35.19±27.0 (g/mL), respectively. The details of the levels of laboratory markers were presented in Table 5.

Discussion

This recent study was conducted to investigate the nutritional status of Epidermolysis bullosa (EB) patients referred to the nutrition clinic and examine the nutritional changes of these patients in relation to referral, intervention, and nutritional monitoring.

In the present study, gastrointestinal complications were not related to BMI-for-age z-score as an indicator related to nutritional status. Contrary to this result, in the study of Reimer et al. (15), the complications of EB patients, including esophageal stenosis, dilatation, and complications related to the side effects of gastrostomy, as well as laboratory markers indicating inflammation and anemia, were related to the developmental status of the patients.

In our study, EB patients were visited in the nutrition clinic regularly every month and were

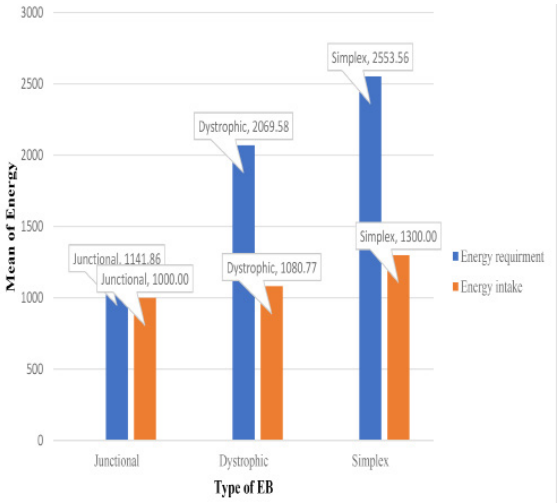

Figure 3. The comparison between energy requirement and energy intake based on type of EB

monitored and received necessary interventions. These interventions included the assessment of nutritional needs and gastrointestinal complications and taking appropriate measures to optimize the nutritional status; the trend of the height of the patients increased significantly compared to the baseline in the second appointment, while the trend of weight was not significant. These findings could be connected to a medical condition that has a greater impact on weight fluctuations (failure to thrive) than on changes in height. In this regard, in the study by Colomb et. al.(16), on severe generalized recessive dystrophic epidermolysis bullosa, who were not able to receive enough food orally, gastrostomy insertion was performed, which led to an increase in weight-for-height and height-for-age; also, people who were less than 10 years old had normal maturity experienced, but the insertion of a gastrostomy could not improve the skin condition of the patients. Similarly, in Haynes et al. study (17), the use of a gastrostomy could lead to an increase in weight standard deviation scores and height standard deviation scores, on average, by 0.9 SDS and 0.42 SDS, respectively. Our results might be related to the disease, which influenced weight gain due to more rapid changes in weight than in height.

Enhancing the growth of these individuals presents a challenge, primarily due to their substantial energy requirements that cannot be met through oral nutrition alone. In this regard, it appears that a sustainable approach, such as the implementation of gastrostomy, could offer a solution with long-lasting effectiveness. Numerous research studies have explored the impacts of PEG (percutaneous endoscopic gastrostomy) in patients with epidermolysis

bullosa (EB). Lynne Hubbard et al (18), presented body mass index (BMI), weight, and height centiles at birth, at gastrostomy placement, and at the age of 18 years. In this pilot study, two groups of EB patients were compared as follows: 12 patients with a mean of 14.5 years who had gastrostomy as group 1, and 5 patients with 18 years who had declined gastrostomy placement as group 2. As a result, compared with group 2, the mean of BMI, weight, and height centiles in the group were significantly higher; and half of group 1 had improved their centile position. In another study conducted by Hubbard et al. in 2014 (19), gastrostomy implantation led to an improvement in the patient's quality of life. The reason for the positive effect of nutritional interventions aimed at optimizing the intake of calories and protein, especially gastrostomy, on the nutritional status of patients can be due to the existence of chronic malnutrition, digestive symptoms that reduce food intake, and chronic inflammation in these patients, as the study of the cohort of Reimer et al. (2020) (15) illustrated that over 50% of children had wasting and/or stunting. At our institution, the routine implementation of this procedure is not standard practice, and as a result, none of our patients have undergone PEG implantation, which may influence the ultimate outcomes.

Epidermolysis bullosa, particularly recessive dystrophic EB (RDEB), often causes chronic anemia due to a complex interplay of factors like iron deficiency, systemic inflammation, poor nutrition, and anemia of inflammation from skin ulcers (20). Gastrointestinal problems further complicate management. Diagnosing iron deficiency is challenging due to poor oral intake, reduced iron absorption, and inconclusive ferritin markers. STfR levels remain unaffected by systemic inflammation, aiding in distinguishing iron-deficiency anemia from inflammation-related anemia using the STfR/ferritin ratio. Standard oral iron therapy may have limited effectiveness, necessitating enteral absorption tests and, in severe cases, erythropoietin. Vitamin C supplements improve iron absorption (21), and monitoring for cardiac toxicity during iron therapy is essential . Tailored approaches are essential for comprehensive anemia management in RDEB patients (15). In EB patients, anemia is a life-threatening problem that is induced by various causes, including iron deficiency, inflammation, poor nutritional status, and blood loss from the wound (15). In Pope et al. reported that hemoglobin (Hb) levels below 10g/dl make wound healing difficult in patients with venous ulcers secondary to decreased tissue oxygenation (11). In our study, among all patients, 24.6% participants were in Hb > 10 g/dl category, 8.7% were included in 8 ≤ Hb ≤10 g/dl category, and 10.1% were belong to hemoglobin 8 < g/dl category. Reimer et al.'s study recommends oral or intravenous iron in patients with iron deficiency anemia; however, iron supplementation was not suggested due to complications such as constipation and gastrointestinal symptoms (15). The strategy for iron deficiency treatment is still under discussion and appropriate management should be considered (15).

Strengths

The strengths of this study include being the first to investigate the relationship between regular visits to a nutrition clinic by EB patients and the nutritional interventions and monitoring that result from these visits. It is also the first study conducted on the Iranian population of patients with epidermolysis bullosa. This study examined the energy requirements of patients with EB and the energy they received based on their disease subgroup, including dystrophic epidermolysis bullosa (DEB), junctional epidermolysis bullosa (JEB), and epidermolysis bullosa simplex.

Limitations

This longitudinal study has several limitations, including a small sample size, no assessment of blood micronutrient status, including vitamins and minerals, a relatively brief duration of the study, existence of some confounding factors such as age, sex, growth hormone levels and nutrients and economic status, and lack of determining the severity of damage to digestive tract tissues. Furthermore, a lack of detailed specification regarding all the interventions conducted individually, the impossibility of using gastrostomy as a supplementary feeding route due to the unwillingness and economic status of the patients, and a failure to distinguish variations in the number of changes among the different types of EB diseases were other limitations of this study.

Recommendations

To address these limitations, it is suggested that future studies should involve larger sample sizes and extend the study duration. Additionally, they should take into account the differences between various types of EB diseases to gain a more comprehensive understanding of the effectiveness of nutritional interventions in improving undernutrition and alleviating disease symptoms. This would contribute to a more robust and nuanced evaluation of the impact of

nutritional management on EB patients.

Conclusion

Patients with Epidermolysis Bullosa benefit from routine clinic visits, and tailored nutritional interventions such as providing nutritional support to ensure sufficient energy and protein intake, prescribing nutrient supplements according to the needs and conditions of each patient, and other necessary measures, as well as managing anemia and deficiencies for their well-being.

Abbreviation

EB: Epidermolysis Bullosa
EBS: Epidermolysis Bullosa Simplex
JEB: Junctional Epidermolysis Bullosa
DEB: Dystrophic Epidermolysis Bullosa
KEB: Kindler Epidermolysis Bullosa
RDEB: Recessive Dystrophic Epidermolysis Bullosa
IDA: Iron Deficiency Anemia
Hb: Hemoglobin

Authors' Contributions

The authors hereby appreciate the great contributions of the study participants. Overall, S.T. and P.R., and H.K. supervised the project and approved the final version of the manuscript to be submitted. P.R., S.T., H.K., F.H. and M.S. designed the research. P.R. analyzed and interpreted the data; S.T. critically reviewed the manuscript; P.R, F.H., and M.S. drafted the initial manuscript.

Ethics approval and consent to participate

The protocol of the present study was approved by the Institute's Ethics Committee of Mashhad University of Medical sciences (IR.MUMS.MEDICAL.REC.1401.288). The written informed was conducted the children or parents of patients (aged less than 18 years).

Consent of publication

Not applicable.

Competing of interest

We do not have any conflict of interest (financial or other) other than those declared. All of authors have read the final version of the manuscript and the corresponding author responsible for what is said in it.

Availability of data and materials

All data from this study are included in the publication article.

Funding

This project was funded by Mashhad University of Medical sciences (MUMS).

Acknowledgments

We express our gratitude to Akbar Children's Hospital for their invaluable contribution to conducting this study.

References

1. Intong LR, Murrell DF. Inherited epidermolysis bullosa: new diagnostic criteria and classification. Clinics in dermatology. 2012;30(1):70-7.
2. Has C, Bauer J, Bodemer C, Bolling M, Bruckner-Tuderman L, Diem A, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. British Journal of Dermatology. 2020;183(4):614-27.
3. Salera S, Tadini G, Rossetti D, Grassi FS, Marchisio P, Agostoni C, et al. A nutrition-based approach to epidermolysis bullosa: Causes, assessments, requirements and management. Clinical Nutrition. 2020;39(2):343-52.
4. Prasad A. Epidermolysis bullosae. Medical Journal, Armed Forces India. 2011;67(2):165.
5. Grover S. Generalised recessive dystrophic epidermolysis bullosa in two sisters. Indian Journal of Dermatology, Venereology and Leprology. 2001;67:205.
6. Farokhforghani S, Fatemi MJ, Ghanooni P, Asadpour F, Araghi S, Nouri A. Epidermolysis bullosa registry data in Iran. World Journal of Plastic Surgery. 2021;10(3):99.
7. Zidorio APC, Dutra ES, Leão DOD, Costa IMC. Nutritional aspects of children and adolescents with epidermolysis bullosa: literature review. Anais brasileiros de dermatologia. 2015;90:217-23.
8. Haynes L. Nutrition in epidermolysis bullosa for children over 1 year of age. DebRA [accessed Sept 02, 2021]; 2008.
9. Manjunath S, Mahajan R, De D, Handa S, Attri S, Behera BN, et al. The severity of malnutrition in children with epidermolysis bullosa correlates with disease severity. Scientific Reports. 2021;11(1):16827.
10. Ingen-Housz-Oro S, Blanchet-Bardon C, Vrillat M, Dubertret L. Vitamin and trace metal levels in recessive dystrophic epidermolysis bullosa. Journal of the European Academy of Dermatology and Venereology. 2004;18(6):649-53.
11. Pope E, Lara-Corrales I, Mellerio J, Martinez A, Schultz G, Burrell R, et al. A consensus approach to wound care in epidermolysis bullosa. Journal of the American Academy of Dermatology. 2012;67(5):904-17.
12. Gruskay DM. Nutritional management in the child with epidermolysis bullosa. Archives of Dermatology. 1988;124(5):760-1.
13. Kianifar H, Talebi S. The effect of oral budesonide liquid therapy to alleviate clinical symptoms in patients with epidermolysis bullosa. Reviews in Clinical Medicine. 2022;9(4):156-8.
14. Simpson B, Tarango C, Lucky AW. Clinical algorithm to manage anemia in epidermolysis bullosa. Pediatric Dermatology. 2018;35(5):e319-e20.
15. Reimer A, Hess M, Schwieger-Briel A, Kiritsi D, Schauer F, Schumann H, et al. Natural history of growth and anaemia in children with epidermolysis bullosa: a retrospective cohort study. British Journal of Dermatology. 2020;182(6):1437-48.
16. Colomb V, Bourdon-Lannoy E, Lambe C, Sauvat F, Hadj Rabia S, Teillac D, et al. Nutritional outcome in children with severe generalized recessive dystrophic epidermolysis bullosa: a short-and long-term evaluation of gastrostomy and enteral feeding. British Journal of Dermatology. 2012;166(2):354-61.
17. Haynes L, Atherton DJ, Ade-Ajayi N, Wheeler R, Kiely EM. Gastrostomy and growth in dystrophic epidermolysis bullosa. Br J Dermatol. 1996;134(5):872-9.
18. Hubbard L, Haynes L, Sklar M, Martinez A, Mellerio J. The challenges of meeting nutritional requirements in children

and adults with epidermolysis bullosa: proceedings of a multidisciplinary team study day. Clinical and experimental dermatology. 2011;36(6):579-84.
19. Hubbard LD, Mayre-Chilton K. Quality of life among adults with epidermolysis bullosa living with a gastrostomy tube since childhood. Qualitative Health Research. 2015;25(3):310-9.
20. Augsburger BD, Lucky AW, Marathe K, Tarango C. Enteral iron absorption in patients with recessive dystrophic epidermolysis bullosa. Pediatric Dermatology. 2020;37(5):817-20.
21. Lynch SR, Cook JD. Interaction of vitamin C and iron. Ann N Y Acad Sci. 1980;355:32-44.