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Nutritional status of pediatric patients with epidermolysis bullosa. A cross-sectional study

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ABSTRACT

Epidermolysis bullosa (EB) is a genetic disorder with continuous formation of blisters and erosions in the skin and mucous membranes as well as multi-systemic involvement. Patients are at high-risk of malnutrition due to decreased food intake and increased nutrient demand. This cross-sectional retrospective study evaluated the daily caloric intake and nutritional status of pediatric patients with EB at a specialized clinic through anthropometric measurements and estimation of the daily intake by 24-hour dietary recall. We used the Waterlow and World Health Organization (WHO) malnutrition classification schemes. Descriptive statistics were used. We included 17 patients with a mean age of 8.4 years (SD 4.6), 82.3% had malnutrition. Those with more severe subtypes, junctional and recessive dystrophic EB, had acute superimposed on chronic malnutrition (100% and 63.4% respectively), wasting (100% and 72.6%), and stunting (0% and 54.4%) more frequently. Most patients required supplementation (caloric 76.4% and vitamin/mineral 100%).

We concluded that there is a high frequency of malnutrition in our EB patients. Although their energy requirements is calculated to be increased in 100-150% of the estimate, our patients only reach 73.1% of that, thus requiring supplementation. Patients with more severe subtypes of EB had chronic malnutrition more frequently. Even though malnutrition is closely linked to wound healing and adequate growth and development of patients, there are few studies about nutrition in EB worldwide. We believe evaluating the nutritional status of these patients is the first step to identifying deficiencies, offering adequate comprehensive medical care and establishing nutritional interventions in a timely manner.

KEY WORDS

Nutritional status, epidermolysis bullosa, malnutrition, pediatrics.

ABBREVIATIONS

EB: Epidermolysis bullosa.

WHO: World Health Organization.

EBS: Epidermolysis bullosa simplex.

JEB: Junctional Epidermolysis bullosa.

DEB: Dystrophic Epidermolysis bullosa.

DDEB: Autosomal dominant dystrophic Epidermolysis bullosa.

RDEB: Recessive dystrophic Epidermolysis bullosa.

FAO: Food and Agriculture Organization.

UNU: United Nations University.

BMI: Body mass index.

CDC: Centers for Disease Control.

HFA: Height-for-age.

WFH: Weight-for-height.

THINC: Tool to Help Identify Nutritional Compromise.

EB CPG: Clinical Practice Guidelines for Nutrition Support in infants and children with EB.

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INTRODUCTION

Epidermolysis bullosa (EB) is a genetic disorder with continuous blister formation and erosions in the skin and mucous membranes due to structural abnormalities in the skin integrity. There are three main types according to altered dermo-epidermal junction structural proteins: EB simplex (EBS), junctional EB (JEB) or dystrophic EB (DEB); and either autosomal dominant EB (DDEB) or recessive EB (RDEB). The prevalence in the United States of America is estimated at approximately 11.07 cases per 1 million population[1,2].

Patients with EB, especially those with JEB and RDEB, have severe multi-systemic involvement and high-risk of malnutrition due to decreased food intake, chronic disease, esophageal stenosis and increased nutrient demand secondary to constant epithelial repair[3] **(Figure 1)**.

The energy requirements in EB range from 100-150% of those estimated for healthy children of the same age[4]. The most frequently associated nutritional deficiencies are vitamin A, D and B6, iron, zinc, selenium and folate. Vitamin C, carnitine and omega-3/n-3 fatty acids supplementation is also suggested[5].

OBJECTIVES

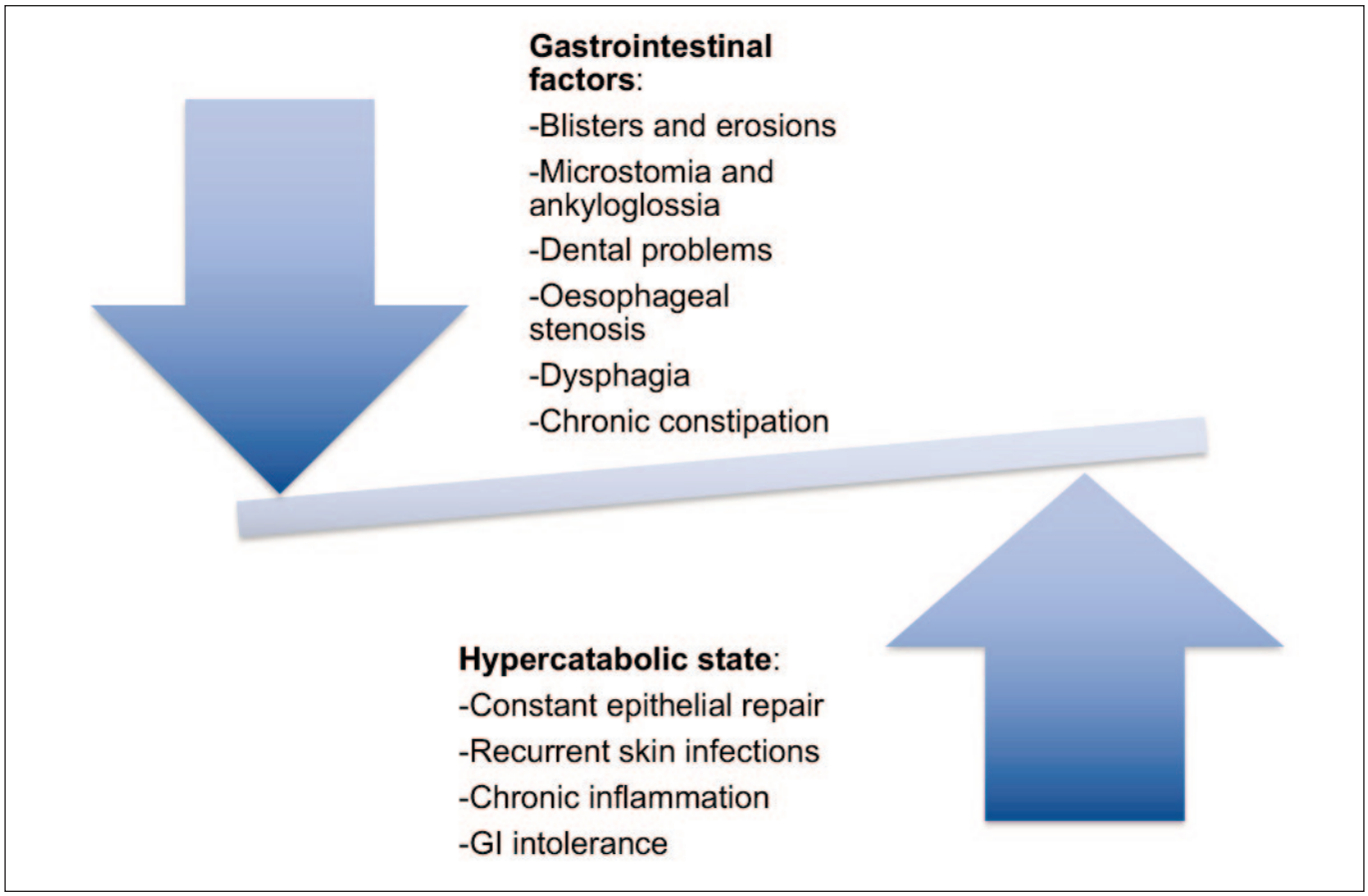
This study aimed to describe the nutritional status of pediatric patients with EB cared for at a reference center.

MATERIALS AND METHODS

We conducted a cross-sectional retrospective study to evaluate the daily caloric intake and nutritional status of pediatric patients with EB. All consecutive patients who attended our institution´s specialized multidisciplinary EB clinic during the period between January 2015 to February 2019 and accepted to participate were included. This resulted in a sample of 17 patients with a mean age of 8.4 years (SD 4.6), 64.7% were male. Almost all (94.1%) had DEB, either dominant (5 patients) or recessive (11 patients), and one patient had JEB**.**

Nutritional status was evaluated through anthropometric measurements, and estimation of the daily caloric intake was conducted by a single 24-hour dietary recall. The energy requirements of each patient were calculated using the Food and Agriculture Organization (FAO)/ World Health Organization (WHO)/ United Nations University (UNU) equation, corrected for stress factors according to nutritional sta-

Figure 1. Factors affecting nutritional balance[1,2]



tus (stress factors of 1.3, 1.4 and 1.5 correspond to mild, moderate and severe malnutrition, respectively), and cutaneous involvement (1.5, 1.4 and 1.2 correspond to mild, moderate and severe involvement).

Given the skin fragility of these patients, the anthropometric measurements consisted only of weight, height and body mass index (BMI).

A trained individual performed measurements using standardized techniques and devices (stadiometer Seca® 213 and digital scale Seca® 954). Percentiles were calculated using reference charts from the WHO for children under 2 years, and from the Centers for Disease Control (CDC) for children aged 2 to 20[6,7]. We used the Waterlow and WHO malnutrition classification schemes[8] (**Table 1)**.

Descriptive statistics were used with dispersion measurements for continuous variables, and percentages and frequencies for categorical variables (SPSS Statistics, 21.0.NY: IBM Corp.).

RESULTS

When classified by EB subtype, the 12 patients with the most severe subtypes (JEB and RDEB) were found to have acute superimposed on chronic malnutrition, wasting, and stunting more frequently. At a mean age of 8.4 years, 81.8% of patients with RDEB had a level of malnutrition, 72.7% had wasting and 54.5% had stunting. One patient with JEB had severe wasting. Patients with DDEB had mild acute malnutrition in 80% or a normal nutritional status in 20% **(Table 2).**

Only 2 patients (11.7%) reached their total daily caloric requirements, the mean total intake being 73.1% of that recommended. Thus, 13 (76.4%) patients required caloric supplementation with either homemade (54%) and/or commercial ready-made supplements (46%). Vitamin/mineral supplementation was prescribed in 100% of the patients [vitamin C (70.58%), zinc (64.7%), vitamin D and omega 3 (52.94%)].

DISCUSSION

In this study, we found a high frequency of malnutrition in EB patients (82.3%). Patients with the more severe subtypes (RDEB and one patient with JEB) had chronic malnutrition, wasting and stunting more frequently, which is consistent with data reported in the literature[3]. In a retrospective study of 200 children with RDEB, weight impairment started at 1 year of age and, by age 8, 50% of patients showed wasting[9]. Kim et al found 97% of patients with EB had appropriate nutritional parameters for gestational age at birth, but as years went by, 60% developed growth failure. Specifically, patients with severe subtypes such as DEB and JEB presented moderate / severe wasting in 85% and 100%, respectively[11]. Patients with these subtypes may require eventual nasogastric tube or gastrostomy placement to maintain adequate nutritional intake. In general terms, nutritional status is less compromised in other EB subtypes such as EBS and DDEB, but patients with severe EBS may also have major complications and poor nutritional status[5]. Even though reports of growth retardation in DDEB patients are rare, 80% of our patients with this subtype had mild acute malnutrition[1].

Table 1. Malnutrition classifications and definitions

	Classification	Grade	Definition
Waterlow	Eutrophic (WFH and HFA > 95%)		
	Acute malnutrition or wasting (WFH < 90% and HFA > 95%)	Mild Moderate Severe	WFH = 80-89% WFH = 70-79% WFH < 70%
	Chronic malnutrition or stunting (WFH > 90% and HFA < 95%)	Mild Moderate Severe	HFA = 90-94% HFA = 85-90% HFA < 90%
	Acute superimposed on chronic malnutrition (WFH < 90% and HFA < 95%)	Mild Moderate Severe	HFA = 90-94% HFA = 85-90% HFA < 90%
World Health Organization (WHO)	Wasting (WFH z score below median WFH)	Moderate Severe	z score = -2 to -3 z score < -3
	Stunting (HFA z scores below median HFA)	Moderate Severe	z score = -2 to -3 z score < -3

HFA, Height-for-age; WFH, Weight-for-height[3].

Table 2. Clinical characteristics of the patients with EB

Clinical characteristic	All patients n=17	JEB n=1	DDEB n=5	RDEB n=11
	Mean (SD), n (%)			
Age in years	8.4 (4.6)	12	7.6 (6)	8.46 (3.9)
Gender Male Female	11 (64.7%) 6 (35.2%)	1 (100%) 0	4 (80%) 1 (20%)	6 (54.5%) 5 (45.4%)
Weight (kg)	21.6 (12.1)	25	25.4 (16.4)	19.5 (9.6)
Height (cm)	117.9 (31.41)	140	118.3 (43.1)	115.7 (25.1)
Height-for-age (HFA)%	93.4 (6.4)	93.9	99.8 (1.6)	90.5 (5.9)
Height Z score	-1.5 (1.4)	-1.24	-0.15 (0.1)	-2.1 (1.3)
Weight-for-height (WFH)%	83.8 (8.03)	75.75	86.3 (5.04)	83.4 (8.8)
Weight Z score	-2.4 (1.9)	-3.03	-0.7 (0.7)	-3.2 (1.9)
Body mass index (BMI) (kg/m^2)	14.2 (2.07)	12.76	16.1 (0.7)	13.6 (2.05)
BMI Z score	-2.2 (1.9)	-3.86	-0.8 (1.2)	-2.7 (1.9)
Nutritional diagnosis				
Waterlow classification				
Normal	3 (17.6%)	0	1 (20%)	2 (18.1%)
Acute malnutrition				
1. Mild	5 (29.4%)	0	4 (80%)	1 (9%)
2. Moderate	0	0	0	0
3. Severe	0	0	0	0
Acute superimposed on chronic malnutrition				
4. Mild	3 (17.6%)	0	0	3 (27.2%)
5. Moderate	4 (23.5 %)	1 (100%)	0	3 (27.2%)
6. Severe	1 (5.8%)	0	0	1 (9%)
Chronic				
7. Mild	1 (5.8%)	0	0	1 (9%)
8. Moderate	0	0	0	0
9. Severe	0	0	0	0
WHO classification				
Wasting	4 (23.5%)	0	0	4 (36.3%)
10. Moderate	5 (29.4%)	1 (100%)	0	4 (36.3%)
11. Severe				
Stunting	3 (17.6%)	0	0	3 (27.2%)
12. Moderate	3 (17.6%)	0	0	3 (27.2%)
13. Severe				

DDEB: dominant dystrophic epidermolysis bullosa; JEB: junctional epidermolysis bullosa; RDEB: recessive dystrophic epidermolysis bullosa.

The aims of nutritional intervention in EB are to reduce the anxiety caused by long feeding times, minimize deficiencies, optimize growth and development, and improve intestinal transit, immunological status, and wound healing[3,10]. Our data is consistent with previous studies that revealed a profound nutritional deficit in EB patients, including micronutrient and vitamin deficiencies[9,11,12]. Vitamin D, zinc and selenium deficiencies are common in patients with EB, especially RDEB and DEB[9]. Reimer et al. suggest that nutritional supplementation should always be administered; Zidorio et al. concluded that it should be recommended based on the patient's dietary intake; and Haynes propose a dose of 150-200% of the normal recommended intake. We recommend that micronutrient supplementation should be administered to all EB patients at the dose proposed by Haynes that ensures intake doesn't exceed tolerable upper intake levels[3,4]. Unfortunately, our patients had suboptimal adherence to the prescription, and only 47% complied with micronutrient supplementation.

In this study, we focused on evaluating nutritional status through anthropometric measurements. However, the natural history of patients with severe subtypes of EB is characterized by a progressive alteration in nutrient levels and markers of anemia; and significant positive correlations have been found between weight Z scores in RDEB and levels of hemoglobin, albumin and micronutrients[9]. Reimer et al found 56% of patients with RDEB and 22% of those with JEB had low albumin levels, and anemia was present in 91% and 75% of patients with these subtypes, respectively[9]. Kim et al report 33% of patients presented a hypoalbuminemic event at some point during follow-up[11]. Thus, it is vital to supplement deficiencies identified in each patient and conduct frequent monitoring, at least every 6 months. Early intervention is a key point for reducing growth impairment. Reimer et al. propose starting nutritional intervention before the age of two years. We suggest beginning the intervention as soon as the patient is diagnosed. Even if the diagnosis is made before the age of two, the intervention can begin with dietary advice and parental nutritional education.

The tools we used in this study to evaluate adequacy of growth in patients are the WHO and CDC charts, and Waterlow and WHO malnutrition classification schemes. It is recommended to use WHO charts for children under 2 years and those from the CDC for children aged 2 to 20[6,7,8]. Although these tools are well-recognized methods of evaluating growth in children, they may have limitations when used to evaluate EB patients, especially those with the more severe subtypes. Nowadays both classifications remain useful[8].

There are other useful tools for managing EB patients, such as Tool to Help Identify Nutritional Compromise (THINC)[13], Clinical Practice Guidelines for Nutrition Support in infa[n]ts and children with EB (EB CPG)[13,], and the recently published personalized growth charts for JEB and RDEB[9].

The THINC's scoring chart measures the risk of nutritional compromise, it is composed of items regarding different aspects of life affected by EB involving three domains: weight and length/height, gastroenterology, and dermatology. There are 2 charts adapted for age groups younger than and older than 18 months. The scores obtained from each item are added and transformed into a score on a scale of 0 to 100; higher values indicate a greater risk of nutritional compromise. Suggested actions for ranges of THINC scores are given in the algorithms found in the EB CPG.

The growth charts developed in 2019 by Reimer et al. result from analysing the course of growth in 200 EB patients aged 0-25 years. These specialized charts (height-for-age, weight-for-age and BMI) are specific for girls and boys with RDEB and JEB. They were calculated using the modified LMS-method. When compared to WHO charts, these new charts have a less smooth appearance of growth curves. Although they may be especially useful for assessing time points for nutritional interventions, they are limited to some subtypes[9]; and unfortunately, were not available at the time of our study.

Even though patients with EB have increased energy requirements[4] (100-150% of the estimate), those included in this cohort only reached 73.1% of it; thus requiring caloric supplementation. Adherence to nutritional therapy may be suboptimal due to either low socioeconomic status[14] or familiar dysfunction / burnout (not uncommon in patients with EB and their families)[13]. This leads to perpetuation of the cycle of malnutrition and, in some cases, worsening of nutritional status. In our institution, caloric supplementation is indicated with either commercially available products (PediaSure® or Ensure®), or, for those patients whose socioeconomic conditions make it impossible, homemade preparations. Our team's nutritionist calculates patients' nutritional requirements and designs the preparation taking into account gastrointestinal function, EB subtype, disease severity, as well as tailoring according to family dynamics and social circumstances like it is recommended[3]. This blenderdized supplement is composed of water and macronutrients (proteins, lipids, and carbohydrates) to which micronutrients (vitamins, minerals, and trace elements) are added in adequate amounts. It is made using fresh food common in our population´s diet[15]. Patients are explained how to prepare the mixture and we provide them a chart of the Equivalent Food System[16] so that they can choose their food according to their indicated rations.

The main limitation of our study is the reduced sample size due to the rareness of EB, and the absence of EBS patients due to selection bias. Due to this, conclusions cannot be generalized. However, there are very few studies on nutrition in EB worldwide, and this is the first in pediatric patients from a middle-income country[4,11,12].

CONCLUSIONS

In this study we found a high frequency (82.3%) of malnutrition in EB patients. Moreover, patients only reached 73.1% of the recommended energy requirements. Evaluating the nutritional status of patients with EB is the first step to identifying deficiencies, offering adequate comprehensive medical care, and establishing interventions to prevent and treat malnutrition timely, as this is closely linked to wound healing and adequate growth and development. Nutritional support is challenging; therefore, it is essential that a specialist in nutrition be part of the multidisciplinary team that cares for patients with EB.

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