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Influence of the nutritional status in the clinical and therapeutical evolution in adults and elderly with American Tegumentary Leishmaniasis

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ABSTRACT

The objective of this study is to describe the nutritional status of adult and elderly patients with American Tegumentary Leishmaniasis (ATL). It was conducted a longitudinal study in 68 adult and elderly patients with ATL treating at the Surveillance Leishmaniasis Laboratory at the Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation (Fiocruz), from 2009 to 2012. The nutritional assessment included the body mass index (BMI) and serum albumin levels. The clinical evolution (epithelialization and wound healing) was measured up to two years after ATL treatment. Most of the sample was composed of men (71%), adults (73%), with household income of 1–5 minimum wages (79%), and incomplete elementary school (48.5%). The predominant ATL form was cutaneous (72%), and 39% presented comorbidities, the most frequent was hypertension (30.8%). The most prevalent clinical and nutritional events were: recent decrease in food intake (23.9%); nasal obstruction (22.1%); oral ulcer (14.7%), anorexia and dysphagia (13.2% each) and odynophagia (10.3%). The total healing time was 115.00 (IR = 80–230) days for skin lesions, and 120.00 (IR = 104.50–223.50) days for mucous membrane lesions. Low body weight in 10%, and hypoalbuminemia in 12% of the patients have been observed. Low body weight was associated with age, mucosal leishmaniasis (ML), nasal obstruction, recent decrease in food intake and hypoalbuminemia. As for serum albumin depletion, association with the ML, dyspnea, dysphagia, odynophagia, recent decrease in food intake, absence of complete healing of the skin lesions, and increased healing time for mucous membrane lesions, was observed. The ML and their events that affect the alimentary intake have been related to the impairment of the nutritional status. Additionally, serum albumin depletion negatively affected the healing of the lesions, suggesting that a nutritional intervention can increase the effectiveness of the ATL treatment.

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1. Introduction

American Tegumentary Leishmaniasis (ATL), an infectious and non-contagious disease caused by *Leishmania* protozoan, is transmitted by the bite of female phlebotomine sandflies, and it affects the skin and mucous membranes of upper airways and upper digestive tube. The main ATL agent in Brazil is *Leishmania (viannia) braziliensis*. In cutaneous leishmaniasis (CL) the wound is painless and located on exposed areas of the skin (Conceição-Silva et al., 1990; Ministry of Health/Brazil, 2010). Mucosal leishmaniasis (ML) may occur several years after the healing of the primary wound (Jones et al., 1987; Ministry of Health/Brazil, 2010).

The nasal mucosa is the area most affected by ML, which can also develop in the pharynx, larynx, and oral cavity. ML is associated with high morbidity, and may lead to deformities and mutilations, impairing food intake, and hindering respiration and phonation. Early diagnosis of ML is important for a more effective therapeutic response, and also to prevent deforming and functional sequels (Lessa et al., 2007; Mota and Miranda, 2011).

Swallowing is a complex process undergoing neural control that involves the oral cavity, pharynx, and esophagus, and allows conduction of the oral content to the stomach. Any difficulty in this process is called dysphagia, and may lead to malnutrition, weight loss, and dehydration (Silva and Ikeda, 2009). Amongst the symptoms of ML, those more related to decrease the food intake are nasal obstruction, dysphagia and odynophagia. Nasal obstruction, in addition to modifying the sense of smell and the food taste, leads to oral breathing, modifying chewing and swallowing patterns (Popoaski et al., 2012).

The immunity and susceptibility to infectious and parasitic diseases are directly related to the nutritional status of the host (Keush, 2003; Malafaia, 2008). Furthermore, the infection causes deterioration of the nutritional status (Keush, 2003). Severe protein-calorie malnutrition decreases humoral and cellular immune function, therefore reducing to fractions the complement system, the number, proliferation, and function of circulating lymphocytes T (thus decreasing the production of cytokines), and modifies the recognition of antigens (Anstead et al., 2001; Schaible and Kaufmann, 2007; Maciel et al., 2008; Malafaia, 2008).

In addition to stimulating the immune system, the macro and micronutrients (vitamins and minerals) also participate in the wounds' healing process (Anderson, 2005). Proteins and amino acids are essential for tissue repairing through neovascularization, fibroblasts and collagenous depositions, and lymphocytes production (Russell, 2001). The protein depletion, in turn, inhibits fibroblastic proliferation and lengthen the inflammatory phase period, decreases collagen synthesis, decreases the wound tensile force, limits the phagocytic capacity of the leukocytes, and increases the infection rate (Anderson, 2005).

Nutritional assessment is a method that allows to determine the nutritional status, quantifying and characterizing the malnutrition degree, as well as tracking the nutritional risk, and assessing the individual's energy requirements (Blackburn and Bistrian, 1977; Ministry of Health/Brazil, 2011).

In CL, some experimental studies have demonstrated the influence of the energy-protein malnutrition in the course of the illness (Pérez et al., 1979; Taylor et al., 1996). However, there are few clinical studies correlating ATL with the nutritional state. It was described that the nutritional status is a factor associated with mucosal leishmaniasis (Machado-Coelho et al., 2005).

Knowing that ATL progresses with cutaneous and mucous wounds, and that several nutrients are important for the activation of the immune system and for healing the wounds, it becomes necessary to assess the nutritional status in patients with this condition. In our belief this is the first study that describes the nutritional status of adult and elderly patients with ATL in order to evaluate its role both in the disease evolution and in the process of healing the wounds.

2. Materials and methods

2.1. Subjects and selection criteria

A longitudinal study was conducted in 68 patients with confirmed diagnosis of ATL, using one or more of the following methods: isolation of promastigote forms in culture, visualization of amastigote forms in direct examination, or the histopathological studies, or parasitic DNA detection by PCR, of patients receiving medical care at the Evandro Chagas Clinical Research Institute (IPEC) in the Oswaldo Cruz Foundation (Fiocruz), for the period of 2009–2012. We included patients over 20 years, prior to starting treatment, and all signed the informed consent form. The project was approved in the Ethics Committee of IPEC.

2.2. Study data collection

Sociodemographic data of the patients (age, sex, level of education, profession, and household income) was collected from the patients' medical records. For analysis, professional activity of the patients was classified in outside home (actual workers and students), and to housework (housewives, retired and unemployed workers).

A clinical and nutritional evaluation was performed in the first appointment. Weight and height were measured to calculate body mass index (BMI). The patients were classified in presence or absence of low body weight, according to BMI and age: in adults (20–59 years old) it was considered based on values of <18.5 kg/m^2, and for the elderly (≥60 years old) based on the values of ≤22 kg/m^2 (Ministry of Health/Brazil, 2011). Serum albumin levels were used as a biochemical parameter to nutritional assessment, and patients were classified as follows: without depletion (>3.5 g/dL) and with depletion (≤3.5 g/dL).

The clinical evaluation included: form of the leishmaniasis, localization of the wounds, comorbidities, nasal obstruction, recent decrease in food intake, dysphagia, odynophagia, anorexia, nausea, vomiting, constipation, diarrhea and time of disease progression.

The evaluation of epithelialization and/or healing of the lesions was performed each visit until two years after drug treatment. When the patient presented more than one lesion, healing time was calculated based on the date of the visit when all the lesions were totally healed. Total healing was considered as the complete cure of the lesion, without remaining inflammatory signs, in patients with CL or with ML.

2.3. Statistical analyses

The frequencies of the categorical variables were estimated. The continuous variables age and BMI have been examined through mean ± standard deviation and serum albumin levels, time of disease progression, time of epithelialization and healing of cutaneous wounds, and time of healing of the mucous wounds have been examined by median and interquartile range (IR). The difference of the medians of the continuous variables according to the nutritional status was evaluated by Student *t* test, in the parametric case and, Mann–Whitney nonparametric. The association among the categorical variables was investigated by the Fisher's exact test. *P* values <0.05 indicate significant statistical tests. For analysis of the data, the Statistical Package for Social Sciences (SPSS) version 16.0 was used.

Table 1
Association of clinical variables with weight and serum albumin levels of 68 patients with ATL in the IPEC/Fiocruz outpatient clinic from 2009 to 2012.

Variables	Low weight			Hypoalbuminemia		
	Yes ($n=7$) n (%)	No ($n=61$) n (%)	P^*	Yes ($n=8$) n (%)	No ($n=60$) n (%)	P^*
ML	5 (71)	14 (23)	**0.016**	5 (63)	14 (23)	**0.034**
Nasal obstruction	5 (71)	10 (16)	**0.005**	4 (50)	11 (18)	0.065
Dyspnea	2 (29)	4 (7)	0.112	3 (38)	3 (5)	**0.019**
Dysphagia	2 (29)	7 (12)	0.230	4 (50)	5 (8)	**0.008**
Odynophagia	2 (29)	5 (8)	0.149	3 (38)	4 (7)	**0.031**
Recent decrease in food intake ($N=67$)	4 (57)	12 (20)	**0.050**	5 (63)	11 (19)	**0.016**
Anorexia	2 (29)	7 (12)	0.230	-	5 (15)	0.585
Cutaneous wounds total healing ($N=57$)	1 (33)	41 (76)	0.166	1 (20)	41 (79)	**0.014**

* Bold values indicate $p<0.05$ in Fisher's exact test.

3. Results

In the 68 evaluated patients, the CL occurred in 72%; the mean age was 47.47 ± 16.30 years and 27% were elderly. The majority was male (71%), with monthly familiar income of up to five minimum wages (each minimum wage corresponding to US$321.770 Brazilian Central Bank) (79%), with extra professional external activity (65%), and having attended incomplete elementary school (49%). Comorbidities were identified in 39% of the samples, and the most prevalent was high blood pressure (31%), followed by an association of more than one comorbidity (19%), *Diabetes mellitus* (15%) and cardiovascular diseases (12%).

The most frequent clinical and nutritional events were: recent decrease in food intake (24%); nasal obstruction (22%); oral ulcer (15%), anorexia and dysphagia (13% each), and odynophagia (10%). There was no occurrence of vomiting in the patients studied.

In patients with ML, compared to CL patients, there was a higher proportion of men (89.5% vs 63.3%; $p=0.04$), elderly (52.6% vs 16.3%; $p=0.005$), with dysphagia (36.8% vs 4.1%; $p=0.001$), odynophagia (31.6% vs 2.0%; $p=0.001$), nasal obstruction (73.7% vs 2.0%; $p<0.0016$), dyspnea (21.1% vs 4.1%; $p=0.047$) and oral ulcers (47.4% vs 2.0%; $p<0.001$)

There was a higher proportion of recent decrease in food intake in patients with anorexia (77.8%; $p<0.001$), dysphagia (77.8%; $p<0.001$), odynophagia (71.4%; $p=0.007$), dyspnea (66.7%; $p=0.026$) and oral ulcers (50%; $p=0.050$).

The median of the average time for disease progression for CL was 4.00 (IR = 3–5) months, and for ML was 24.00 (IR = 9–120.25) months ($p<0.001$). For cutaneous lesion, epithelialization time was 20.00 (IR = 1–32.50) days, and total healing 115.00 (IR = 80–230) days. For the mucous wound the healing time was 120.00 (IR = 104.50–223.50) days.

Mean BMI was 25.47 ± 4.62 kg/m^2, and 10% of the patients had low body weight. The median value for serum albumin levels was 4.00 g/dL, and hypoalbuminemia was observed in 12% of the patients.

In patients, there was an association between low body weight and the clinical form of leishmaniasis, nasal obstruction, recent decrease in food intake, and serum albumin levels. There was an association between serum albumin levels depletion and the ML, dyspnea, dysphagia, odynophagia, recent decrease in food intake and the absence of lesions' healing. We cannot make statements about the relative risk of these variables on low body weight and hypoalbuminemia, due to the small size of the sample (Table 1).

There was an association between low body weight and higher age average, and between hypoalbuminemia and healing time for mucous lesions. No significant difference on the average time of epithelialization, nor of cutaneous wounds healing, was observed related to weight and serum albumin (Table 2).

4. Discussion

This study evaluated the nutritional status of 68 patients with ATL, through BMI and serum albumin levels, having verified the association of the nutritional status impairment with age, ML, events affecting the food intake, and the wound healing. Although this study has some limitations, as non-measuring the weight loss,

Table 2
Distribution of variables age, serum albumin level, disease progression time, epithelialization time and healing time according to low weight and hypoalbuminemia in 68 ATL patients seen at IPEC/Fiocruz outpatient clinic on 2009–2012.

Variables	Low weight			Hypoalbuminemia		
	Yes	No	p	Yes	No	p
Age (years) – mean ± SD	60.71 ± 10.93 ($N=7$)	45.95 ± 16.19 ($N=61$)	**0.022**	48.25 ± 15.50 ($N=8$)	47.37 ± 16.54 ($N=60$)	0.887
Albumin (g/dL)	3.60 ± (3.10–4.10) ($N=7$)	4.10 ± (2.90–4.60) ($N=61$)	**0.004**	–	–	–
Cutaneous wound epithelialization time (days)	50.00± (1.0–140) ($N=3$)	20.00± (1.00–30.00) ($N=51$)	0.271	10.00± (1.00–15.00) ($N=5$)	1.00± (1.00–40.00) ($N=49$)	0.155
Cutaneous wound epithelialization time (days)	230± (230–230) ($N=1$)	110.00± (80.00–190.00) ($N=41$)	0.278	110.00± (110.00–110.00) ($N=1$)	120.00± (80.00–230.00) ($N=41$)	0.707
Mucous wound epithelialization time (days)	213.00± (123.50–264.00) ($N=5$)	120.00± (91.00–171.50) ($N=13$)	0.216	213.00± (145.50–362.00) ($N=5$)	120.00± (76.00–168.50) ($N=13$)	**0.033**

Q_1 = Quartile 1; Q_3 = Quartile 3; interquartile range (IR = $Q_3 - Q_1$).

and the absence of other anthropometric parameters to evaluate the nutritional status; no similar studies have been found in the literature consulted.

In this study there was a prevalence of patients with incomplete elementary school and monthly familiar income of less than US$321.770. Socioeconomic factors, as low familiar income and lesser schooling are limiting factors to alimentary safety, i.e., the access to a healthy and adjusted eating, potentially leading to malnutrition (PAHO/WHO, 2012). Moreover, poverty is related with higher malnutrition rates and infectious illnesses, potentially increasing the seriousness of the individuals' clinical manifestations. It is also known that leishmaniasis is distributed in the poorest segments of global population (Alvar et al., 2006; Werneck et al., 2011).

Although the decreased prevalence of low body weight and hypoalbuminemia in the study population, the group of individuals' with weight below the normal were elderly. This relation between low body weight and age has already been observed in other studies, and may be related to the decreased muscle mass occurring with aging (Nascimento et al., 2011; Campos et al., 2006) or even to different classification criteria used in accordance with the Ministry of Health (2011). Another possibility is that the known association between ML and old age (Machado-Coelho et al., 2005), also observed in the present study, may have played as a confounding factor.

It was observed an association of ML with low body weight and depletion of blood albumin levels. Malnutrition is known as a risk factor for ML (Machado-Coelho et al., 2005). However, the association of ML with clinical events as nasal obstruction, dyspnea, dysphagia, odynophagia, and oropharyngeal ulcers, makes us assume that actually the wounds and related symptoms of this clinical form of ATL are responsible for a decrease in food intake and consequent malnutrition. Supporting this reasoning, it is described that the nasal obstruction interferes with the taste of food, and that dysphagia and odynophagia are symptoms that impair the swallowing of food, leading to decreased food intake, and potentially leading to depletion of the nutritional status (Rios, 2003; Ferreira, 2005). Likewise, it is reported that the depletion of serum albumin levels occurs more frequently when the wound is located in the oropharynx (Sampaio and Mannarino, 2007).

It is possible that the healing time has been overestimated, since the wounds may have healed before the visit in which it was evidenced. Futhermore, the evaluation of serum albumin levels has been more representative to the nutritional status of the studied patients. The BMI measured only one time before the treatment, did not allow the evaluation of the recent weight loss. This would explain why we do observe an association between the healing process and the hypoalbuminemia, but not with the BMI. Therefore, the association found between the healing time and the serum albumin levels depletion, supports the negative impact on the immunity, the health, and the healing process of the protein and caloric malnutrition, being in accordance with other authors (Keush, 2003; Anderson, 2005; França et al., 2009). It is known that the nutrients, mainly the proteins, participate actively on the healing process of the wounds (Mandelbaum et al., 2003; Anderson, 2005; Balbino et al., 2005), justifying thus that the hypoalbuminemia leads to a less favorable therapeutical result.

To evaluate the cause-effect relation between malnutrition and ML, a longitudinal study on the nutritional evolution of ATL patients before and after treatment is ongoing.

In conclusion, ML is associated with nutritional events, as dysphagia, odynophagia, nasal obstruction, dyspnea and oral ulcers. These symptoms may be responsible for a decrease in food intake, that can lead to a nutritional status impairment. Furthermore, the hypoalbuminemia may have negatively affected the healing of skin and mucous membrane lesions. Thereby, a nutritional intervention could increase the effectiveness of the ATL treatment, as an appropriate food intake, both quanti- and qualitatively, would assure a good nutritional status, essential for tissue recovery.

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