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Influence of Obesity on Clinical Manifestations and Response to Therapy in Cutaneous Leishmaniasis Caused by *Leishmania braziliensis*

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Background. Cutaneous leishmaniasis (CL) caused by *Leishmania braziliensis* is characterized by a single ulcer or multiple cutaneous lesions with raised borders. Cure rates <60% are observed in response to meglumine antimoniate therapy. We investigated the impact of obesity on CL clinical presentation and therapeutic response.

Methods. A total of 90 age-matched patients with CL were included (30 obese, 30 overweight, and 30 with normal body mass index [BMI]). CL was diagnosed through documentation of *L. braziliensis* DNA by polymerase chain reaction or identification of amastigotes in biopsied skin-lesion samples. Serum cytokine levels were determined by chemiluminescence. Antimony therapy with Glucantime (Sanofi-Aventis; 20 mg/kg/day) was administered for 20 days.

Results. Obese CL patients may present hypertrophic ulcers rather than typical oval, ulcerated lesions. A direct correlation between BMI and healing time was noted. After 1 course of antimony, cure was achieved in 73% of patients with normal BMI, 37% of overweight subjects, yet just 18% of obese CL patients ($P < .01$). Obese CL cases additionally presented higher leptin levels than overweight patients or those with normal BMI ($P < .05$).

Conclusions. Obesity modifies the clinical presentation of CL and host immune response and is associated with greater failure to therapy.

Keywords. cutaneous Leishmaniasis; *Leishmania braziliensis*; obesity; atypical lesions; immune response.

Cutaneous leishmaniasis (CL) is a vector-borne disease caused by *Leishmania* protozoan parasites. *Leishmania* (*Viannia*) *braziliensis* is the main causal agent of this disease in Central and South America [1, 2]. Cutaneous leishmaniasis is observed in more than 90% of patients infected with *L. braziliensis*. Nasal mucosal lesions develop concomitantly or months after primary infection in approximately 3% of patients with CL. Moreover, approximately 6% of infected patients present with more than 10 and up to 1000 lesions, thus characterizing disseminated leishmaniasis. Genotypic differences among isolates of *L. braziliensis* may underlie different clinical presentations of disease [3]. Both parasite burden and genotypic differences among isolates have been associated with failure to antimonial therapy [4, 5]. In CL, elevated production of interferon-γ activates macrophages, promoting parasite killing [6]. The impairment of a T-helper (Th) 1 (Th1) immune response, as observed in pregnant women, subjects with human immunodeficiency virus (HIV), or in patients with CL with a negative leishmanin skin test, can lead to poor therapeutic outcomes [7–9]. In addition, an exaggerated Th1 immune response in *L. braziliensis* infection can also play an important role in ulcer development, as activated CD8+ T cells kill infected host cells, yet present a limited capacity to kill *Leishmania* [10]. In mice infected with *L. braziliensis,* it was recently shown that the neutralization of granzyme and interleukin (IL)-1β either prevented or attenuated ulcer development [11].

Obesity, defined as excess body fat, is considered a chronic inflammatory disease that affects people of all ages and ethnicities [12]. In Brazil, obesity is on the rise and more than 50% of the population is classified as overweight [13]. Associations have been established between obesity and immune-mediated diseases, such as psoriasis, bronchial asthma, and atherosclerosis [14–16]. Obesity and CL are both considered important public health concerns [17, 18]. Obesity is characterized by low-grade systemic chronic inflammation, with high levels of leptin (a proinflammatory adipokine) production and reduced levels of adiponectin (an adipokine with anti-inflammatory effects). Leptin mediates appetite and energy balance in the body, and its secretion, mainly by adipose tissue, is directly correlated to the degree of adiposity [19, 20]. While it is recognized as an inflammatory cytokine associated with IL-1 and IL-6 production [21,

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22], it may also be associated with Th2 activation, as observed in obese patients with asthma [23].

Considering that both obesity and leishmaniasis are characterized by a potent inflammatory response, here we endeavored to evaluate whether obesity modifies clinical presentation and the response to therapy in patients with CL.

METHODS

Study Type and Area

The present ambispective study involved 90 age-matched patients with CL (range: 18–60 years), 30 of whom were obese, 30 overweight, and 30 who had a normal body mass index (BMI) (controls). Moreover, to determine whether patient weight, regardless of BMI, had an effect on therapeutic response, we also evaluated 44 patients with CL who weighed more than 60 kg but had a normal BMI; these patients were concurrently seen during the same period as the obese patients. Patients were seen at the Corte de Pedra Health Post, located in the municipality of Tancredo Neves, Bahia, Brazil, an area recognized for significant *L. braziliensis* transmission. The village of Corte de Pedra is surrounded by Atlantic forest, and agricultural activities provide the main source of income for most of the region's inhabitants.

In addition, a cross-sectional study was carried out to compare serum cytokine levels in biological samples available from 16 obese patients with CL and 13 patients with CL with normal BMI with those observed in 16 obese patients without CL and 16 healthy subjects with a normal BMI, all of whom resided in a nonendemic area of leishmaniasis.

Study Design and Case Definition

A prospective pilot study conducted in 2019 involving 30 patients with CL (10 were obese, 10 overweight, and 10 had a normal BMI) revealed that obesity was associated with high rates of failure to therapy. Thus, we retrospectively included patients with CL seen at the Corte de Pedra Health Post over the previous 2 years who were obese, overweight, or had a normal BMI. For the retrospective study, we selected an obese CL patients, the first CL case with normal BMI and the first CL with overweight seen in the same month of the obese patients. The obese individuals without CL and the healthy subjects (HS) used for determination of serum cytokine levels were recruited from an area that was not endemic for leishmaniasis. All patients had the diagnosis confirmed by detection of *L. braziliensis* DNA by polymerase chain reaction (PCR) in biopsy specimens obtained from the borders of the lesions [24]. Patients were classified as obese when their BMI (kg/m^2) was 30 or greater, as overweight when their BMI was 25 or greater and 29.9 or less, or as controls when their BMI was 18.5 or greater and 24.9 or less. Patients included in the retrospective study were consecutively enrolled; for each obese or overweight patient with CL, we added a control CL case matched by ±5 years of age. The inclusion criteria for all patients with CL consisted of the presence of a typical CL ulcer and documentation of *L. braziliensis* DNA by PCR [24]. The following exclusion criteria were applied: age less than 18 years or older than 60 years; diagnosis of diabetes, heart, and/or kidney failure; HIV positivity; or use of corticosteroids and/or immunosuppressants.

Patient demographic characteristics, illness duration, number of lesions, and ulcer location and size were recorded at the time of enrollment, while therapeutic response was evaluated at 30, 60, 90, and 180 days. All patients were treated with Glucantime (Sanofi-Aventis) at a dose of 20 mg/kg body weight per day (maximum, 1200 mg/day) for 20 days.

As the recommended dose of meglumine antimoniate for leishmaniasis treatment is 20 mg/kg per day, at a maximum level of 1200 mg/day, patients weighing over 60 kg received a lower dose of antimony when compared with patients who weighed 60 kg or less. To determine whether higher rates of therapeutic failure resulted from reduced relative dosage in the overweight and obese patients whose weight was greater than 60 kg, we compared cure rates in 44 patients with CL who weighed more than 60 kg but had a normal BMI. These patients were diagnosed in the same study period as the other 60 obese or overweight patients included above.

Cytokine Determination

Reagents used to determine leptin levels were purchased from R&D Systems, while those used to quantify IFN-γ, IL-4, IL-5, IL-15, and eotaxin were obtained from Bio-Rad Laboratories. Serum cytokine levels were measured by chemiluminescence in accordance with the manufacturer's instructions; results are expressed in picograms per milliliter.

Statistical Analysis

Due to the lack of normally distributed data, most statistical analyses employed nonparametric testing. Ages are presented as means ± standard deviation and were compared by the Student's *t* test. Other continuous variables are presented as medians and interquartile range (IQR). The Mann–Whitney *U* test was used for comparisons between 2 groups, while the Kruskal–Wallis test was applied for comparisons between 3 or more groups. Categorical data were compared using Fisher's exact test. Correlations were evaluated by calculating Spearman correlation coefficients. Kaplan–Meier survival estimates were also evaluated to compare differences in healing time between the 3 studied groups. Statistical analyses were conducted using Prism (version 8.0; GraphPad Software) and differences were considered significant when $P < .05$.

Ethics Statement

This study was approved by the Institutional Review Board of the Federal University of Bahia Medical School (no. 3.677.777). All included patients provided written informed consent.

RESULTS

Table 1 lists the demographic and clinical features of 90 patients with CL classified according to BMI. Males predominated among the patients with CL classified as overweight or with a normal BMI, while females were more frequently obese. No differences were seen between the groups with regard to age, illness duration, or number/size of lesions. Although a higher frequency of obese patients with CL presented ulcers above the waist than controls or overweight patients with CL, this finding did not achieve statistical significance. The cure rate in obese patients was 2-fold lower than in overweight and 4-fold lower than in patients with CL with a normal BMI ($P < .001$, Mann–Whitney U test). Additionally, obese and overweight patients received more courses of meglumine antimoniate than patients with a normal BMI ($P < 005$). A lengthier healing time was noted in the obese and overweight patients compared with controls, as it took twice as long for obese patients to heal compared with patients with CL with a normal BMI ($P < .001$, Mann–Whitney U test).

Figure 1 illustrates correlations between BMI and lesion-healing time in all 90 study participants. A direct correlation between BMI and healing time was observed ($r = 0.4$, $P < .0001$, Spearman's rank correlation coefficient).

To investigate associations between BMI and healing time in patients with CL treated with meglumine antimoniate, survival analysis was conducted using the Kaplan–Meier method (Figure 2). Obese patients exhibited a longer healing time than overweight patients with CL and those with a normal BMI ($P < .05$, log-rank test).

Since patients weighing over 60 kg received proportionally lower doses of antimony (maximum recommended daily dose: 1200 mg), the cure rate in obese patients was compared with that observed in patients with a normal BMI who weighed more than 60 kg. The cure rate in patients weighing over 60 kg with a normal BMI was 50%, compared with 20% in the obese subjects ($P < .05$, Fisher's exact test).

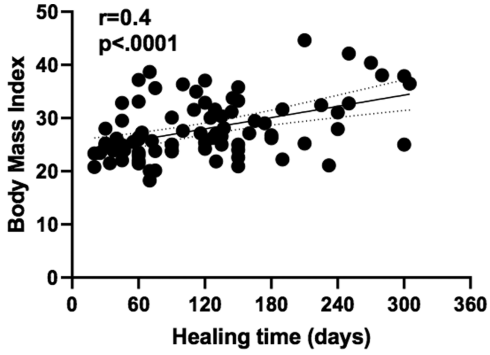

Figure 1. Correlation between BMI and lesion healing time in 90 patients with CL. Analysis of BMI and healing rate indicates that higher BMI values correlated with prolonged CL lesion healing time, considering the number of days from the onset of therapy until when cure was achieved ($r = 0.4$, $P < .0001$). Statistical analysis was performed by Spearman's correlation coefficient test. Abbreviations: BMI, body mass index; CL, cutaneous leishmaniasis.

Figure 3 illustrates a representative clinical picture of cutaneous ulcers from 3 obese patients. A hypertrophic ulcer in an obese patient is shown in Figure 3A, an ulcer with a poorly demarcated border in Figure 3B, and a well-defined ulcer, with raised and infiltrated edges similar to those observed in patients with classical CL, is shown in Figure 3C.

Figure 4 depicts median serum levels of leptin, IFN-γ, IL-15, and eotaxin in obese patients with CL, in patients with CL with a normal BMI, in obese individuals without CL, and in healthy subjects. Obese patients with CL presented higher leptin levels (median: 2581 pg/mL; IQR: 2515–2692 pg/mL) ($P < .0001$). Interestingly, leptin levels in patients with CL with a normal BMI (median: 1799 pg/mL; IQR: 1196–2176 pg/mL)

Table 1. Demographic and Clinical Features of Patients With Cutaneous Leishmaniasis Stratified by Body Mass Index Classification: Obese, Overweight, or Normal

				P Value	
Demographic and Clinical Features	Obese (n = 30)	Overweight (n = 30)	Control (n = 30)	Obese vs Control	Overweight vs Control
Age, mean (SD), years	34.83 ± 9.5	33.53 ± 11.72	33.90 ± 10.06	NS	NS
Sex					
Male, n/N (%)	8/30 (27)	22/30 (73)	17/30 (57)	.05*	NS
Illness duration, mean (SD), days	43 ± 17	40 ± 17	37 ± 14	NS	NS
Size of largest lesion, mm^2, median (IQR)	29.5 (17.5–40)	22 (16.5–35.2)	22.5 (16.7–29.2)	NS	NS
Ulcers on lower limbs, n/N (%)	17/30 (57)	27/30 (90)	22/30 (73)	NS	NS
Response to therapy, n/N (%)					
Cure achieved after 90 days	5/28 (18)	11/30 (37)	22/30 (73)	.001***	.01**
Courses of Sb^V therapy, n/N (%)					
1 Course	9/30 (30)	13/30 (43.3)	23/30 (76.6)	.001***	.01**
>1 Course	21/30 (70)	17/30 (56.7)	7/30 (23.4)	.001***	.01**
Therapeutic failure, n/N (%)	25/28 (82)	19/30 (63)	8/30 (37)	.001***	.05*
Healing time, median (IQR), days	139 (102–236)	127 (63–165)	60 (36–97)	.001***	.01**

*$P < .05$; **$P < .01$; ***$P < .001$. Abbreviations: IQR, interquartile range; NS, not significant; SB^V, pentavalent antimony; SD, standard deviation.

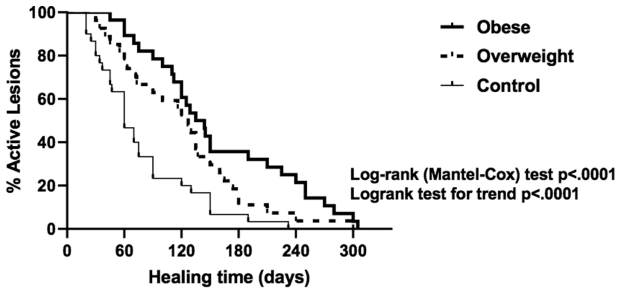

Figure 2. Survival analysis in 90 patients with CL. Kaplan–Meier survival analysis of differences in healing time among obese, overweight, and control patients treated with meglumine antimoniate revealed longer CL lesion healing times in obese patients compared with those with a normal BMI ($P < .05$, log-rank test). Abbreviations: BMI, body mass index; CL, cutaneous leishmaniasis.

were similar to those in obese individuals without CL (median: 1786 pg/mL; IQR: 362–2423 pg/mL), yet higher than in controls (median: 1307 pg/mL; IQR: 626–1651 pg/mL) ($P < .05$). IFN-γ levels in obese patients with CL were similar to those observed in patients with CL with a normal BMI ($P > .05$), but higher than obese individuals without CL or healthy subjects. A similar pattern was seen in IL-15 levels, as obese patients with CL and patients with CL with a normal BMI presented similarly higher levels than obese individuals without CL or healthy subjects ($P < .05$). The median level of eotaxin in obese patients with CL was 7 pg/mL (IQR: 2–21 pg/mL), lower than in patients with CL with a normal BMI (median: 22 pg/mL; IQR: 13–40 pg/mL) ($P < .001$) and healthy subjects (median: 42 pg/mL; IQR: 27–75 pg/mL) ($P < .05$). Low levels of IL-4 and IL-5 were detected across all groups ($P > .05$).

DISCUSSION

Obesity has been associated with the severity of autoimmune and chronic inflammatory diseases, with increasing prevalence in poor countries where leishmaniasis is also highly prevalent [25, 26]. The literature contains few studies on associations between BMI and leishmaniasis. C57BL/6 mice fed a hypercaloric diet presented thicker lesions, higher parasite burden, and more intense inflammatory infiltrate [27]. In an area endemic for leishmaniasis in Brazil, patients with CL presented a higher BMI than controls [28]. Here we attempted to evaluate whether obesity modified the clinical presentation and response to therapy in patients with CL infected with *L. braziliensis*. We found obesity to be associated with large hypertrophic ulcers

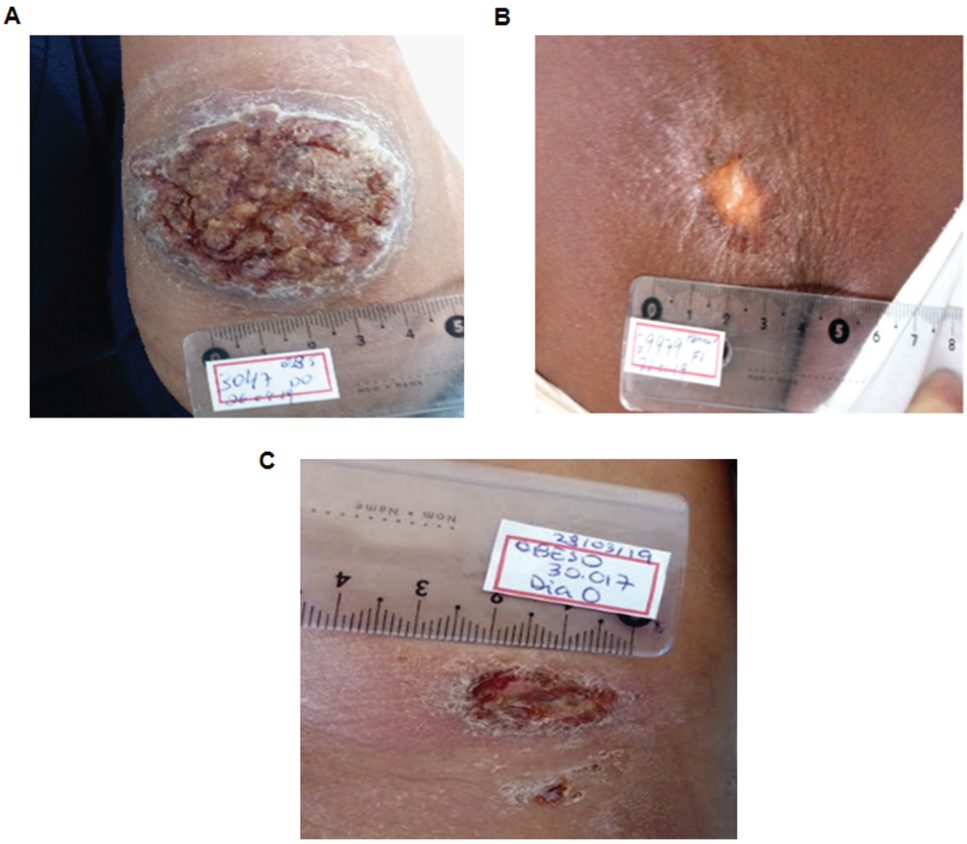

Figure 3. Clinical features of cutaneous leishmaniasis in 2 obese patients with CL and 1 patient with a normal BMI. The clinical spectrum of CL ulcers in obese patients: hypertrophic ulcers (*A*), ulcers lacking well-defined borders (*B*), and typical well-delimited CL ulcers with raised borders (*C*). Photographs were obtained at time of patient enrollment, prior to onset of therapy. Abbreviations: BMI, body mass index; CL, cutaneous leishmaniasis.

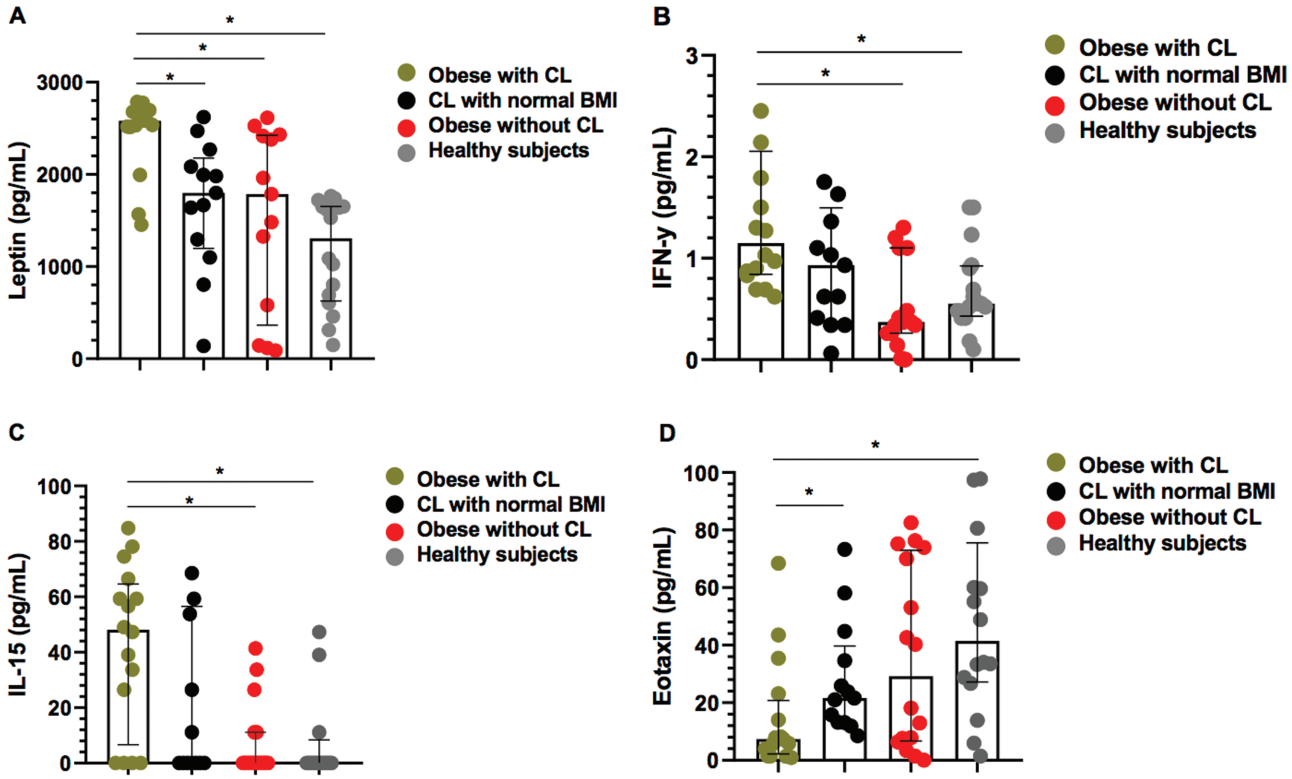

Figure 4. Serum levels of proinflammatory molecules. Serum levels of leptin (*A*), IFN-γ (*B*), IL-15 (*C*), and eotaxin (*D*) were determined by ELISA prior to the introduction of therapy in obese patients with CL and others with a normal BMI, as well as in the sera of obese individuals without leishmaniasis or any other chronic inflammatory disease, and in healthy subjects living outside an area endemic for *Leishmania braziliensis* transmission. Statistical analysis was performed using medians and interquartile range; Mann–Whitney *U* test was used for comparisons between the 2 groups. Abbreviations: BMI, body mass index; CL, cutaneous leishmaniasis; ELISA, enzyme-linked immunosorbent assay; IFN-γ, interferon-γ; IL-15, interleukin-15.

and higher rates of failure to pentavalent antimonial therapy. While no differences were seen in serum levels of IFN-γ, IL-4, and IL-5 between obese patients with CL and those with CL and a normal BMI, higher levels of leptin and lower levels of eotaxin were observed in the obese patients with CL.

Our comparative analysis of demographic and clinical features revealed that the frequency of women was significantly higher in obese patients with CL than in the other groups studied. Men are typically predominant in CL infection due to *L. braziliensis,* at a frequency generally over 60% [29, 30]. However, it is known that the frequency of obesity in women is higher than in men [31], which may explain this difference between the groups. The most important observation regarding the clinical findings was a high rate of failure to antimony therapy among the obese subjects. Risk factors for therapy failure in CL include age, duration of illness, and number of lesions [32–34]. Children exhibit greater rates of failure to antimony therapy and miltefosine than adults when administered at identical drug dosages per kilogram [34, 35]. In patients with an illness duration of less than 30 days who are in the preulcerative phase of disease, failure rates are 2-fold higher than in patients with ulcerated lesions [36, 37]. With regard to the number of lesions, the presence of a second CL ulcer increases failure rates by 1.7 times [35] and more than 70% of patients with disseminated leishmaniasis do not respond to the initial course of meglumine antimoniate [38]. Considering there were no differences detected in age, illness duration, and number of lesions between the groups studied herein, we therefore conclude that obesity was the main factor associated with failure to therapy. Moreover, we noted a direct correlation between a patient's BMI and healing time.

The recommended dose of meglumine antimoniate used to treat CL is 20 mg/kg/day, with a maximum daily dose of 1200 mg. In this scenario, patients who weigh more than 60 kg receive the same amount of antimony as those who weigh 60 kg. A retrospective study of patients with CL infected with *L. braziliensis* found higher rates of failure to therapy in those who weighed more than 68 kg (odds ratio: 4.3; 95% confidence interval: 1.5–11.9) [39]. We found lower cure rates in obese patients than in nonobese patients weighing more than 60 kg, which suggests that higher BMI represents an important risk factor for treatment failure.

Atypical lesions have been well described in CL. In addition to classical ulcers with raised borders, patients may present verrucous, nodular, or large ulcerated lesions [40–42]. Verrucous lesions have been observed in pregnant women,

and larger lesions are seen in patients coinfected with HIV [10, 41]. It is known that since *L. braziliensis* is polymorphic, genotypic differences among isolates of this species may be associated with atypical lesions, such as multiple nodules in 1 segment of the body [41]. Of interest, the atypical ulcers seen in the obese patients studied herein presented a different pattern than that described above. Moreover, the site of atypical ulcers in obese patients was different than that observed in nonobese patients. Ulcers are more frequent in the lower extremities in patients with CL and 2 studies recently published in the endemic area studied by our group reported a frequency ranging from 65.4% to 82% for cutaneous lesions in the lower limbs [43, 44]. By contrast, in obese patients we documented that 43% of lesions were located on the trunk or superior limbs, which is also where atypical ulcers are more frequently observed.

IFN-γ produced by CD4+ T cells is the most important cytokine involved in the control of *Leishmania* infection. In CL, despite high IFN-γ production, parasites are not eradicated, and an exaggerated inflammatory response is associated with disease pathology [45, 46]. In mice, IL-15 is associated with severity of *L. braziliensis* infection [47]. High levels of leptin are observed in obesity [48], and leptin has been shown to enhance the production of IFN and IL-1β [49, 50]. Our observation that patients with CL with a normal BMI produce leptin at levels similar to obese subjects not infected with CL provides evidence that leptin production is upregulated in CL. Considering that leptin may exacerbate the proinflammatory response, and that obese patients with CL presented the highest serum levels of leptin among the groups studied herein, we speculate that, through the enhancement of proinflammatory response in CL, leptin may contribute not only to disease severity but also to failure to therapy.

The present study has some limitations. As most data were obtained retrospectively from patient records, we were not able to provide photographic documentation of lesions in many patients. This prevented us from accurately determining the frequency of atypical CL lesions in most obese patients, as well as evaluating whether atypical lesions are more frequent above the waistline in obese patients with CL, as was observed in some cases.

Conclusions

Obesity enhances the proinflammatory response, modifies the clinical presentation of CL caused by *L. braziliensis*, decreases cure rates in patients treated with meglumine antimoniate, and delays healing time. Leptin seems to be a trigger that encourages this proinflammatory response, thus contributing to more severe disease and therapeutic failure in obese individuals.

Notes

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References

1. Cupolillo E, Grimaldi G Jr, Momen H. Genetic diversity among Leishmania (Viannia) parasites. Ann Trop Med Parasitol **1997**; 91:617–26.
2. Burza S, Croft SL, Boelaert M. Leishmaniasis. Lancet **2018**; 392:951–70.
3. Queiroz A, Sousa R, Heine C, et al. Association between an emerging disseminated form of leishmaniasis and Leishmania (Viannia) braziliensis strain polymorphisms. J Clin Microbiol **2012**; 50:4028–34.
4. Silva SC, Guimarães LH, Silva JA, et al. Molecular epidemiology and in vitro evidence suggest that Leishmania braziliensis strain helps determine antimony response among American tegumenary leishmaniasis patients. Acta Trop **2018**; 178:34–9.
5. Amorim CF, Novais FO, Nguyen BT, et al. Variable gene expression and parasite load predict treatment outcome in cutaneous leishmaniasis. Sci Transl Med **2019**; 11:eaax4204.
6. Ameen M. Cutaneous leishmaniasis: advances in disease pathogenesis, diagnostics and therapeutics. Clin Exp Dermatol **2010**; 35:699–705.
7. Morgan DJ, Guimaraes LH, Machado PR, et al. Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. Clin Infect Dis **2007**; 45:478–82.
8. Carvalho AM, Guimarães LH, Costa R, et al. Impaired Th1 response is associated therapeutic failure in patients with cutaneous leishmaniasis caused by *Leishmania braziliensis*. J Infect Dis **2021**; 223:527–35.
9. Lindoso JA, Barbosa RN, Posada-Vergara MP, et al. Unusual manifestations of tegumentary leishmaniasis in AIDS patients from the New World. Br J Dermatol **2009**; 160:311–8.
10. Cardoso TM, Machado Á, Costa DL, et al. Protective and pathological functions of CD8+ T cells in Leishmania braziliensis infection. Infect Immun **2015**; 83:898–906.
11. Novais FO, Carvalho AM, Clark ML, et al. CD8+ T cell cytotoxicity mediates pathology in the skin by inflammasome activation and IL-1β production. PLoS Pathog **2017**; 13:e1006196.
12. Bray GA, Kim KK, Wilding JPH; World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev **2017**; 18:715–23.
13. Vigitel Brazil. Surveillance of risk and protective factors for chronic diseases by telephone survey. Vigitel; **2018**. Available at: https://abeso.org.br/wp-content/uploads/2020/01/vigitel-brasil-2018.pdf. Accessed 1 May 2020.
14. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol **2005**; 125:61–7.
15. Farah CS, Salome CM. Asthma and obesity: a known association but unknown mechanism. Respirology **2012**; 17:412–21.
16. Yoo HJ, Choi KM. Adipokines as a novel link between obesity and atherosclerosis. World J Diabetes **2014**; 5:357–63.
17. Desjeux P. Leishmaniasis. Clin Dermatol **1966**; 14:417–423.
18. Agha M, Agha R. O aumento da prevalência da obesidade: parte A: impacto na saúde pública. Jornal internacional de cirurgia. Oncology **2017**; 2:e17.
19. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature **1994**; 372:425–32.
20. Carter S, Caron A, Richard D, Picard F. Role of leptin resistance in the development of obesity in older patients. Clin Interv Aging **2013**; 8:829–44.
21. Yang WH, Liu SC, Tsai CH, et al. Leptin induces IL-6 expression through OBRl receptor signaling pathway in human synovial fibroblasts. PLoS One **2013**; 8:e75551.
22. La Cava A. Leptin in inflammation and autoimmunity. Cytokine **2017**; 98:51–8.

23. Zheng H, Zhang X, Castillo EF, Luo Y, Liu M, Yang XO. Leptin enhances TH2 and ILC2 responses in allergic airway disease. J Biol Chem **2016**; 291:22043–52.
24. Weirather JL, Jeronimo SM, Gautam S, et al. Serial quantitative PCR assay for detection, species discrimination, and quantification of Leishmania spp. in human samples. J Clin Microbiol **2011**; 49:3892–904.
25. Nour NN. Obesity in resource-poor nations. Rev Obstet Gynecol **2010**; 3:180–4.
26. Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev **2014**; 13:981–1000.
27. Martins VD, Silva FC, Caixeta F, et al. Obesity impairs resistance to Leishmania major infection in C57BL/6 mice. PLoS Negl Trop Dis **2020**; 14:e0006596.
28. Cunha DF, Cunha SF, Nunes AG, Silva-Vergara ML. Is an increased body mass index associated with a risk of cutaneous leishmaniasis? Rev Soc Bras Med Trop **2009**; 42:494–5.
29. Jirmanus L, Glesby MJ, Guimarães LH, et al. Epidemiological and clinical changes in American tegumentary leishmaniasis in an area of Leishmania (Viannia) braziliensis transmission over a 20-year period. Am J Trop Med Hyg **2012**; 86:426–33.
30. Teles GC, Fonseca FR, Goncalves MJF. American tegumentary leishmaniasis in the Brazilian Amazon from 2010 to 2014. Rev Inst Med Trop Sao Paulo **2019**; 61:e22.
31. World Health Organization. Obesity and overweight. Geneva, Switzerland: World Health Organization, **2018**. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 1 May 2020.
32. Llanos-Cuentas A, Tulliano G, Araujo-Castillo R, et al. Clinical and parasite species risk factors for pentavalent antimonial treatment failure in cutaneous leishmaniasis in Peru. Clin Infect Dis **2008**; 46:223–31.
33. Valencia C, Arévalo J, Dujardin JC, Llanos-Cuentas A, Chappuis F, Zimic M. Prediction score for antimony treatment failure in patients with ulcerative leishmaniasis lesions. PLoS Negl Trop Dis **2012**; 6:e1656.
34. Castro MDM, Cossio A, Velasco C, Osorio L. Risk factors for therapeutic failure to meglumine antimoniate and miltefosine in adults and children with cutaneous leishmaniasis in Colombia: a cohort study. PLoS Negl Trop Dis **2017**; 11:e0005515.
35. Suprien C, Rocha PN, Teixeira M, et al. Clinical presentation and response to therapy in children with cutaneous leishmaniasis. Am J Trop Med Hyg **2020**; 102:777–81.
36. Machado P, Araújo C, Da Silva AT, et al. Failure of early treatment of cutaneous leishmaniasis in preventing the development of an ulcer. Clin Infect Dis **2002**; 34:E69–73.
37. Unger A, O'Neal S, Machado PR, et al. Association of treatment of American cutaneous leishmaniasis prior to ulcer development with high rate of failure in northeastern Brazil. Am J Trop Med Hyg **2009**; 80:574–9.
38. Turetz ML, Machado PR, Ko AI, et al. Disseminated leishmaniasis: a new and emerging form of leishmaniasis observed in northeastern Brazil. J Infect Dis **2002**; 186:1829–34.
39. Rodrigues AM, Hueb M, Santos TARR, Fontes CJF. Fatores associados ao insucesso do tratamento da leishmaniose cutânea com antimoniato de meglumina. Rev Soc Bras Med Trop **2006**; 39:139–145.
40. Guimarães LH, Machado PR, Lago EL, et al. Atypical manifestations of tegumentary leishmaniasis in a transmission area of Leishmania braziliensis in the state of Bahia, Brazil. Trans R Soc Trop Med Hyg **2009**; 103:712–5.
41. Guimarães LH, Queiroz A, Silva JA, et al. Atypical manifestations of cutaneous leishmaniasis in a region endemic for Leishmania braziliensis: clinical, immunological and parasitological aspects. PLoS Negl Trop Dis **2016**; 10:e0005100.
42. Meireles CB, Maia LC, Soares GC, et al. Atypical presentations of cutaneous leishmaniasis: a systematic review. Acta Trop **2017**; 172:240–54.
43. Brito G, Dourado M, Guimarães LH, et al. Oral pentoxifylline associated with pentavalent antimony: a randomized trial for cutaneous leishmaniasis. Am J Trop Med Hyg **2017**; 96:1155–9.
44. Prates FV, Dourado ME, Silva SC, et al. Fluconazole in the treatment of cutaneous leishmaniasis caused by *Leishmania braziliensis*: a randomized controlled trial. Clin Infect Dis **2017**; 64:67–71.
45. Bacellar O, Lessa H, Schriefer A, et al. Up-regulation of Th1-type responses in mucosal leishmaniasis patients. Infect Immun **2002**; 70:6734–40.
46. Da-Cruz AM, Oliveira-Neto MP, Bertho AL, Mendes-Aguiar CO, Coutinho SG. T cells specific to leishmania and other nonrelated microbial antigens can migrate to human leishmaniasis skin lesions. J Invest Dermatol **2010**; 130:1329–36.
47. Novais FO, Nguyen BT, Scott P. Granzyme B inhibition by tofacitinib blocks the pathology induced by CD8 T cells in cutaneous leishmaniasis. J Invest Dermatol **2021**; 141:575–85.
48. Ekmen N, Helvaci A, Gunaldi M, Sasani H, Yildirmak ST. Leptin as an important link between obesity and cardiovascular risk factors in men with acute myocardial infarction. Indian Heart J **2016**; 68:132–7.
49. Mattioli B, Straface E, Quaranta MG, Giordani L, Viora M. Leptin promotes differentiation and survival of human dendritic cells and licenses them for Th1 priming. J Immunol **2005**; 175:3446.
50. Santos CL, Bobermin LD, Souza DO, Quincozes-Santos A. Leptin stimulates the release of pro-inflammatory cytokines in hypothalamic astrocyte cultures from adult and aged rats. Metab Brain Dis **2018**; 33:2059–63.