



## ORIGINAL ARTICLE

# The influence of periodontal status and serum biomarkers on salivary leptin levels in systemic lupus erythematosus patients

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## KEYWORDS

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**Abstract** *Objective:* This study aimed to investigate the influence of periodontal status, clinical data, and serum markers on salivary leptin levels in patients with systemic lupus erythematosus (SLE).

*Methods:* A case–control study was conducted with 38 patients with SLE and 29 healthy controls. Periodontal data included periodontal probing depth (PPD), clinical attachment level (CAL), and gingival bleeding on probing (BOP). Stimulated saliva samples were collected to analyze salivary leptin levels. Clinical and serum data were collected from the SLE group. Statistical analysis included the *t*-test, Mann–Whitney test, Spearman correlation coefficient, and a structural equation model.

*Results:* The SLE group had a lower salivary leptin level than the control group ( $P = 0.002$ ). The model revealed that SLE had an inverse and independent effect on salivary leptin (standardized estimate =  $-0.289$ ,  $P = 0.023$ ). Moreover, salivary leptin level negatively correlated with the serum levels of triglyceride, creatinine, and leukocytes, positively correlated with the serum total cholesterol, but was not significantly correlated with the periodontal status.

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*Conclusion:* These findings suggest that patients with SLE have a lower salivary leptin level. In addition, the level of salivary leptin does not appear to be related to periodontal status in patients with SLE.

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## 1. Introduction

Systemic lupus erythematosus (SLE) and periodontal disease are chronic diseases that stimulate the body's inflammatory response and are associated with several changes in serum and salivary markers of immune receptors, cytokines, and other biomarkers (Marques et al., 2016; Sojod et al., 2021). Periodontal disease has an inflammatory and infectious nature, related to dysbiosis caused by well-characterized periodontopathogens, usually formed by anaerobes, influences the activation of immune response mechanisms with inflammatory stimuli with repercussion in cells and defense substances, and is associated with the development of other systemic diseases (Tonetti et al., 2018; Van Dyke et al., 2020).

Among these inflammatory-related markers, leptin is a peptide hormone mainly produced by adipocytes and plays the role as a metabolic mediator, a cellular energy homeostasis regulator, and neuroendocrine actor (Pérez-Pérez et al., 2020). Moreover, leptin exhibits structural similarities to the long chain of the helical cytokine family, such as the tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 6 (IL-6), playing a key role in modulating the inflammatory response (Chougule et al., 2018; Han and Zhou, 2019; Ghadge and Khair, 2019).

The autoimmune manifestations of SLE have a systemic effect, with expressive activation of inflammatory mechanisms, and a massive increase in cells and defense substances. This imbalance can result in an exacerbated activation of the immune response that impairs cell homeostasis, with consequent damage to the functioning of various organs (Pabón-Porras et al., 2019; Tsokos, 2020). Studies have shown that leptin plays an important role in the pathogenesis of SLE caused by several molecular pathways, including immunocyte activation and modification in antibody reactivities leading to aberrant activation of T cells and B cells (Mercado and Martínez-García, 2020; Yuan et al., 2020).

Evidence has shown increased serum leptin levels in SLE, and the leptin blockade promotes a reduction in the production of autoantibodies (Lourenço et al., 2016). However, studies on salivary leptin levels in patients with SLE are still scarce (Stanescu et al., 2018), both investigating their association with periodontal inflammation and their relationship with systemic disorders in this population. These findings could help provide data for the clinical monitoring of patients with SLE. Therefore, this study aimed to investigate the influence of periodontal status, clinical data, and serum biomarkers on the salivary leptin levels of patients with SLE.

## 2. Materials and Methods

### 2.1. Study design and sample

A case-control study was conducted in the city of São Luís, Maranhão, Brazil, with a sample of 38 patients with SLE

and 29 healthy controls. The study was approved by the Ethics and Research Committee of the University Hospital of the Federal University of Maranhão (No. 460.888). All participants were informed about the objectives and procedures of the study and signed an informed consent form.

The patients in the SLE group were selected at the University Hospital of the Federal University of Maranhão, São Luís, Brazil. Healthy participants (control group), as identified by clinical and laboratory examination, were selected from the patients attending the Dentistry School of the Federal University of Maranhão. The study sample included participants of both sexes aged 18–60 years. The exclusion criteria were as follows: patients with diabetes, smokers or ex-smokers for < 10 years, users of orthodontic appliances, participants who received periodontal treatment 6 months before the survey. Patients were also excluded if they had clinically evident infectious diseases and presence of nodules and/or edema in the regions around the salivary glands (evaluated through a visual examination and digital palpation). Women who were pregnant or breastfeeding and participants who had used antibiotics 6 months before data collection were excluded.

### 2.2. Clinical and serum data

The clinical data and the list of medicines used by the patients were collected using an individual questionnaire and medical records. Body mass index (BMI) was measured during the clinical examination. Serum variables that were measured included triglycerides (TG), total cholesterol, blood glucose, creatinine, creatinine clearance, urea, glutamic oxaloacetic transaminase (GOT), glutamate-pyruvate transaminase (GPT), leukocytes, hemoglobin, and platelets.

### 2.3. Periodontal data

Periodontal examination was performed by a single examiner previously trained under artificial light using a clinical mirror and Williams periodontal probe (Trinity, São Paulo, Brazil). The intra-examiner agreement was calculated before data collection, with 10 patients reexamined within a 7-day interval, obtaining a coefficient > 0.8 for the probing pocket depth (PPD) and clinical attachment level (CAL). The PPD was measured as the distance (in mm) from the gingival margin to the bottom of the gingival sulcus or the periodontal pocket. The CAL was measured as the distance (in mm) from the cement-enamel junction to the bottom of the gingival sulcus or periodontal pocket. The PPD and CAL were measured in the six sites of all the teeth present: distobuccal, buccal, mesiobuccal, distolingual, lingual, and mesiolingual. Gingival bleeding on probing (BOP) was evaluated in the four dental sites of the teeth present: buccal, lingual, mesial, and distal (Ainamo and Bay, 1975).

#### 2.4. Saliva collection and analysis

Saliva samples were obtained after stimulation by chewing a piece of 2-cm latex, between 7 and 10 am, with an interval of at least 1 h after the last meal (Rodrigues et al., 2016). A protease inhibitor cocktail (Sigma-Aldrich, USA) was added to the collected saliva, and it was stored at  $-80^{\circ}\text{C}$  until analysis. The leptin concentration in the saliva was measured using the MAGPIX® System (Merck Millipore, USA) automatic analyzer and an HBNMAG-51 K kit, Milliplex MAP (Millipore, Massachusetts, USA), following the manufacturer's instructions, and samples were evaluated in duplicate.

#### 2.5. Theoretical model

A theoretical model was constructed to investigate the potential effect of SLE and periodontal disease on the changes in salivary leptin levels (Fig. 1). In this model, the response variable was the salivary leptin level, and the explanatory variables were age, SLE, and latent variable periodontal status as described by the mean of PPD, mean of CAL, and BOP. Latent variables are unobservable variables constructed from indicators that must measure the same construct, thus reducing the measurement error of variables that are difficult to define or diagnose (Wang and Rhemtulla, 2021).

#### 2.6. Statistical analysis

Data were analyzed using the Stata software version 18 (Stata Corp., College Station, Texas, USA). The Lilliefors test was used to evaluate the normality of the distribution. An independent *t*-test was used in the comparative analysis of salivary leptin levels. The Mann-Whitney test was used to analyze the

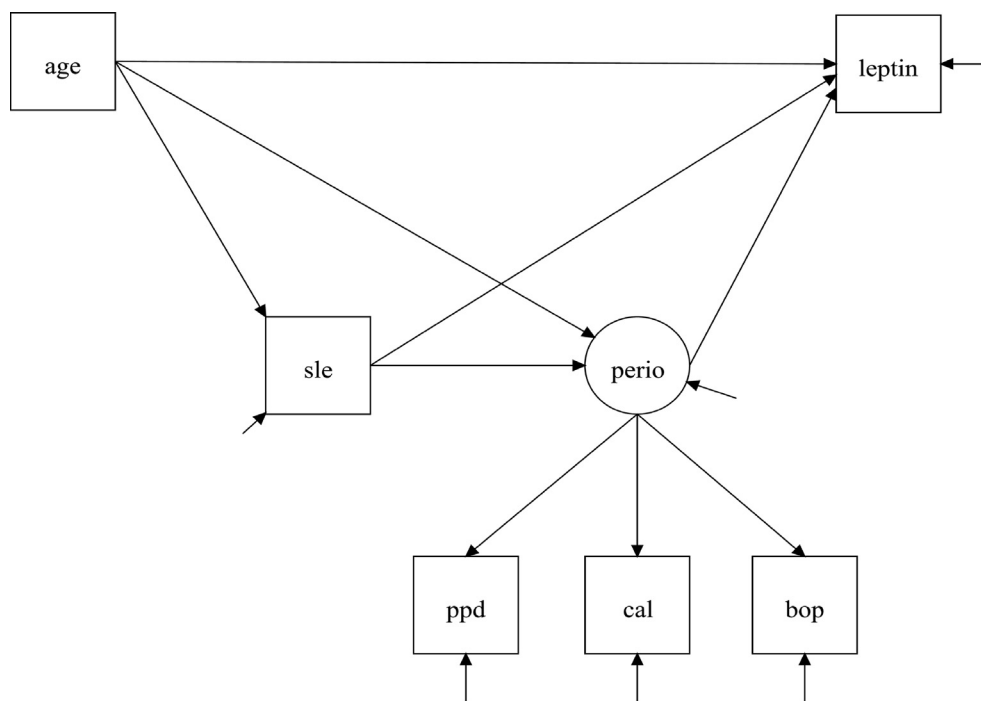
salivary leptin level according to the type of medicine. In addition, Spearman's coefficient was calculated to estimate the correlation between variables. The significance level adopted for all tests was 5 %.

For model adjustment, structural equations modeling (SEM) was used to investigate the association between SLE, periodontal disease, and salivary leptin levels. Mplus software version 7.0 (Muthén & Muthén, Los Angeles, CA, USA) was used to analyze the structural equation. The values of the standardized estimates were adjusted to determine the effects on the model. The following indices were considered to evaluate the model fit: a *p*-value  $> 0.05$  for the chi-square test ( $\chi^2$ ), Tucker-Lewis index (TLI) and comparative fit index (CFI)  $> 0.95$ , root mean square error of approximation (RMSEA)  $< 0.05$ , and standardized root mean square residual (SRMR)  $< 0.05$ .

### 3. Results

A total of 38 patients with SLE (all women; mean age,  $39.6 \pm 10.5$  years) and 29 without SLE (20 women, 9 men; mean age,  $46.3 \pm 11.8$  years) were included in this study. In the SLE group, 63.2 % patients had a BMI  $< 25$  and 36.8 % had one higher or equal to 25, but BMI did not correlate with the salivary leptin level ( $P = 0.385$ ).

Fig. 2 shows that patients with SLE had a lower salivary leptin level than patients without SLE ( $P < 0.05$ ). A correlation analysis between salivary leptin levels and levels of the serum markers and periodontal variables collected from patients with SLE was also performed (Table 1). Data showed that the salivary concentration of leptin presented an inverse proportional correlation with triglycerides ( $R_s = -0.534$ ,  $P = 0.003$ ), creatinine ( $R_s = -0.331$ ,  $P = 0.048$ ), creatinine clearance ( $R_s = -0.445$ ,  $P = 0.025$ ), and leukocyte



**Fig. 1** Theoretical model of the study. BOP, bleeding on probing; CAL, mean clinical attachment level; LEPTIN, salivary leptin; PPD, mean probing pocket depth; PERIO, periodontal disease (latent variable); SLE, systemic lupus erythematosus.

( $R_s = -0.331, P = 0.041$ ), in addition to a positive correlation with total cholesterol ( $R_s = 0.434, P = 0.016$ ). In Table 2, no association was found between leptin salivary levels and type of medicine.

Fig. 3 and Table 3 present the results of the structural equation analysis. Each indicator of the latent variable presented a factorial load higher than 0.3 and  $P < 0.001$ . The age variable presented an inverse effect on SLE and a direct effect on the periodontal condition, whereas SLE presented an inverse effect on the periodontal status. As regards the direct effects on salivary leptin, only SLE had an inverse and independent effect on salivary leptin (estimate =  $-0.289; P = 0.023$ ). The model presented satisfactory adjustment indexes.

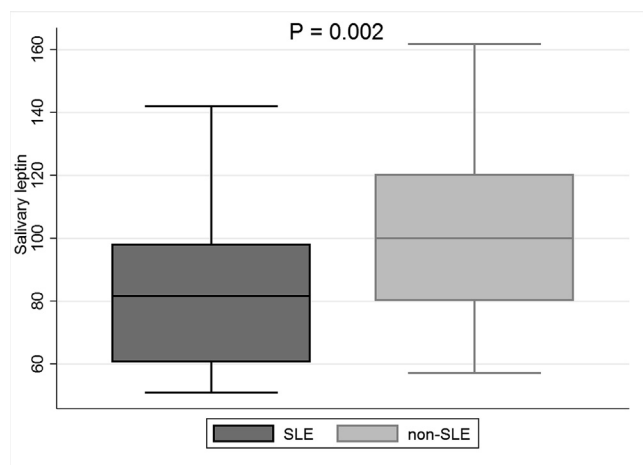


Fig. 2 Comparative analysis of salivary leptin levels among patients with SLE and healthy controls.

**Table 1** Correlation between salivary leptin levels and serum markers and periodontal data in patients with SLE.

Variables	Leptin	
	$R_s$	p value
<b>Serum markers</b>		
Total cholesterol	0.434	<b>0.016*</b>
Triglycerides	-0.534	<b>0.003*</b>
Glycemia	-0.298	0.122
Creatinine	-0.331	<b>0.048*</b>
Creatinine Clearance	-0.445	<b>0.025*</b>
Urea	-0.324	0.065
GOT	0.167	0.322
GPT	0.002	0.989
Leukocyte	-0.331	<b>0.041*</b>
Hemoglobin	-0.047	0.789
Platelet	-0.223	0.176
<b>Periodontal Parameters</b>		
BOP	0.121	0.465
PPD	0.069	0.680
CAL	0.009	0.950

$R_s$ , Spearman correlation coefficient; GOT, glutamic oxaloacetic transaminase; GPT, glutamate-pyruvate transaminase; BOP, bleeding on probing; PPD, probing pocket depth; CAL, clinical attachment level.

\* Statistically significant correlation.

**Table 2** Comparative analysis of salivary leptin levels and type of medicine in patients with SLE.

Variables	n (%)	Leptin	
		means $\pm$ sd	p value
<b>Folic acid</b>			
No	32 (84.2)	87.3 $\pm$ 24.8	0.078
Yes	6 (15.8)	70.7 $\pm$ 17.8	
<b>Azathioprine</b>			
No	21 (55.3)	90.5 $\pm$ 24.9	0.101
Yes	17 (44.7)	77.5 $\pm$ 22.3	
<b>Pulse therapy</b>			
No	33 (86.8)	86.4 $\pm$ 23.9	0.377
Yes	5 (13.2)	73.5 $\pm$ 27.3	
<b>Prednisolone</b>			
No	8 (21.1)	95.4 $\pm$ 17.4	0.098
Yes	30 (78.9)	81.8 $\pm$ 25.4	
<b>Reuquinol</b>			
No	19 (50.0)	85.2 $\pm$ 26.5	0.897
Yes	19 (50.0)	84.2 $\pm$ 22.6	
<b>Hydrochlorothiazide</b>			
No	33 (86.8)	86.5 $\pm$ 25.6	0.261
Yes	5 (13.2)	72.9 $\pm$ 7.7	
<b>Losartan</b>			
No	28 (73.7)	87.1 $\pm$ 22.7	0.384
Yes	10 (26.3)	78.1 $\pm$ 28.7	
<b>Omeprazole</b>			
No	31 (81.6)	81.7 $\pm$ 23.4	0.165
Yes	7 (18.4)	97.9 $\pm$ 26.1	
<b>Hydroxychloroquine</b>			
No	29 (76.3)	85.8 $\pm$ 22.7	0.675
Yes	9 (23.7)	81.1 $\pm$ 30.3	

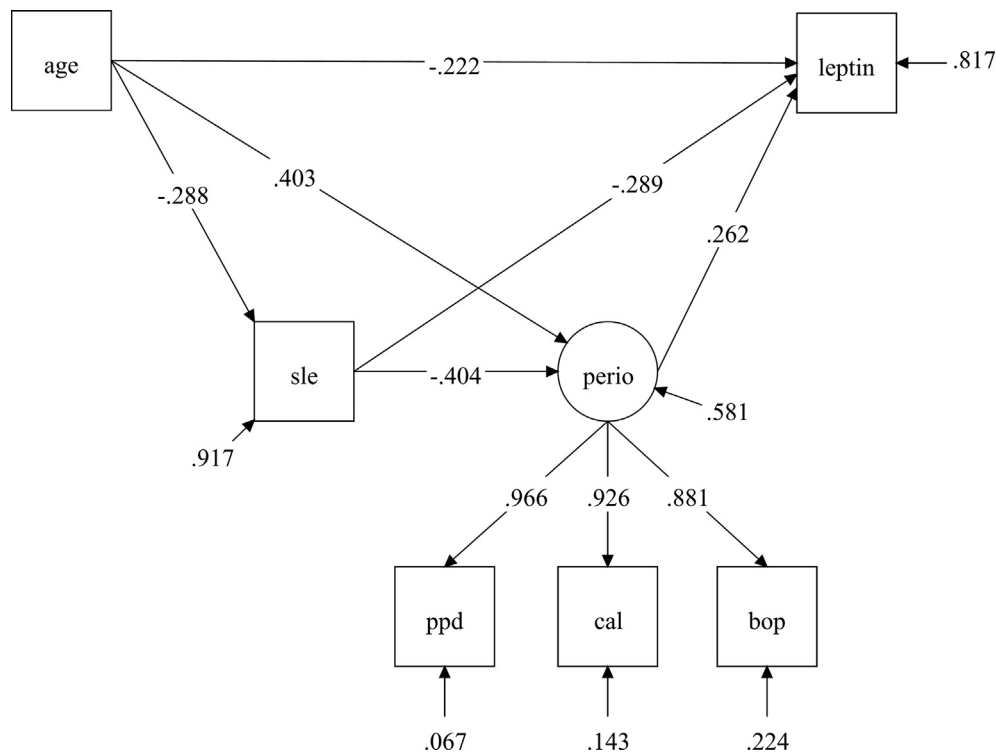
Sd, standard deviation.

#### 4. Discussion

The findings revealed a reduction in the salivary leptin levels in individuals with SLE from the study sample, and this reduction appears to be independent of the periodontal status. In addition, the salivary leptin levels positively correlated with total cholesterol and inversely correlated with serum triglycerides, creatinine, creatinine clearance, and leukocytes in patients with SLE.

Previous studies have shown a direct relationship between body fat levels and circulating leptin levels independent of the presence of other inflammatory diseases (Van Dielen et al., 2001; Vendrell et al., 2004; Sáinz et al., 2015). In the present study, BMI was not correlated with the salivary leptin level in patients with SLE, which corroborates the results of previous studies that identified leptin alterations in patients with SLE independent of other factors such as age, sex, and BMI (Chung et al., 2009; McMahon et al., 2011; Wang et al., 2017).

Evidence indicates that the salivary leptin level is higher in patients with periodontitis, and this level is further increased by diabetes (Jeevitha et al., 2021). Nisha et al. (2022) showed that salivary leptin levels were higher in patients with periodontitis; however, non-surgical periodontal therapy had no effect on salivary leptin levels. These findings suggest that salivary leptin analysis could be useful for monitoring periodontal



**Fig. 3** Results of the structural equations model. BOP, bleeding on probing; CAL, mean clinical attachment level; LEPTIN, salivary leptin; PERIO, periodontal disease (latent variable); PPD, mean probing pocket depth; SLE, systemic lupus erythematosus.

**Table 3** Factorial load of the direct effects in the proposed theoretical model.

	Standardized estimate	Standard error	P value
Latent periodontal condition (perio)			
Probing pocket depth (ppd)	0.966	0.018	< 0.001*
Clinical attachment level (cal)	0.926	0.024	< 0.001*
Bleeding on probing (bop)	0.881	0.031	< 0.001*
Effect on SLE			
Age	-0.288	0.112	0.010*
Effect on periodontal condition (perio)			
Age	0.403	0.098	< 0.001*
SLE	-0.404	0.096	< 0.001*
Effect on salivary leptin (leptin)			
Periodontal condition (perio)	0.262	0.148	0.077
Age	-0.222	0.129	0.085
SLE	-0.289	0.127	0.023*

\* Statistically significant effect (P value < 0.05). RMSEA of 0.004 (< 0.05 indicates a good fit), a CFI of 0.938 (> 0.90 indicates a good fit), and an SRMR of 0.036 (< 0.05 indicates a good fit), but TLI was 0.84, slightly outside the recommended standard (> 0.90 indicates a good fit).

status, although further clinical trials with longitudinal follow-up are needed to understand the possible use in periodontal therapy evaluation.

This study showed lower salivary leptin levels in the SLE group. [Stanescu et al. \(2018\)](#) showed no significant difference in the salivary leptin levels between the SLE group and the control group. In addition, salivary leptin did not correlate with serum inflammatory markers, such as IL-6, or serum leptin levels. That suggests that salivary leptin levels appear to have no linear correlation with the serum concentration in patients with patients SLE. The imbalance in the immune response can explain these findings; however, further studies should be addressed to elucidate the molecular pathways and SLE clinical repercussions of these molecular relationships.

In the correlation analysis, periodontal disease variables did not correlate with the salivary leptin levels. These results appear to indicate that SLE can alter the level of salivary leptin independently of local factors that may contribute to salivary leptin changes. The reason for the reduction of the salivary leptin level in this autoimmune disease has not yet been elucidated. [Johnson and Serio \(2001\)](#) speculated that during inflammation, the salivary leptin concentration is decreased following vascular network expansion caused by vascular endothelial growth factor, which may increase the net rate of leptin removal from the gingival tissue while elevating serum leptin levels.

Another possible mechanism may be related to the fact that leptin presents differently in different parts of the body, as demonstrated by [Schapher et al. \(2009\)](#), which indicates that leptin is secreted into the salivary glands as oligomers, not

breaking these bonds under different denaturation conditions. On the contrary, leptin is secreted as a dimer in the gastrointestinal tract, thus presenting a greater number of molecules in the rest of the body than in the saliva.

Pharmacotherapy used in SLE treatment is characterized by the excessive use of glucocorticoids to obtain a potent anti-inflammatory and immunosuppressive action, but the action of these medicines has several side effects, such as weight gain, fluid retention, and effect on circulating leptin (Cimmino et al., 2010). In the present study, a correlation between the type of medicine and salivary leptin level was not observed. Pharmacological interaction can present effects on oral tissues, alter the immune response because of concomitant intake of multiple drugs (Isola et al., 2015), and affect salivary gland secretions (Grisius, 2001).

The results of this study also showed that the salivary leptin levels demonstrated a negative correlation with serum creatinine, creatinine clearance, and leukocytes. Creatinine and creatinine clearance are frequently altered in patients with SLE and are used to assess renal damage, which is primarily responsible for the increased morbidity and mortality of this disease (Ge et al., 2021).

Patients with SLE also have a higher susceptibility to heart diseases. Cholesterol is an important risk indicator of atherosclerosis, and patients with SLE have accelerated disease course (Chung et al., 2009). Leptin has been associated with both an increased risk of developing atherosclerosis and increased cholesterol levels (Chung et al., 2009; McMahon et al., 2011). Regarding the triglyceride level, this study demonstrated a negative correlation between salivary leptin and this serum marker, which is in agreement with studies that evaluated the correlation between serum leptin and triglyceride in cardiovascular diseases (Chung et al., 2009; Vadacca et al., 2009).

As strengths of this study, the use of SEM enabled us in a single analysis to evaluate different ways of explaining the association between SLE and salivary leptin level. As limitations, the study has a small sample size, which can be explained by the use of a strict criterion for the control group, including initial screening using clinical and serum markers, and the difficulty of evaluating the disease activity in patients with SLE. Longitudinal studies are needed to better investigate the mechanism involved in the interaction between SLE activity and periodontal repercussions.

## 5. Conclusions

The findings of this study suggest that patients with SLE have a reduction in their level of salivary leptin independent of the periodontal status. Salivary leptin level appears to be related to serum markers such as triglycerides, total cholesterol, leukocytes, and creatinine in patients with SLE.

## Ethical approval and consent to participate

The study was approved by the Ethics and Research Committee of the University Hospital of the Federal University of Maranhão (No. 460.888). All participants were informed about the objectives and procedures of the study and signed an informed consent form.

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