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Original article

Mild and moderate Mannose Binding Lectin deficiency are associated with systemic lupus erythematosus and lupus nephritis in Brazilian patients☆

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ABSTRACT

Objective: The potential association of mannose binding lectin (MBL) deficiency and systemic lupus erythematosus (SLE) has been investigated in several studies, but results have been mixed. One explanation for the conflicting results could be differences in ethnic background of study subjects. In this study we investigated the association of MBL deficiency and SLE in a large cohort of Brazilian SLE patients and controls.
Methods: Serum MBL and Complement levels were determined for 286 Brazilian adult SLE patients and 301 healthy Brazilian adults as controls. MBL deficiency was classified as mild (<1000 and ≥500 μg/L), moderate (<500 and ≥100 μg/L) or severe (<100 μg/L).
Results: SLE patients presented higher frequency of mild and moderate MBL deficiency compared to controls. SLE patients with MBL deficiency presented higher frequency of lupus nephritis compared to those without MBL deficiency. MBL deficiency was not associated with any other clinical manifestation, use of immunosuppressant therapy, disease activity, disease severity serum or Complement levels.
Conclusion: This study shows that an association between MBL deficiency and SLE does exist in the Brazilian population. We also found an association between MBL deficiency and lupus nephritis. These findings support the hypothesis that MBL deficiency contributes to the development of SLE and lupus nephritis.

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As deficiências leve e moderada de lectina ligadora de manose estão associadas ao lúpus eritematoso sistêmico e à nefrite lúpica em pacientes brasileiros

Palavras-chave:
Deficiência de LLM
Lúpus eritematoso sistêmico
Imunodeficiência
Nefrite lúpica

RESUMO

Objetivo: Vários estudos já investigaram a potencial associação entre a deficiência de lectina de ligação a manose (LLM) e o lúpus eritematoso sistêmico (LES), mas os resultados obtidos são mistos. Uma explicação para esses resultados conflitantes poderia estar nas diferenças étnicas dos indivíduos estudados. Este estudo investigou a associação entre a deficiência de LLM e o LES em uma grande coorte de pacientes brasileiros com LES e controles.

Métodos: Determinaram-se os níveis séricos de LLM e complemento em 286 pacientes adultos brasileiros com LES e 301 adultos brasileiros saudáveis que atuaram como controles. A deficiência de LLM foi classificada como leve (<1000 e ≥ 500 μg/L), moderada (<500 e ≥ 100 μg/L) ou grave (<100 μg/L).

Resultados: Os pacientes com LES apresentaram uma maior frequência de deficiência leve e moderada de LLM em relação aos controles. Os pacientes com LES com deficiência de LLM apresentaram uma maior frequência de nefrite lúpica em comparação com aqueles sem deficiência de LLM. A deficiência de LLM não esteve associada a qualquer outra manifestação clínica, uso de terapia imunossupressora, atividade da doença, gravidade da doença ou níveis séricos de complemento.

Conclusão: Este estudo mostra que há uma associação entre a deficiência de LLM e o LES na população brasileira. Encontrou-se também uma associação entre a deficiência de LLM e a nefrite lúpica. Esses resultados apoiam a hipótese de que a deficiência de LLM contribui para o desenvolvimento do LES e da nefrite lúpica.

Introduction

Mannose binding lectin (MBL), an important component of the innate immune defense system, has the capacity to bind microorganism surface polysaccharides and subsequently activate the Complement system through the MASP (MBL associated serine proteases) family of proteases. MBL is functionally similar and structurally homologous to C1q, the first component of the classical Complement pathway.[1]

The MBL gene contains 4 exons and its chromosome location is 10q11.2–q21. Five single nucleotide polymorphisms (SNPs) have been reported to be associated with reduced MBL serum protein levels. The most common SNPs are located on exon 1, at codons 52 (+223), 54 (+230), and 57 (+239), respectively designated alleles D, B and C (the "wild" type allele is designated A).[2] In addition, polymorphisms of the MBL promoter region are also reported to influence serum protein levels.[3] The frequency of the abnormal alleles differs significantly according to ethnic background.[4]

MBL polymorphism has been reported in association with several autoimmune diseases, including type I diabetes[5] and rheumatoid arthritis.[6] Several studies suggest an association between MBL deficiency or gene polymorphism and systemic lupus erythematosus (SLE).[7] It has been postulated that MBL deficiency might result in inefficient clearance of apoptotic cells and predisposition to infections. This, in turn, may lead to over-expression of autoantigens that could contribute to autoantibody generation and SLE development.[7] A meta-analysis of 8 studies published in 2001 showed that the presence of abnormal alleles confers a 1.6 fold increase in risk for developing SLE.[8] Four years later, Lee et al.[9] demonstrated that a SNP at MBL codon 54 (designated allele B) and polymorphisms in the MBL promoter region were risk factors of SLE development. However, several other studies failed to demonstrate an association between SLE and MBL deficiency. This discrepancy may be related to the heterogeneous ethnic backgrounds of subjects in those studies.[10,11] It is possible that other genetic factors, perhaps related to ethnic background, are required for the development of SLE in individuals with MBL deficiency or gene polymorphism.[2] Therefore, it is important to investigate the influence of MBL deficiency on development of SLE in distinct ethnic groups.

Here we report on a study of a large cohort of Brazilian lupus patients and healthy controls aimed to determine whether low serum MBL level is a risk factor for SLE in this population.

Materials and methods

Study subjects

286 patients meeting the 1997 updated American College of Rheumatology (ACR) criteria for SLE[12] were sequentially selected from the Autoimmune Rheumatic Diseases Out-Patient Clinic at Federal University of Sao Paulo (UNIFESP) during an eighteen-month period. Three hundred and one healthy blood donors were recruited after showing no evidence of autoimmune disease according to a structured medical interview. Patients and controls were at least 18 years old; each signed the Informed Consent Form, previously approved by UNIFESP Ethics Committee (CEP n. 0330/09).

Table 1 – Distribution of subjects with systemic lupus erythematosus according to demographic variables, presence of co-morbidity, clinical characteristics and medications taken.

	n (%)		*n* (%)
Gender (F:M)[a]	271:15	Current immunosuppressant[d]	196 (68.5)
Age (years)[b]	39.29 ± 12.23	• Antimalarials[e]	198 (69.2)
Disease duration (years)	10.58 ± 7.91	• Corticosteroids	153 (53.4)
SLICC-DI (median/25%–75%)	1/0–2	≥20 mg (prednisone)	67 (23.4)
SLEDAI (median/25%–75%)	0/0–2	<20 mg (prednisone)	86 (30.1)
Autoimmune rheumatic diseases	20 (6.9)	• Azathioprine	65 (22.7)
• APS	14 (4.9)	• Methotrexate	48 (16.8)
• Sjögren's syndrome	6 (2.1)	• Cyclophosphamide	23 (8)
Other non-rheumatic autoimmune diseases	14 (4.8)	• Mycophenolate	25 (8.7)
• Hashimoto's thyroiditis	14 (4.8)	• Leflunomide	14 (4.9)
Miscellaneous[c]	134 (43.8)	• Cyclosporine	7 (2.4)
		• Tacrolimus	4 (1.4)
		• Dapsone	3 (1.0)
		• Thalidomide	2 (0.7)
		Previous immunosuppressant	186 (65)

APS, antiphospholipid syndrome; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI, Systemic Lupus International Collaborating Clinics-Damage Index.

[a] Healthy controls: 286:15 ($p = 0.856$).
[b] Healthy controls: 35.1 ± 11.10 ($p = 0.070$).
[c] Miscellaneous: non autoimmune diseases, such as arterial hypertension, dyslipidemia, osteoarthritis, etc. Healthy controls: 43 (14.2%; $p < 0.001$).
[d] The sum of subjects using each drug results in a number greater than the total number of patients because some subjects used two or more medications.
[e] Antimalarial was not considered immunosuppressant.

Exclusion criteria were: (a) any kind of infection within 30 days before data collection; (b) use of immunobiological medication (infliximab, adalimumab, etanercept, rituximab or abatacept) within the last 6 months; (c) coexistence of malignant diseases; and (d) HIV infection. Patients underwent a detailed clinical evaluation, with emphasis on SLE clinical manifestations, recurrent infections, current and previous medications, age at SLE onset, evidence of other autoimmune diseases, family history, and determination of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[13] and Systemic Lupus International Collaborating Clinics-Damage Index (SLICC-DI).[14] Patients with inactive autoimmune disease and altered MBL tests had a second blood sample drawn after 60 days for re-testing. Patients with any evidence of active autoimmune disease (SLEDAI ≥ 1) and MBL deficiency were followed up to the end of the flare and only then were submitted to a second blood draw and retesting. Patients were classified as deficient exclusively after the confirmation of initial results. In all the cases who were submitted to retest, laboratorial data analyzed were restricted to the second blood drawn. In regards to the clinical manifestations and disease activity, clinical data used were restricted to the last activity period. Lupus nephritis subtypes were defined according to previous biopsies, when available. Patients with abnormal results who continued to exhibit active disease throughout the study period were excluded.

Evaluation of serum Complement and MBL levels

The analysis of the Complement components included determination of total Hemolytic Complement (CH50), C2, C3, and C4. CH50 and C2 were determined by immunohemolytic assays, as previously reported.[15] C3 was determined by immunoturbidimetry (Olympus®, San Mateo, USA) and C4 by immunonephelometry (Beckman Coulter®, Brea, USA). Serum MBL was determined by ELISA (Bioporto Diagnostics®, Gentofte, Denmark) and MBL deficiency was defined as serum levels lower than 1000 μg/L and graded according to severity into mild (<1000 and ≥500 μg/L), moderate (<500 and ≥100 μg/L) and severe (<100 μg/L), as validated by previous studies.[16–20]

Statistical analysis

Continuous variables with normal distribution were analyzed with Student's *t* test and those with non-parametric distribution were analyzed with the Mann–Whitney test. Qualitative parameters were analyzed by the Chi-square test and the Fisher's exact test when appropriate. Multiparametric analyses were calculated with the ANOVA one-way test and post-ANOVA tests (Bonferroni) when appropriate. Correlation analysis was performed by the Pearson's correlation method. Statistical inference level was set at 0.05.

Results

Study population characteristics

Among the 286 SLE patients there were 271 women and 15 men, with age varying from 18 to 75 years old (39.29 ± 12.23). Among the 301 normal controls, there were 286 women and 15 men, with age varying from 18 to 61 years old (35.1 ± 11.1). Patients and controls did not differ with regard to age and

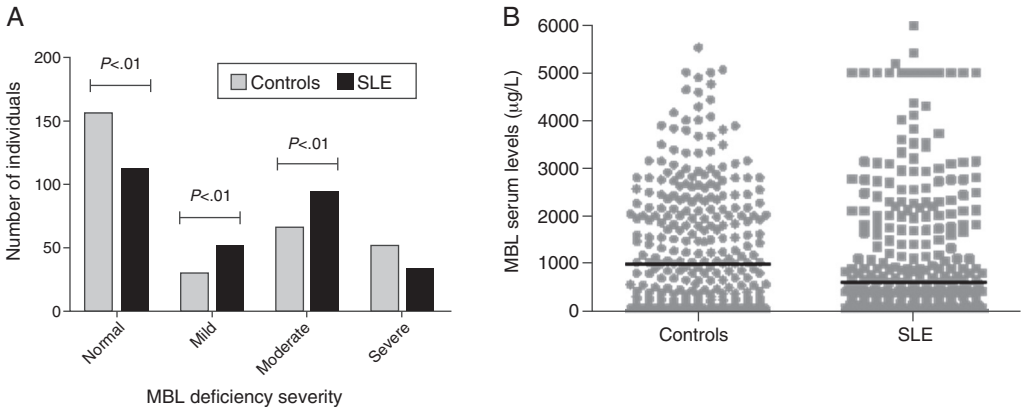

Fig. 1 – Systemic lupus erythematosus (SLE) is associated with mild and moderate MBL deficiency. A, distribution of SLE patients and controls according to severity of MBL deficiency; B, MBL serum levels in SLE patients and controls. Definition of MBL deficiency (present in 146 controls and 175 SLE patients), serum MBL <1000 µg/L; mild, serum MBL <1000 and ≥500 µg/L; moderate, serum MBL <500 and ≥100 µg/L; severe, serum MBL <100 µg/L.

gender distribution, and all of them were descendant from a blend of different ethnicities, presenting, therefore, a mixed background. Patients presented SLEDAI varying from 0 to 14 (1.62 ± 2.81, median: 0) and SLICC-DI varying from 0 to 5 (0.95 ± 1.12, median: 1). Duration of disease varied from 1 to 53 years (10.58 ± 7.91). Table 1 depicts the distribution of SLE patients according to the presence of distinct clinical manifestations and medications used.

Mild and moderate MBL deficiency is more frequent in SLE patients

SLE patients ($n = 175$; 61.18%) presented higher frequency of MBL deficiency compared to controls ($n = 146$; 48.50%; $p < 0.01$), especially due to mild and moderate MBL deficiency (Fig. 1A). However, the overall distribution of MBL serum levels was similar in SLE patients and healthy controls (Fig. 1B). There was no correlation between MBL deficiency and serum Complement component levels, regardless of the severity of MBL deficiency (Table 2).

Clinical features of SLE patients with MBL deficiency

As the laboratory data referred to patients without relevant disease activity (clinical quiescence), all the clinical data refer to previous manifestations. Patients with MBL deficiency presented higher frequency of previous lupus nephritis (class II, III, IV or V) compared to those without MBL deficiency, regardless of the severity of MBL deficiency (Table 3). No other clinical manifestation, including recurrent infections, presented different frequency in SLE patients with and without MBL deficiency (Table 3). There was also no difference between these two subgroups regarding the presence of other autoimmune rheumatic diseases, non-rheumatic autoimmune diseases or other non-autoimmune diseases (miscellaneous), disease severity, cumulative damage, current age, disease duration, age at SLE onset (Table 3), and previous or current use of immunosuppressant (Table 4). Finally, no correlation between MBL serum levels and disease severity or cumulative damage was observed (Table 5).

Discussion

In the present study, we determined the frequency and possible clinical implications of MBL deficiency in a large cohort of Brazilian SLE patients. We observed an increased frequency of mild and moderate MBL deficiency in SLE patients compared to healthy controls. Interestingly, our results showed higher frequency of lupus nephritis in association with MBL deficiency regardless of the severity of MBL deficiency. One concern was the possibility that the low serum MBL observed

Table 2 – Lack of correlation between serum MBL levels and Complement levels in subjects with systemic lupus erythematosus.

MBL deficiency	CH50		C2		C3		C4	
	Pearson	*p*	Pearson	*p*	Pearson	*p*	Pearson	*p*
Overall	0.041	0.491	0.118	0.067	0.019	0.751	−0.125	0.233
Mild	0.064	0.657	−0.026	0.857	0.154	0.285	0.215	0.363
Moderate	0.113	0.284	0.204	0.051	0.024	0.819	0.022	0.907
Severe	−0.044	0.807	−0.037	0.839	−0.289	0.102	−0.011	0.979

MBL deficiency, serum levels lower than 1000 µg/L; mild, serum MBL level <1000 and ≥500 µg/L; moderate, serum MBL level <500 and ≥100 µg/L; severe, serum MBL level <100 µg/L.

Table 3 – Distribution of subjects with systemic lupus erythematosus according to the severity of MBL deficiency and the previous clinical manifestation and demographic characteristics of the disease.

Clinical features		No MBL deficiency $n=111$	MBL deficiency			
			Overall $n=175$	Mild $n=50$	Moderate $n=92$	Severe $n=33$
Gender	M:F	3:108	12:163	2:48	7:85	3:30
Cutaneous	%[a]	94.6	89.7	92.0	88.0	90.9
Oral ulcers	%	18.9	22.9	32.0	21.7	12.11
Arthritis	%	83.8	88.6	88.0	88.0	90.9
Nephritis	%	47.7	60.6[b]	74.0[c]	61.1[b]	66.7[b]
II	%	1.3	1.8	2.1	1.5	1.6
III	%	8.6	8.5	8.1	9.6	7.9
IV	%	13.2	12.2	13.6	13.2	13.9
V	%	5.7	6.2	6.1	4.8	5.0
No biopsy available	%	18.9	19.4	18.5	18.9	19.8
Hematologic disease	%	68.5	65.1	60.0	66.3	69.7
Serositis	%	21.6	32.0	24.0	33.7	39.4
Neuropsychiatric	%	18.9	22.9	28.0	20.7	21.2
Recurrent infection	%	9.0	8.6	2.0	10.9	12.11
Other SARD	%	8.1	6.9	4.0	7.6	9.1
NRAID	%	1.8	6.9	12.0	3.3	9.1
Miscellaneous	%	48.6	45.7	56.0	40.2	45.5
Age	Mean ± SD	38.7 ± 11.8	39.2 ± 12.9	38.7 ± 12.1	37.9 ± 13.0	43.3 ± 13.0
Disease duration		9.7 ± 7.1	10.8 ± 8.0	10.3 ± 7.4	11.0 ± 8.5	11.0 ± 7.6
Age at SLE onset		28.9 ± 10.4	28.3 ± 11.0	28.4 ± 10.9	26.8 ± 10.7	32.2 ± 11.14
SLEDAI	Median (min–max)	0 (0–11)	0 (0–12)	0 (0–6)	0 (0–8)	1 (0–12)
SLICC-DI		1 (0–4)	1 (0–5)	1 (0–4)	1 (0–5)	1 (0–3)

MBL deficiency, serum levels lower than 1000 μg/L; mild, serum MBL level <1000 and ≥500 μg/L; moderate, serum MBL level <500 and ≥100 μg/L; severe, serum MBL level <100 μg/L; SARD, systemic autoimmune rheumatic diseases; NRAID, non-rheumatic autoimmune diseases; miscellaneous, any non-rheumatic and non-autoimmune disease; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI, Systemic Lupus International Collaborating Clinics-Damage Index.

[a] Percentages refer to the frequency of any given clinical manifestation.

[b] $p<0.05$.

[c] $p<0.01$.

Table 4 – Distribution of subjects with systemic lupus erythematosus according to the severity of MBL deficiency and use of immunosuppressant therapy.

		No MBL deficiency	MBL deficiency			
		$n=111$	Overall $n=175$	Mild $n=50$	Moderate $n=92$	Severe $n=33$
Current immunosupressant[a]	%[b]	64.0	71.4	68.0	71.7	75.8
Previous immunosupressant[a]	%	63.6	66.7	74.0	63.7	63.6
Corticosteroids						
Total[a]	%	52.3	54.9	66.0	45.7	57.6
Low doses[a]	%	32.4	28.6	32.0	26.1	36.4
High doses[a]	%	19.80	25.7	34.0	19.6	21.2
Anti-malarials[a]	%	73.0	66.9	70.0	59.8	81.8
Azathioprine[a]	%	21.6	23.40	24.0	25.0	18.2
Mycophenolate[a]	%	9.9	8.0	8.0	6.5	12.1
Methotrexate[a]	%	13.5	18.9	16.0	17.4	27.3
Cyclophosphamide[a]	%	7.2	8.6	6.0	10.9	6.1
Leflunomide[a]	%	5.4	4.6	4.0	3.3	9.1
Dapsone[a]	%	1.8	0.6	2.0	0	0
Thalidomide[a]	%	0.9	0.6	0	1.1	0
Tacrolimus[a]	%	0.9	1.7	2.0	2.2	0
Cyclosporine[a]	%	1.8	2.9	6.0	1.1	3.0

MBL deficiency, serum levels lower than 1000 μg/L; mild, serum MBL level <1000 and ≥500 μg/L; moderate, serum MBL level <500 and ≥100 μg/L; severe, serum MBL level <100 μg/L.

[a] No statistically significant association.

[b] Percentages refer to the frequency of any given clinical manifestation.

Table 5 – Lack of correlation between MBL serum levels and disease activity or cumulative damage in subjects with systemic lupus erythematosus.

MBL deficiency	SLEDAI		SLICC-DI	
	Correlation[a]	*p*	Correlation	*p*
Overall	−0.068	0.256	−0.05	0.945
Mild	0.037	0.800	−0.090	0.631
Moderate	0.107	0.310	0.163	0.160
Severe	0.036	0.840	−0.322	0.154

SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI, Systemic Lupus International Collaborating Clinics-Damage Index; MBL deficiency, serum levels lower than 1000 μg/L; mild, serum MBL level <1000 and ≥500 μg/L; moderate, serum MBL level <500 and ≥100 μg/L; severe, serum MBL level <100 μg/L.

[a] Calculated according to Pearson's test.

in some patients could be secondary to disease activity or immunosuppressant therapy. However, this seems not to be the case, since follow up assessment after SLE disease activity has confirmed the initial MBL deficient classification in all cases. In addition, there was no difference in the frequency of MBL deficiency according to SLE activity and severity. No association was observed between MBL deficiency and immunosuppressant use or recurrent infections.

Traditionally, immunodeficient states are associated with increased susceptibility to infection. MBL deficiency has been described as a risk factor for infectious diseases.[21–23] However, microbicide activity is not the sole function of MBL: it can also bind apoptotic cells and initiate their uptake by macrophages.[24,25] Therefore, it is possible that MBL deficiency could lead to decreased clearance of autoantigens, which could in turn contribute to the development of autoimmunity. We propose that mild or moderate immunologic deficits such as MBL deficiency may impact the inflammatory process and eventual development of autoimmune diseases even without increasing susceptibility to infections.

The association between MBL deficiency and SLE is still controversial and disparate results have been obtained in different ethnic groups, including American[11] and African[10] populations. In this regard, the present study makes an important contribution, since it confirms the association in a sample of the Brazilian population, which represents a unique blend of European, African and native American Indian descendants. Another source of controversy is the lack of a clear definition of MBL deficiency. In this study we defined three degrees of MBL deficiency severity based on serum MBL levels, as has been done in several previous studies.[16–20] There is some concern that anti-MBL autoantibodies in the serum of SLE patients might lead to secondary MBL deficiency without underlying MBL genetic abnormality. This could partially explain conflicting findings on the association between MBL deficiency and SLE.[8,11,26] As an alternative, some studies have used MBL polymorphisms in the promoter region or the coding region as criteria for definition of MBL deficiency.[3,4,7–9] However, there is no perfect correlation between the presence of MBL polymorphisms and protein expression, and therefore the real value of this approach is still unclear.

In this study, we observed a higher frequency of lupus nephritis in subjects with SLE and MBL deficiency than in subjects with SLE and normal MBL levels. Several previous studies have suggested links between MBL levels and lupus nephritis. Anti-MBL autoantibodies can bind to MBL deposited in tissues and contribute to local injury, as demonstrated in kidneys of SLE patients.[27] It has been also reported that the nucleic acid-binding capacity of MBL plays an important role in the clearance of DNA, an important autoantigen for lupus nephritis development.[28] Piao et al.[29] in a North American population and Asgharzadeh et al.[30] in an Azerbaijan population in Iran demonstrated that homozygosis for MBL variants is a disease-modifying factor, particularly for renal involvement. However, the relationship between MBL deficiency and lupus nephritis may be affected by ethnic background, since Bertoli et al.[31] showed in a large multiethnic lupus cohort composed by Hispanics, African American and Caucasians that carriers of variant alleles for MBL gene had lower frequency of lupus nephritis and serositis, but higher frequency of leukopenia.

Besides the decrease in antigen clearance, homozygosis for MBL variant alleles is also associated with an increase in risk of infections, mainly in children.[32,33] Consequently, patients with MBL deficiency are at higher risk of being exposed more frequently and for longer periods of time to pathogens that may play a role in SLE pathogenesis. It should be pointed out that a previous report found no association between MBL deficiency and severe infections in SLE patients,[34] and this was confirmed in the present study. Furthermore, it has been reported that MBL-deficient adults do not present increased frequency of infectious diseases, leading to the assumption that a second immune defect might be needed to trigger susceptibility to infection.[35]

The exact mechanism underlying the effect of MBL deficiency on the pathogenesis and clinical outcome of SLE is not clear. Takahashi et al.[36] showed positive, although weak, correlation between serum CH50 activity and serum MBL levels, suggesting that MBL could also be used as a marker for disease activity in SLE patients. In the present study, we could not demonstrate any correlation between serum MBL levels and Complement levels, SLE disease activity or cumulative damage. Regardless of the pathophysiology involved, MBL deficiency per se is probably not enough to induce autoimmunity. Additional, yet unknown factors may act in concert with MBL deficiency to trigger development of autoimmunity. Further studies are needed to address this question.

In summary, analysis of serum MBL levels in a large cohort of adult Brazilian SLE patients and healthy controls showed that mild and moderate MBL deficiency is associated with SLE in this study population. Moreover, we observed that SLE

patients with MBL deficiency had higher prevalence of lupus nephritis, regardless of the severity of MBL deficiency, than SLE patients with normal MBL levels. These results obtained in the ethnically unique and complex Brazilian population framework add another piece to the puzzle of the association of MBL deficiency and SLE.

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Conflicts of interest

The authors declare no conflict of interest.

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