Estudo longitudinal do anticorpo antilipoproteína lipase e sua relação com atividade de doença nos indivíduos com lúpus eritematoso sistêmico sem anticorpos anti-dsDNA

Longitudinal fluctuation of anti-lipoprotein lipase antibody is related with disease activity in systemic lupus erythematosus patients without anti-dsDNA antibodies

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RESUMO

Introdução: O Lúpus Eritematoso Sistêmico (LES) se caracteriza por períodos de exacerbação e remissão clínica que frequentemente são acompanhados por alterações nos níveis séricos de anticorpos específicos, como o anti-dsDNA, que está presente em 40% dos casos, associado principalmente à atividade renal. Recentemente houve a descrição de duas subpopulações de anticorpos antilipoproteína lipase (anti-LPL) no LES: uma com e a outra sem atividade anti-dsDNA. A possível relação desse último grupo de anticorpos com a atividade inflamatória de doença ainda não foi analisada no LES. **Objetivos:** Avaliar longitudinalmente a associação dos níveis séricos dos anticorpos anti-LPL com atividade do LES em pacientes com anti-dsDNA persistentemente negativo. **Pacientes e Métodos:** Cinco pacientes com LES com anti-dsDNA persistentemente negativo mensurado por ELISA e por imunofluorescência indireta em *crithidia luciliae* e altos títulos de anti-LPL por ELISA (≥ 5 desvios-padrão (DP) da média de 20 controles normais) foram selecionados e acompanhados longitudinalmente durante um período mínimo de dois anos. **Resultados:** Caso 1: Homem, 24 anos com LES desde 2001 apresentou hemorragia alveolar, proteinúria, hipertensão arterial sistêmica, eritema malar, aftas, artrite, FAN+, com SLEDAI (*systemic lupus erythematosus*

ABSTRACT

Introduction: *Systemic lupus erythematosus (SLE) is characterized by periods of clinical flares and remission that are followed by alterations of sera specific autoantibodies such as anti-dsDNA, present in 40% of the cases and strongly associated with renal involvement. Recently, there was a description of two subpopulations of anti-lipoprotein lipase antibodies (anti-LPL) in SLE: with and without anti-dsDNA activity. A possible relationship between these antibodies with inflammatory activity of SLE was not analyzed.* ***Objectives:*** *To evaluate longitudinally the association between anti-LPL with lupus activity in patients persistently negatives for anti-dsDNA antibodies.* ***Patients and methods:*** *Five SLE patients with persistently negative anti-dsDNA measured by ELISA and indirect immunofluorescence using crithidia luciliae and high titers of anti-LPL by ELISA (≥ 5 SD) were selected and followed for at least 2 years.* ***Results:*** *Case 1: A 24-year-old male with SLE since 2001, presented with alveolar hemorrhage, proteinuria, systemic hypertension, malar rash, oral ulcers, polyarthritis, positive ANA, SLEDAI=16 and anti-LPL=144U. He was treated with intravenous (IV) methylprednisolone followed by prednisone and had an excellent response. SLEDAI=0, anti-LPL decreased to 109U. New renal flare in April 2002, SLEDAI=10 and a*

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disease activity index) = 16 e anti-LPL = 144UA. Tratado com pulso de metilprednisolona e prednisona com melhora clínica e SLEDAI = 0 e redução do anti-LPL (109UA). Nova atividade com acometimento renal em abril de 2002, SLEDAI = 10 e aumento de anti-LPL (150UA). Iniciada pulsoterapia de ciclofosfamida e metilprednisolona com boa resposta, SLEDAI = 0 e diminuição de anti-LPL (77UA) até a sua total negativação acompanhando a remissão do quadro no ano de 2003. Caso 2: Mulher, 32 anos, com LES desde 1997. Em setembro de 2001 iniciou vasculite cutânea, febre e *rash*, SLEDAI = 10, anti-LPL = 80UA. Em janeiro de 2002, teve atividade renal e HAS, SLEDAI = 8 e anti-LPL = 25UA, mas com a introdução de CE e ciclofosfamida evoluiu com melhora importante. Em 2003, assintomática, apresentava SLEDAI = 2 e anti-LPL = 12UA. Caso 3: Homem, 39 anos, com LES desde 1997. Estável em uso de cloroquina, sem atividade durante 3 anos, SLEDAI = 0 em todas as ocasiões e sem variação dos títulos de anti-LPL no período do estudo: 85UA (2001),100UA (2002) e 86UA (2003). Caso 4: Mulher**,** 58 anos com LES desde 1996. Remissão do LES desde agosto de 2001 e com SLEDAI = 0 no período do estudo. Títulos de anti-LPL sem flutuações significativas: 71UA (2001), 42UA (2002) e 61UA (2003). Caso 5: Mulher, 55 anos com LES desde 1989. Estável desde 2000 em uso de cloroquina, SLEDAI = 0, e títulos de anti-LPL também sem variações: 71UA (1999), 92UA (2001), 71UA (2002) e 90UA (2003). **Conclusão**: A avaliação longitudinal dos pacientes selecionados mostrou-se estar associada à flutuação dos títulos de anti-LPL com o SLEDAI, sugerindo ser essa variação um novo marcador de atividade do LES, na ausência de anticorpos anti-dsDNA.

Palavras-chave: lúpus eritematoso sistêmico, antilipoproteína lipase, anti-dsDNA, SLEDAI, autoanticorpos.

new increment of anti-LPL (150U). IV Cyclophosphamide and methylprednisolone were started and he achieved remission, SLEDAI=0 and a decrease of anti-LPL (77U) until become negative in 2003. Case 2: A 32-year-old female had SLE since 1997. In September 2001 began cutaneous vasculitis, fever and rash, SLEDAI=10, anti-LPL=80U. In January 2002, she had renal involvement and systemic hypertension, SLEDAI=8 and anti-LPL= 25U. She received corticosteroid and cyclophosphamide and improved. In 2003, she was asymptomatic, SLEDAI=2 and anti-LPL=12U. Case 3: A 39-year-old male has SLE since 1997. He was stable, under chloroquine use, without disease activity for 3 years, SLEDAI=0 in all period studied and no fluctuation of anti-LPL titers: 85U (2001),100U (2002) e 86U (2003). Case 4: A 58-year-old female had SLE since 1996. She was in remission since August 2001 with a SLEDAI=0 during all this study. Anti-LPL titers did not significantly change: 71U (2001), 42U (2002) e 61U (2003). Case 5: A 55-year-old female had SLE since 1989. She was stable since 2000 using chloroquine, SLEDAI=0, and anti-LPL titers without variations: 71U (1999), 92U (2001), 71U (2002) e 90U (2003). ***Conclusion:*** *The longitudinal evaluation of the selected patients showed a positive correlation between the fluctuations of the titers of anti-LPL with the SLEDAI score. These findings suggest that this variation may be a new marker for lupus activity in patients without anti-dsDNA antibodies.*

Keywords: *systemic lupus erythematosus, anti-lipoprotein lipase, anti-dsDNA, SLEDAI, autoantibodies.*

INTRODUÇÃO

O lúpus eritematoso sistêmico (LES) é uma doença caracterizada por períodos de exacerbação e remissão e pela presença de certos anticorpos específicos, e a flutuação dos títulos destes correlaciona-se com a atividade da doença. O anticorpo anti-dsDNA, presente em cerca de 40% dos casos, correlaciona-se com a atividade renal, e o anti-P ribossomal, presente em 10-20% dos pacientes, está associado a manifestações neuropsiquiátricas e renais.[1-3] Pela paucidade desses marcadores, a busca de novos anticorpos que se correlacionem com atividade do LES seria de grande auxílio para a clínica.

Nesse sentido, os anticorpos antilipoproteína lipase (anti-LPL), recentemente descritos no LES[4], foram correlacionados à hipertrigliceridemia, à proteína C-reativa de alta sensibilidade e à atividade de doença através do *systemic lupus erythematosus disease activity index* (SLEDAI).[5] A lipoproteína lipase (LPL) é uma enzima presente na superfície endotelial que tem como função a hidrólise de quilomícrons e triglicérides[6] e já foi demonstrada que a sua função reduzida está relacionada à hipertrigliceridemia.[7]

Os objetivos do presente estudo foram estabelecer se existe flutuação dos anticorpos anti-LPL ao longo do tempo em pacientes com LES e se essa flutuação poderia estar associada à atividade da doença.

PACIENTES E MÉTODOS

Dos 900 pacientes acompanhados no Ambulatório de Lúpus do Serviço de Reumatologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, 200 foram selecionados consecutivamente para a realização de anticorpos anti-LPL, todos preenchiam os critérios do Colégio Americano de Reumatologia (*American College of Rheumatology, ACR*) para LES.[8,9] Dessa população, apenas 66 foram incluídos para a realização de um trabalho anterior já publicado.[5] A partir dessa população e da aplicação dos critérios de inclusão do presente trabalho (positividade dos anticorpos anti-LPL > 5, os desvios-padrão e ausência de anticorpos anti-dsDNA) por dois métodos nos levaram a cinco pacientes. Todos eles foram analisados através de entrevista clínica e preenchimento de ficha padronizada do protocolo, revisão de prontuário, dados

atividade clínica ou laboratorial e com SLEDAI persistentemente de zero, os anticorpos anti-LPL estavam presentes em altos títulos e sem variação significante dos seus valores. Isso sugere a presença de duas subpopulações de anticorpos anti-LPL, uma relacionada à atividade de doença e que acompanha a evolução de atividades e remissões dos indivíduos e outra subpopulação de anticorpos que se mantém elevada persistentemente, não se correlacionando com atividade ou mesmo com níveis dos lipídios sanguíneos, como já explicado anteriormente.[4]

Este estudo traz a possibilidade de um novo e possível marcador de atividade do LES quando os anticorpos anti-dsDNA estão ausentes no soro de alguns pacientes com essa conectivopatia.

Longitudinal fluctuation of anti-lipoprotein lipase antibody is related with disease activity in systemic lupus erythematosus patients without anti-dsDNA antibodies

INTRODUCTION

Systemic lupus erythematosus (SLE) is characterized by periods of clinical flares and remission and for certain specific antibodies whose titer fluctuation is correlated with disease activity. Antibody anti-dsDNA, present in 40% of the patients and related to renal involvement, and anti-ribosomal P protein antibodies, present in 10-20% of patients, associated with neuropsychiatryc and renal manifestations.[1-3] Due to the low frequency of such markers, searching for new antibodies that correlate with SLE activity should be helpful for clinical pratice.

Recently described in SLE,[4] anti-lipoprotein lipase antibodies (anti-LPL), was correlated to hypertriglyceridemia, and to highly sensitive C-reactive protein, and the Systemic Lupus Erythematosus Activity Index (SLEDAI).[5] Lipoprotein lipase (LPL) is an enzyme present in endothelial surface, which function is hydrolysis of chylomicrons and triglycerides,[6] and it has already been demonstrated that its reduced function is related to hypertriglyceridemia. [7]

The purpose of this study were to verify anti-LPL antibody fluctuation over time in lupus patients and correlate this fluctuation to disease activity.

PATIENTS AND METHODS

Two hundred consetive SLE patients were selected to perform anti0LPL antibodies from among 900lupus patients attending the Lupus Clinic at the Rheumatology Division of Sao Paulo University. All patients fulfilled the revised American College of Rheumatology (ACR) criteria for SLE.[8,9] Out of this population, only 66 were included to perform a study previously published.[5] From this population and the inclusion criteria application of this present study (positivity of anti-LPL antibodies > 5), standard deviations and lack of anti-dsDNA antibody by two methods led us to five patients. All of them were clinically evaluated, completed a standardized form, had the medical records review, necessary data to complete SLEDAI,[10] and blood taking for laboratory tests. The local ethics committee approved the study, and informed consent was obtained from all participants.

Anti-LPL antibody detection: Serum were analyzed by ELISA techniques, using lipoprotein lipase purified from commercial bovine milk (*Sigma Chem Company, US*) standardized in our laboratory, in order to identify IgG isotype antibody presence specific for this enzyme, as previously described.[5] For this study and in order to assure high antibody positivity, only those patients with high antibody titers had been included, that is, more than five standard deviations from the average of 20 normal controls. Outcomes had been stated in arbitrary units (AU), corresponding to optical density of sample x100. Cut-off for this study was 15AU.

Biochemical determinations, inflammatory markers and blood count: Total cholesterol dosing and fractions, as well as triglycerides, were done in serum obtained after a 12-hour fast. *Total cholesterol (TC)* was established using colorimetric enzymatic method,[11] adapted to chemical analyzer RA 1000 System (Technicon), using Boehringer Mannheim's diagnosis set (Argentina). *Triglycerides (TG),* using enzymatic method[12] adapted to biochemical analyzer RA 1000 System (Technicon), using Merck diagnosis set (Germany). For cholesterol fraction detections: High density lipoprotein (HDL) cholesterol was obtained after precipitation of very low-density lipoprotein (VLDL) cholesterol from serum, and low-density lipoprotein (LDL) cholesterol by phosphotungstic acid and magnesium chloride;[13] VDLD cholesterol (VLDL) were calculated based on triglyceride level division by 5, since triglyceride values previously obtained were lower than 400 mg/dL,[14] and finally, LDL was calculated by the formula: LDL cholesterol = total cholesterol - (HDL + VLDL).[14]

Blood count was performed using automated technique by flow cytometry. Erythrocyte sedimentation rate (ESR) speed

was established by modified Westergren technique, the high-sensitivity C-reactive protein (CRP) by nephelometry and gamma globulin by protein electrophoresis.

Anti-dsDNA antibody detection: Exclusion of patients with anti-dsDNA antibodies was performed by two techniques to assure reliability. These procedures had been performed using ELISA for anti-dsDNA, with the addition of anti-S1-nuclease enzyme to assure the absence of anti-ssDNA antibodies, and using indirect immunofluorescence technique with hemoflagellate *crithidia luciliae* as substrate.[3]

Determination of hemolytic activity of the Complement system and its components: The evaluation of total Complement activity (CH100) in sera had been performed by hemolysin-sensitive erythrocyte method in subagglutinating doses incorporated to agarose gel.[15] Normal value limit ranges from 150 to 350 U/mL. C3 and C4 complement fraction measurement was quantified by radial immunodiffusion, using plates with monospecific antibodies dispersed homogeneously in agarose (Behring, Germany). Normal values established by manufacturer are: C3 = 55-120 mg/dL and C4 = 20-50 mg/dL.

Disease's activity: Clinical and laboratory activity was assessed in each patient, using *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI).[10]

RESULTS

Case 1*:* A 24-year-old male with SLE since July 2001, presented with alveolar hemorrhage, confirmed by hemosiderophage in bronchoalveolar lavage, malar rash, oral ulcers, arthritis and renal involvement with proteinuria, systemic hypertension, presented positive ANA with a speckled pattern, and negative anti-dsDNA by two methods, normal complement, ESR 37mm/h and CRP 10,7mcg/L, 1.1 mg/dL gamma-globulin, lymphopenia (900 cells/mm³) and SLEDAI=16. Serum at that time showed the presence of high titer anti-LPL144AU (> 5 SD). He was treated with intravenous (IV) methylprednisolone for three days, and after one week, presented alveolar hemorrhage recurrence, and new pulse therapy after 7 days. At that time, TG were 255 mg/dL and TC was 315 mg/dL (LDL-c 201 mg/dL and HDL-c 62 mg/dL). Clinically stable, with anti-LPL titer reduction to 109UA and SLEDAI = 0. He was started on IV monthly cyclophosphamide (average doses 1,2g). In January 2002, presented malar rash and renal recurrence, SLEDAI=10, with new anti-LPL titer elevation to 150UA, with lack of anti-dsDNA and normal complement. After prednisone return to 1 mg/kg/day, cyclophosphamide maintenance, and dapsone introduction due to cutaneous involvement, the patient presented a progressive improvement of the renal involvement until complete remission, SLEDAI = 0, reducing anti-LPL titer to 77UA (Figure1).

Case 2*:* a 32-year-old African-American female had SLE since 1997 characterized by malar rash, photosensitivity, arthritis, serositis, cutaneous vasculitis and lymphopenia, with positive ANA with a speckled pattern, negative anti-dsDNA. In 1998, had two episodes of ischemic stroke, in addition to livedo reticularis, IgG and IgM anticardiolipin were positive at the same occasion and after 12 weeks, Antiphospholipid Syndrome was diagnosed and oral anticoagulation started. In September and October of 2001, she presented with fever, digital vasculitis, palpable purpura of lower limbs, photosensitivity and a nasal erythematous skin lesion. At the time, CH100 slightly reduced 140 UI/mL, with normal C3 and C4, SLEDAI = 8, presented 80AU anti-LPL. She was treated with IV cyclophosphamide and corticosteroids, with clinical improvement and reduction of anti-LPL titer to 25UA. In the beginning of 2001, she presented with an arterial obstruction in the left foot, requiring amputation. In February 2002, she started a renal involvement with proteinuria, hematuria and systemic hypertension (SLEDAI 8). She was again treated with corticosteroids and cyclophosphamide with higher anti-LPL titer reduction and SLEDAI regression to 2, as may be verified in Figure 2.

Case 3*:* a 39-year-old Caucasian male has SLE since 1997 characterized by malar rash, photosensitivity, polyarthritis, oral

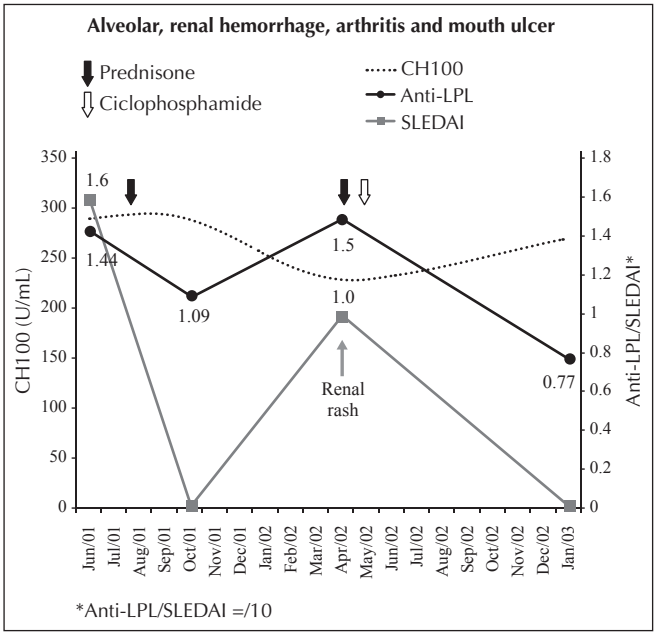

Figure 1. Case 1: longitudinal variation of anti–lipoprotein lipase (anti-LPL) levels, total hemolytic complement activity (CH100), *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI) and clinic manifestations.

ulcers, pleurisy, and cutaneous vasculitis. He presented a positive ANA with a speckled pattern and negative anti-dsDNA. He had used corticosteroids and azathioprine, additionally to chloroquine diphosphate (250 mg/day). During the whole study period, he did not have disease activity (SLEDAI zero) and high anti-LPL titer, with no titer fluctuation, as may be confirmed in Figure 3. Normal lipid profile, with TC of 154 mg/dL (HDL-c 39 mg/dL, LDL-c 102 mg/dL) and TG of 70 mg/dL.

***Case 4*:** a 58-year-old Caucasian female had SLE characterized by malar rash, photosensitivity, Raynaud's phenomenon, arthritis, and thrombocytopenia, with positive ANA with a speckled pattern, negative anti-dsDNA. She had diet-controlled for diabetes mellitus and primary systemic hypertension, and used captopril (100 mg/day) and chlorthalidone (25 mg/day). Her SLE was stable, with normal platelets, using azathioprine (75 mg/day) and prednisone (5 mg/day). These drugs had been gradually reduced during the study period and then completely removed. She always presented normal complement and negative anti-dsDNA by two methods. During follow-up of this study, patient had never presented clinical or laboratory activity (SLEDAI zero) and always maintained anti-LPL titer extremely high, as demonstrated in Figure 3. Normal lipid profile with TC 195 mg/dL (HDL-c 47. LDL-c 132) and TG 195 mg/dL.

***Case 5*:** a 55-year-old female, SLE since 1989 characterized by malar rash, photosensitivity, polyarthritis**,** with positive ANA with a speckled pattern, negative anti-dsDNA. She had systemic hypertension and neurocysticercosis, both under suitable control. Her SLE was stable (SLEDAI zero) since 2000 on chloroquine. Anti-LPL titer 71UA in 1999, 92UA in 2001, 71UA in 2002 and 90UA in 2003 (Figure 3).

DISCUSSION

The findings of the present study suggest that anti-LPL antibodies in SLE may fluctuate, following exacerbation periods of the disease, in some negative anti-dsDNA patients.

Anti-LPL antibodies were recently described,[4,5] and our group extended the initial findings of these antibody correlations. Thus, in addition to anti-LPL association with hypertriglyceridemia already described, our previous results demonstrated a strong association with disease's activity, measured by SLEDAI score, by reduced complement levels, either by total hemolytic activity or by fractions in the same system (C3 and C4), as well as high sensitive CRP levels.[5] In those two patients with clinical activity of the disease, there was a trend to present normal or lower than normal complement levels during the severe disease's activity period. In one of those patients, there was an increment of total cholesterol levels and triglycerides during the first activity, with very high anti-LPL titer. In those patients who did not presented clinical and laboratory activity of disease, these antibody levels were maintained high and with no important fluctuation of their values.

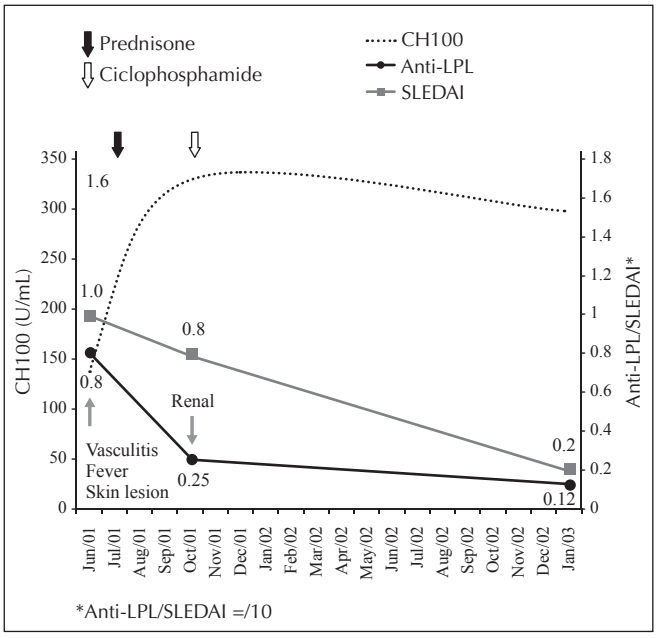

Figure 2. Case 2: longitudinal variation of anti-lipoprotein lipase (anti-LPL) levels, total hemolytic complement activity (CH100), *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI) and clinic manifestations.

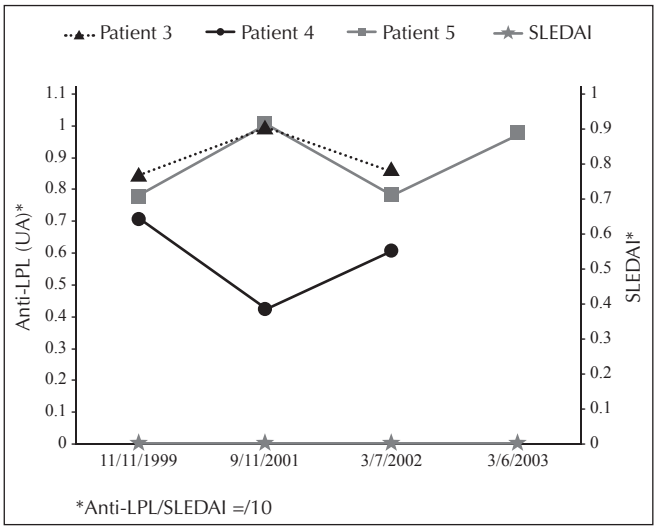

Figure 3. Case 3, 4 and 5: insignificant variation of anti-lipoprotein lipase antibodies (anti-LPL). Patients were in remission and Systemic lupus erythematosus disease activity index (SLEDAI) zero.

To corroborate such findings, anti-LPL antibodies were also associated with lupus nephritis, especially when concomitant with ribosomal anti-P antibodies. This finding provides a strong synergistic effect to predict renal disease in SLE.[16] In the present study, renal disease was found in both patients whose anti-LPL titers fluctuated; one of them had two episodes of renal disease activity marked by proteinuria and concomitant anti-LPL increment. In the other patient, in the second SLE's exacerbation, LPL-antibody was present. In both cases systemic hypertension was noticed, possibly related to renal disease activity. Additionally to the lupus nephritis, vasculitis was found in such disease's exacerbation episodes. In fact, one of the patients presented with alveolar hemorrhage and the other with cutaneous vasculitis as first SLE manifestations. Our group has demonstrated in previous work, the association of anti-ribosomal P and lupus nephritis, more specifically with the histological features of membranous glomerulonephritis.[3]

Anti-LPL antibodies were also described in systemic sclerosis, in fact, 35% of these patients can present such antibodies. In this disease, antibodies were also correlated to hypertriglyceridemia, but also to disease's activity measured by a longer extension of cutaneous fibrosis and a higher frequency of pulmonary fibrosis. In scleroderma, anti-LPL antibodies were correlated with anti-topoisomerase I antibodies, as well as higher rates of cardiac involvement.[17] In this systemic sclerosis study, the authors could demonstrate that anti-LPL antibodies were capable to inhibit lipoprotein lipase enzyme activity in a functional *in vitro* trial.[17] As for the lipid profile in the present study, only case 1 presented with hypercholesterolemia and hypertriglyceridemia,, other individuals had their lipid profile within normality, although presenting high antibody titers. None of them had been taking hypolipemiant drugs. This brings to light the question previously raised by Reichlin of distinct subpopulations of autoantibodies against LPL, perhaps there is a population that has an inhibitory activity on the enzyme and other population not functionally active.[4]

Our study showed titer fluctuation of anti-LPL antibodies in those individuals with concomitant lupus clinical and laboratory activity. On the other hand, in those other patients who were in remission for years, anti-LPL antibodies were present, in high titers and with no significant variation. Taken together, the above findings suggest the presence of two subpopulations of anti-LPL antibodies: one related to disease activity that fluctuates accordingly to exacerbation and remission periods and. another antibody subpopulation that stays persistently high and does not correlate with disease activity or lipid profile, as stated before. [4]

Our findings suggest the possibility of a new potential marker of SLE activity, especially for those lupus patients with anti-dsDNA antibodies absent in the serum.

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