Acta Medica Okayama

Volume 31, *Issue* 5 1977 *Article* 4

OCTOBER 1977

Decreased plasma postheparin lipolytic activity in systemic lupus erythematosus

Koichi Kawanishi* Hidenori Ueda†

Masayuki Nagase‡ Tadashi Ofuji**

*Okayama University,

†Okayama University,

‡Okayama University,

**Okayama University,

Decreased plasma postheparin lipolytic activity in systemic lupus erythematosus*

Koichi Kawanishi, Hidenori Ueda, Masayuki Nagase, and Tadashi Ofuji

Abstract

Plasma postheparin lipolytic activity (PHLA) was measured on 50 patients with systemic lupus erythematosus (SLE). Plasma PHLA was significantly decreased in SLE patients. This decrease was most striking in the acute phase of the disease. There was a close relationship between decreased PHLA and immunologic factors indicative of the acute phase of SLE. These immunologic factors included shaggy antinuclear antibody pattern, low serum complement titer, high DNA antibody titer, mixed cryoglobulin and lumpy glomerular pattern by immunofluorescent staining.

*PMID: 146403 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **31**, 319—324 (1977)

DECREASED PLASMA POSTHEPARIN LIPOLYTIC ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Koichi KAWANISHI, Hidenori UEDA, Masayuki NAGASE and Tadashi OFUJI

Third Department of Internal Medicine, Okayama University Medical School, Okayama 700, Japan (Director: Prof. T. Ofuji)

Received July 25, 1977

Abstract. Plasma postheparin lipolytic activity (PHLA) was measured on 50 patients with systemic lupus erythematosus (SLE). Plasma PHLA was significantly decreased in SLE patients. This decrease was most striking in the acute phase of the disease. There was a close relationship between decreased PHLA and immunologic factors indicative of the acute phase of SLE. These immunologic factors included shaggy antinuclear antibody pattern, low serum complement titer, high DNA antibody titer, mixed cryoglobulin and lumpy glomerular pattern by immunofluorescent staining.

Hyperlipoproteinemia may be present in various collagen diseases (1). Type 1 and type 3 hyperlipoproteinemias combined with decreased postheparin lipolytic activity (PHLA) have been reported in a few cases of systemic lupus erythematosus (SLE) (2-4). In a previous study of 67 SLE patients, we found that about 40% of patients had type 2a hyperlipoproteinemia and 40% had type 4 hyperlipoproteinemia (5). In the present study, plasma PHLA and some selected immunological measures were studied in a group of SLE patients.

MATERIALS AND METHODS

A total of 50 consecutive hospitalized SLE patients was examined (5 males, 45 females; aged 12-51). The criteria of SLE diagnosis were according to Cohen *et al.* (6). A few patients were examined during both the acute and remission periods, as defined by Schur and Sandson (7). The diagnoses were made by one author (H.U.) independent of the PHLA values. All patients were being treated with steroids. Most patients in the acute phase were receiving a daily dose of 30 mg of prednisolone, and most patients in remission were receiving a daily dose of 10 mg of prednisolone. Other immunosuppressive agents used together with prednisolone were: cyclophosphamide (100 mg/day in acute phase and 50 mg/day in remission, 11 patients); azathioprin (100mg/day in acute phase and 50mg/day in remission, 7 patients); and 6-mercaptopurine (50 mg/day in acute phase and 25 mg/day in remission, 5 patients). Thirty, non-obese hospital staff members served as control subjects (15 males, 15 females;

aged 20-40). None of the control subjects had plasma lipid abnormalities. In SLE patients, blood samples were obtained 10, 20 and 30 min after an intravenous injection of heparin sodium at 0.1 mg/kg of body weight. In normal controls, blood samples were obtained at the same time periods after the same dose of heparin injection as the patients.

Plasma PHLA was determined by a slight modification of the technique of Fredrickson *et al.* (8). Glass-stoppered tubes containing 0.5 ml of 5% bovine albumin (Fraction V), 5 mg of coconut oil emulsion (Ediol), 0.2 ml of ammonium chloride and 0.2 ml of plasma in a total volume of 1.0 ml were incubated at 37°C for 30 min. Free fatty acid (FFA) concentrations in 0.2 ml of the substrate-plasma mixture were determined by the method of Itaya and Ui (9). PHLA was calculated from the difference in FFA concentration between the incubated tube and control tube. The values were expressed as μEqFFA/ml/min plasma.

Results were obtained from most patients for each of the following: antinuclear antibodies (ANA) separated into shaggy, diffuse and speckled patterns (10, 11); serum complement titer (CH50) (12); DNA antibody titer (13); cryoglobulin of IgG and IgG-IgM mixed type (15); and immunofluorescent staining of biopsied kidney differentiated into linear, mesangial, granular or lumpy patterns of glomeruli (16). In biopsied patients plasma PHLA values were determined no later than 2 weeks after biopsy. Histologic examinations were conducted on biopsied specimens stained by hematoxylin-eosin.

RESULTS

Mean plasma PHLA values (μEqFFA/ml/min) of normal subjects were 0.249 at 10 min; 0.192 at 20 min; and 0.099 at 30 min. There were no differences between the sexes in the result for the control plasma PHLA. SLE plasma PHLA was significantly lower compared to normal subjects (Fig. 1). The SLE patient response was prominent in the acute phase of the disease. The mean acute patient values were 0.059 at 10 min; 0.057 at 20 min, and 0.019 at 30 min. PHLA values in remission were 0.111 at 10 min; 0.070 at 20 min; and 0.040 at 30 min. There were no differences between the sexes in the results for the plasma PHLA of SLE patients PHLA values were not related to the type of immunosuppressive agents used in treatment.

Patients with the shaggy ANA pattern showed significantly lower plasma PHLA compared with patients with diffuse or speckled patterns (Table 1). A positive correlation was present between PHLA and serum complement titer (Fig. 2). The DNA antibody titer showed an inverse correlation with PHLA (Fig. 3). Patients with positive cryoglobulin showed lower plasma PHLA values than patients with negative cryoglobulin; patients with IgG-IgM mixed cryoglobulin showed decreased plasma PHLA values compared with IgG type cryoglobulin (Table 1). Patients with lumpy immunofluorescent patterns showed a

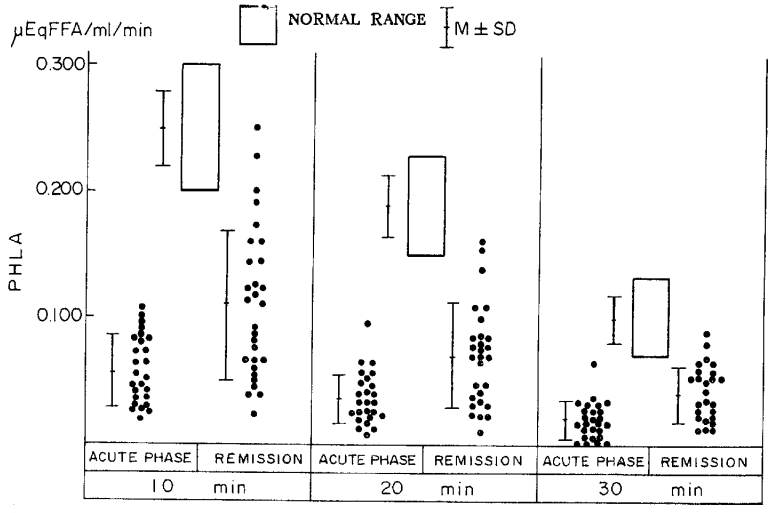

Fig. 1. Plasma PHLA levels at three time periods after heparin administration (0.1 mg/kg) in the acute and remission periods of SLE patients. Plasma PHLA was significantly lower in SLE patients compared to the control values ($P<.001$ at 10, 20 and 30 min). Plasma PHLA levels during the acute phase were depressed compared to PHLA levels during remission ($P<.01$ at 10, 20 and 30 min).

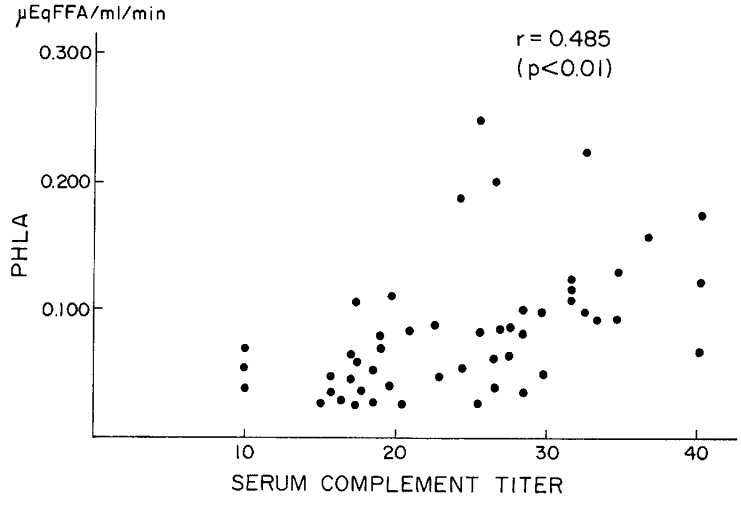

Fig. 2. Relationship between plasma PHLA 10 min after heparin administration and serum complement titer in SLE patients. Plasma PHLA level correlated positively with serum complement titer ($r=0.485$).

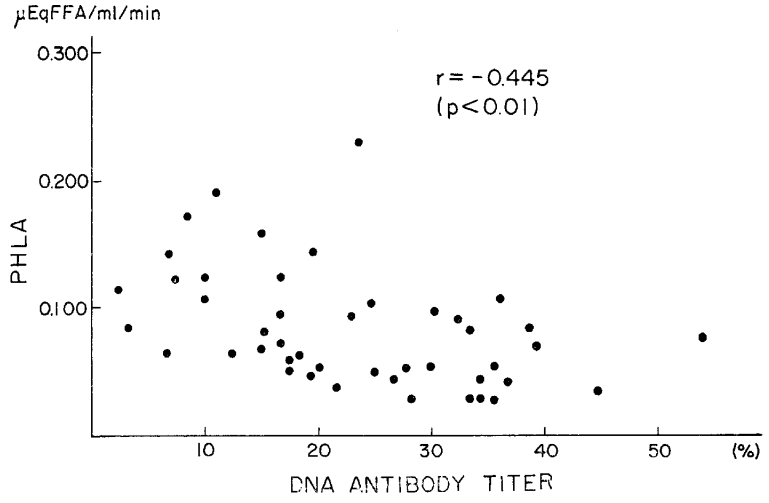

Fig. 3. Relationship between plasma PHLA 10 min after heparin administration and DNA antibody titer in SLE patients. Plasma PHLA level correlated inversely with DNA antibody titer ($r = -0.445$).

TABLE 1. RELATIONSHIPS BETWEEN IMMUNOLOGIC MEASURES AND PLASMA PHLA LEVELS (μEQFFA/ML/MIN) IN SLE PATIENTS

Antinuclear antibodies (number of patients)	Shaggy (23)	Diffuse (21)	Speckled (11)
PHLA (Mean ± SD) 10 min after heparin injection	0.058 ± 0.029*	0.095 ± 0.044	0.131 ± 0.066
Cryoglobulin (number of patients)	IgG-IgM (8)	IgG (13)	Negative (5)
PHLA (Mean ± SD) 10 min after heparin injection	0.060 ± 0.022+	0.095 ± 0.037	0.116 ± 0.033
Immunofluorescent patterns of glomeruli (number of patients)	Lumpy (4)	Granular (14)	Mesangial and linear (12)
PHLA (Mean ± SD) 10 min after heparin injection	0.042 ± 0.013++	0.073 ± 0.029	0.110 ± 0.035

* $P < .05$ with diffuse pattern; $p < .01$ with speckled pattern

\+ $P < .05$ with IgG; $P < .01$ with negative cryoglobulin

\++ $P < .01$ with mesangial and with linear immunflouorescent patterns

significant PHLA depression compared to patients with mesangial or linear immunofluorescent patterns (Table 1). Most patients with mesangial and linear patterns showed normal or minimal histological changes in the glomeruli. Patients with granular patterns showed focal or diffuse proliferative glomerulonephritis and membranous glomerulonephritis. Most cases with lumpy patterns showed membranous glomerulonephritis including wire-loop lesions.

DISCUSSION

Several distinctive immunologic features have been reported in the acute phase of SLE. These include shaggy ANA pattern (11), low complement levels (7), high DNA antibody titers (14), the presence of mixed (IgG-IgM) cryoglobulin (15), and a lumpy immunofluorescent pattern of biopsied glomeruli (16). In the present study, plasma PHLA was measured on 50 patients with SLE. Plasma PHLA was significantly decreased in SLE patients and most strikingly in the acute phase of the disease. A close relationship was present between decreased PHLA and immunologic factors indicative of the acute phase of SLE.

Glueck *et al.* (2, 3) reported SLE accompanied by acquired type 1 hyperlipoproteinemia, dysglobulinemia and heparin resistance in three patients. In these cases a decrease was found in plasma PHLA, triglyceride lipase and monoglyceride hydrolase. These investigators demonstrated that the plasma PHLA depression was due to the association of the heparin-binding immunoglobulin with exogenous hyperlipoproteinemia. Beaumont and Lemort (17) also reported immunoglobulins with antiheparin activity. Stern *et al.* (4) reported acquired type 3 hyperlipoproteinemia in two patients with SLE. PHLA was decreased in both patients. In one of these patients after adrenocortical steroid treatment, the PHLA value returned to normal concomitantly with the disappearance of the type 3 hyperlipoproteinemia. In a previous study in our laboratory (5), SLE patients with decreased PHLA often showed elevated plasma triglyceride. The pathophysiology of SLE is extremely complicated, and various factors are likely to be involved in the SLE lipid metabolism. The decreased PHLA is probably related not only to heparin binding with serum but to other factors of immunologic, metabolic and therapeutic consequence.

REFERENCES

1. Parra, C. A., Abaurre, R. and Rivero, I.: Collagen diseases associated with type 4 hyperlipoproteinemia. *Arch. Dermatol. Forsch.* **251**, 123-127, 1974.
2. Glueck, C. J., Levy, R. I., Glueck, H. I., Gralnick, H. R., Greten, H. and Fredrickson, D. S.: Acquired type 1 hyperlipoproteinemia with systemic lupus erythematosus, dysglobulinemia and heparin resistance. *Am. J. Med.* **47**, 318-324, 1969.
3. Glueck, C. J., Kaplan, A. P., Levy, R. I., Greten, H., Gralnick, H. and Fredrickson, D. S.: A new mechanism of exogenous hyperglyceridemia. *Ann. Intern. Med.* **71**, 1051-1062, 1969.

4. Stern, M. P., Kolterman, O. G., McDevitt, H. and Reaven, G. M.: Acquired type 3 hyperlipoproteinemia. *Arch. Intern. Med.* **130**, 817-821, 1972.
5. Nagase, M., Kawanishi, K., Ueda, H., Kurata, N. and Ofuji, T.: Serum lipids in SLE patients. *The Ryumachi* **13**, 497, 1973 (in Japanese).
6. Cohen, A. S., Reynolds, W. E., Franklin, E. C., Kulka, J. P., Ropes, M. W., Schlman, L. E. and Wallase, S. L.: Preliminary criteria for the classification of systemic lupus erythematosus. *Bull. Rheum. Dis.* **21**, 643-648, 1971.
7. Schur, P. H. and Sandson, J.: Immunologic factors and clinical activity in systemic lupus erythematosus. *N. Engl. J. Med.* **278**, 533-538, 1968.
8. Fredrickson, D. S., Ono, K. and Davis, L. L.: Lipolytic activity of postheparin plasma in hyperglyceridemia. *J. Lipid Res.* **4**, 24-33, 1963.
9. Itaya, K. and Ui, M.: Calorimetric determination of free fatty acids in biological fluids. *J. Lipid Res.* **6**, 16-20, 1965.
10. Beck, J. S.: Variations in the morphological patterns "autoimmune" nuclear fluorescence. *Lancet* **1**, 1203-1205, 1961.
11. Casals, S. P., Friou, G. J. and Teague, P. O.: Specific nuclear reaction of antibody to DNA in lupus erythematosus sera. *J. Lab. Clin. Med.* **62**, 625-631, 1963.
12. Mayer, M. M.: Procedure for titration of complement. In *Experimental Immunochemistry*, ed. E. A. Kabat and M. M. Mayer, C. C. Thomas, Springfield, Illinois, pp. 149-153, 1961.
13. Carr, R. I., Koffler, D., Agnello, V. and Kunkel, H. G.: Studies on DNA antibodies using DNA labelled with actinomycin D(^{3}H) or dimethyl (^{3}H) sulphate. *Clin. Exp. Immunol.* **4**, 527-536, 1969.
14. Casals, S. P., Friou, G. J. and Myers, L. L.: Significance of antibody to DNA in systemic lupus erythematosus. *Arthritis Rheum.* **7**, 376-390, 1964.
15. Barnett, E. V., Bluestone, R. and Cracchiola, A. III.: Cryoglobulinemia and disease. *Ann. Intern. Med.* **73**, 95-107, 1970.
16. Koffler, D., Agnello, V., Carr, R. I. and Kunkel, H. D.: Variable patterns of immunoglobulin and complement deposition in the kidneys of patients with systemic lupus erythematosus. *Am. J. Pathol.* **56**, 305-316, 1969.
17. Beaumont, J. L. and Lemort, N.: Une immunoglobuline anti-héparine dans un sérum hyperlipidémique. (Une nouvelle variété d'hyperlipidémie par auto-anticorps). *C. R. Acad. Sc. Paris*, **271**, 2452-2454, 1970.