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Plasma Soluble Fibrin Monomer Complexes in Nephrotic Syndrome — with Reference to Hypoalbuminemia

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IIOKA, Y., KIKUCHI, K., TADA, H., ISOGAI, S. and URAYAMA, T. *Plasma Soluble Fibrin Monomer Complexes in Nephrotic Syndrome —— with Reference to Hypoalbuminemia.* Tohoku J. exp. Med., 1984,**143**(1) 53-57 —— Plasma soluble fibrin monomer complexes (SFMC) in 10 patients with nephrotic syndrome were measured to demonstrate the contribution of hypoalbuminemia to the SFMC formation. The levels of SFMC as well as plasma fibrinogen (Fbg) levels were significantly higher than those in control subjects. There was a negative correlation between the levels of SFMC and serum albumin, and also between Fbg and serum albumin. The increase in SFMC levels which indicates the intravascular generation of thrombin might be correlated to hypoalbuminemia in nephrotic syndrome with hypercoagulability. ———— soluble fibrin monomer complexes; hypoalbuminemia; nephrotic syndrome; hypercoagulability

It is well known that nephrotic syndrome is often associated with hypercoagulability and a risk of the thromboembolism (Kendall et al. 1971). The patients showed significant elevations of coagulant factors I (i.e. fibrinogen ; Fbg), V and VIII (Thomson et al. 1974). The role of plasma soluble fibrin monomer complexes (SFMC), however, has not been studied enough. SFMC are the complexes of fibrin monomer and Fbg or fibrin degradation products in plasma. The increase in the levels of SFMC is thought to be an indicator of the thrombin generation in the blood (Isogai et al. 1982). The present study was carried out to investigate the levels of SFMC, and their relationship to the levels of serum albumin in nephrotic syndrome.

SUBJECTS AND METHODS

Clinical details of the subjects are shown in Table 1. Ten patients (6 males and 4 females) at the ages ranging from 34 to 71 years (43.0 years as a mean) were involved in this study. Four cases had hypertension with higher than 161 mmHg systolic and 95 mmHg diastolic blood pressures. All cases had proteinuria ranging from 1.3 to 19.5 g/24 hr (6.05 g/24 hr as a mean). Kidney biopsy was carried out in 6 out of 10 cases, and revealed that

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membranous type of glomerulonephritis in 5 cases (Nos. 2, 3, 8, 9 and 10) and mesangial proliferative type in one (No. 6). Fourteen healthy subjects matched with the patients with regard to age and sex were studied as controls. None of the control subjects had hypertension or proteinuria. Blood samples were drawn for the determination of plasma glucose, serum albumin, SFMC and Fbg concentrations.

Plasma glucose was determined by the glucose-oxidase method using a Beckman Glucose Analyser (Kadish et al. 1968), serum albumin by the method of bromocresol green, SFMC according to the method of Shoda and Masukata (1980), Fbg by the tyrosine method (Matsuoka et al. 1958) and plasminogen by a single radial immunodiffusion method.

Data were expressed as mean±S.D. Statistical analysis was performed by Student's

TABLE 1. *Clinical characteristics of the subjects*

Case No	Age (years)	Sex	Blood pressure (mmHg)	Urinary protein (g/24 hr)	Kidney biopsy
Healthy control					
1	66	M	126/ 70	—	
2	56	M	130/ 66	—	
3	50	M	126/ 70	—	
4	67	M	114/ 80	—	
5	55	M	122/ 78	—	
6	45	M	132/ 78	—	
7	58	M	134/ 68	—	
8	60	F	138/ 76	—	
9	60	F	130/ 64	—	
10	53	F	120/ 70	—	
11	43	F	112/ 64	—	
12	40	F	114/ 60	—	
13	46	F	122/ 76	—	
14	41	F	128/ 82	—	
M±S.D.	52.9± 8.6				
Nephrotic syndrome					
1	37	M	156/100	2.0	
2	32	F	160/120	5.1	Membranous type
3	27	F	110/ 60	5.7	Membranous type
4	56	M	130/ 86	6.2	
5	37	M	170/ 70	4.6	
6	46	F	176/120	4.4	Mesangial proliferative type
7	67	M	124/ 54	4.5	
8	24	F	118/ 88	1.3	Membranous type
9	33	M	110/ 70	7.2	Membranous type
10	71	M	140/ 80	19.5	Membranous type
M±S.D.	43.0±15.6			6.05±4.79	

unpaired t-test.

Results

The laboratory findings are shown in Table 2. Overnight fasting plasma glucose levels in the patients were similar to those in control subjects with no significant difference. The concentrations of serum albumin in patients were

Table 2. *Laboratory findings on the patients with nephrotic syndrome and healthy controls*

Case No.	Overnight fasting plasma glucose (mg/100 ml)	Serum albumin (g/100 ml)	SFMC (mg/100 ml)	Fibrinogen (mg/100 ml)	Plasminogen (mg/100 ml)
Healthy control					
1	84	3.9	3.8	384	10.8
2	103	4.3	4.0	250	11.3
3	108	4.4	6.0	240	13.2
4	89	4.2	4.0	244	9.5
5	112	4.4	2.5	238	12.9
6	86	3.8	7.0	248	10.7
7	100	4.0	8.0	284	12.2
8	96	3.8	3.5	286	11.2
9	97	3.8	5.8	314	10.8
10	92	4.1	6.0	232	11.9
11	91	4.2	6.0	260	11.5
12	80	4.6	3.8	202	10.7
13	95	4.0	5.0	292	12.4
14	80	4.6	3.5	236	12.9
M±S.D.	93.8 ± 1.5	4.15±0.27	4.9 ± 1.5	265.0 ± 43.4	11.57±1.1
Nephrotic syndrome					
1	95	2.9	13.0	292	10.8
2	115	3.6	32.0	450	11.3
3	97	2.5	24.2	242	8.4
4	104	4.2	21.7	256	12.3
5	85	4.3	11.7	176	7.5
6	82	2.1	86.9	622	10.0
7	83	1.9	66.4	196	11.8
8	68	2.4	21.5	280	9.8
9	90	2.8	22.0	488	10.1
10	99	2.4	42.5	672	8.9
M±S.D.	91.8±12.5	2.91±0.80	34.2±23.3	367.4±169.2	10.1±1.5

SFMC, plasma soluble fibrin monomer complexes.

significantly ($p<0.001$) lower than those in control subjects. The levels of SFMC in the patients were significantly ($p<0.001$) higher than those in control subjects. Fbg levels of the patients were also higher than those of control subjects ($p<0.05$). There was no significant difference in the levels of plasminogen between the patients and control subjects. There was a significant negative correlation between the levels of serum albumin and SFMC ($r=-0.80$, $p<0.001$, $n=24$), and also between the levels of serum albumin and Fbg ($r=-0.53$, $p<0.01$, $n=24$) in all the subjects. A positive correlation ($r=+0.58$, $p<0.01$) was recognized between the levels of SFMC and Fbg.

Discussion

It has been stated that nephrotic syndrome is often associated with hypercoagulability (Kanfer et al. 1970; Kendall et al. 1971; Thomson et al. 1974). The cause is, however, still uncertain. Previous investigators have reported supernormal activities of several procoagulant factors (Kendall et al. 1971; Thomson et al. 1974). Fbg is one of these factors, and the increase of this factor was thought to be induced as a nonspecific hepatic response to heavy proteinuria (Takeda 1967). In agreement with the previous reports (Kanfer et al. 1970), the majority of our patients showed increased levels of Fbg and proteinuria with hypoalbuminemia. Plasminogen levels were not elevated in any cases, so that SFMC formation took place without extensive fibrinolysis. Hyperfibrinogenemia may be induced as a rebound phenomenon which can be observed in chronic intravascular coagulation as described by Ultin and Ultin (1975).

Hypoalbuminemia with hyperfibrinogenemia brings about a high degree of red cell aggregation, and may induce sludged or granular flow (Little 1976). The present study revealed that SFMC levels in such patients increased, and this increase was correlated possitively to the levels of Fbg and negatively to decreasing concentrations of serum albumin. High levels of SFMC probably represented the intravascular generation of some quantity of thrombin, because SFMC production essentially requires thrombin for the partial proteolysis of Fbg to make fibrin monomer, the material for the complex formation. Therefore, hypoalbuminemia in nephrotic syndrome may play an important role to promote hypercoagulability or thromboembolism induced by not only high levels of procoagulant factors but also a direct acceleration of thrombin production in the blood with abnormal hemorrheodynamics.

References

1) Isogai, S., Kikuchi, K., Kameyama, M., Oshima, Y., Urayama, T. & Komoto, M. (1982) Plasma soluble fibrin monomer complexes in the development of diabetic retinopathy. *Thohoku J. exp. Med.*, **137**, 409-413.
2) Kanfer, A., Kleinknecht, D., Broyer, M. & Josso, F. (1970) Coagulation studies in 45 cases of nephrotic syndrome without uremia. *Thromb. Diath. Haemorr.* **24**, 562-571.
3) Kadish, A.H., Litle, R.L. & Sternberg, J.C. (1968) A new and rapid method for the

determination of glucose by measurement of oxygenconsumption. *Clin. Chem.*, **14**, 116-131.

4) Kendall, A.G., Lohmann, R.C. & Dossetor, J.B. (1971) Nephrotic syndrome — A hypercoagulable state. *Arch. intern. Med.*, **127**, 1021-1027.
5) Little, H.L. (1976) The role of abnormal hemorrheodynamics in the pathogenesis of diabetic retinopathy. *Trans. Amer. Ophthalmol. Soc.*, **74**, 573-636.
6) Matsuoka, M., Satake, K. & Fukasawa, E. (1958) The determination of plasma fibrinogen concentration by tyrosine method. *Rinsho Kensa*, **2**, 61-63. (Japanese)
7) Shoda, H. & Masukata, E. (1980) Calorimetric determination of soluble fibrin monomer complexes. *J. med. Soc. Toho Jap.*, **27**, 669-673. (in Japanese with English abstract)
8) Takeda,Y. & Chen,A.Y.(1967) Fibrinogen metabolism and distribution in patients with the nephrotic syndrome. *J. Lab.clin. Med.*, **70**, 678-685.
9) Thomson, C., Forbes,C.D., Prentice,C.R.M. & Kennedy, A.C. (1974) Changes in blood coagulation and fibrinolysis in the nephrotic syndrome. *Q.J. Med., New series*, **43**, 339-407.
10) Ultin, O.N. & Ultin, S.B. (1975) Acquired storage pool deficiency of platelets in chronic disseminated intravascular coagulation. In : *Platelets*, edited by O.N. Ultin, Excepta Medica, Amsterdam, pp. 329-333.