Tohoku J. exp. Med., 1982, 137, 409–413

Plasma Soluble Fibrin Monomer Complexes in the Development of Diabetic Retinopathy

Syo Isogai, Kazuyoshi Kikuchi, Masaaki Kameyama, Yasuo Oshima, Tsutomu Urayama* and Michiji Komoto†

*The Second Department of Internal Medicine, *the Department of Biochemistry, and †the Department of Ophthalmology, Toho University School of Medicine, Tokyo 143*

Isogai, S., Kikuchi, K., Kameyama, M., Oshima, Y., Urayama, T. and Komoto, M. *Plasma Soluble Fibrin Monomer Complexes in the Development of Diabetic Retinopathy.* Tohoku J. exp. Med., 1982, **137** (4), 409–413 —— To elucidate the relationship between plasma soluble fibrin monomer complexes (SFMC) and retinal or vitreous hemorrhages, 11 diabetics were studied for 15 months. The levels of SFMC in 3 out of the 11 cases were elevated prior to hemorrhages and in the other 8 cases SFMC levels were elevated after hemorrhages. With regard to fibrinogen (Fbg) concentrations, there was no significant difference between the values before and after hemorrhages. The plasma glucose levels did not change significantly during the observation. It was concluded that the SFMC level was not only an indicator of the intracapillary generation of thrombin but an important factor affecting the development of diabetic retinopathy.

diabetic retinopathy; retinal hemorrhage; soluble fibrin monomer complexes; fibrinocoagulopathy

Fibrinocoagulopathy in diabetic angiopathy has been reported by some investigators (Banerjee et al. 1973, 1974; Fukuda 1972). The relationship between levels of soluble fibrin monomer complexes (SFMC) and retinal or vitreous hemorrhages, however, has not yet been studied. SFMC are the complexes of fibrin monomer and fibrinogen (Fbg) or fibrin degradation products as shown in Fig 1. Fibrin monomer production essentially requires thrombin for the partial proteolysis of Fbg. If thrombin is generated in the capillaries, fibrin monomers may be producted, and SFMC are formed. The increase in the level of SFMC therefore, is an indicator of the generation of thrombin in the blood. The present study was designed to investigate the relationship between the levels of SFMC and retinal or vitreous hemorrhages in the development of diabetic retinopathy.

Subjects and Methods

Clinical characteristics of the patients are shown in Table 1. Eleven diabetics involved in this study were 5 males and 6 females, with ages ranging from 48 to 70 years (59.9 years as a mean) and with mean history of diabetes of 7.8 years. Five out of the 11 diabetics were treated with dietary therapy alone, 4 cases with sulphonylurea and 2 cases

Received for publication, December 11, 1981.

TABLE 1. *Clinical characteristics of the patients*

Case No.	Age (years)	Sex	Duration of diabetes mellitus (years)	Treatment	
				Diet (kcal/day)	Drugs
1	66	F	8	1200	Insulin
2	60	F	3	1300	None
3	57	M	13	1600	None
4	48	F	2	1200	None
5	58	M	2	1800	Tolbutamide
6	61	M	4	1500	Tolbutamide
7	57	M	14	1300	None
8	70	F	6	1200	Tolbutamide
9	67	M	22	1400	Glybenclamide
10	54	F	4	1500	None
11	61	F	8	1200	Insulin

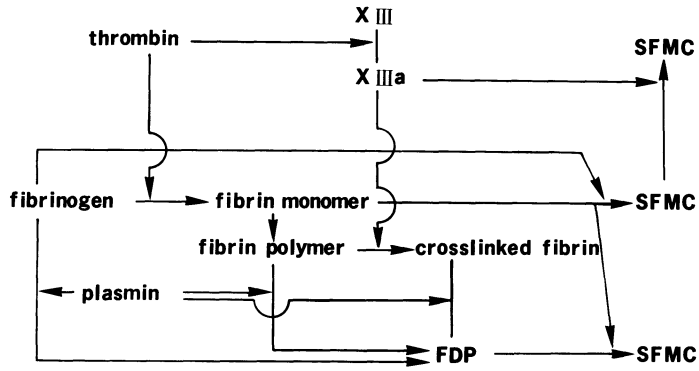

Fig. 1. Diagram illustrating the formation of various soluble fibrin monomer complexes. XIII, coagulant factor XIII; XIIIa, activated coagulant factor XIII; FDP, fibrinogen or fibrin degradation products; SFMC, soluble fibrin monomer complexes.

with insulin. Plasma glucose levels after overnight fasting were from 92 to 194 mg/100 ml. None had hypertension. Ocular findings by ophthalmoscopy were as follows: No diabetic change in 5 cases (Nos. 1–5), microaneurysm in 4 cases (Nos. 6–9), hard exudates in 1 case (No. 10), and advanced proliferation in 1 case (No. 11). Ophthalmoscopic examinations and photography were repeated twice a month for 15 months at the Out Patient Clinic of Toho University Hospital. Simultaneously, venous blood was drawn from each patient after overnight fasting for the determinations of SFMC, Fbg and glucose concentrations.

SFMC were determined according to the methods of Shoda and Masukata (1980). Fbg concentrations were determined by the tyrosine method (Matsuoka et al. 1958) and glucose by the glucose-oxidase method using Beckman Glucose Analyser (Kadish et al. 1968).

Data were expressed as mean±S.D. Statistical analysis was performed by Student's paired and unpaired t test.

with retinal and vitreous hemorrhages

Blood pressure (mmHg)	Changes of ocular findings and location of hemorrhage	Time until hemorrhage (months)
138/82	No retinopathy → Intraretinal	14
114/72	No retinopathy → Intraretinal	7
142/78	No retinopathy → Intraretinal	3
128/80	No retinopathy → Intraretinal	3
124/76	No retinopathy → Intraretinal	12
128/76	Microaneurysm → Intraretinal	8
138/82	Microaneurysm → Intraretinal	13
148/82	Microaneurysm → Intraretinal	11
138/78	Microaneurysm → Intraretinal	12
142/82	Hard exudates → Intraretinal & superficial	1
100/58	Proliferation Vitreous	7

Results

Intraretinal hemorrhage was seen in 10 cases and vitreous hemorrhage in 1 case within 1–14 months after the beginning of the study (Table 1).

The laboratory findings are summarized in Table 2. SFMC levels within 1 month after hemorrhage were significantly higher than those before hemorrhage ($p<0.05$). Furthermore, SFMC levels within 1 month and 2 months after hemorrhage were significantly higher than those at the first time of the determination ($p<0.01$, and $p<0.02$, respectively). There was no significant difference in Fbg concentrations between before and after hemorrhage, though the values within 1 month after hemorrhage were seemingly higher in comparison with those before hemorrhage. No significant changes were seen in the fasting plasma glucose levels during the study.

Discussion

Fukuda (1972) reported that when new hemorrhages or new cotton wool spots were discovered in diabetics with retinopathy, the plasma Fbg concentrations increased and blood fibrinolytic activity decreased. The present data showed that there was no significant difference between the values before and after hemorrhages. This discrepancy seems to be due to the different subjects; the subjects in Fukuda's study included many patients with advanced retinopathy as compared with ours.

Kameyama (1981) reported that high levels of SFMC were seen in the diabetics with advanced proliferative retinopathy. A recent study on the pathogenesis of diabetic retinopathy in rats (Ishibashi et al. 1981) has revealed the presence of microthrombi in the retinal vessels of various sizes. These findings strongly suggest the generation of a small amount of thrombin, and the high levels of SFMC should be due to intravascular, especially intracapillary generation of thrombin. The high levels of SFMC were not necessarily associated with the decrease in plasma antithrombin-III (Isogai et al. 1982). Thus, it was suspected that fibrin mono-

TABLE 2. *Changes of soluble fibrin monomer complexes, fibrinogen and fasting plasma glucose levels before and after hemorrhage*

Case No.	At first	Before hemorrhage	After hemorrhage	
			within 1 month	within 2 months
Soluble fibrin monomer complexes				
1	13.7	16.8	21.0	—
2	1.2	9.5	4.1	9.8
3	4.0	4.4	12.5	14.5
4	1.8	—	21.0	14.3
5	14.2	11.8	23.3	30.0
6	2.2	3.3	20.0	8.8
7	20.0	5.3	15.5	17.0
8	6.7	14.3	18.3	3.0
9	1.5	5.3	16.0	10.5
10	3.9	—	5.7	21.3
11	3.6	18.5	19.8	14.5
M±S.D.	6.6±6.3	9.9±5.7	16.1±6.3	14.3±7.4
Fibrinogen				
1	316	268	240	—
2	324	318	314	316
3	280	328	380	290
4	332	—	312	260
5	276	234	226	218
6	194	268	288	276
7	284	366	290	312
8	378	296	360	268
9	278	300	300	300
10	394	—	500	348
11	296	276	294	320
M±S.D.	304.7±54.3	294.0±39.0	318.0±74.8	290.8±36.9
Fasting plasma glucose				
1	155	76	148	—
2	131	142	129	130
3	104	151	144	123
4	154	—	159	138
5	130	175	176	156
6	194	116	92	186
7	150	187	182	198
8	114	113	144	130
9	96	133	145	130
10	92	—	115	96
11	107	88	86	98
M±S.D.	129.7±31.2	142.3±33.3	138.2±30.8	138.5±33.4

The unit of the values in the Table is mg/100 ml.

mers were produced by such a small amount of thrombin generation as to be unable to influence the Fbg and antithrombin-III concentrations.

High levels of SFMC after hemorrhages may be the result of the retinal hemorrhages. Besides, high levels of SFMC were observed in several cases (Nos. 1, 8, 11) prior to their retinal and vitreous hemorrhages, and therefore hemorrhages should be provocated by the preceding intracapillary coagulation. It remains unknown at present whether the high levels of SFMC are the cause or result of diabetic retinopathy.

In the clinical respect, high levels of SFMC were thought not only as an indicator of thrombin generation in the blood but also as a reflection of protective reaction to prevent the intravascular coagulation (Kopec et al. 1970; Brass et al. 1976). The formation of SFMC in the blood may be reaction to prevent the silting of fibrin fiber. The high levels of SFMC in the blood may give rise to a possibility to cause the fibrin deposit on the retinal or vitreous vessel walls in some pathological circumstances, because of the fact that the solubilizing capacity of Fbg by the complexes formation was reduced with the lowering of blood pH (Shainoff and Page 1964) and that SFMC are not so stable as their short in vivo half-life suggests (Kikuchi et al. 1981).

It is possible to conclude from the present study that the high levels of SFMC have a close relation to retinal or vitreous hemorrhages and may play an important role in developing the diabetic retinopathy.

Acknowledgment

This work was supported, in part, by Chiyoda Seimei Health Developing Foundation.

References

1) Banerjee, R.N., Sahni, A.L. & Kumar, V. (1973) Fibrinocoagulopathy in maturity onset diabetes mellitus and atherosclerosis. *Thromb. Diathes. Haemorrh.*, **30**, 123–132.
2) Banerjee, R.N., Sahni, A.L., Kumar, V. & Arya, M. (1974) Antithrombin-III deficiency in maturity onset diabetes mellitus and atherosclerosis. *Throm. Diathes. Haemorrh.* **31**, 339–345.
3) Brass, E.B., Forman, W.B., Edward, R.V. & Lindan, O. (1976) Fibrin formation; the role of fibrinogen-fibrin monomer complex. *Thrombos. Haemostas.*, **36**, 37–48.
4) Fukuda, M. (1972) Blood fibrinolytic activity and fibrinogen concentration in diabetic retinopathy. *Eye Ear Nose & Throat Monthly*, **51**, 266–272.
5) Ishibashi, T., Tanaka, K. & Taniguchi, Y. (1981) Platelet aggregation and coagulation in the pathogenesis of diabetic retinopathy in rats. *Diabetes*, **30**, 601–606.
6) Isogai, S., Kameyama, M. & Urayama, T. (1982) Plasma soluble fibrin monomer complexes in diabetic microangiopathy. *Jap. J. Med.*, **21**, 96–100.
7) Kadish, A.H., Litle, R.L. & Sternberg, J.C. (1968) A new and rapid method for the determination of glucose by measurement of rate of oxygenconsumption. *Clin. Chem.*, **14**, 116–131.
8) Kameyama, M. (1981) Plasma soluble fibrin monomer complexes in diabetic angiopathies. *J. Jap. Diab. Soc.*, **23**, 379–387. (in Japanese with English abstract)
9) Kikuchi, K., Kameyama, M., Oshima, Y., Ogaki, H., Ishii, M., Iioka, Y., Inokuchi, T., Isogai, S., Abe, T. & Urayama, T. (1981) Development of diabetic retinopathy and plasma soluble fibrin monomer complexes. *J. Jap. Diab. Soc.*, **24**, 297. (Japanese)
10) Kopec, M., Wegrzynowicz, Z. & Latallo, Z.S. (1970) Precipitation of soluble fibrin monomer complexes SFMC by cellular basic proteins, and the antagonistic effect of sulfonated mucopolysaccharides. *Proc. Soc. exp. Biol. Med.*, **135**, 675–684.
11) Matsuoka, M., Satake, K. & Fukasawa, E. (1958) The determination of plasma fibrinogen concentration by tyrosin method. *Rinsho Kensa*, **2**, 61–63. (Japanese)
12) Shainoff, J.R. & Page, I.H. (1964) Fibrin deposition and atherosclerosis. *Nat. Conf. Cardiovasc. Dis.*, **2**, 374–375.
13) 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)