

## The Fibrinogen Degradation Products (FgDP) Levels in Liver Disease

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*We measured plasma levels of fibrinogen degradation products (FgDP) with newly developed enzyme-linked immunosorbent assay based on monoclonal antibody to assess the fibrinogenolytic state in 52 patients with various liver diseases (27 patients with liver cirrhosis, 10 with chronic hepatitis, 7 with acute hepatitis, 6 with hepatocellular carcinoma, 2 with intrahepatic cholestasis). As compared with 20 healthy subjects (upper limit: 580 ng/ml), elevated plasma levels (660~32000 ng/ml) of FgDP were found in 19 (36.5%) patients. When analyzed according to the underlying disease categories, the magnitude of elevations of FgDP were most prominent in patients with chronic hepatitis. No correlation was found between plasma FgDP levels and serum AST or ALT activity. These findings indicate that increased primary fibrinogenolysis is not rare in liver disease, but poorly correlates with liver function.*

**Key Words:** Fibrinogen degradation products, hepatitis, liver cirrhosis, primary fibrinogenolysis

Disseminated intravascular coagulation (DIC) can occur in both acute and chronic liver disease (Verstraete *et al.* 1974; Bloom 1975; Hughes *et al.* 1985) and recently, Paramo *et al.* (1991) have suggested that a low grade DIC may occur by demonstration of increased thrombin-antithrombin (TAT) complex and fibrin degradation products (FbDP) in liver cirrhosis. In addition, Kroneman *et al.* (1991) have observed the good correlation between fibrinogen degradation products (FgDP) and D-dimer levels, and suggested that secondary fibrinolysis appears to be accompanied by fibrinogenolysis in patients with liver cirrhosis. However, Takahashi *et al.* (1990b) observed normal FgDP in the majority of patients with liver disease indicating

that accelerated fibrinolysis observed in liver disease is due to fibrinolysis secondary to thrombin generation but not due to primary fibrinogenolysis in its nature. So, we measured the FgDP in plasma of patients with liver disease in order to evaluate the presence or absence of an enhanced fibrinogenolytic state in liver disease.

### PATIENTS AND METHODS

Fifty-two patients with liver disease were studied. They consisted of twenty seven patients with liver cirrhosis, ten patients with chronic hepatitis, seven patients with acute viral or toxic hepatitis, six patients with hepatocellular carcinoma, and two patients with intrahepatic cholestasis. Twenty healthy subjects were also included as controls. Basic laboratory findings in these patients are shown in Table 1.

Fibrinogen degradation products (FgDP) were quantitated with a recently developed

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**Table 1. Basic laboratory findings in patients with liver disease (Mean and range) and in normal subjects (Range)**

		Albumin (g/L)	AST (U/L)	ALT (U/L)	Billrubin ( $\mu$ mol/L)	Prothrombin time(s)	Platelet count ( $\times 10^9$ /L)
LC	n=27	25 (17~34)	198 (30~1770)	119 (26~798)	157 (15~649)	20.2 (12~36)	71 (22~151)
CH	n=10	27 (21~39)	99 (37~724)	217 (44~37)	56 (18~121)	17.5 (13~25)	131 (28~344)
AH	n=7	33 (26~41)	564 (97~2304)	477 (39~1300)	324 (27~738)	38.5 (15~65)	149 (44~303)
HC	n=6	23 (20~29)	396 (45~1085)	177 (23~455)	147 (23~227)	24.4 (12~61)	103 (40~153)
IC	n=2	30 (28~32)	180 (139~222)	102 (67~138)	359 (324~410)	25.5 (13~28)	386 (206~566)
Normal	range	34~53	7~25	8~25	6~25	12~14	140~450

Abbreviations: LC: liver cirrhosis, CH: chronic hepatitis, AH: acute hepatitis, HC: hepatocellular carcinoma, IC: intrahepatic cholestasis.

enzyme-linked immunosorbent assay (ELISA, Fibrinostika FgDP; Organon Teknika, Turnhout, Belgium)(Koppert *et al.* 1987). Diluted plasma samples (twenty fold or higher) or calibrators were added to the wells which had been coated with a murine monoclonal anti-FgDP/FbDP. Anti-FgDP/FbDP is a catching antibody specific for degradation products of both fibrin and fibrinogen (Koppert *et al.* 1986). After 15 min at 37°C, each well was washed with phosphate buffer. The peroxidase-conjugated monoclonal anti-FgDP, which reacts exclusively with the captured degradation products of fibrinogen, not with those of fibrin (Koppert *et al.* 1985), was then added. After 15 min at 37°C, each well was washed and a substrate tetramethylbenzidine solution containing urea peroxide was introduced. After 10 min at 37°C, the reaction was stopped by adding sulphuric acid, and the absorbance was read at 450nm with micro-ELISA reader. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined by standard methods.

The elevated FgDP results are expressed as mean/SD in each group, excluding one extremely increased value (32,000) in the group of liver cirrhosis. Variable comparisons between the groups were performed by ANOVA with multiple comparison test. Dif-

**Table 2. Proportion of Patients with high\* FgDP level in various liver diseases**

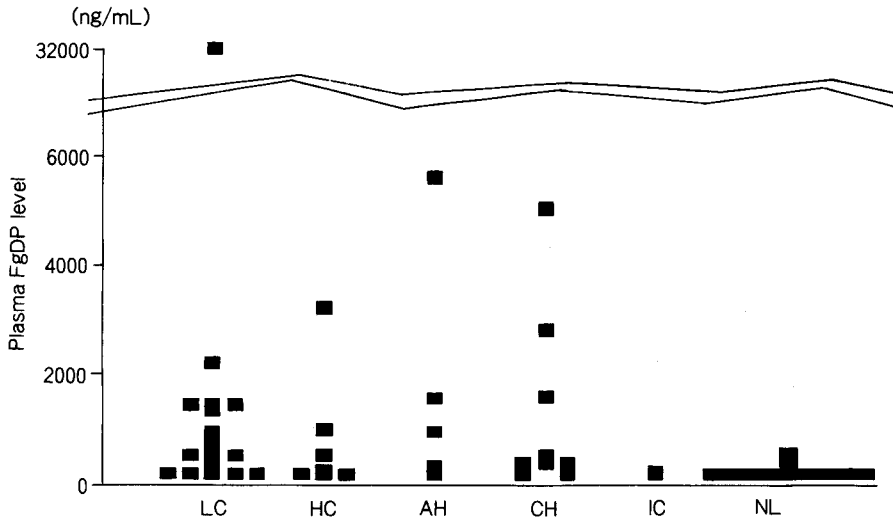
	No. Patients	No. of Patients with Elevation (%)
Liver cirrhosis	27	11(40.7%)
Chronic hepatitis	10	3(30.0%)
Acute hepatitis	7	3(42.9%)
Hepatocellular carcinoma	6	2(40.7%)
Intrahepatic cholestasis	2	0 (0.0%)
Total	52	19 (36.5%)

\*: Higher FgDP level than upper limit of healthy subjects(580ng/ml).

ferences between groups were considered significant at a P value of <0.05. Correlation analysis was performed, and the Pearson correlation coefficient(r) was calculated.

## RESULTS

Of the 52 patients with various liver disease, 19 (36.5%) had elevation of plasma FgDP levels, compared with 20 healthy subjects (upper limit: 580 ng/ml). Incidences of el-



**Fig. 1.** Plasma FgDP level in various liver diseases. Abbreviations: LC: liver cirrhosis, CH: chronic hepatitis, AH: acute hepatitis, HC: hepatocellular carcinoma, IC: intrahepatic cholestasis.

**Table 3.** Plasma FgDP levels in patients with high FgDP levels (higher than upper limit of healthy subjects)

	n	Mean ng/ml	SD ng/ml	Range ng/ml
Liver cirrhosis*	10	1168	488	660~2200
Chronic hepatitis	3	3146	1746	1600~5040
Acute hepatitis	3	2713	2519	960~5600
Hepatocellular Carcinoma	2	2100	1555	1000~3200

\*: One patient with liver cirrhosis who had extremely high FgDP (32,000 ng/ml) was excluded.

evaluation according to the underlying disease categories are shown in Table 2 and Figure 1. In 7 patients with acute hepatitis, 3 (42.9%) had elevation of FgDP and none of the patients with intrahepatic cholestasis had elevation of FgDP level. However, there was no statistically significant difference of plasma FgDP levels between disease subgroups. When considering the magnitude of elevation among the patients with increased plasma FgDP, there was a statistically significant difference between liver cirrhosis and chronic hepatitis ( $p < 0.05$ ) (Table 3). No correlation between plasma FgDP level and AST or ALT could be demonstrated in either the patients with elevated FgDP levels or when considering all cases (AST;  $r = 0.15$   $p = 0.33$  and

ALT;  $r = 0.24$   $p = 0.11$ ).

## DISCUSSION

The development of a bleeding diathesis is a frequent accompaniment of liver disorders, particularly when there is severe parenchymal damage as in acute fulminant hepatic failure and end stage hepatic cirrhosis (Dymock, 1976). This coagulation defect is complex in origin and may arise from a number of different mechanisms including failure of synthesis of clotting factors and inhibitors (Knot *et al.* 1984), malabsorption of vitamin K, platelet dysfunction and/or deple-

tion, formation of ineffective fibrinogen (Francis and Arstrong 1982), disseminated intravascular coagulation (DIC) (Clark *et al.* 1973; Jones *et al.* 1973) and accelerated fibrinolysis (Hersch *et al.* 1987). Especially, alpha2-plasmin inhibitor, the major inhibitor of plasmin in blood is synthesized in the liver (Aoki and Yamanaka, 1978) and impaired synthesis of this protein as well as decreased clearance of plasminogen activators (PA) (Brommer *et al.* 1988) correlates with the increased plasmin activity and the presence of enhanced fibrinolytic and fibrinogenolytic activity in the blood (Furie, 1991). Findings consistent with DIC or accelerated fibrinolysis include an increase in fibrinogen/fibrin degradation products (FDP) in the blood and shortened survival of plasma fibrinogen, which is improved by administration of heparin (Colman *et al.* 1972). However, FDP may be formed as a consequence of ongoing proteolysis in ascitic fluid (Solomon, 1991).

Moreover, the latex agglutination test for FDP often gives false positive values in patients with liver disease (VanDeWater *et al.* 1986). Recently it has become possible to measure directly different forms of FDP in plasma by ELISA techniques based on the use of monoclonal antibodies, which do not cross react with fibrinogen (Whitaker *et al.* 1984; Koopman *et al.* 1987). These newly developed assays specific for FgDP and FbDP may also provide more useful information about the nature of accelerated fibrinolysis or DIC. According to Takahashi *et al.* (1990a), besides fibrinolysis, fibrinogenolysis is markedly accelerated in the majority of patients with DIC complicated with malignancy, sepsis or vascular disorders as judged by elevation of both FgDP and FbDP. However, interestingly, Takahashi *et al.* (1990b) reported that FgDP employing the same technique was normal in the majority of patients with liver disease and suggested that increased primary fibrinogenolysis is rare in acute and chronic liver disease. Our finding of increased FgDP levels in some patients with liver disease are not consistent with results by Takahashi *et al.* (1990b) but are consistent with those of Kroneman *et al.* (1991), who reported a good correlation between FgDP and D-dimer levels in liver cirrhosis suggesting that secondary fibrinolysis appeared to be accompanied by

fibrinogenolysis. Recently Paramo *et al.* (1991) reported that there was a significant increase of thrombin-antithrombin (TAT) complex in patients with severe liver disease suggesting increased thrombin activity followed by hyperfibrinolysis. In addition, Hughes *et al.* (1985) reported that there was a significant increase in B 1-42 fibrinogen degradation products cleaved by plasmin, in chronic liver disease. Altogether, thrombin generation in liver disease followed by plasmin generation appear to be evident but the degree of fibrinolysis may be different according to the individual patients due to mechanisms unknown at present. If impaired hepatic clearance is the main cause of increased TAT, D-dimer, or FgDP levels in liver disease, one would expect a relationship between these thrombin or plasmin generation markers and the severity of the liver disease. In the present study we found no relation between FgDP and the liver function test.

Increased FgDP in liver disease may be also associated with high plasma levels of t-PA (Brommer *et al.* 1988). Tornai *et al.* (1993) have recently reported that the baseline t-PA values in the liver cirrhosis is significantly higher than the normals. However, according to Takahashi *et al.* (1989), t-PA levels showed no correlation with TAT or cross-linked fibrin derivatives. A study by Hersch *et al.* (1987) also stressed the critical role of PAI-1 in the pathogenesis of accelerated fibrinolysis. According to Takahashi *et al.* (1989), t-PA and t-PA/PAI-1 ratios in liver cirrhosis were lower than acute or chronic hepatitis while PAI-1 levels were higher than chronic hepatitis. Plasmin-antiplasmin complex (PAP) were also lower in liver cirrhosis than in chronic hepatitis or acute hepatitis. These findings may be associated more with the lower mean value of FgDP elevations in liver cirrhosis than in acute or chronic hepatitis. More experience with these new assays may provide useful information about the mechanism of fibrinogenolysis and fibrinolysis in these various liver diseases.

## REFERENCES

- Aoki N, Yamanaka T: The alpha2-plasmin inhibitor levels in liver disease. *Clin Chim Acta* 84:

99-105, 1978

- Bloom AL: Intravascular coagulation and the liver. *Br J Haematol* 30: 1-7, 1975
- Brommer EJP, Derkx FHM, Schalekamp MADH, Dooijewaard G, v.d. Klaauw MM: Renal and hepatic handling of endogenous tissue-type plasminogen activator (t-PA) and its inhibitor in man. *Thromb Haemostas* 59: 404-411, 1988
- Clark R, Rake MO, Flute PT, Williams R: Coagulation abnormalities in acute liver failure; pathogenesis and therapeutic implications. *Scand J Gastroenterol* 8: 63-68, 1973
- Colman RW, Robboy SJ, Minna JD: Disseminated intravascular coagulation (DIC): An approach. *Amer J Med* 52: 679-689, 1972
- Dymock IW: Liver disease. In: Israels MCG and Delamore IW, eds. *Hematological aspects of systemic disease*. London: WB Saunders Co, 1976, 479-485
- Francis JL, Armstrong DJ: Acquired dysfibrinogenemia in liver disease. *J Clin Pathol* 35: 667-672, 1982
- Furie B: Coagulation disorders associated with liver disease. In: Hoffman R, eds. *Hematology*. New York: Churchill Livingstone, 1991, 1378
- Hersch SL, Kunelis T, Francis RB, Jr: The pathogenesis of accelerated fibrinolysis in liver cirrhosis: A critical role for tissue plasminogen activator inhibitor. *Blood* 69: 1315-1319, 1987
- Hughes RD, Lane DA, Ireland H, Langley PG, Gimson AES, Williams R: Fibrinogen derivatives and platelet activation products in acute and chronic liver disease. *Clin Sci* 68: 701-707, 1985
- Jones CTA, Birch CR, Poller D, Dymock IW: Disseminated intravascular coagulation associated with hepatitis in late pregnancy. *Gut* 14: 891-894, 1973
- Knot E, Ten Cate JW, Drijfhout HR, Kahle LH, Tytgat GN: Antithrombin III metabolism in patients with liver disease. *J Clin Pathol* 37: 523-530, 1984
- Koopman J, Haverkate F, Koppert P, Nieuwenhuizen W, Brommer EJP, van der Werf WGC: New enzyme immunoassay of fibrin-fibrinogen degradation products in plasma using monoclonal antibody. *J Lab Clin Med* 109: 75-84, 1987
- Koppert PW, Huijsmans CMGH, Nieuwenhuizen W: A monoclonal antibody, specific for human fibrinogen, fibrinopeptide A-containing fragments and not reacting with free fibrinopeptide A. *Blood* 66: 503-507, 1985
- Koppert PW, Koopman J, Haverkate F, Nieuwenhuizen W: Production and characterization of a monoclonal antibody reactive with a specific neoantigenic determinant (comprising BB 54-118) in degradation products of fibrin and fibrinogen. *Blood* 68: 437-441, 1986
- Koppert PW, Huipers W, Hooged Nobel B, Brommer EJP, Koopman J, Nieuwenhuizen W: A quantitative enzyme immunoassay for primary fibrinogenolysis products in plasma. *Thromb Haemostas* 57: 25-28, 1987
- Kroneman H, Nieuwenhuizen W, Knot EA, van Bergen PF, De Maat MP: Correlation between plasma levels of fibrin (ogen) derivatives as quantified by different assays based on monoclonal antibodies. *Thromb Res* 61: 441-452, 1991
- Paramo JA, Rifon J, Fernandez J, Cuesta B: Thrombin activation and increased fibrinolysis in patients with chronic liver disease. *Blood Coagul Fibrinolysis* 2: 227-230, 1991
- Solomon LR: Hematologic complications of liver disease and alcoholism. In: Hoffman R, eds. *Hematology*. New York: Churchill Livingstone, 1991, 1685
- Takahashi H, Tatewaki W, Wada K, Yoshikawa A, Shibata A: Thrombin and plasmin generation in patients with liver disease. *Amer J Hematol* 32: 30-35, 1989
- Takahashi H, Tatewaki W, Wada K, Niwano H, Shibata A: Fibrinolysis and fibrinogenolysis in disseminated intravascular coagulation. *Thromb Haemostas* 63: 340-344, 1990a
- Takahashi H, Tatewaki W, Wada K, Niwano H, Shibata A: Fibrinolysis and fibrinogenolysis in liver disease. *Amer J Hematol* 34: 241-245, 1990b
- Tornai I, Harsfalvi J, Boda Z, Udvardy M, Pfiogler G, Rak K: Endothelium release more von willebrand factor and tissue type plasminogen activator upon venous occlusion in patients with liver cirrhosis than in normals. *Haemostas* 23: 58-64, 1993
- VanDeWater L, Carr JM, Aronson D, McDonagh J: Analysis of elevated fibrin (ogen) degradation product levels in patients with liver disease. *Blood* 67: 1468-1473, 1986
- Verstraete M, Vermeylen J, Collen D: Intravascular coagulation in liver disease. *Ann Rev Med* 25: 447-455, 1974
- Whitaker AN, Elms MJ, Masci PP, Bundesen PG, Rylatt DB, Webber AJ, Bunce IH: Measurement of crosslinked fibrin derivatives in plasma: an immunoassay using monoclonal antibodies. *J Clin Pathol* 37: 882-887, 1984