Dysfibrinogenemia Associated with Liver Disease

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ABSTRACT To test the possibility that a functionally abnormal fibrinogen may exist in some patients with liver disease, we studied the plasma and purified fibrinogens of five patients whose plasma thrombin times were prolonged at least 40% over normal controls. In no patient was there evidence of disseminated intravascular coagulation and/or fibrinolysis. No abnormalities were detected by immunoelectrophoresis of plasmas or purified fibrinogens. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of reduced patient fibrinogens showed normal mobility and amount of Aα, Bβ, and γ chains. Alkaline polyacrylamide gel electrophoresis and gradient elution, DEAE-cellulose chromatography of admixtures of radioiodinated patient 125I-fibrinogen and normal 125I-fibrinogen showed identical mobility in the gel and simultaneous elution from the column, respectively. Thrombin and Reptilase (Abbott Scientific Products Div., Abbott Laboratories, South Pasadena, Calif.) times of purified patient fibrinogens were prolonged, and calcium ions improved but did not completely correct these defects. Increasing amounts of thrombin progressively shortened the clotting times of patient fibrinogens but not to the level of normal. Addition of equal amounts of patient fibrinogen to normal fibrinogen resulted in a prolongation of the thrombin time of the normal protein. Thrombin-induced fibrinopeptide release was normal. Fibrin monomers prepared from patient plasmas and purified fibrinogens demonstrated impaired aggregation at low (0.12) and high (0.24) ionic strength. These studies demonstrate that some patients with liver disease and prolonged plasma thrombin times have a dysfibrinogenemia functionally characterized by an abnormality of fibrin monomer polymerization.

INTRODUCTION

Most coagulation proteins are synthesized by the liver, and patients with liver disease often exhibit multiple coagulation defects (1, 2). Prolongation of the plasma thrombin time in the presence of normal or even elevated levels of plasma fibrinogen is often observed in these patients. In several cases, this abnormality has been explained on the basis of increased antithrombin activity in the plasma, probably due to circulating fibrinogen-fibrin degradation products (3) whose clearance by the diseased liver may be delayed (4). It has also been suggested that the fibrinogen molecule itself is abnormal in patients with liver disease. In one study of plasmas of patients with cirrhosis and hepatitis, impairment of thrombin-induced fibrin monomer aggregation was described. However, when studies were performed with the euglobulin fraction of the same plasmas, the functional abnormality was no longer demonstrated (5). Since the system utilized did not involve purified protein, the influence of other plasma factors cannot be excluded in these studies.

To examine the possibility that an abnormal fibrinogen may exist in patients with liver disease, we have studied the fibrinogen of five patients with clinically and histologically documented liver disease (three with alcoholic liver disease and two with postnecrotic cirrhosis of undetermined etiology). The plasma thrombin times in all five patients were at least 40% longer than normal in the absence of clinical and laboratory evidence of disseminated intravascular coagulation and/or fibrinolysis.

METHODS

Blood was collected with plastic syringes into 1/9 volume 3.8% sodium citrate or 2% disodium EDTA. Samples were then centrifuged at 4°C for 15 min at 2,500 g. The platelet-poor plasma was removed and tested immediately, or quick-frozen in acetone-dry ice, and then stored at −80°C.

Fibrinogen purification. Normal fibrinogen was purified from Anticoagulant Citrate Dextrose Solution U. S. P.
fibrinogen dissolved was tested. Patient fibrinogen was purified and acid to a (Fenwal Inc., Ashland, Mich.) was then allowed to clot at room temperature for 30 min and the clot was removed by winding it onto a wooden applicator stick. The serum was then placed at 4°C for 30 min and any additional clot was removed. The resultant serum was then tested for the presence of fibrinogen-fibrin-related antigens by a latex agglutination test (13).

The thrombin clotting time was performed by adding to 0.1 ml of citrated plasma 0.2 ml of imidazole-buffered saline (0.15 M NaCl, 0.045 M imidazole, pH 7.4) and 0.1 ml of bovine thrombin (10 U/ml imidazole-buffered saline). The thrombin clotting times of normal and patient purified fibrinogens were also determined. To 0.1 ml of fibrinogen at a concentration of 2.0 mg/ml in 0.02 M sodium citrate, 0.15 M NaCl, pH 7.4, was added 0.2 ml of imidazole-buffered saline and 0.1 ml of bovine thrombin (10 U/ml imidazole-buffered saline). When calcium was used, the imidazole-buffered saline contained 0.01 M CaCl₂. Reptilase times were performed with the lyophilized venom of Bothrops atrox (Abbott Scientific Products Div., Abbott Laboratories, South Pasadena, Calif.) reconstituted with distilled water. The system was identical to that described for the thrombin time except that 0.1 ml of Reptilase (20 μg/ml water) was substituted for thrombin. Thrombin times were also performed using a highly purified human thrombin obtained through the kindness of Dr. John Fenton, N. Y. State Department of Health Laboratories, Albany, N. Y.

Plasma fibrinogen concentration was measured by the thrombin clottability method of Ellis and Stransky (14), and by quantitative immunodiffusion using commercial antobody-containing agar plates (Behringwerke AG, Marburg-Lahn, West Germany).

Fibrinopeptide release of normal and patient fibrinogens was studied by measuring TCA-soluble arginine at timed intervals after the addition of thrombin (15).

Recent coagulation studies were done by one of two methods. One was based on the procedure described by von Felten et al. (16). Plasma, or purified fibrinogen at a concentration of 2.0 mg/ml, containing disodium EDTA and 250 μM of Trasylol (Calbiochem, San Diego, Calif.) was diluted 1:5 with 0.15 M NaCl and treated with bovine thrombin. The mixture was incubated at 37°C for 3 h and then at 4°C for 48 h, after which the clots were recovered by centrifugation. The clots were then washed five times with 0.025% disodium EDTA in 0.15 M NaCl, and then dissolved in 5 M urea, and dialyzed against three changes of barbitalsodium acetate buffer, pH 4.6, ionic strength 0.05 at 4°C over 72 h. After dialysis, the fibrin monomer concentration was adjusted to 1.0 mg/ml. A 0.5-ml aliquot of this solution (0.5 mg) was transferred to a cuvette to which had been added 0.5 ml of 0.1 M phosphate buffer, pH 6.8, with NaCl to a final ionic strength of 0.20. Absorbance was followed at 350 nm over 30 min in a Gilford spectrophotometer (Gilford Instrument Laboratories, Inc., Oberlin, Ohio). Fibrin monomer aggregation was also measured at a final ionic strength of 0.24 by adding an aliquot of the monomer solution to an equal volume of 0.1 M phosphate buffer, pH 6.8, adjusted with NaCl to a final ionic strength of 0.43. Final pH of the aggregation mixtures was 6.7. Fibrin monomer aggregation was also measured in patients, 1, 2, and 4, by the method of Belitser et al. as modified by Gralnick et al. (15).

The formation of cross-linked fibrin was studied by clotting plasma with thrombin in the presence of calcium, incubating the clots in 9 M urea for 24 h, and then measuring the absorbance of the supernate at 280 nm (17).

Electrophoretic and chromatographic studies. Immuno-electrophoretic studies were performed in 1% agarose, at pH 8.6, in barbital buffer with commercial goat anti-human fibrinogen antiserum (Meloy Laboratories Inc., Springfield, Va.). Sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis of normal and patient purified fibrinogens reduced with β-mercaptoethanol was performed using 7.5% gels according to the method of Weber and Oshorn (18). Densitometric scans of the stained gels were made with a Gilford gel scanner. Polyacrylamide gel electrophoresis of labeled purified proteins was performed by the method of Davis (19) with 5% gels and pH 8.5 Tris-glycine. DEAE-cellulose (DE32, Schwarz/Mann Div., Becton, Dickinson & Co., Orangeburg, N. Y.) chromatography was performed at 4°C using a continuous concave gradient with Tris-phosphate buffer (20). For these experiments, admixtures of normal fibrinogen and patient fibrinogen, both labeled by the iodine monochloride method of McFarlane (21) modified as previously described, were run in the same gel or column (22). After electrophoresis, the gels were stained with Coomasie blue, cut into 1-mm segments, and the radioactivity in each gel segment was counted in an Isodyne model 1185 two-channel counter (Searle Analytic, Inc., Des Plaines, Ill.). Absorbance at 280 nm, radioactivity, and pH were measured on column effluents.

RESULTS

Coagulation studies. The plasma thrombin times were prolonged in three patients who had normal levels of plasma fibrinogen and in two patients with slightly decreased plasma fibrinogen (Table I). The serial dilution protamine sulfate test was negative. Fibrinogen-fibrin-related antigens were negative or very low in patients 1, 2, and 4. Fibrin monomer aggregation studies were done by one of two methods. One was based on the procedure described by von Felten et al. (16). Plasma, or purified fibrinogen at a concentration of 2.0 mg/ml, containing disodium EDTA and 250 μM of Trasylol (Calbiochem, San Diego, Calif.) was diluted 1:5 with 0.15 M NaCl and treated with bovine thrombin. The mixture was incubated at 37°C for 3 h and then at 4°C for 48 h, after which the clots were recovered by centrifugation. The clots were then washed five times with 0.025% disodium EDTA in 0.15 M NaCl, and then dissolved in 5 M urea, and dialyzed against three changes of barbitalsodium acetate buffer, pH 4.6, ionic strength 0.05 at 4°C over 72 h. After dialysis, the fibrin monomer concentration was adjusted to 1.0 mg/ml. A 0.5-ml aliquot of this solution (0.5 mg) was transferred to a cuvette to which had been added 0.5 ml of 0.1 M phosphate buffer, pH 6.8, with NaCl to a final ionic strength of 0.20. Absorbance was followed at 350 nm over 30 min in a Gilford spectrophotometer (Gilford Instrument Laboratories, Inc., Oberlin, Ohio). Fibrin monomer aggregation was also measured at a final ionic strength of 0.24 by adding an aliquot of the monomer solution to an equal volume of 0.1 M phosphate buffer, pH 6.8, adjusted with NaCl to a final ionic strength of 0.43. Final pH of the aggregation mixtures was 6.7. Fibrin monomer aggregation was also measured in patients, 1, 2, and 4, by the method of Belitser et al. as modified by Gralnick et al. (15).

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Abbreviation used in this paper: SDS, sodium dodecyl sulfate.
within the range of normal for this method. Of the individual coagulation factors tested, the only abnormal findings common to all patients were a decreased level of Factor X and an increased level of Factor VIII. The thrombin and Reptilase times of purified patient fibrinogens adjusted to concentrations of 2.0 mg/ml are shown in Table II. Both thrombin and Reptilase times were prolonged. The prolongation of the thrombin time was similar in the respective patient plasma and purified fibrinogen systems. The addition of calcium improved but did not always completely correct the thrombin and Reptilase times of the patient fibrinogens. Similar prolongation of the thrombin time was noted in two patients whose fibrinogens were treated with human thrombin. The effect of increasing concentrations of thrombin on the clotting of two patient fibrinogens is shown in Fig. 1. Increasing concentrations of thrombin shorten the clotting time of the patient fibrinogens, but not to the level of the normal at the concentrations of thrombin employed. The addition of equal amounts of purified patient fibrinogen to purified normal fibrinogen caused a significant prolongation of the thrombin time of the normal fibrinogen (Fig. 1).

Thrombin-induced fibrinopeptide release of normal and patient purified fibrinogens is shown in Fig. 2. Fibrinopeptide release was normal in rate and amount for each of the patient fibrinogens tested.

Fibrin monomer aggregation was studied in each of the patients by treating both plasma and purified fibrinogen with thrombin according to a modification of the method of von Felten et al. (16) described above. Patient fibrin monomers derived from plasma and from purified fibrinogen showed impaired aggregation at both low and high ionic strength. Results for purified fibrinogen are shown in Fig. 3. The normal represents the mean of duplicate determinations of purified fibrinogen from each of two normal donors. Fibrin monomer aggregation in patients 1, 2, and 4 tested according to a modification of the method of Belitser et al. (15) was also impaired at low and high ionic strength (Fig. 4). The degree of impairment of fibrin monomer aggregation appears to correlate with the extent of prolongation of the patient plasma thrombin times.

### Table I

**Coagulation Studies**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Patient 1*</th>
<th>Patient 2*</th>
<th>Patient 3</th>
<th>Patient 4*</th>
<th>Patient 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin time, s</td>
<td>20–23</td>
<td>38.0</td>
<td>40.0</td>
<td>32.9</td>
<td>47.7</td>
<td>39.0</td>
</tr>
<tr>
<td>Fibrinogen, mg/100 ml</td>
<td>232–444</td>
<td>303</td>
<td>438</td>
<td>157</td>
<td>220</td>
<td>270</td>
</tr>
<tr>
<td>Thrombin-clottable</td>
<td>§</td>
<td>347</td>
<td>426</td>
<td>138</td>
<td>174</td>
<td>280</td>
</tr>
<tr>
<td>Immunoreactive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serial dilution protamine sulfate test</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Fibrinogen-fibrin-related antigen, μg/ml</td>
<td>≤8</td>
<td>18.8</td>
<td>18.5</td>
<td>14.0</td>
<td>16.3</td>
<td>16.1</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>12–15</td>
<td>60–90</td>
<td>84.7</td>
<td>75.0</td>
<td>97.5</td>
<td>80.1</td>
</tr>
<tr>
<td>Factor V, U/ml</td>
<td>0.47–1.53</td>
<td>0.56</td>
<td>0.72</td>
<td>0.46</td>
<td>0.56</td>
<td>0.80</td>
</tr>
<tr>
<td>Factor VIII, U/ml</td>
<td>0.48–1.52</td>
<td>1.64</td>
<td>1.64</td>
<td>1.64</td>
<td>4.99</td>
<td>1.72</td>
</tr>
<tr>
<td>Factor IX, U/ml</td>
<td>0.62–1.38</td>
<td>0.83</td>
<td>1.04</td>
<td>0.72</td>
<td>0.77</td>
<td>0.78</td>
</tr>
<tr>
<td>Factor X, U/ml</td>
<td>0.58–1.42</td>
<td>0.56</td>
<td>0.40</td>
<td>0.39</td>
<td>0.56</td>
<td>0.50</td>
</tr>
<tr>
<td>Factor XI, U/ml</td>
<td>0.52–1.48</td>
<td>0.94</td>
<td>1.17</td>
<td>0.98</td>
<td>0.70</td>
<td>0.66</td>
</tr>
</tbody>
</table>

* Alcoholic liver disease.
† Postnecrotic cirrhosis of undetermined etiology.
§ Measured against standard normal plasma.

### Table II

**Thrombin and Reptilase Times of Purified Normal and Patient Fibrinogens**

<table>
<thead>
<tr>
<th></th>
<th>Thrombin time</th>
<th>Reptilase time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Ca++</td>
<td>With Ca++</td>
</tr>
<tr>
<td></td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Normal*</td>
<td>23.2±2.0</td>
<td>12.3±1.0</td>
</tr>
<tr>
<td>Patient 1</td>
<td>41.7</td>
<td>16.3</td>
</tr>
<tr>
<td>2</td>
<td>39.8</td>
<td>15.2</td>
</tr>
<tr>
<td>3</td>
<td>41.2</td>
<td>12.5</td>
</tr>
<tr>
<td>4</td>
<td>75.1</td>
<td>15.7</td>
</tr>
<tr>
<td>5</td>
<td>31.5</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Fibrinogen concentrations were 2.0 mg/ml in 0.02 M sodium citrate, 0.15 M sodium chloride, pH 7.4. The mixture consisted of 0.1 ml of fibrinogen solution, 0.2 ml imidazole-buffered saline, and 0.1 ml bovine thrombin (10 U/ml) or Reptilase (20 μg/ml). Where indicated, CaCl₂ was 0.005 M final concentration.

* The normal is expressed as the mean±1 SD.
thrombin time except for patient 3. The lack of correlation for patient 3 is unclear at present.

Electrophoretic and chromatographic studies. Immunoelectrophoresis of each patient plasma and purified fibrinogen revealed an immunoprecipitin arc of normal mobility. SDS-polyacrylamide gel electrophoresis of each of the five reduced patient fibrinogens showed normal mobility and amount of $\alpha$, $\beta\beta$, and $\gamma$ chains with no evidence of proteolysis. Results for patients 1 and 4 are shown in Fig. 5. Alkaline polyacrylamide gel electrophoresis and DEAE-cellulose chromatography were performed with radiolabeled fibrinogen of patients 1 and 4. Patient $^{131}$I-fibrinogen and normal $^{131}$I-fibrinogen migrated identically when studied by alkaline polyacrylamide gel electrophoresis (Fig. 6). Gradient elution chromatography on DEAE-cellulose of a mixture of patient $^{125}$I-fibrinogen and normal $^{125}$I-fibrinogen revealed simultaneous elution in two major peaks (Fig. 7) as previously described for normal fibrinogen (20).

**DISCUSSION**

Most of the dysproteinemias described in patients with liver disease have been due to quantitative abnormalities. However, the presence of qualitative abnormalities of plasma proteins in this group of patients is becoming increasingly recognized. In several patients with hepatoma, an acquired abnormality of fibrin monomer polymerization has been reported (23, 24). High levels of an R-type $B_12$-binding protein with increased sialic acid content have also been demonstrated in patients with hepatoma (25). In addition,

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increased levels of partially desialylated thyroxine-binding globulin have been described in patients with alcoholic and biliary cirrhosis, primary and metastatic liver carcinoma, and hepatitis, presumably due to decreased removal of the altered protein by damaged hepatocyte membranes (26).

We have studied the plasma and purified fibrinogens of five patients (three with alcoholic liver disease and two with postnecrotic cirrhosis) who had prolonga-

![Figure 4](image1.png)

**Figure 4** Aggregation of fibrin monomers of purified normal (N) and patients 1, 2, and 4 fibrinogens at ionic strength of 0.12 and 0.24. Final pH was 6.7 and protein concentration was 0.21 mg/ml (μ = ionic strength).

![Figure 6](image2.png)

**Figure 6** Electrophoretic mobility of 131I-labeled normal fibrinogen mixed with 125I-labeled patient 4 fibrinogen in 5% polyacrylamide gel. The gel was cut into 1-mm segments and 125I and 131I radioactivity was counted.

![Figure 7](image3.png)

**Figure 7** DEAE-cellulose chromatography of 15 mg of normal fibrinogen (dash-dot line) mixed with tracer amounts of 131I-labeled normal fibrinogen (dashed line) and 131I-labeled patient 1 fibrinogen (solid line). A concave gradient from 0.005 M Tris-phosphate, pH 8.6, to 0.5 M Tris-phosphate, pH 4.2, was used.
conversion of fibrinogen to fibrin by thrombin in the
presence of Factor XIII and calcium involves three
steps: (a) thrombin-induced fibrinopeptide release re-
sulting in the production of fibrin monomer, (b) poly-
merization of fibrin monomers, and (c) formation of
cross-linked fibrin. The thrombin time is affected by al-
terations in the first two steps of the conversion of
fibrinogen to fibrin. In all five patients, the prolonga-
tion of their plasma thrombin times was comparable
to the prolongation of the thrombin times of their
purified fibrinogens. Reptilase times of purified patient
fibrinogens were likewise prolonged. Calcium ac-
celerated clotting in both systems but did not always
completely correct the defect. Thrombin-induced fi-
brinopeptide release of patient fibrinogens was equal
in rate and amount to that of normal fibrinogen.
Therefore, the prolongation of the thrombin times
could be explained by defective aggregation of patient
fibrin monomers. Our studies demonstrate impaired ag-
gregation of patient fibrin monomers prepared from
plasma and from purified fibrinogen at both low and
high ionic strength, and localize the functional defect
specifically to the phase of monomer polymerization.
The degree of impairment of fibrin monomer poly-
merization appears to correlate with the extent of pro-
longation of the thrombin times. The improvement in
the thrombin times with calcium can be explained by
the known enhancement of fibrin monomer ag-
gregation by this ion (27). The third step in the con-
version of fibrinogen to covalently cross-linked fibrin
was grossly normal as indicated by the insolubility in
9 M urea of patient fibrinogen clotted with thrombin
in the presence of Factor XIII and calcium.
Several of the genetic dysfibrinogenemias have
been distinguished by differences on immunoelectro-
phoresis and DEAE-cellulose chromatography (28).
The functionally abnormal fibrinogen reported here
shows normal mobility on immunoelectrophoresis of
plasma and purified protein, identical mobility with
normal fibrinogen on polyacrylamide gel electropho-
resis, and simultaneous elution with normal fibrino-
gen on DEAE-cellulose chromatography. These results
suggest that the patient fibrinogen has an electrical
charge similar to that of normal fibrinogen. In addition,
SDS-polyacrylamide gel electrophoresis of patient re-
duced fibrinogens showed intact Aα, Bβ, and γ chains
with no evidence of proteolysis (29). Although cleavage
products of fibrinogen may be present in patients with
liver disease due to disseminated intravascular coagula-
tion and/or fibrinolysis (3, 30, 31), the normal elution
pattern on DEAE-cellulose chromatography and the
presence of intact Aα, Bβ, and γ chains on SDS-
polyacrylamide gel electrophoresis indicate that the
abnormality we are describing is not secondary to
proteolysis by plasmin but is intrinsic to the molecule.
The demonstration of a functional abnormality of the

circulating fibrinogen molecule does not necessarily
mean that the molecule secreted by the diseased liver
is abnormal. It is conceivable that a normal fibrino-
gen is secreted by the abnormal liver and undergoes
rapid alteration in the circulation due to an abnormal
plasma environment.

Accumulation of altered proteins in the plasma of
patients with liver disease may occur due to their im-
paired removal by the diseased liver. Most asialoglyco-
proteins are rapidly removed from the circulation by
the liver as the result of binding of their terminal
galactosyl residues to the hepatocyte membrane (32).
Impairment of this clearance mechanism might be
responsible for the finding of elevated levels of al-
tered thyroxine-binding globulin in patients with liver
disease (26). The liver also appears to play a role in
the removal of activated coagulation factors (33, 34).
Abnormal removal of altered coagulation proteins by
the diseased liver might affect the hemostatic balance
in these patients.

The occurrence of a dysfibrinogenemia in these five
patients with two types of liver disease suggests that
the abnormality may be a consequence of liver damage
rather than a manifestation of any single type of liver
disease. As can be seen from Table I, these patients
exhibited a variety of coagulation abnormalities. How-
ever, since coagulation factors are usually assayed on
the basis of their biological activity, what is generally
interpreted as reduced levels of these factors in liver
disease may reflect instead impaired biological activity
of altered molecular species present in reduced, nor-
mal, or increased amounts. The protein abnormalities
detected thus far in liver disease may be indicative of
generalized qualitative protein abnormalities in
these patients. Further investigations into the nature of
these alterations may ultimately provide the basis for
a better understanding of the pathogenetic mechanism
responsible for the dysproteinemias found in patients
with liver disease.

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