Antithrombin III metabolism in patients with liver disease

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SUMMARY Liver diseases are associated with complex haemostasis defects, in which platelets, coagulation, and fibrinolysis may all be affected. The low plasma concentrations of clotting factors often found can be the result of many changes such as impaired synthesis, increased catabolism due to intravascular coagulation, or alternate distribution.

In this study, we investigated the metabolism of purified human antithrombin III (AT III) labelled with $^{125}$I in 25 patients with histologically established liver disease and in nine control subjects. The results showed that, in general, low plasma concentrations of AT III in liver cirrhosis are not due to consumption in the central compartment but rather to altered transcapillary flux ratio. Such altered transcapillary flux ratios may already exist even with normal plasma AT III concentrations. Altered ratios are not only found for coagulation proteins but also for albumin and thus may be a general phenomenon of liver disease. In micronodular cirrhosis the $\alpha$ phase, the transcapillary efflux ($k_{1,2}$) and influx ($k_{2,1}$) were significantly increased compared with the normal subjects.

Liver disease is associated with a complex haemostasis defect, in which platelets, coagulation, and fibrinolysis may all be affected. In this study we describe the metabolism of human antithrombin III (AT III) in patients with chronic liver disease.

Antithrombin III neutralises thrombin and several other activated serine proteases of the coagulation system. Congenital or acquired AT III deficiencies are associated with recurrent thromboembolism. Plasma concentrations of this physiological inhibitor of the coagulation system are low in severe chronic liver disease and Tytgat et al have evidence for low grade diffuse intravascular coagulation. They found a shorter $\beta$ half life of radiolabelled fibrinogen in patients with liver disease, which could be prolonged by heparinisation. Other studies have shown that selective correction of AT III activity with human AT III concentrate reverses the increased turnover of radiolabelled fibrinogen in these patients.

These observations indicate that decreased AT III activity contributes to a major part of the increased radiolabelled fibrinogen turnover. In order to determine whether low plasma concentrations of AT III are due to impaired synthesis and/or low grade diffuse intravascular coagulation or alternate distribution, turnover studies are necessary using highly purified radiolabelled AT III. One study, using radiolabelled AT III in patients with severe liver disease, showed normal $\beta$ half life values. In this paper we report a further turnover study in patients with liver disease.

Material and methods

SUBJECTS AND CLINICAL DETAILS

Twenty five patients with histologically proved chronic liver disease were studied. Twelve had micronodular cirrhosis due to alcoholism and nine had macronodular cirrhosis with positive hepatitis B surface antigen (HBsAg). One patient had cirrhosis and an associated hepatocellular carcinoma of the liver. Two patients had micronodular cirrhosis of unknown aetiology and one had Budd-Chiari syndrome. None of the patients was receiving anticoagulant therapy. All patients were studied as outpatients. Three patients had mild ascites.

The mean age was 47.3 yr. The mean weight was
80 ± 10·9 kg and 72 ± 6·7 kg in the micronodular and macronodular groups respectively. In the micronodular and macronodular cirrhosis groups there were two and three patients respectively with transaminase activities more than twice the upper limit of the normal range. Three patients in the micronodular cirrhosis group had alkaline phosphatase and \( \gamma \)-glutamyltransferase activities more than twice the upper limit of the normal range. The mean albumin concentration of the whole group of patients was 38·3 ± 6·10 g/l. (micronodular cirrhosis 35·8 ± 6·5 g/l; macronodular 41·1 ± 5·4 g/l; normal 35-50 g/l). Nine healthy male volunteers were screened as controls.

**PREPARATION OF RADIOACTIVE TRACER**

The AT III was purified from HBsAg negative plasma.\(^{14}\) One unit of AT III was defined as the thrombin inactivity present in 1 ml of pooled plasma (40 donors, M:F = 1:1). The specific heparin cofactor activity was 5·6 U/mg per absorbency unit at 280 nm. SDS-polyacrylamide gel electrophoresis\(^{15}\) showed one band with a molecular weight of about 67 000 daltons when stained for protein with Coomassie brilliant blue. Amino acid composition and N-terminal sequencing (Prof Dr D Collen, Leuven) showed a protein similar to a highly purified internal AT III standard preparation.

The purified AT III was labelled with \(^{125}\)I using the Iodigen method\(^{16}\) (1 \( \mu \)g AT III labelled with 1·3-4 \( \mu \)Ci). The \(^{125}\)I-AT III was separated from free iodine by gel filtration on Sephadex G25. The \(^{125}\)I-labelled tracer was applied to a heparin Sepharose column (1 cm × 8 cm). The non-heparin binding tracer was removed by washing with phosphate saline buffer (pH 7·4) and the heparin binding \(^{125}\)I-AT III was eluted with 1·5 mol/l NaCl in phosphate saline buffer (pH 7·4).

Fractions were pooled, made isotonic with sterilised distilled water, sterilised by millipore filtration (0·45 \( \mu \)m), and stored in small aliquots at \(-70\)°C. Each batch was negative for HBsAg and for endotoxins.\(^{17}\)

**IN VITRO CHARACTERISATION OF \(^{125}\)I-AT III**

Crossed immunoelectrophoresis\(^{18}\) of a mixture of human plasma and purified radiolabelled AT III against rabbit antihuman serum (Behringwerke, Marburg Lahn, West Germany) showed a single precipitation peak when stained for protein with the same mobility as the radioactivity peak on autoradiography (Kodak XAR) (Fig. 1).

Gel filtration of a mixture of \(^{125}\)I-AT III and normal human plasma on Sephadex G100 showed one radioactivity peak with a similar elution pattern and biological activity as AT III antigen.

The specific activity of the preparation after labelling was unchanged.

Turnover data obtained with this preparation can therefore be assumed to reflect that of the total body AT III pool.

**TURNOVER STUDIES**

Before injection and daily throughout the course of the study each subject received sodium-iodide capsules (100 mg) to avoid thyroidal uptake of \(^{125}\)I. Ten \( \mu \)Ci \(^{125}\)I-AT III was injected intravenously and blood samples were taken at 10, 30, and 60 min; 2, 4, and 6 h; and then twice daily for six days.

Urine was collected at 24 h intervals. At the end of the study the radioactivity of the samples was counted with a Beckmann gammacounter.

Trichloroacetic acid precipitation was performed on plasma and urine samples. Less than 2% of the radioactivity was found in the plasma supernatant, while no precipitable \(^{125}\)I was found in the urine samples.

**TRACER DATA**

The tracer data were analysed using a two compart-
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Fig. 2  Two compartment model.19

The mathematical model (Fig. 2). A sum of two exponential terms, \( P_0 = A e^{-\alpha t} + B e^{-\beta t} \), was fitted to the plasma radioactivity data. \( P_0 \) is the concentration of protein in plasma during the time. \( A \) and \( B \) are the intercepts and \( \alpha \) and \( \beta \) the slopes of the curves of distribution and elimination phase respectively.

From the exponents and coefficients of this formula the following metabolic parameters were calculated:

Fractional catabolic rate constant \( k_{1,0} = \frac{Y(P_0)\alpha\beta}{(A\beta + B\alpha)} \)

Transcapillary efflux rate constant \( k_{1,2} = \frac{A\beta(\beta-\alpha)^2}{(P_0(A\beta + B\alpha))} \)

Transcapillary influx rate constant \( k_{2,1} = \frac{A\beta + B\alpha}{P_0} \)

The \( \beta \) half life = \( \ln(2) \). The apparent volume of distribution, \( V_d = V_p \left( \frac{1 + k_{2,1}^2}{k_{1,2}} \right) \), where \( V_p \) is the plasma volume.

COAGULATION AND FIBRINOLYTIC DATA

Venous blood was collected using a 20G Wasserman needle in plastic tubes containing either solid K_2EDTA (1.5 mg/ml blood) or trisodium citrate dihydrate 3.2% (one volume to nine volumes of blood). Plasma was prepared by centrifugation for 10 min at 1700g and rendered platelet free by a second run at 12 000g. Platelet free reference plasma was obtained from 40 volunteers, sex ratio 1:1. Plasma samples were stored in small aliquots at -70°C. EDTA plasma was used for the automated aminolytic determination of factor II, factor X, plasminogen, \( \alpha_2 \)-antiplasmin, and AT III.20-23

Citrate plasma was used for the following laboratory tests: prothrombin time,24 kaolin-cephalin clotting time,25 thrombin time,26 fibrinogen,27 ethanol gelation test,28 and the procoagulant activity of factors V and VII as determined by one stage assays using specific factor deficient human plasma.26 AT III antigen was measured by the method of Laurell.29

Serum containing tranexamic acid was used for the assay of fibrin/fibrinogen degradation products using a latex agglutination test (Thromb-Wellcotest, Wellcome).

Platelets were counted using cell counter 134 (Analytic Instruments, Sweden).

STATISTICAL ANALYSIS

Student’s \( t \) test and the Wilcoxon test were used and a \( p \) value of 0.05 was considered to be significant. The test was used for establishing the incidence of abnormal values outside the 95% confidence interval of the respective control values.

Results

RESULTS OF COAGULATION AND FIBRINOLYTIC DATA

The mean values of the activated partial thromboplastin time and the prothrombin and thrombin times of the micronodular and macronodular groups were prolonged by 11, 2, and 4 seconds respectively. The mean plasma concentrations of factors V and VII were 0.69 ± 0.23 U/ml and 0.50 ± 0.22 U/ml respectively (n = 11) (normal values 0.70–1.4 U/ml).

Fig. 3  Turnover data of 125I-AT III in a healthy volunteer (a) and in a patient with macronodular cirrhosis (b).
The mean plasma concentrations of AT III, $\alpha_2$-antiplasmin, and plasminogen in the whole group of patients were $0.70 \pm 0.24$ U/ml, $0.71 \pm 0.16$ U/ml, and $0.66 \pm 0.20$ U/ml respectively (normal values $0.80$-$1.40$ U/ml). In the micronodular group the mean AT III and antigen values were $0.67 \pm 0.30$ U/ml and $87.0 \pm 29.3$ g/100ml respectively. The AT III:antigen ratio was 0.74 (normal 1.0); the biologically measured AT III was significantly lower compared with the control subjects ($p < 0.005$ Wilcoxon). The mean values in the micronodular group were significantly lower than those for the macronodular group ($p < 0.05$ Wilcoxon). The mean fibrinogen degradation levels were within the normal range. Fibrinogen degradation products were present in raised concentrations in only the one patient with primary liver cell carcinoma. None of the patients had a positive ethanol gelation test. Ten patient had a thrombocytopenia.

RESULTS OF TURNOVER DATA
Two representative examples of the plasma radioactivity disappearance in a healthy volunteer and one patient from the micronodular group with a shortened $\beta$ half life are shown in Fig. 3.

NORMAL SUBJECTS (TABLE 1)
All data of the normal subjects are seen in Table 1 and are compatible with other studies. The mean $\beta$ half life was 58.6 $\pm$ 5.2 h.

MICRONODULAR CIRRHOSIS (TABLE 2)
In the micronodular group the mean $\alpha$ value was significantly increased (0.380) compared with norm-

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<td>$\alpha$ AT III</td>
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<td>$k_{\alpha}$(h$^{-1}$)</td>
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<td>$k_{\beta}$(h$^{-1}$)</td>
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Table 3 Macronodular cirrhosis (HBsAg positive) data

<table>
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<tr>
<th>No</th>
<th>AT III (U/ml)</th>
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<th>T½β(h)</th>
<th>α</th>
<th>T½α(h)</th>
<th>k½β(h⁻¹)</th>
<th>k½α(h⁻¹)</th>
<th>k₁(h⁻¹)</th>
<th>k₂(h⁻¹)</th>
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<td>20</td>
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Elementary statistics

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<th>SEM</th>
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<th>Minimum</th>
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<td>AT III (U/ml)</td>
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<td>0.2</td>
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<td>1.10</td>
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<td>β AT III</td>
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<td>4.465E-04</td>
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<td>α AT III</td>
<td>0.199</td>
<td>0.048</td>
<td>0.016</td>
<td>0.252</td>
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<td>k₁(h⁻¹)</td>
<td>0.109</td>
<td>0.003</td>
<td>0.011</td>
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<td>β half life (h)</td>
<td>52.728</td>
<td>5.432</td>
<td>1.811</td>
<td>61.449</td>
<td>44.951</td>
<td>16.498</td>
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The mean β half life of 46.8 h was significantly shorter compared with normal subjects (p < 0.005 Student's t test, p < 0.001 Wilcoxon) and also compared with the macronodular group (p < 0.005 Student's t test). The fractional catabolic rate constant (k₁,α) in this group was not significantly different from the control group.

The transcapillary efflux (k₁,h⁻¹) and influx (k₂,h⁻¹) were both significantly increased in the group with micronodular cirrhosis (0.195 h⁻¹ and 0.172 h⁻¹ respectively) (p < 0.05 Wilcoxon and p < 0.005 Wilcoxon) compared with the control group (0.072 h⁻¹ and 0.071 h⁻¹ respectively).

MACRONODULAR CIRRHOSIS (HBsAg) (TABLE 3)

In the macronodular group the mean α value was not significantly different from the control group.

The β half life was 52.7 h, which was significantly shorter compared with normal subjects (58.6 h) (p < 0.025 Student's t test and Wilcoxon).

The transcapillary influx rate constant (k₂,h⁻¹) (0.109 h⁻¹) was also significantly increased compared with normal subjects (0.071 h⁻¹) (p < 0.005 Wilcoxon).

The fractional catabolic rate constant (k₁,α) and the transcapillary efflux (k₁,h⁻¹) were not significantly different from the control group.

The relation between β plasma half life of all the patients and the AT III plasma concentration is shown in Fig. 4. The relation between the fractional catabolic rate constant (k₁,α) and the AT III plasma concentration is shown in Fig. 5. Correlation with the plasma AT III concentration was found neither with the β half life nor with the k₁,α.

A significant regression was seen between the transcapillary influx (k₂,h⁻¹) and the apparent distribution volume (Vd). γ(k₂,h⁻¹) = 1.28 × 10⁻⁸ × Vd + 0.1

Fig. 4 Relation between β half life and plasma antithrombin III values.

Fig. 5 Relation between the fractional catabolic rate constant (k₁,α) and plasma antithrombin III values.
Knot, Cate, Drijfhout, Kahlé, Tytgat

Table 4 Data for other liver diseases

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<thead>
<tr>
<th>No</th>
<th>PLC</th>
<th>AT III (U/ml)</th>
<th>$T\frac{1}{2}\beta(h)$</th>
<th>$k \alpha(h^{-1})$</th>
<th>$k \beta(h^{-1})$</th>
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<tr>
<td>22</td>
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<td>0-23244</td>
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<td>MLC</td>
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<td>54-407</td>
<td>0-44760</td>
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PLC = primary liver cell carcinoma.
MLC = macronodular liver cirrhosis, no alcoholic aetiology.
BUD = Budd-Chiari syndrome.

± 5-9, p < 0-025 for regression. Although the correlation coefficient was poor (0-435), this trend was seen in all patients taken together as well as when calculated separately for the groups mentioned.

LIVER CELL CARCINOMA (TABLE 4)
The patient with primary liver cell carcinoma had a very fast $\beta$ phase, a high fractional catabolic rate constant ($k_{1\alpha}$), high transcaval efflux and influx rate constants which were five, three, ten, and five times higher respectively than the mean values of the control group. This patient had also a very short $\beta$ half life of 23-9 h.

Discussion

The mechanisms involved in the pathogenesis of catabolism defects in liver disease may be due to impaired hepatic synthesis of coagulation factors or their increased catabolism. One of the reasons for increased catabolism is low grade intravascular coagulation in severe liver disease. There is substantial evidence for the occurrence of low grade diffuse intravascular coagulation: this includes the presence of circulating thromboplastin like factors from necrotic hepatocytes, ascitic fluid activating the circulating factors, and platelet activation by circulating endotoxins. In addition, clearance of procoagulants thus generated may also be less effective because of liver insufficiency.

Turnover studies of coagulation proteins are required to substantiate the suspected increased catabolism in the course of diffuse intravascular coagulation. Most turnover studies so far performed employing radiolabelled fibrinogen have been in patients in the final stage of their disease and in patients with acute and chronic HBsAg positive hepatitis. All investigations have reported a shortened $\beta$ half life of the radiolabelled fibrinogen and some of them have also found an increased fractional catabolic rate constant ($k_{1\alpha}$). During heparinisation the $\beta$ half life was increased sometimes to normal values, supporting the hypothesis that increased fibrinogen removal is dependent on activation of the coagulation system.

These studies have been criticised, however, because in some a single injection of radiolabelled fibrinogen was used to determine both the base line and the effect of heparin treatment on this survival when plasma radioactivity had dropped below 10% of its initial level. As a result possible contamination of the fibrinogen preparation with other proteins may have played an important role. In another study data obtained in the first two and a half days were used, when equilibration had not yet been reached.

Because of these deficits there is still no direct proof for the existence of low grade diffuse intravascular coagulation in liver cirrhosis.

In our study radiolabelled AT III was found to be similar to plasma AT III measured biologically and immunologically, including affinity for heparin measured by chromatography. Thus we suggest that the total body AT III could be reflected by turnover data obtained from a $^{125}$I-AT III preparation.

The results of the control group are compatible with the data reported by other groups. We found a mean $\beta$ plasma half life of 58-6 h, a fractional catabolic rate constant ($k_{1\alpha}$) of 0-26 h$^{-1}$, and transcaval efflux and influx rate constants ($k_{1\beta}$ and $k_{1\gamma}$) of 0-071 h$^{-1}$ and 0-072 h$^{-1}$ respectively. In the group with macronodular and macronodular cirrhosis the mean plasma AT III concentrations were 0-67 and 0-76 U/ml respectively, with an AT III antigen concentration of 196 mg/l and 272 mg/l respectively.

A significantly higher $\alpha$ value was seen in the group with macronodular cirrhosis (0-380) but not in those with macronodular cirrhosis when compared with the control subjects (0-157). This suggests that the equilibrium state in the group with macronodular cirrhosis is reached sooner. This phenomenon was also found for other radiolabelled coagulation proteins but not for radiolabelled albumin.

The mean $\beta$ half lives in the group with macronodular cirrhosis (46-8 h) and macronodular cirrhosis (52-7 h) were both significantly shorter compared with the control value.

The $\beta$ half life of the group with macronodular cirrhosis was significantly shorter when compared with the group with macronodular cirrhosis and normal subjects; this may be due to differences in the severity of liver cirrhosis reflected by significant differences in the mean serum albumin values. These results differ from those of Chan et al.
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who found only normal $\beta$ half lives in their patients, perhaps explicable by their choice of patients. Unfortunately no data on the $k_{2,1}$ are given by these investigators (see below).

We found no correlation between the $\beta$ half life and the plasma AT III level in either group; this has also been reported in two other studies.$^{11,45}$

In both groups the mean value of the fractional catabolic rate constant $k_{1,0}$ was similar to the control group. This suggests that there was no increased consumption in the central compartment. In addition, we found no correlation in either group between the fractional catabolic rate constant and plasma AT III values; this was also seen in two other studies.$^{11,45}$

The shorter $\beta$ half life with a normal fractional catabolic rate constant must be due to a change in transcapillary efflux:influx ratio.

We found significantly raised values of the transcapillary influx rate constant ($k_{2,1}$) in both groups ($0.172 \text{ h}^{-1}$ and $0.108 \text{ h}^{-1}$ respectively), whereas the mean value of the transcapillary efflux rate constant ($k_{1,2}$) was only significantly raised in the micronodular group compared with the control group, although the $k_{2,1}$ was always higher than the $k_{1,2}$.

Similar results have been found by others$^{11,45}$ not only for coagulation proteins but also for radio-labelled albumin.$^{46,47}$

It is unlikely that the high apparent $V_d$ is a result of ascites as the apparent volume sometimes increases more than the total body volume and some investigators who injected radiolabelled fibrinogen intraperitoneally recovered only 4-8% of the injected doses in the circulation.$^{44}$

Only two exceptions to this general pattern were found. One was the patient with primary liver cell carcinoma and the other was a patient with micronodular cirrhosis with an extremely low plasma AT III concentration (0.24 U/ml). In both patients a raised fractional catabolic rate constant was found suggesting consumption in the central compartment, which was substantiated by the occurrence of high concentrations of fibrinogen degradation products and clinical signs of diffuse intravascular coagulation in the patient with primary liver cell carcinoma at necropsy.

Unlike the other patients the value of the transcapillary efflux rate constant ($k_{1,2}$) was higher than the influx constant ($k_{2,1}$). Chan et al reported but did not publish this finding in severe patients (TK Chan, personal communication, 1983).

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