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RESEARCH ARTICLE

Albumin and fibrinogen synthesis rates in advanced chronic liver disease

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Abstract

Synthesis of plasma proteins is an important function of the liver that has sparsely been investigated by modern techniques in patients with advanced chronic liver disease (CLD). Twenty-eight well-characterized patients with CLD under evaluation for liver transplantation were included. Albumin and fibrinogen synthesis rates were measured by the flooding dose technique using stable isotope-labeled phenylalanine. Transcapillary escape rate of albumin and plasma volume were assessed by radioiodinated human serum albumin. The absolute albumin synthesis rates were low (65 mg/kg/day, range: 32–203) and were associated with impaired liver function, as reflected by the risk-scores Child-Pugh ($P = 0.025$) and model for end-stage liver disease ($rs = -0.62$, $P = 0.0005$). The fibrinogen synthesis rate (12.8 mg/kg/day, range: 2.4–52.9) was also negatively associated with liver function. The synthesis rates of albumin and fibrinogen were positively correlated. Plasma volume was high (51 ± 9 mL/kg body wt), which contributed to an almost normal intravascular albumin mass despite low plasma concentration. Autoimmune inflammatory etiologies to CLD were associated with higher fibrinogen synthesis. De novo synthesis rates of albumin and fibrinogen in advanced chronic liver failure were negatively correlated to prognostic scores of liver disease. Albumin synthesis rate was low and associated with both liver failure and autoimmune inflammation, whereas fibrinogen synthesis was often normal and positively associated with chronic inflammation. This is different from acute inflammatory states in which both albumin and fibrinogen synthesis rates are high.

NEW & NOTEWORTHY Albumin and fibrinogen synthesis were positively correlated, but the high variation indicates that these are probably influenced by different mechanisms. There might be a limited metabolic reserve for the liver to increase both albumin and fibrinogen synthesis in response to longstanding inflammation in CLD and fibrinogen seems to be prioritized.

Child-Pugh; chronic inflammation; inflammatory liver disease; MELD; protein turnover

INTRODUCTION

Synthesis of plasma proteins, such as albumin and fibrinogen, is one of many important liver functions. Albumin is the most abundant plasma protein, with a turnover rate of ~11 g per day in healthy subjects. Albumin has many important physiological functions including regulation of plasma oncotic pressure, transport of fatty acids, and other non-water-soluble compounds. Albumin also has antioxidant and scavenger functions. Low plasma albumin concentration has a prognostic significance in liver failure, predicts death in the general population (1), and predicts complications after major surgery (2–4). Plasma albumin concentration only poorly reflects albumin synthesis rate (5–7).

Fibrinogen is synthesized in the liver with a turnover rate of ~2 g per day in healthy subjects (8). Fibrinogen is important in coagulation where it is enzymatically converted to fibrin in response to tissue or vascular injury. Serum fibrinogen concentration is often reduced in liver failure, but portal hypertension probably reflects bleeding risk better than serum fibrinogen concentration (9).

Knowledge and documentation on the effect of liver failure on the synthesis rates of liver proteins is incomplete. Only two small case series in the 1990s measured synthesis of albumin or fibrinogen in liver failure in patients with moderately severe viral liver disease (10, 11), and another one was from a recent study that included patients with decompensated alcohol-related liver disease (12).

In this study, we explore how synthesis rates of albumin and fibrinogen were influenced by severity of chronic liver disease (CLD), as assessed by the Child-Pugh score (13) and the model for end-stage liver disease (MELD) score (14), and the separate components thereof. We explored which factors are associated with the absolute synthesis rates of albumin and fibrinogen in patients with advanced chronic liver disease.

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MATERIALS AND METHODS

This prospective exploratory study in patients with advanced CLD was performed at the Karolinska University Hospital in Huddinge, Sweden between September 2015 and May 2018. Karolinska University Hospital is one of the two referral centers for severe liver disease and liver transplantation in Sweden. Patients were eligible for this study if admitted to the Department of Upper Gastrointestinal Diseases for assessment of suitability for liver transplantation due to CLD. Before a 2- to 4-day outpatient assessment for possible liver transplantation, patients received written study information from a study nurse. They were then approached by one of the investigators for further information and for agreement on a convenient study day within the outpatient assessment period. Written informed consent was obtained on the study day.

Inclusion criteria were written informed consent and Child-Pugh score of 7 or more (B or C) as assessed by referral documentation. Patients younger than 40 yr were excluded to avoid treatment with potassium iodine in conjunction with ^{125}iodine exposure due to the use of labeled albumin in the study based on the recommendation by the World Health Organization (WHO) (15). Other exclusion criteria were pregnancy or breastfeeding, paracentesis, or gastrointestinal bleeding in the previous 7 days, and participation in other studies involving radiation or stable isotopes in the previous 30 days.

The study was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice. The protocol was approved by the Regional Ethics Review Board in Stockholm (Dnr 2015/1048-31/2) and by the Swedish Medical Product Agency (EudraCT 2015–002567-42). The study protocol was published before the start of the study at EudraCt (Clinical Trials Register, EudraCT; No. 2015–002567-42). All patients gave written informed consent after being informed orally and in writing about the investigational procedure and the possible risks involved.

Study Procedure

The study procedure started with a standardized meal (nutrition drink: 200 mL Fortimel compact, 240 kcal/100 mL, 9.6 g protein/100 mL) after a monitored fasting period of at least 4 h. Urinary HCG was tested in all females between ages 40 and 55 yr to exclude pregnancy. Blood samples for plasma albumin and fibrinogen concentrations and complete blood count were drawn after insertion of two peripheral venous lines, followed by a resting period of 30 min in the semirecumbent position.

Measurements of albumin and fibrinogen synthesis rates were then commenced with the patient remaining in the same resting position for 90 min.

Phenylalanine at a concentration of 20 mg/mL and with 10 mol percent excess of L-[$^2H_5$]phenylalanine was infused for 10 min at a dose of 0.45 g/kg body wt. Plasma was sampled immediately before and 5, 15, 30, 50, 60, 70, and 90 min after the start of the infusion to determine the ratio of L-[$^2H_5$]phenylalanine to phenylalanine as an index of the precursor pool enrichment (16). Analysis was performed on a quadrupole gas chromatography-mass spectrometer (Agilent, Kista, Sweden).

Albumin and fibrinogen were first extracted from the plasma samples taken at 50, 60, 70, and 90 min. Then incorporation of L-[$^2H_5$]phenylalanine into albumin and fibrinogen was measured as described in detail before (17).

The fractional synthesis rate (FSR) is the fraction of the intravascular pool that is synthesized every day and was calculated as previously described (7), and the absolute synthesis rate (ASR) was calculated as the product of FSR and the total plasma pool of albumin or fibrinogen obtained from plasma volume and plasma albumin or fibrinogen.

Measurement of transcapillary escape rate (TER) and plasma volume was performed using radiolabeled albumin (SERALB-125, CIS Bio International, Gif-sur-Yvette Cedex, France). A dose of 200 kBq in <0.1 g of albumin was injected intravenously 20 min after the start of the FSR measurement procedure as described earlier, followed by blood sampling on nine occasions over 70 min, for analysis of plasma albumin concentration and radioactivity. The radioactivity was measured by scintillation counting (Wallac Compu-gamma CS 1282, energy window 20–82 keV). TER was derived from the slope of the logarithm of counts per minute versus time plot. Radioactivity at the time of injection was obtained from back extrapolation of the slope of the same plot. Plasma volume was derived by dividing the radioactive dose administered by the back extrapolated radioactivity at the time of injection (18). Furthermore, anthropometric plasma volume was calculated according to Nadler et al. (19). Intravascular albumin and fibrinogen mass were calculated as the product of plasma albumin and plasma volume.

During the investigation, vital signs (blood pressure, heart rate, and saturation) were recorded every 15 min. Nutrition status assessment was done by a dietician during the pretransplantation evaluation and included subjective global assessment (SGA A-C), where A is well nourished, B is moderately malnourished, and C is severely malnourished (20, 21). Anthropometric measurements including triceps skinfold thickness (TSF), midarm circumference (MAC), and midarm muscle circumference (MAMC = MAC-3.14*TSF) were also recorded as previously described (22). Child-Pugh and MELD scores, presence of portal hypertension, hepatic encephalopathy, splenomegaly, and esophageal varices were recorded by a transplant hepatologist as part of the liver transplantation evaluation protocol. Autoimmune etiologies (autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis) were considered inflammatory CLD.

Reference values for albumin and fibrinogen synthesis rates were obtained from a group of 16 healthy volunteers from a previous study by our research group (16). Median age of the volunteers was 40 yr (range: 21–67), seven were females, and the mean body mass index was 26.2 ± 3.8 kg/m^2. The same study protocol was used for this study, with a standardized meal before the investigation, and synthesis of albumin and fibrinogen were measured in our laboratory by an identical flooding dose of L-[$^2H_5$]phenylalanine and laboratory methods. In that study, repeated experiments using different tracers were investigated, but the first measurement was used as the reference value.

Statistics

Data are presented as mean (± standard deviation) or median (range) as appropriate by Shapiro–Wilk's test of

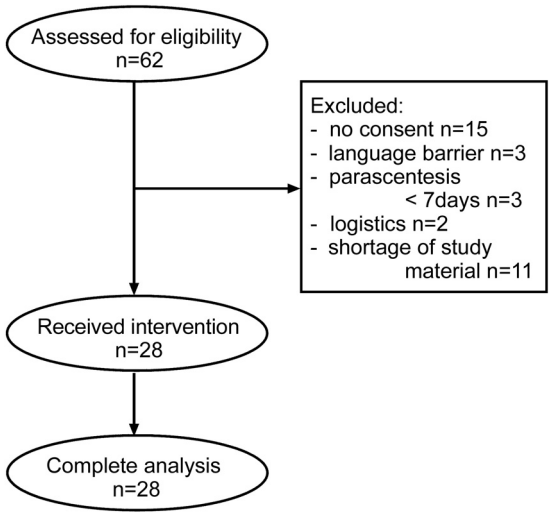

Figure 1. CONSORT flow chart.

normality. Parametric data were analyzed by *t* test between groups, and the Welch correction was used to account for unequal variances between groups, and Pearson correlation (*r*). Nonparametric data were analyzed by the Mann–Whitney test and Spearman rank correlation (r_S.) Absolute synthesis rates of albumin and fibrinogen were correlated with Child-Pugh score, MELD components, nutrition status, plasma C-reactive protein (CRP), and portal hypertension. The nonnormality of the data prevented multiple regression analysis. Demographic data such as age, height, weight, BMI, sex, routine laboratory parameters, and liver diagnoses are presented as numbers, means, or medians, as applicable.

Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software, Inc., San Diego, CA). With 28 subjects there is a power of 80% to detect a correlation of 0.5 between two parameters by a two-sided *t* test and a significance level of 5%. *P* values <0.05 were considered statistically significant.

RESULTS

Patients

The investigation included 6 female and 22 male patients (Fig. 1) aged 60 ± 8 yr, with a body weight of 86 ± 18 kg, and a body mass index of 28 ± 4 kg/m^2. Nineteen patients had Child-Pugh score B and 7 had Child-Pugh C, whereas 2 patients with Child-Pugh B at referral that later turned out to have Child-Pugh A at the time of investigation. Two of the patients with Child-Pugh C had alcohol cirrhosis, and one had a combination of alcohol-related disease hepatitis C and hepatocellular carcinoma. The main cause of the pretransplantation investigation was hepatocellular carcinoma in 10 patients and alcoholic liver cirrhosis in 8 patients (Table 1). Comorbidities were compromised of renal function with serum creatinine exceeding 100 μmol/L (>1.13 mg/dL) (n = 8), arterial hypertension (n = 6), insulin-dependent diabetes mellitus (n = 4), noninsulin-dependent diabetes mellitus (n = 3), cerebrovascular lesion (n = 2), and one each of ulcerative colitis, Crohn's disease, obesity, asthma, and chronic obstructive pulmonary disease.

Table 1. *Patients under investigation for possible liver transplantation, individual diagnosis*

Etiology with Existing Associations	Number of Patients	Etiology with Existing Associations	Number of Patients
Alcohol	8	PSC	2
Alcohol + HCC	2	AIH	2
Alcohol + HCC + HCV	2	AAT	1
HCC + HCV	2	AAT + NAFLD	1
HCC + cryptogenic cirrhosis	1	NAFLD	2
HCC + NAFLD	2	NAFLD + HPS	1
HCC + PSC	1	PBC	1

AAT α-1, α-1-antitrypsine deficiency; AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; HCV, hepatitis C; HPS, hepatopulmonary syndrome; NAFLD, non-alcoholic fatty liver disease; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis. n = 28 patients.

Albumin Synthesis and Distribution

Albumin kinetic parameters are presented in Table 2. Plasma albumin was 26.5 ± 4.5 g/L and was lower in Child-Pugh C than in Child-Pugh B. Plasma volume estimated by radioiodine-labeled albumin was 4.3 ± 0.7 L corresponding to 51 ± 9 mL/kg body wt and intravascular albumin mass was estimated to be 113 ± 29 g. Plasma volume calculated from sex, body weight, and length was 3.6 ± 0.6 L corresponding to 42 ± 5 mL/kg body wt (19). Albumin absolute synthesis rate was higher in patients with Child-Pugh B (66 mg/kg/day) than in patients with Child-Pugh C (44 mg/kg/day), P = 0.026. Both fractional and absolute albumin synthesis rates were negatively correlated to the Child-Pugh score (Fig. 2, *A* and *C*) and to the MELD score (Fig. 2, *B* and *D*). A MELD score of ≥15 and a Child-Pugh of ≥9 were both consistently associated with an absolute synthesis rate of albumin below the 95% confidence interval for that of the control group of healthy volunteers, 169 mg/kg/day (95% CI 153–184, n = 16) (17).

Fibrinogen Synthesis Rate

Fibrinogen kinetic parameters are presented in Table 3. Plasma fibrinogen was lower in Child-Pugh C than in Child-Pugh B (P = 0.0010). Patients with Child-Pugh C also had a lower intravascular fibrinogen mass (P = 0.0054). The reference interval for plasma fibrinogen in healthy subjects is 2.0–4.2 g/L in our hospital. Absolute, but not fractional, synthesis rate of fibrinogen was negatively correlated to Child-Pugh and MELD scores (Fig. 3). There was a positive correlation (r_S = 0.717, P < 0.0001) between albumin and fibrinogen absolute synthesis rates (Fig. 4). None of the MELD score or Child-Pugh score were associated with an absolute synthesis rate of fibrinogen outside the 95% confidence interval for that of healthy volunteers 14 mg/kg/day (95% CI 11–16, n = 16) (17).

Factors Associated with Protein Synthesis Rates in CLD

Albumin ASR was low in the patients compared with volunteers (Fig. 2) and positively correlated with plasma

Table 2. *Albumin pharmacokinetic parameters' relation to Child-Pugh and MELD scores, respectively, in 28 patients with chronic liver failure*

		Child-Pugh			MELD	
	All	*B*, *n* = 19	*C*, *n* = 7	p *B vs. C*	*r* or r_S	*P*
Plasma albumin, g/L	26.5 ± 4.5	27.3 ± 4.3	23.1 ± 3.8	0.033	−0.356	0.063
Plasma volume, L	4.3 ± 0.7	4.2 ± 0.7	4.6 ± 0.5	0.125	0.215	0.273
Intravascular albumin mass, g	113 ± 29	115 ± 33	106 ± 22	0.421	−0.117	0.554
Fractional synthesis rate, %/day	4.6 (2.0–17.9)	5.4 (2.0–17.9)	3.9 (2.7–4.5)	0.0215	−0.554	0.0022
Absolute synthesis rate, mg/kg/day	65 (30–203)	66 (32–203)	44 (30–66)	0.0255	−0.617	0.0005
Transcapillary escape rate, %/h	6.2 ± 2.1	6.2 ± 2.2	5.5 ± 1.9	0.418	−0.121	0.541
Albumin mass flow, g/h	6.9 ± 2.8	7.0 ± 2.9	5.7 ± 2.1	0.239	−0.246	0.208

Parametric data are presented as means ± SD and analyzed by *t* test between *groups B* and *C*, and Pearson correlation *r* to MELD score, nonparametric data are given as median (range) and analyzed by Mann–Whitney test between Child-Pugh *B* and *C* and Spearman rank correlation r_s and corresponding *P* value. *n* = number of patients. MELD, model for end-stage liver disease.

fibrinogen and plasma albumin (see Supplemental Table S1). Albumin ASR was also negatively correlated with MELD score, Child-Pugh score, INR (international normalized ratio), and blood bilirubin, with the overall strongest correlation to MELD ($r_S = -0.62$, $P = 0.0004$, Supplemental Table S1).

Fibrinogen ASR varied greatly (2.4 to 53 mg/kg/day) and was positively correlated to plasma fibrinogen ($r_s = 0.708$, $P < 0.0001$) and CRP (Supplemental Table S1) but negatively correlated to BMI ($r_s = -0.6413$, $P = 0.0002$), INR, MELD, and Child-Pugh. Eleven patients had ascites (mild: 7, moderate: 2, severe: 2), and three patients had Westhaven grade 1 hepatic encephalopathy (HE). Signs of portal hypertension were common, such as splenomegaly ($n = 15$), esophageal varices ($n = 21$), or thrombocyte count below 145 10^9/L ($n = 22$). All associations between protein synthesis and these dichotomous variables (ascites, HE, portal hypertension) had *P* values below 0.28. Subjective global assessment class A (well nourished) corresponded to fibrinogen ASR 9.1 mg/kg/day (interquartile range: 6.1–16.7, $n = 17$), but class B (moderately malnourished) and C (severely malnourished) had a significantly higher fibrinogen ASR of 20.5 mg/kg/day (interquartile range: 9.1–39.5, $n = 11$, $P = 0.0228$, see Supplemental Table S2).

DISCUSSION

Albumin and Fibrinogen Synthesis Rates and Distribution

The albumin synthesis rate was low in the patients with advanced CLD compared with healthy volunteers ($n = 16$) (17). Albumin synthesis was negatively correlated to Child-Pugh and MELD scores and to some components thereof, suggesting that the albumin synthetic capacity of the liver is proportional to the degree of liver failure.

Plasma albumin concentration was low, but because measured plasma volumes were 20% higher than anthropometrically calculated values, i.e., an increased volume of distribution, the total intravascular albumin mass was only slightly lower than normal values. This implies a slower turnover rate of albumin in liver-insufficient patients.

Fibrinogen synthesis was distributed within the same range as healthy volunteers but also showed a negative correlation to MELD and Child-Pugh scores.

Similar lower synthesis rates for albumin and fibrinogen in liver failure have been described in smaller groups of selected patients with viral hepatitis or decompensated alcoholic liver disease (10–12). However, our study included

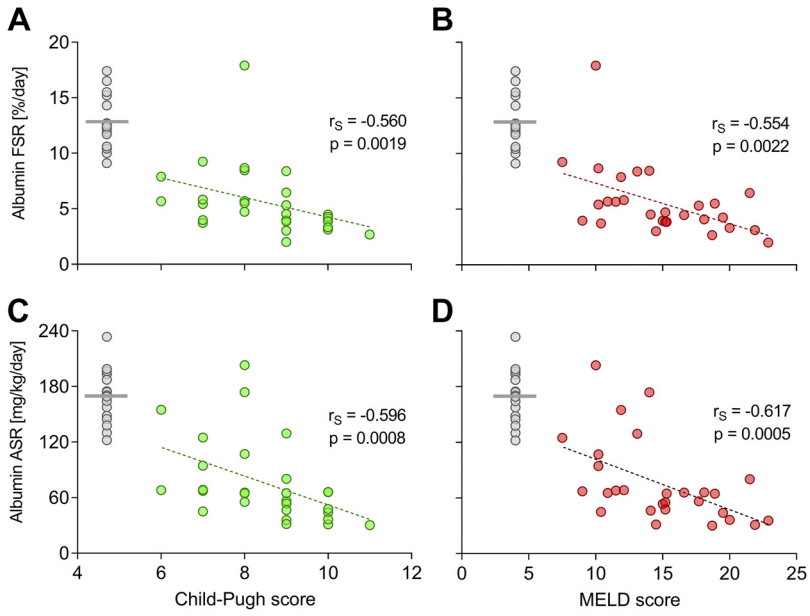

Figure 2. Child-Pugh score (*A* and *C*) and MELD score (*B* and *D*) vs. albumin fractional and absolute synthesis rates in 28 patients with chronic liver disease. Gray symbols denote 16 healthy volunteers analyzed by a similar study protocol (16). ASR, absolute synthesis rate; FSR, fractional synthesis rate; MELD, model for end-stage liver disease; r_s, Spearman rank correlation.

Table 3. *Fibrinogen pharmacokinetic parameters correlated to Child-Pugh and MELD scores, respectively, on study day in 28 patients with chronic liver failure*

	Child-Pugh			MELD	
	***B*, *n* = 19**	***C*, *n* = 7**	***P***	***r* or r_S**	***P***
Plasma fibrinogen, g/L	2.4 (1.6–6.0)	1.2 (0.9–2.2)	0.0010	−0.637	0.0003
Intravascular fibrinogen mass, g	10.7 ± 3.7	6.7 ± 2.5	0.0054	−0.532	0.004
Fractional synthesis rate, %/day	13.4 ± 6.2	11.3 ± 4.4	0.375	−0.170	0.388
Absolute synthesis rate, mg/kg/day	15.4 (2.4–40.9)	7.0 (3.8–28.3)	0.031	−0.479	0.0099

Parametric data are presented as means ± SD and analyzed *t* test between *groups B* and *C*, and Pearson correlation to MELD score. Nonparametric data are given as median (range) and analyzed by Mann–Whitney between Child-Pugh *B* and *C* and Spearman rank correlation r_S. *n* = number of patients. MELD, model for end-stage liver disease.

more patients with a wider range of liver failure, which allowed us to better study correlations and subgroups.

The significant association between albumin and fibrinogen syntheses, illustrated in Fig. 4, seems to be formed by distinct different patient groups, i.e., those with a generally poor protein synthesis and those with an inflammatory disease that presents with relatively high synthesis of both proteins. The large plasma volume, especially in patients with autoimmune inflammatory liver disease, and high fibrinogen synthesis, separates these patients from the healthy volunteers when absolute synthesis rates are presented as in Fig. 4.

Autoimmune Inflammation

Patients with autoimmune inflammatory CLD had elevated CRP and high fibrinogen synthesis rate (Table 4 and Supplemental Table S1), whereas there was no difference in albumin concentrations and albumin absolute synthesis rates.

Fibrinogen is an acute-phase protein and both the plasma concentration and fibrinogen absolute synthesis rates were positively correlated to CRP in this group of patients, indicating that inflammation is the cause of the high fibrinogen synthesis.

Transcapillary escape rate of albumin is a marker of capillary leakage, which is elevated in inflammation and after surgery. In contrast to earlier studies in patients after major abdominal surgery (18) or liver transplantation (23), we found no correlation between the plasma concentration of CRP and albumin or albumin synthesis rate.

High plasma fibrinogen and high fibrinogen synthesis rates were associated with poor nutritional scores and low body mass index. These findings can be indicative of a chronic inflammation leading to both loss of lean mass and increased fibrinogen synthesis.

Our group has previously demonstrated that albumin synthesis is increased in acute inflammation (5, 7, 18, 24). There might be a limited metabolic reserve for the liver to increase both albumin and fibrinogen synthesis in response to long-standing inflammation in CLD and fibrinogen seems to be prioritized. This has also been shown following major liver resection, where fibrinogen synthesis increased dramatically, and albumin synthesis did not change in comparison with pancreas resection where both increased (25). This supports our hypothesis that a limited liver capacity, due to the major resection, limits the metabolic reserve to increase the synthesis of both proteins when needed to fight a major stress with inflammation.

The strength of this study is the well-characterized study population as a modern case mix of advanced chronic liver disease and the use of both stable isotope-labeled phenylalanine and radioiodinated albumin to

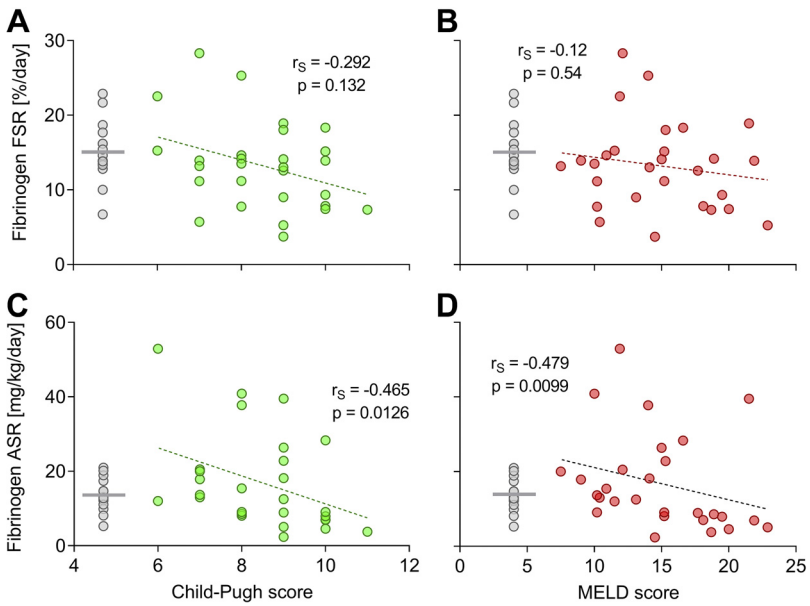

Figure 3. Child-Pugh score (*A* and *C*) and MELD score (*B* and *D*) vs. fibrinogen fractional and absolute synthesis rates in 28 patients with chronic liver failure. Gray symbols denote 16 healthy volunteers analyzed by an identical study protocol (17). ASR, absolute synthesis rate; FSR, fractional synthesis rate; MELD, model for end-stage liver disease; r_S, Spearman rank correlation.

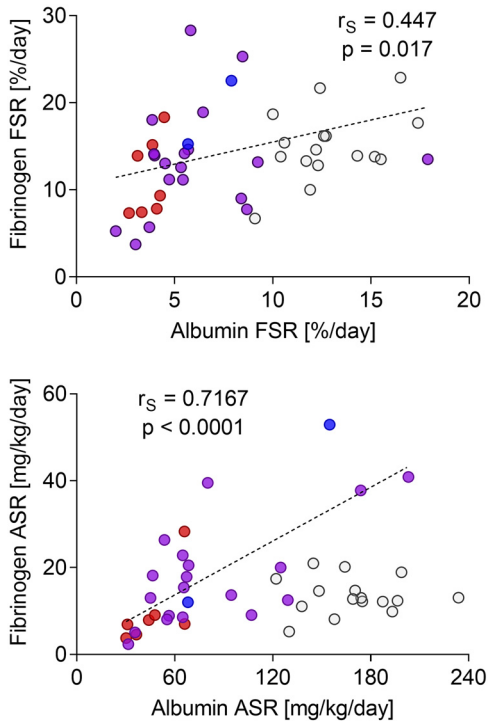

Figure 4. Correlation between albumin and fibrinogen FSR and ASR, respectively, in 28 patients with advanced chronic liver disease. Blue symbols Child-Pugh A, violet symbols Child-Pugh B, red symbols Child-Pugh C, and light gray symbols represent 16 healthy volunteers (17). ASR, absolute synthesis rate; FSR, fractional synthesis rate; r_s, Spearman rank correlation.

calculate absolute synthesis rates of albumin and fibrinogen. Measurement of plasma protein synthesis by the direct incorporation of a stable isotope-labeled amino acid as opposed to the disappearance of radioiodinated serum albumin gives a 90-min snapshot of the direct synthesis rate rather than an estimated average over several days or weeks. All three factors contribute to the accuracy of our results.

Our study also has some limitations. The first is the small meal before the measurement in our protocol that was given to standardize the patient's metabolic status. It might have increased the measured synthesis rates (26) if the feeding effect reported in healthy volunteers prevails in states of liver failure. However, a similar small meal was also served in our control experiment (16). The inclusion of a historical reference group is also a limitation of the present study. Another limitation is the rather limited number of patients with Child-Pugh C due to the exclusion of patients who had undergone paracentesis.

In conclusion, we showed that albumin synthesis rate was low and associated with both liver failure and autoimmune inflammation, whereas fibrinogen synthesis was often normal and positively associated with chronic inflammation. Albumin and fibrinogen synthesis were positively correlated, but the high variation indicates that these are probably influenced by different mechanisms.

Table 4. *Anthropometric and pharmacokinetic parameters in patients with chronic liver failure associated with inflammation: a post hoc analysis*

	Inflammatory Disease, $n = 6$	Other Disease, $n = 22$	P
Female	2	4	
MELD score	15.5 ± 3.3	14.7 ± 4.5	0.62
Child-Pugh score	8.5 ± 1.4	8.5 ± 1.3	> 0.99
Body weight, kg	68.7 ± 8.3	90.5 ± 17.8	0.0005
Body mass index, kg/m^2	23.5 ± 2.1	29.0 ± 4.2	0.0003
Plasma C reactive protein, mg/L	18.5 (7–48)	4.0 (1–20)	0.0019
Blood white blood cell count, 10^9/L	2.8 (2.0–11.3)	6.4 (2.8–16.2)	0.21
Plasma volume, mL/kg body wt	64 (53–72)	50 (37–58)	0.0009
Plasma fibrinogen, g/L	2.8 (2.1–3.8)	2.0 (0.9–6.0)	0.037
Intravascular fibrinogen mass, g	12.7 (9.7–14.1)	8.3 (4.3–20.3)	0.016
Fibrinogen absolute synthesis rate, mg/kg/day	33 (18–53)	9.1 (2.4–41)	0.0003
Plasma albumin, g/L	24.2 ± 5.3	27.1 ± 4.2	0.25
Albumin absolute synthesis rate, mg/kg/day	73 (47–174)	65 (30–203)	0.26

Data are presented as mean (± SD) or median (range) as appropriate and analyzed by t test or Mann–Whitney test between groups. n = number of patients. MELD, model for end-stage liver disease.

DATA AVAILABILITY

Data will be made available upon reasonable request.

SUPPLEMENTAL DATA

Supplemental Tables S1 and S2: https://doi.org/10.5281/zenodo.8187750.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.A., J.W., O.R., and A.N. conceived and designed research; M.A., A.S., S.W., and A.N. performed experiments; M.A., J.W., O.R., and A.N. analyzed data; M.A., A.S., S.W., J.W., O.R., and A.N. interpreted results of experiments; A.N. prepared figures; M.A. and A.N. drafted manuscript; M.A., A.S., S.W., J.W., O.R., and A.N. edited and revised manuscript; M.A., A.S., S.W., J.W., O.R., and A.N. approved final version of manuscript.

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