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ORIGINAL PAPER

Clinical Significance of Haemostatic Tests in Chronic Liver Disease

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Objective: To determine different haemostatic tests in patients with various degrees of liver parenchymal damage and to rule out their role in assessing parenchymal hepatocyte dysfunction. **Methods**: Seventy-five patients with chronic liver disease were included and due to their degree of liver damage categorized into three groups: group one patients with chronic viral hepatitis and early stage of fibrosis (n=30), group two patients with compensated cirrhosis (n=17) and group three patients with decompensated liver cirrhosis (n=28). The following haemostatic tests were measured: activated partial thromboplastin time, prothrombin time, plasma fibrinogen, antithrombin III and protein C and plasma D-dimer. **Results**: Antithrombin III levels showed significant reduction in compensated (83.86 ± 19.49%) and decompensated cirrhosis (52.64 ± 14.31%; p<0.001), while protein C activity exhibited significant decrease in all the patients group, including patients with chronic viral hepatitis (90.58 ± 11.03, 74.65± 19.56, 41.11 ± 18.35%; p<0.001) in comparison with controls. Correlation between antithrombin III (Pearson ro= -,931, p<0,01) and protein C (Pearson ro= -,789, p<0,01) and clinical degree of chronic liver disease were found. D-dimer levels were significantly increased in decompensated cirrhosis (832.26 ± 537.19 μg/L; p<0.001) and no significant difference was found in group two and three when compared with healthy controls. **Conclusions**: In advanced chronic liver disease anticoagulant activitiy may reflect hepatocellular dysfunction. Protein C activity may be used as a senstive marker of hepatocellular damage even in those patients with mild liver affection whereas D-dimer levels may be considered as an important sign of decompensation in cirrhotic patients. Further studies are necessary to approve whether these parameters could be used as clinical routine markers of hepatocyte function in chronic liver disease. Keywords: chronic liver disease, chronic hepatitis B and C, haemostatic tests, D-dimer.

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1. INTRODUCTION

The liver plays a central role in blood coagulation proces because it is the site of synthesis of most of the coagulation factors and their inhibitors (1, 2) . Chronic liver disease is commonly associated with complex haemostatic defects that include impaired synthesis of clotting factors (3, 4, 5, 6) and coagulation inhibitors (7, 8, 9), abnormalities of fibrinolytic activitiy (10), disseminated intravascular coagulation and platelet defects (11). Previous studies have shown diminished circulating levels of natural anticoagulants in those with chronic liver disease (12) as well as acute liver failure (13) as a result of impaired liver synthetic function.

These earlier studies were not well correlated with histological and clinical findings of chronic liver disease and therefore the clinical significance of haemostatic disturbances due to different stages of liver disease is still unclear.

The aim of the study was to evaluate various haemostatic parameters in patients with well defined histological and clinical stages of parenchymal damage ranging from mild liver affection through to patients with advanced liver impairment and clinical signs of decompensation and to elucidate their possible role as markers of hepatocyte damage in clinical practice.

2. MATERIALS AND METHODS

2.1. Study Patients

From july 2007 to november 2009, we studied seventy five consecutive patients referred to the Department of Gastroenterology and Hepatology of the Clinical Center Universitiy of Sarajevo for various types of chronic liver disease. The basic epidemiological and laboratory parameters of all patients are summarized in Table 1.

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethical Committee of the Medical Centre University of Sarajevo. Informed consent was taken from all patients who

enrolled in the study.

All patients with chronic hepatitis B and C had undergone liver biopsy except when previous histological diagnosis of cirrhosis had been made. All participants had screening abdominal ultrasonography at the time of recruitment into the study and proximal enodscopy was performed.

The patient group was divided into three groups. In the first group (n=30) patients with diagnosed chronic viral hepatitis B and C and histological findings of mild/moderate fibrosis (Ishak fibrosis score 0-3) were included. The diagnosis of chronic viral hepatitis was based on biochemical tests, positive RNA and DNA PCR assays and confirmed by liver biopsy. Histological changes of chronic hepatitis were evaluated according to the classification system proposed by Ishak and colleagues (14) .

Group two (n=17) consisted of patients with compensated liver cirrhosis. The diagnosis of liver cirrhosis was established histologically (Ishak fibrosis score 4 and 5) together with ultrasonographic evidence of cirrhosis and no signs of decompensated disease (no presence of ascites, no evidence of oesophageal varices on endoscopy).

The third group consisted of patients with decompensated liver cirrhosis (n=28) defined by typical clinical picture together with sonographic features consistent with cirrhosis and evidence of ascites as well as oesophageal varices on endoscopy.

	Group 1	Group 2	Group 3	Total
Chronic hepatitis B	9	7	10	26
Chronic hepatitis C	21	9	5	35
Alcohol consumption			8	8
Cryptogenic			4	4
Autoimmune hepatitis		1	1	2

Table 1. Aetiology of chronic liver disease.

The aetiology of chronic liver disease of the overall study group is summarized in Table 1.

Haemostatic screening tests were obtained in all patients on day of admission to our department. Exclusion criteria were the following: history of deep venous thrombosis and current anticoagulation therapy, hepatocellular carcinoma or other known malignancy, other chronic liver disease, hepatitis B and C virus coinfection.

2.2. Control group

A control group consisted of 30 healthy individulas with normal results of physical examination and laboratory blood findings were selected from the general public.Their basic epidemiological and laboratory parameters are summarized in Table 2.

	Chronic hepatitis B/C Group 1	Compensated Cirrhosis Group 2	Decompensated cirrhosis Group 3	Control	p
n	30	17	28	30	
Sex (M/F)	15/15	10/7	20/8	17/13	p=0,4135
Age (years)	43.4 ± 11.68	46.06 ± 9.99	54.64 ± 11.21	40.17± 12.29	p<0.001
Platelet count(x10^3/l)	214.37 ± 63.67	180.79 ± 63.67	78.37 ± 63.67	252.78 ± 55.12	p<0.001
ALT (IU/l)	143.82 ± 73.38	102.33 ± 63.19	59.75 ± 83.19	24.04 ± 8.82	p<0.001
AST (IU/l)	74.70 ± 30.44	65.70 ± 66.14	55.58 ± 78.34	23.63 ± 8.29	p=0,002
GGT (IU/l)	69.41 ± 48.35	53.22 ± 42.61	83.22 ± 58.61	27.89 ± 9.90	p<0.001
Albumin (g/l)	41.80 ± 3.22	39.94 ± 2.75	24.32 ± 2.99	41.90 ± 2.72	p<0.001

Table 2. Epidemiological and biochemical characteristics of healthy controls and patients with chronic liver disease. Quantitative values are expressed as mean (SD); ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT gamma-glutamyl-transpeptidase;

2.3. Laboratory Assays

Blood samples were collected by venipuncture directly into vacuum tubes containing trisodium citrate. The blood samples tube were centrifuged at 2.000 x g for 15 min at room temperature. The assay were performed on fresh plasma or on aliquots which were immedately stored at -70^{0}C until analysis was performed. Blood samples were obtained from each patient on day of admission to our department. Coagulation screening tests included: activated partial thromboplastin time (aPTT) and prothrombin time expressed as international normalized ratio (INR) were performed by the conventional methods. Plasma fibrinogen was measured by the turbidometric method of Clauss (Dade Thrombin Reagent) (15). Natural anticoagulants were assayed using commercial reagent kits (Dade Behring, Marburg, Germany) according to the manufacturer's instructions: Activities of AT III were determined by colorometric assay (Berichrom AT III), and PC activity by kinetic testing (Berichrom C). Plasma D-dimer was measured by a latex-enhanced, immunoturbidimetric test using a commercially available kit (Dade Behring, Marburg, Germany).

2.4. Statistical analysis

All data are presented as mean ± standard deviation. Statistical analysis was performed using the Student t-test to compare the means of independent groups. Logarithmic transformation was applied to the group of data that did not show normal distribution to reduce variances before applying t-test using the new tranasformed values. For one-way analysis of variance ANOVA test was used to evaluate difference between different groups. Correlations coefficient was evaluated by the Pearson's test. A two tailed p-value below 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the statistical package SPSS 19.0.

3. RESULTS

3.1. Patient Characteristics

Epidemiological and biochemical characteristics of healthy controls (n=30) and patients with chronic liver disease (n=75) are presented in Table 2. The age at the time of the study was significantly higher among patients with decompensated liver disease, whereas gender distribution was not significantly different across all groups. The mean serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl-transpeptidase (GGT) were significantly different across study groups. Mean platelet count and albumin level were significantlay lower among patients with decompensated cirrhosis.

3.2. Coagulation screening tests

The mean fibrinogen levels showed

	Group 1 Chronic hepatitis B/C	Group 2 Compensated cirrhosis	Group 3 Decompensated cirrhosis	Control
Fibrinogen (g/l)	3.47 ± 0.44	3.24 ± 0.52	2.18 ± 0.70 *p<0.001 **p<0.001 #p<0.001	3.36 ±0.59
APTT(s)	31.01 ± 3.19	33.74 ± 3.25 *p<0.001 **p<0.05	46.05 ± 5.54 *p<0.001 **p<0.001 #p<0.001	30.80± 2.11
INR (%)	1.04 ± 0.10	1.14 ± 0.09 *p<0.005 **p=0.001	2.18 ± 0.54 *p<0.001 **p<0.001 #p<0.001	1.03 ± 0.12
AT III (%)	98.97±9.51	83.86 ± 19.49 *p<0.001 **p<0.001	52.64 ± 14.31 *p<0.001 **p<0.001 #p<0.001	99.81 ± 14.65
PC (%)	90.58 ± 11.03 *p<0.001	74.65± 19.56 *p<0.001 **p<0.001	41.11 ± 18.35 *p<0.001 **p<0.001 #p<0.001	111.59 ± 10.94
D-dimer (µg/L)	100.63 ± 29.16	104.35 ± 31.12	832.26 ± 537.19 *p<0.001 **p<0.001 #p<0.001	98.07 ± 31.03

Table 3. Results and comparison of haemostatic assays in chronic liver disease patients . Quantitative values are expressed as mean ± standard deviation, APTT: activated partial thromboplastin time, INR: international normalized ratio, AT:antithrombin, PC: protein C *significant difference in comparison with controls **significant difference in comparison with group 1

significant reduction in patients with advanced liver disease and signs of decompensation (2.18 ± 0.70 g/l) in comparison with normal controls (3.36 ±0.59 g/l) (p<0.001). No fluctuation of fibrinogen levels were achieved in patients with chronic hepatitis B and C infection and mild/moderate stage of fibrosis (3.47 ± 0.44 g/l) as well as in patients with cirrhosis (3.24 ± 0.52 g/l) (p=0.42, p=0.49).

Prolongation of INR was noted in patients with compensated cirrhosis (1.14 ± 0.09 %) and patients with decompensated cirrhosis (2.18 ± 0.54%) when compared with healthy controls (1.03 ± 0.12%) (p<0.005, p<0.001).

APTT levels showed remarkable alterations in patient group 2 (33.74 ± 3.25 s) and patient group 3 (33.74 ± 3.25s) in comparison with controls (30.80± 2.11s) (p<0.001). No significant prolongation of both INR and aPTT was noted in patient group 1 (Table 3).

3.3. Natural coagulation inhibitors

The mean level of AT III showed significant reduction in patients with cirrhosis (83.86 ± 19.49%) as well as in patients with decompensated liver disease (52.64 ± 14.31%) when compared with the normal control level (99.81 ± 14.65%) (p<0.001). However, there was no significant decrease in AT III levels in group one patients with mild liver affection (98.97±9.51%) (p=0.79).

At the same time the mean PC level exhibited a significant reduction in all the patient groups (90.58 ± 11.03, 74.65± 19.56, 41.11 ± 18.35%) when compared with the normal control group (111.59 ± 10.94; p<0.001) (Table 3).

3.4. Fibrinolytic parameter

The mean D-dimer levels showed significantly higher levels only in patients with signs of decompensated cirrhosis (832.26 ± 537.19 µg/L) when compared with controls (98.07 ± 31.03 µg/L) (p<0.001). In patient group 1 and 2 D-dimer levels were not significantly different from the controls (Table 3).

When comparing haemostatic parameters in different patients groups, significant differences between individual groups were observed in INR, aPTT, PC and AT III levels while fibrinogen and D-dimer levels did not exhibited significant differences between group 1 and 2 (Table 3).

Anticoagulant activity (AT III, PC) was also evaluated with respect to the clinical degree of liver damage. Statistically significant correlation between AT III levels and clinical degree of liver damage (Pearson ro= -,931, *p<0,01*) as well as correlation between PC levels and clinical degree of liver damage was found (Pearson ro= -,789, *p<0,01*) (Figure 1, Figure 2).

No statistically significant correlation was found between different haemostatic parameters and other liver synthetic and function tests.

It is of interest to note that in the first patient group only PC levels showed significant decrease in comparison with the healthy control group (90.58 ± 11.03) (p<0.001). (Table 2).

4. DISCUSSION

It is well-known that chronic liver disease is characterized by variable haemostatic defects that involves primary

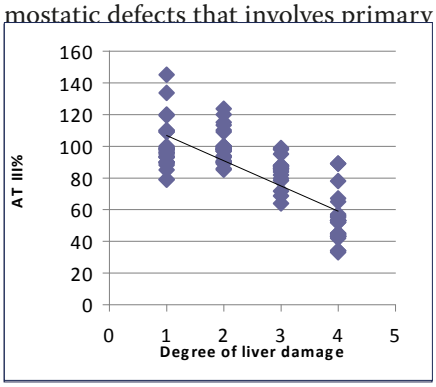

Figure 1. Correlation between AT III levels and clinical degree of liver damage. 1-no liver damage (healthy control group), 2-chronic heaptitis patients, 3-compensated cirrhosis patients, 4-decompensated cirrhosis patients (Pearson ro = -,931, p<0,01, significant negative correlation)

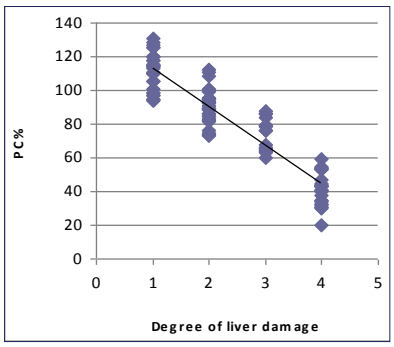

Figure 2. Correlation between PC levels and clinical degree of liver damage. 1-no liver damage (healthy control group), 2-chronic heaptitis patients, 3-compensated cirrhosis patients, 4-decompensated cirrhosis patients (Pearson ro = -,789, p<0,01, significant negative correlation)

haemostasis, fibrinolysis and coagulation (16). Coagulation indices because of their relationship to liver synthetic function are well established as prognostic markers in a variety of settings in both acute and chronic liver disease (17, 18). Previous studies have shown in patients with chronic liver disease a marked decrease in liver synthesis of

coagulation factors as well as inhibitors (19). Recently, anticoagulation proteins were approved not only to reflect hepatocyte impairment (8, 9, 12) but also to have predictive value in chronic liver disease (20).

It is therefore justified to assume that diverse haemostatic assays reflect hepatocyt damage in chronic liver disease and could be of great value in the clinical assessment of liver damage.

The present study shows significant prolongation of prothrombin time (PT), expressed as INR, in patients with compensated as well as decompensated liver cirrhosis. This is in line with many earlier reports (21, 22) and PT has kept its place as one of the parameters of common prognostic indices in advanced liver disease (23). However, in patients with chronic hepatitis B and C and moderate liver affection no significant prolongation of INR and APTT were noted. This is in concordance with previous investigations (9, 12, 24) and confirms that prolongation of conventional coagulation screening tests appear in advanced liver disease and are not sensitive markers of liver damage. Furthermore, recent studies have shown that these global tests are not predictive of bleeding in patients with cirrhosis (25).

Our findings of normal fibrinogen values in chronic hepatitis patients are in line with previous findings (26). Plasma fibrinogen as an acute-phase reactant remains normal or increases in chronic liver disease (27). Our findings of reduced fibrinogen levels in decompensated liver cirrhosis is in line with earlier reports in cirrhotic patients (12). Fibrinogen is synthesized almost exclusively in the liver and low levels in cirrhotics are generally attributed to decreased liver synthetic capacity. However, our results obtained normal values in patients with compensated liver cirrhosis. This disagreement in fibrinogen levels confirm the hypothesis that its decreased levels in severe liver insufficiency are attributed not only to decreased liver synthesis but also to extravascular loss (ascites) or concomitant DIC (27).

In the current report, the plasma levels of natural anticoagulants AT III and PC exhibited significant reduction in patients with decompensated as well as compensated cirrhosis. This is in line with previous studies which reported low levels of natural anticoagulants not only in chronic liver disease (8, 9, 20) but also in acute hepatitis (12).

We noticed with much interest that in patients with chronic hepatitis PC levels exhibited significant reduction in comparison with healthy controls. All other haemostatic assays did not show any significant fluctuation in this patient group. This is in concordance with previous investigations which demonstrated markedly reduced PC anticoagulant activity in chronic hepatitis patients as a sign of reduced hepatocyte synthetic capacity (12, 20, 24). A recent study from Italy even showed that in chronic liver disease reduction in plasma levels of PC correlate with a higher model for end-stage liver disease (MELD) score (28). Another recent published investigation documented PC as a potential predictor of hepatic fibrosis in chronic liver disease (20). These findings, including the present one, confirm that levels of PC are sensitive markers of hepatocyte impairment.

Mean AT III levels did not show any marked reduction in chronic hepatitis patients and this could be interpreted as AT III to be a less sensitive protein reflecting hepatocyte malfunction. AT III was shown to be a good marker of liver cell synthetic function in cirrhosis (29, 30, 31), acute hepatitis (12, 32) and HCC (33, 34), but in chronic viral hepatitis AT III did not show any significant decrease (12).

In the present study we found high D-dimer levels in patients with decompensated liver cirrhosis while in all other patients group no significant increase of D-dimer levels were observed. Plasma levels of fragment D-dimer represent an accurate marker of fibrinolytic activity and increased fibrinolysis is a common finding in advanced liver disease. Our finding is in agreement with that of Agarwal *et al* who reported increased plasma D-dimer values in 93% of patients with cirrhosis and ascites (35). Another recent study confirmed the association between circulating high D-dimer levels and the presence of ascites found in cirrhotic patients (36). In the current report in all patients with decompensated cirrhosis (patient group three) ascites was present and 96% showed plasma levels above the normal range while in cirrhotics without ascites only 13% showed increased D-dimer levels. On the basis of these findings we approve that in liver cirrhosis ascites counts to the main factors to be associated with increased fibrinolytic activity. We concluded that high D-dimer levels in cirrhotics is a strong indicator of decompensation. The underlying mechanism for these observation remains to be clarified. Increased levels of D-dimer has been detected in ascitic fluid as well, suggesting that ascites reabsorption into systemic circulation contributes to hyperfibrinolytic state in patients with advanced liver disease (35, 37). Piscaglia et al proposed that the association between high circulating D-dimer levels and ascites might be due only to advanced liver imparment with portal hypertension and bacterial translocation (38).

5. CONCLUSION

On the basis of our results we concluded that natural anticoagulants AT III and PC reflect hepatocellular impairment in chronic liver disease. This is supported further by the negative correlations between the levels of these parameters and clinical stage of liver disease. PC levels exhibited significant reduction in all patients groups and its levels seems to reflect hepatocyte malfunction accurately. Our study further shows that patients with high D-dimer levels require careful monitoring since this observation is associated with decompensated liver disease. Whether these parameters coul be used in the clinical assessment of liver impairment need to be confirmed by future larger studies

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