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Assessment of Thrombin Generations in Patients with Chronic Liver Diseases

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Abstract:

Background: The area of hyper coagulability in cirrhosis and its potential contribution to certain clinical aspects have received a lot of attention. The clinical manifestations of the haemostatic disorders of cirrhosis have been traditionally related to bleeding due to multiple procoagulant factor defects, excessive fibrinolysis and thrombocytopenia. Aim: Asses the function of blood coagulation in patients with chronic liver diseases and improve the knowledge of the pathophysiology of haemostatic.

Patients and methods: This is a prospective case control study which was conducted at outpatient clinic of internal medicine dept., Minia University Hospital, Minia governorate, during the period from March 2017 to August 2018.

Results: Protein C and S concentrations decreased significantly in Group (II A, II B and IIC) compared to control and also, group (II C) decreased significantly than Group (II A, II B). Regarding Thrombin fragments (F 1+2), Child score A patients had significantly higher concentration compared to the other three groups. However, as regard, Thrombin-ant thrombin (TAT), Child score C group had the significantly higher level compared to other groups.

Conclusion: Thrombin fragments and thrombin ant thrombin complex are considered as the main specific markers for thrombin generations which were elevated strongly depending upon the pathogenesis and the severity of the liver diseases.

Keywords: Thrombin Generations, Chronic Liver Diseases

Introduction

Liver cirrhosis is characterized by a reduce capacity of the liver to synthesize coagulation factors. In addition, some patients with cirrhosis show hyper- fibrinolysis or, less frequently, chronic intravascular coagulation, which may combine to further reduce plasma coagulation factors (1). The complex defects can be documented through the measurement of coagulation factors which are, with the only exception of factor VIII, below normal limits, or through the prolongation of such global tests as the prothromin time (PT) and the activated partial thromboplastin ' time (APTT) (2). While portal hypertension is recognized as the main cause of bleeding in patients with cirrhosis (3). The role played by coagulation defects in the occurrence of bleeding is still unclear. This may reflect a partial association between the severity of bleeding and the degree of coagulation abnormalities,10 as well as the fact that conventional coagulation tests fail to reflect blood coagulation as it occurs in vivo (3).

Coagulation and fibrin formation may be conveniently seen as a two-sided coin, the first side is the procoagulant drive triggered by tissue factor when this cellular receptor forms a complex with plasmatic factor VII, which in turn ignites a series of reactions ultimately leading to thrombin generation and fibrin clot formation (4). The other side is the anticoagulant drive originating from thrombin itself, which, once complexed with its endothelial receptor thrombomodulin, activates plasmatic protein C (2). Activated protein C is a potent anticoagulant that, in combination with its cofactor protein S, downregulates thrombin generation through the inactivation of the activated forms of factor VIII and factor V (5).

The balance between the procoagulant and anticoagulant drives is essential to ensure unwanted thrombin generation in physiological conditions. This balance is usually investigated by means of laboratory tests such as the PT and APTT that are based on the rate of conversion of fibrinogen to fibrin. A limitation of conventional laboratory tests is that plasma starts to clot soon after as little as 5% of the whole thrombin is generated, thus leaving the remaining 95% undetected (8).

Patients and Methods

This is a prospective case control study which was conducted at outpatient clinic of internal medicine dept., Minia University Hospital, Mania governorate, during the period from March 2017 to August 2018. The study protocol was approved by our research ethical committee, faculty of medicine, Minia University at the initiation of the study and appropriate uniform consent obtained from each patient. A total of 80 subjects were included in this study, they were classified to three groups as follow:

Group (I): Control: Included 20 healthy subjects apparently healthy with no history of bleeding and comparable for age, sex, served as a control group.

Group (II): Patients: Included 60 patients with chronic liver disease classified according to the severity of disease and child-Turcotte-pugh score into:

Group (II A): Included 20 patients with child-Pugh score A.

Group (II B): Included 20 patients with child- Pugh score B.

Group (II C): Included 20 patients with child- Pugh score C.

All included subjects were chosen according to the following criteria's:

1. **Inclusion criteria**

- Patients with no bleeding or haemostatic disorders.
- Patients with no medications known to affect blood coagulation.

1. **Exclusion Criteria**

1) Use of medications known to affect blood coagulation.

2) Recent bleeding (within the last 6 months).

3) Bacterial infection.

4) Hepatocellular carcinoma and extra hepatic malignancy.

5) Known haemostatic disorders other than liver disease.

All included mothers and newborns were subjected to the following:

1. Full history taking including

1. Personal history: name, age, sex and educational and economic status, alcohol etc.

2. Medical history: Diabetes, hypertension, Bilharzias, using antiplatlet drugs, Blood transfusion.

2. Examinations including:

1. General and clinical examination.
2. Local and physical examinations.
3. Abdominal ultrasound.
4. Detection of the severity of the disease. Severity of disease was estimated according to Child-Turcotte-Pugh classification.

Table (1): Child-Turcotte-Pugh (CTP) classification.

	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

CTP score is obtained by adding the score for each parameter, CTP class:

A = 5-6 points

B = 7-9 points

C = 10-15 points

3. Laboratory investigations:

A 10 ml blood shamble was drawn without stasis by clean venepuncture and collected in vacuum tubes containing 105 mmol/L trisodium citrate as an anticoagulant (Vacutainer; Becton Dickinson, Meylan, France) at a bloodanticoagulant ratio of 9:1. Then blood was centrifuged within 30 minutes at controlled room temperature for 15 minutes at 2,000g. Plasma was then harvested and filtered through 0.22-m cellulose acetate filters (Millipore, Bedford, MA) to eliminate residual platelets. The platelet-free plasma was subsequently aliquoted in plastic-capped tubes, quickly frozen in liquid nitrogen, and stored at 70°C until it was tested for thrombin generation (see Methods), which was performed no later than 6 months after blood collection.

The studied laboratory investigations:

Complete blood count: It was determined in a whole blood sample (of mothers and newborns) using Automated cell counter Sysmex, NE (TAO, Medical Incorporation, Ono, Japan).

Liver Enzymes: AST and ALT and albumin were assessed using fully automated clinical chemistry auto-analyzer system Konelab 60i (Thermo Electron Incorporation, Finland) by commercial kits.

Prothrombin time and concentration: PT was measured with human relipidated recombinant thromboplastin (Recombiplastin, Instrumentation Laboratory) in combination with a fully automated photo-optical coagulometer (ACL, Instrumentation Laboratory).

Activated partial thromboplastin time (APTT): The APTT was measured with the automated APTT reagent (bioMerieux, Durham, NC), and results were expressed as ratios of test to reference plasma. Factor II (prothrombin) activity was measured using S2238 (Instrumentation Laboratory) as the chromogenic substrate and Echis Carinatus (Sigma, St. Louis, MO) as the activator.24 The test was performed on an automated coagulometer (Electra 1600C, Instrumentation Laboratory).

Protein C and S: Protein C and S were measured by the by Elisa kits of SinoGeneClon Biotech Co. Ltd.

Principle of test: The kits is for the quantitative level of Protein (C and S) in the sample, adopt purified human P C& S antibodies, to coat microtiter plate, make solid-phase antibodies, then add P C& S to walls, then combine the antibodies with labeled HRP to form antibody - antigen - enzyme-antibody complex, After washing completely, add TMB substrate solution, TMB substrate becomes blue color at HRP enzyme-catalyzed, reaction is terminated by the addition of a stop solution and the color change is measured at a wavelength of 450 nm. The concentration of protein C& S in the samples is then determined by comparing the O. D. of the samples to the standard curve.

Human Thrombin-antithrombin complex (TAT): It was measured by the kits of Glory Science company Ltd.

Principle of test: The kit is for the quantitative level of TAT in the sample, adopt purified human TAT to coat microtiter plate, make solid-phase antibody, then add samples or standards to wells with a labeled antibody specific to TAT, then add labeled HRP to the wall. After washing completely, add TMB substrate solution, TMB substrate becomes blue color in wells that contains antibody - antigen - enzyme-antibody complex, reaction is terminated by the addition of a stop solution and the color change is measured at a wavelength of 450 nm. The concentration of TAT in the samples is then determined by comparing the O. D. of the samples to the standard curve.

Human Prothrombin fragment 1+2 (F1+2): It was measured by the kits of Glory Science company Ltd.

Principle of test: This kit is for quantitative level of F1+2 in the sample, adopt purified Human F1+2 to coat microtiter plate, make solid phase antibody, then add F1+2 to walls, combine F1+2 antibody with labeled HRP to form antibody-antigin enzyme antibody complex, after washing completely, add TMB substrate solution, TMB substrate become blue color at HRP enzyme-catalyzed, reaction is terminated by the addition of a stop solution and the color change is measured at a wavelength of 450nm. The concentration of F1+2 in the samples is then determined by comparing the O. D. of the sample to the standard curve. The reference range for protein S was 0.5:1.20 µg/ml and for protein C was 0.2:5.0 µg/ml.

Statistical analyses:

- Data entry and all statistical analyses were performed using Statistical Package for Social Science (SPSS) version 21 under windows 7 operating system.
- Results are expressed as means ± SD for quantitative data and by No. (%) for qualitative data.
- Analyses were done for quantitative variables using one way ANOVA test for comparison between three groups and post Hoc Tukey's correction between each two groups. The nonparametric quantitative variables analyzed by the same tests after logarithmic transformation. However, Chi square test was used for qualitative data between groups.
- Correlation between two quantitative variables was done by using Pearson's correlation coefficient and for non-parametric variables using Spearman's rho correlation test and Multiple linear regression analysis was done.
- Probability level (P-value) was assumed significant if less than 0.05 and highly significant if P-value was less than 0.01. P-value was considered non-significant if greater than or equal to 0.05.

Results

The study included 80 subjects, all of these were classified to the following groups:

Group (I): Control: Included 20 healthy subjects apparently healthy as a control group.

Group (II): Patients: Included 60 patients with chronic liver disease classified according to the severity of disease and child- Turcotte-pugh score into:

Group (II A): Included 20 patients with child-Pugh score A.

Group (II B): Included 20 patients with child- Pugh score B.

Group (II C): Included 20 patients with child- Pugh score C.

Table (2) showed the demographic and some clinical presentations of studied groups. The results revealed that there was no significant differences between groups regarding age and sex distribution. Also, group (II B) and group (II C) had significant higher number of cases with diabetes, HTN and blood transfusion and we noticed that higher number of cases was found in child score C (group, II C) (fig. 10).

Table (2): Demographic and some clinical presentations & of studied groups

Variable		groups				P. value (Sig.)
		Group (I) Control (n=20)	Group (II A) Child. S. (A) (n=20)	Group (II B) Child. S. (B) (n=20)	Group (II C) Child. S. (C) (n=20)	
Age (year)		$43.4^{c} \pm 5.7$	$44.1^{b} \pm 6.9$	$46.0^{b} \pm 7.8$	$47.4^{a} \pm 6.4$	0.23^{NS}
Sex	Male	11 (55.0%)	9 (45.0%)	10 (50.0%)	12 (60.0%)	0.80^{NS}
	Female	9 (45.0%)	11 (55.0%)	10 (50.0%)	8 (40.0%)	
Diabetes		0	8 (40.0%)	11 (45.0%)	19 (95.0%)	<0.01**
Hypertension		0	4 (20.0%)	5 (25.0%)	9 (45.0%)	<0.01**
Blood transfusion		0	2 (10.0%)	5 (25.0%)	8 (40.0%)	<0.01**

Qualitative data presented as No. (%). Quantitative data presented as Mean ± SD

One way ANOVA was used to test significance among groups.

**** Significant ($p<0.01$). NS Not significant.**

a, b, c Means in the same row with different superscript are significantly different.

Result of table (3) showed that Child. score group (group II C) had significantly higher cases with Jaundice (100.0%) compared to other groups, also the same trend was found in ascites, LL odema, history of Hematemesis, history of Hep. Encephalopathy and splenomegaly and we noticed that the incidence of these findings increased with increase child score (disease severity). However, no significant difference was found among groups as regard liver size

Table (3): Some clinical and sonogarphic findings of studied groups.

Variable	groups				P. value (Sig.)
	Group (I) Control (n=20)	Group (II A) Child. S. (A) (n=20)	Group (II B) Child. S. (B) (n=20)	Group (II C) Child. S. (C) (n=20)	
Jaundice	0	4 (20.0%)	9 (45.0%)	20 (100.0%)	<0.01**
Ascites	0	0	8 (40.0%)	13 (65.0%)	<0.01**
LL odema	0	1 (5.0%)	9 (45.0%)	14 (70.0%)	<0.01**
History of Hematemesis	0	0	7 (35.0%)	13 (65.0%)	<0.01**
History of Hep. encephalopathy	0	1 (5.0%)	3 (15.0%)	10 (50.0%)	0.47^{NS}
Liver size	0	4 (20.0%)	6 (30.0%)	2 (10.0%)	<0.01**
Splenomegaly	0	4 (20.0%)	9 (45.0%)	14 (70.0%)	<0.01**

Qualitative data presented as No. (%). Quantitative data presented as Mean ± SD

One way ANOVA was used to test significance among groups.

****Significant ($p<0.01$). NS Not significant.**

a, b, c Means in the same row with different superscript are significantly different.

Table (4) showed the liver function among studied groups. Regarding liver enzymes (AST and ALT), group (II A) and (II B) had significantly higher level compared to control and group (II A). Serum albumin, Prothrombin time, and activated partial thromboplastin time (APTT) were increased significantly by increasing child score (disease severity), however, in contrast Prothrombin concentration was decreased. Regarding INR, group (II C) had significantly higher INR compared to the other three groups

Table (4): Liver function among studied groups.

Variable	groups				P. value (Sig.)
	Group (I) Control (n=20)	Group (II A) Child. S. (A) (n=20)	Group (II B) Child. S. (B) (n=20)	Group (II C) Child. S. (C) (n=20)	
ALT (U/L)	$24.5^{b} \pm 10.4$	$59.4^{a} \pm 18.7$	$65.9^{a} \pm 16.3$	$30.4^{b} \pm 12.3$	<0.01**
AST (U/L)	$21.5^{b} \pm 11.1$	$50.9^{a} \pm 12.9$	$52.3^{a} \pm 12.8$	$26.4^{b} \pm 12.7$	<0.01**
Albumin (g/dL)	$4.58^{a} \pm 0.40$	$3.82^{b} \pm 0.49$	$3.14^{c} \pm 0.51$	$2.71^{d} \pm 0.46$	<0.01**
Prothrombin time (PT)	$10.94^{c} \pm 1.20$	$11.29^{c} \pm 1.11$	$12.76^{b} \pm 1.15$	$14.70^{a} \pm 1.86$	<0.01**
Prothrombin con. (PC)	$98.7^{a} \pm 2.63$	$96.8^{b} \pm 2.48$	$95.1^{b} \pm 5.78$	$58.7^{c} \pm 10.5$	<0.01**
INR	$1.00^{b} \pm 0.01$	$1.03^{b} \pm 0.04$	$1.01^{b} \pm 0.04$	$1.33^{a} \pm 0.19$	<0.01**
Activated partial thromboplastin time (APTT)	$21.3^{d} \pm 4.7$	$27.4^{c} \pm 4.4$	$33.7^{b} \pm 3.9$	$38.9^{a} \pm 4.2$	<0.01**

One way ANOVA was used to test significance among groups.

****Significant ($p<0.01$). NS Not significant.**

a, b, c Means in the same row with different superscript are significantly different.

Table (5) presents the results of CBC among studied groups. Blood hemoglobin concentration was decreased significantly In group (II C) compared to other groups. While, platelets concentration was decreased significantly by increase child score. No significant differences were found among groups regarding WBCs concentration

Table (5): CBC among studied groups.

Variable	groups				P. value (Sig.)
	Group (I) Control (n=20)	Group (II A) Child. S. (A) (n=20)	Group (II B) Child. S. (B) (n=20)	Group (II C) Child. S. (C) (n=20)	
Hb (%)	$13.6^{a} \pm 1.71$	$13.2^{a} \pm 1.21$	$13.1^{a} \pm 1.28$	$10.3^{b} \pm 1.77$	<0.01**
WBCs (10^9/L)	6.96 ± 2.35	7.12 ± 1.95	7.30 ± 2.01	6.94 ± 2.40	0.81^{NS}
Platelets (10^9/L)	$293.5^{a} \pm 51.8$	$249.3^{b} \pm 38.9$	$237.4^{b} \pm 44.5$	$111.1^{c} \pm 32.2$	<0.01**

One way ANOVA was used to test significance among groups.

**** Significant ($p<0.01$). NS Not significant.**

a, b, c Means in the same row with different superscript are significantly different.

Table (6) presents the results of Protein C, Protein S, Theombin fragments (F 1+2) and Thrombin-antithrombin (TAT) among studied groups. Protein C and S concentrations decreased significantly in Group (II A, II B and IIC) compared to control and also, group (II C) decreased significantly than Group (II A, II B). Regarding Thrombin fragments (F 1+2), Child score A patients had significantly higher concentration compared to the other three groups. However, as regard, Thrombin-antithrombin (TAT), Child score C group had the significantly higher level compared to other groups

Table (6): Protein C, Protein S, Theombin fragments (F 1+2) and Thrombin-antithrombin (TAT) among studied groups.

Variable	groups				P. value (Sig.)
	Group (I) Control (n=20)	Group (II A) Child. S. (A) (n=20)	Group (II B) Child. S. (B) (n=20)	Group (II C) Child. S. (C) (n=20)	
Protein C (μg/ml)	$0.34^{a} \pm 0.06$	$0.31^{a} \pm 0.07$	$0.26^{b} \pm 0.05$	$0.22^{c} \pm 0.06$	<0.01**
Protein S (μg/ml)	$0.83^{a} \pm 0.11$	$0.79^{a} \pm 0.13$	$0.61^{b} \pm 0.10$	$0.47^{c} \pm 0.08$	<0.01**
Thrombin fragment (F 1+2, nmol/l)	$32.4^{b} \pm 6.9$	$39.2^{a} \pm 7.4$	$34.3^{b} \pm 9.4$	$31.5^{b} \pm 8.7$	0.02*
Thrombin-antithrombin, TAT (ng/ml)	$8.41^{b} \pm 1.79$	$9.12^{b} \pm 1.82$	$9.51^{b} \pm 2.10$	$10.15^{a} \pm 2.24$	0.05*

One way ANOVA was used to test significance among groups.

****Significant (p<0.01). NS Not significant.**

a, b, c Means in the same row with different superscript are significantly different (Duncan test).

Results of table (7) presents the correlations between PC and thrombin markers in the three studied subgroups of patients group. Non-significant weak correlation was found between prothrombin concentration and therombin generation markers in the three groups .

Table (7): Correlations between PC and thrombin markers in the three studied groups.

Correlation	groups		
	Group (II A) Child. S. (A) (n=20)	Group (II B) Child. S. (B) (n=20)	Group (II C) Child. S. (C) (n=20)
PC * Protein C	0.02^{NS}	0.18^{NS}	0.16^{NS}
PC * Protein S	-0.32^{NS}	-0.26^{NS}	-0.05^{NS}
PC * F+2	-0.26^{NS}	-0.05^{NS}	-0.03^{NS}
PC * TAT	-0.02^{NS}	0.14^{NS}	0.17^{NS}

Person correlation coefficient was used to get the correlation between parameters.

NS Not significant.

Correlation coefficient ranges from (0-1):- weak (r=0-0.24), fair (r=0.25-0.49), moderate (r=0.5-0.74), strong (r=0.75-1)

Discussion

Thrombin generation is fully preserved or even increased in patients with cirrhosis provided that platelet numbers are sufficient (>60 $\times 10^9$ /L) to support the normal TG elicited by plasma **(9)**. Moreover, it has been shown that chronic liver disease display a procoagulant imbalance that may be detected by measuring TG, **(10)** consistent with a state of hypercoagulability. These findings are in keeping with earlier observations that patients with cirrhosis are not protected from hypercoagulant events, such as portal vein thrombosis (PVT) or other deep venous thromboses, despite their substantial prolongation of conventional coagulation times **(11)**.

Nowadays, the area of hypercoagulability in chronic liver disease and its potential contribution to certain clinical aspects have received a lot of attention **(11)**. In this regard, it was recently reported that prophylaxis with enoxaparin in patients with advanced chronic liver disease not only is effective in preventing PVT but also reduces the risk of decompensation and improves survival without bleeding complications **(12)**. These findings suggest a possible connection between anticoagulation and reduction of portal hypertension (PH). Yet, no study has investigated the relationship between thrombotic potential, evaluated by TG and anticoagulant activity, and clinical consequences of PH or mortality in patients with advanced chronic liver disease **(11)**.

The clinical manifestations of the hemostatic disorders of chronic liver disease have been traditionally related to bleeding due to multiple procoagulant factor defects, excessive fibrinolysis and thrombocytopenia **(10)**.

In recent years, however, there is growing recognition that hypercoagulability associated with diminished production of natural anticoagulant factors may play a poorly appreciated but important role in many clinical aspects of cirrhosis **(11)**. Routine coagulation tests, such as the PT and APTT, cannot evaluate the thrombotic tendency in cirrhosis **(11)**. By contrast, several lines of evidence indicate that TG could assess the global coagulation status and detect hypercoagulability in this setting **(9)**.

This is a prospective case control study included a total of 80 subjects were included in this study who were classified to three: **group (I): Control:** Included 20 healthy subjects (free of any acute or chronic liver or medical disease and comparable for age, sex) served as a control group, **group (II): Patients:** Included 60 patients with chronic liver disease classified according to the severity of disease and child- Turcotte-pugh score into, group (II A): included 20 patients with child-Pugh score A, group (II B): included 20 patients with child- Pugh score B and group (II C): Included 20 patients with child- Pugh score C. The aim of this study was to asses the function of blood coagulation in patients with chronic liver diseases and improve the knowledge of the pathophysiology of haemostasis.

The present results revealed that group (II B) and group (II C) had significant higher number of cases with diabetes, HTN and blood transfusion and we noticed that higher number of cases was found in child score C (group, II C). Also, group (II C) had significantly higher cases with Jaundice (100.0%) compared to other groups, also the same trend was found in ascites, LL odema, history of Hematemesis, history of Hep. Encephalopathy and splenomegaly and we noticed that the incidence of these findings increased with increase child score (disease severity). These results are in agreement with many authors **(8-11)**.

The present results revealed that protein C and S concentrations decreased significantly in Group (II A, II B and IIC) compared to control and also, group (II C) decreased significantly than Group (II A, II B). Regarding Thrombin fragments (F 1+2), Child score A patients had significantly higher concentration compared to the other three groups. However, as regard, Thrombin-antithrombin (TAT), Child score C group had the significantly higher level compared to other groups. To the best of our knowledge, this is the first attempt ever made to investigate blood coagulation in patients with cirrhosis (at least in Egypt). These results agreed with **Tripodi, et al., (13)** who found that Protein C, Protein S concentrations decreased with the advance of Child-Pugh score..

The present results agreed with a recent study by of **Georgios et al., (14)** who studied Thrombin generation measured as thrombin–antithrombin complexes predicts clinical outcomes in patients with cirrhosis. They found that Child score C patients had significantly higher TAT concentration compared to controls. Also, they found that protein C and S concentrations were decreased significantly in by advancement of child score compared to control group.

Thrombin generation assays are very convenient laboratory tools for assessing the endogenous thrombin potential in plasma after activation of coagulation. These assays provide a unique opportunity to investigate mechanistically the coagulation balance under standardized conditions, however, until recently, these investigations were limited only to plasma, because the presence of cells makes the reaction medium too turbid and therefore unsuitable for chromogenic measurements **(11)**.

Tripodi et al., (10) investigated whether plasma from cirrhotic patients has an imbalance of pro- vs anti-coagulation factors. They analyzed blood samples from 134 cirrhotic patients and 131 healthy subjects (controls) for levels of pro- and anti-coagulants and for thrombin generation in the presence or absence of thrombomodulin (the main physiologic activator of the protein C anticoagulant pathway). They found that the median ratio of thrombin generation (with/without thrombomodulin) was higher in patients (0.80; range, 0.51-1.06) than controls (0.66; range, 0.17-0.95), indicating that cirrhotic patients are resistant to the action of thrombomodulin. This resistance resulted in greater hypercoagulability of plasma from patients of Child-Pugh class C than of class A or B. The hypercoagulability of plasma from patients of Child-Pugh class C (0.86; range, 0.70-1.06) was slightly greater than that observed under the same conditions in patients with congenital protein C deficiency (0.76; range, 0.60-0.93). Levels of factor VIII, a potent pro-coagulant involved in thrombin generation, increased progressively with Child-Pugh score (from Child-Pugh class A to C). Levels of protein C, one of the most potent naturally occurring anti-coagulants, showed the opposite trend. Finally, they concluded that the hypercoagulability of plasma from patients with cirrhosis appears to result from increased levels of factor VIII and decreased levels of protein C-typical features of patients with cirrhosis. These findings might explain the risk for venous thromboembolism in patients with chronic liver disease.

Conclusion

- Thrombin fragments and thrombin antithrombin complex are considered as the main specific markers for thrombin generations which were elevated strongly depending upon the pathogenesis and the severity of the liver diseases.
- As in chronic liver diseases haemotemesis process was impaired not only for the defect of coagulation factors synthesis but also due to impaired the clearance of these factors.
- In chronic liver diseases, it was thought to only hypo coagulation but recently hyper coagulable was presented also in chronic liver diseases more prominent and the elevations of thrombin generations in patients with chronic liver disease more significant than the reduction in anticoagulants.
- In early liver disease, it was noticed that elevations of thrombin generations in correlation with the ordinary coagulation tests which were normal despite of the liver pathogenesis resulting in disruption of the liver parenchyma.

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