Asian Journal of Research and Reports in Hepatology

3(1): 22-30, 2021; Article no.AJRRHE.68193

Naturally Occurring Anti-coagulant Proteins in Patients with Liver Cirrhosis: Is it Valuable Markers for Disease Severity?

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Authors' contributions

This work was carried out in collaboration among all authors. Author SME performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SSA managed the analyses of the study. Author HG do the laboratory part of the study. Author SK managed the analyses of the study. Author AAA help in editing and revision. Author SMH designed the study and managed the literature searches. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Kuldip Singh, Government Medical College, India.
Reviewers:
(1) Simonovska Natasha, Sts Cyril and Methodius University in Skopje, Republic of North Macedonia.
(2) Ankur Singhal, Sardar Patel Medical College, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/68193

Original Research Article

Received 12 March 2021
Accepted 18 May 2021
Published 31 May 2021

ABSTRACT

Background: Hemostatic systems in cirrhotic patients are delicately balanced between pro- and anticoagulant factors and can be easily tipped to a hypo- or hypercoagulable status, resulting from decreased levels of procoagulant and anticoagulant factors synthesized by hepatocytes and sinusoidal cells. Hypercoagulability has an underestimated but crucial role in many aspects of LC and can encounter thrombotic complications.
Aim: Assessment of the activity of protein C, protein S and anti-thrombin III in patients with liver cirrhosis and their level with the degree of liver cirrhosis and to correlate the level of procoagulants markers (prothrombin concentration, prothrombin time) with the level of anticoagulant proteins in LC.

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Methods: Case control study, included 136 patients were allocated into 3 groups according to Child Pugh scoring system as well as 44 apparently heathy persons as control group. All patients subjected to assessment of prothrombin time (PT), prothrombin concentration (PC), international normalized ratio (INR) and partial thromboplastin time (PTT) as well protein C, protein S and antithrombin III.
Results: Serum levels of protein C, protein S and Antithrombin III were significantly lower in the studied cases than controls and were significantly lower in patients with severe LC than in patients with mild LC. They negatively correlated with the disease severity and with levels of procoagulant markers.
Conclusion: Proteins C, protein S, and AT III decreased in patients with liver cirrhosis and its levels were correlated negatively to severity of liver disease as well as levels of procoagulant markers.

Keywords: Anti-coagulant proteins; liver cirrhosis; protein C; protein S.

1. INTRODUCTION

Liver has an essential role in the haemostatic system [1]. The balanced levels of procoagulant and anticoagulants determine the risk of hemorrhage and thrombosis under the physiological conditions. In chronic liver disease (CLD) due to chronic hepatitis and underlying cirrhosis, this haemostatic imbalance leads to hyper-coagulability which favors thrombosis despite the longer coagulation times of their plasma, compared with that of healthy individuals [2]. However, end stage liver disease is predominately associated with bleeding tendency [1].

Protein C (PC) and protein S (PS) are vitamin K-dependent glycoproteins, that act as natural anticoagulants [3]. Antithrombin III (AT III) is a natural anticoagulant that is synthesized exclusively in parenchymal cells of the liver [4]. The cause of hypercoagulability in CLD is the reduced level of protein C and increased level of factor VIIIa [5]. As a consequence of hypercoagulability, the deep vein thrombosis, pulmonary embolism, hepatic and portal vein thrombosis may occur [6].

Patients with CLD were (and are still) subjected to laboratory screening with the prothrombin time (PT) and activated partial thromboplastin times (APTT), and those with abnormal values to correct the abnormalities and to prevent haemorrhage during invasive procedures or to stop bleeding from the gastrointestinal tract are treated with plasma or procoagulant agents [1].

It was reported that protein C value was significantly lower in both chronic hepatitis and cirrhosis group when compared with control group. It is a sign of reduced hepatocyte synthetic capacity in chronic hepatitis. Zocco et al. showed that in CLD reduction in plasma levels of protein C correlated with a higher Model For End-Stage Liver Disease (MELD) score [7]. The levels of AT III and aminotransferase activity may be used in patients with liver disease for differential diagnosis and the monitoring of disease progression [4].

We aimed in this work to investigate patients with LC in our locality for both pro an anti-coagulants and its relation to disease severity.

2. PATIENTS AND METHODS

Recruited patients with LC were diagnosed based on clinical criteria of LC; biochemical confirmation (low serum albumin and prolonged PT) and suggestive ultrasonographic confirmation (coarse liver, irregular surface ± reduced size, attenuated hepatic veins, enlarged caudate lobe). Severity of cirrhosis was assessed according to Child-Pugh score and MELD score. Patients with history of thrombotic disorder on anticoagulant therapy, renal disease, recent pregnancy, recent history of transfusion of blood products within one-month, current anticoagulation therapy, hepatocellular carcinoma were excluded from the study.

The included 136 patients were allocated into 3 groups according to Child Pugh score as well as 44 apparently heathy persons as control group. Patients were classified: group I: 45 patients of LC with Child Pugh score A, group II: 46 patients of LC with Child Pugh score B, group III: 45 patients of LC with Child Pugh score C.

All patients were subjected to full history and thorough clinical examination, abdominal ultrasonography, liver function and coagulation profile.

Assay of Protein C, protein S, antithrombin III activity was done using automated blood coagulation analyzer CA-1500 (Sysmex corporation, Japan), serial number A7463.

2.1 Statistical Analysis

Data entry and data analysis were done using SPSS version 22 (Statistical Package for Social science). Data were presented as number, percentage, mean, median and standard deviation. Chi-square test and Fisher Exact test was used to compare qualitative variables. Independent samples t-test was used to compare quantitative variables between groups for parametric data and Mann-Whitney test for non-parametric data. Spearman correlation was done to measure correlation between quantitative variables. P-value was considered significant if < 0.05.

3. RESULTS

The studied cases were 88 males (64.7%) and 48 females (35.3%) with age ranged from 18 to 81 years (57.73±12.66). The controls group were 26 male (59.1%) and 18 female (40.9%) with age ranged from 20 to 39 years (29.75±5.11). The etiology of LC in the studied patients were HCV in 108 patients (79.4%), HBV in 8 patients (5.9%), mixed HCV & HBV in 1 case (0.7%), autoimmune in 5 cases (3.7 %), NAFLD in 1 patient (0.7%) and cryptogenic in 13 patients (9.6%) respectively. The studied patients were classified according to Child score into three subgroups [group A 45 (33.1%), group B 46 patients (33.8%) and group C 45 patients (33.1%)]. MELD score mean value for the studied patients was 16.49 ± 7.11. These data presented on Table (1).

There was significantly lower platelets count (119.16 ± 65.74) in the studied cases than in the controls (256.52 ± 55.35). There were significantly higher serum mean levels of PT, INR and PTT in the studied cases than in the controls (P<0.0001 for each). Also, there was significantly lower serum mean level of prothrombin concentration in the studied cases than in the controls (P<0.0001).

There was significantly lower median platelets count in group C (89) than in group A (123) and in group B (112.5). There were significantly higher PT, INR and PTT in group C than in group A and group B as well as in group B than in group A (P < 0.0001 for each). Also, there was significantly lower prothrombin concentration in group C than in group A and group B as well as in group B than in group A (P < 0.0001 for each) (Table 2).

There were significantly lower serum median levels of protein C, Protein S and AT III in the studied cases than in controls (P<0.0001 for each) (Table 3).

Table 1. Clinical data of the studied patients

	No. (136)	%
Etiology of cirrhosis:		
HCV	108	79.4%
HBV	8	5.9%
HCV and HBV	1	0.7%
Autoimmune	5	3.7%
NAFLD	1	0.7%
Cryptogenic	13	9.6%
Child score:		
A (5-6)	45	33.1%
B (7-9)	46	33.8%
C (10-15)	45	33.1%
Mean ± SD	8.28 ± 2.48	
Range	5.0-15.0	
MELD score:		
Mean ± SD	16.49 ± 7.11	
Median (Range)	15.0 (6.0-37.0)	

Data expressed as mean (SD), median (range), frequency (percentage); Data expressed median (range). P-value is significant if <0.005. PS: protein S; ATIII: Antithrombin III.
Statistical test used in this table was Mann-Whitney test.

Table 2. Platelets and procoagulant markers in the different patients' subgroups

	Group A (n= 45)	Group B (n= 46)	Group C (n= 45)	P-value[1]	P-value[2]	P-value[3]
Platelets (X103/ul)						
Median (Range)	123.0 (39.0-325.0)	112.5 (31.0-386.0)	89.0 (19.0-240.0)	0.905	0.018*	0.025*
Prothrombin time (PT) (seconds)						
Mean ± SD	13.15± 1.85	15.25± 2.04	19.16 ± 4.43	<0.001	<0.001	<0.001
Range	9.6-19.0	12.0-21.7	12.7-35.0			
Prothrombin Concentration %						
Mean ± SD	80.31 ± 20.76	60.71 ± 11.40	45.06 ± 11.34	<0.001	<0.001	<0.001
Range	45.0-139.1	37.8-82.5	24.6-69.5			
International randomized ratio (INR)						
Mean ± SD	1.12 ± 0.15	1.34 ± 0.17	1.68 ± 0.37	<0.001	<0.001	<0.001
Range	0.8-1.5	1.0-1.8	1.1-2.8			
Activated partial thromboplastin time (PTT) (seconds)						
Mean ± SD	34.39 ± 6.33	41.82 ± 7.42	51.50 ± 14.22			
Range	24.2-54.0	30.6-63.2	32.4-90.0	<0.001	<0.001	<0.001

Data expressed as mean (SD), range. P-value is significant if <0.005. PT: prothrombin time; INR: International randomized ratio; PTT: Activated Partial thromboplastin time.

P value[1]: comparison between group A and group B.

P value[2]: comparison between group A and group C.

P value[3]: comparison between group B and group C.

**Means statistically significant; Statistical tests used in this table were Independent samples t-test, Mann-Whitney test.*

Table 3. Anticoagulant markers serum activity levels in the studied cases and controls

	Cases (n= 136)	Controls (n= 44)	P-value
Protein C %			<0.001
Median (Range)	38.1 (11.2-138.4)	103.2 (84.5-129.2)	
Protein S (PS) %			<0.001
Median (Range)	49.1 (16.5-130.0)	85.8 (64.3-123.0)	
Anti-thrombin III (ATIII) %			<0.001
Median (Range)	44.8 (4.7-105.5)	94.4 (74.0-133.0)	

Table 4. Anticogulant markers serum activity levels in the different patients' subgroups

	Group A (n= 45)	Group B (n= 46)	Group C (n= 45)	P-value[1]	P-value[2]	P-value[3]
Protein C %				<0.001	<0.001	<0.001
Median (Range)	57.0 (30.7-138.4)	37.6 (11.2-81.1)	26.1 (11.2-56.2)			
Protein S (PS)%				0.205	<0.001	<0.001
Median (Range)	62.0 (21.6-130.0)	52.9 (18.7-123.0)	41.0 (16.5-81.0)			
Anti-thrombin III (ATIII) %						
Median (Range)	69.0 (33.8-105.5)	43.7 (15.4-98.0)	30.6 (4.7-60.5)	<0.001	<0.001	<0.001

Data expressed median (range). P-value is significant if <0.005. PS: protein S; ATIII: Antithrombin III.
P value[1]: comparison between group A and group B.
P value[2]: comparison between group A and group C.
P value[3]: comparison between group B and group C.
Statistical test used in this table was Mann-Whitney test.

Regarding the studied anticoagulant markers in the different patients' subgroups, there were significantly lower serum median levels of protein C and AT III in group C than in group A and group B (P<0.0001 for each) as well as significantly lower serum median levels of protein C and AT III in group B than in group A (P<0.0001 for each). Also, there were significantly lower serum median levels of Protein S in group C than in group B and group A (P<0.0001 for each) (Table 4).

There were significant negative correlation between the protein C, PS and AT III with CHILD score and MELD score (p value <0.001 for each) (Table 5).

Protein C, Protein S and Antithrombin III were significant negatively correlated with PT, PTT, INR (p value <0.001), but significant positively correlated with prothrombin concentration (p value <0.001) (Table 6).

4. DISCUSSION

Hemostatic systems in cirrhotic patients are delicately balanced between pro- and anticoagulant factors and can be easily tipped to a hypo- or hypercoagulable status, resulting from decreased levels of procoagulant and anticoagulant factors synthesized by hepatocytes and sinusoidal cells. Hypercoagulability has an underestimated but crucial role in many aspects of LC. In fact, they can encounter thrombotic complications. Patients with cirrhosis appear to have a higher incidence of unprovoked DVT and pulmonary embolism compared with the general population [8].

In this study, we aimed to estimate the level of protein C, PS, AT III in patients with LC and to correlate their level with the degree of LC and with level of procoagulants. We found that serum levels of protein C, PS and AT III were lower in the studied cases than in controls.

Tripodi and his colleagues had shown that in comparison with controls the cirrhotic patients had significantly decreased protein C levels in their study that was conducted on 50 cirrhotic patients [9]. Also, El Bokl et al. found similar results in their study on a total of 102 adult subjects: 51 cirrhotic patients and 51 healthy controls [10]. A study by Sheikh and Viunytska study done in Ukrain measuring the plasma level of AT-III and serum activity of aminotransferase in 60 participants: 20 patients with chronic hepatitis, 20 patients with cirrhosis, and 20 healthy individuals (controls) found that the level of AT-III in plasma was significantly lower in patients with cirrhosis compared to patients with chronic hepatitis and the level of AT-III in plasma was lower in patients with liver disease in comparison to healthy participants [4]. Flores and his colleagues found that patients with Child-Pugh Class C cirrhosis have been found to have as low as 40% Protein C concentration compared to those without cirrhosis [11].

In a study by Saray et al., the mean level of AT-III showed significant reduction in patients with extensive fibrosis in comparison to mean level of patients with mild fibrosis and mean level of normal control [12]. Youngwon et al. studied the coagulation inhibitor protein C in patients with various liver diseases. Protein C level was significantly decreased in patients with cirrhosis as compared to patients with steatosis and it can be used for assessment of fibrosis [13].

Our study showed that there were significantly lower serum levels of protein C and AT III in cirrhotic patients with Child-pugh score C than in cirrhotic patients with Child-pugh score A and Child-pugh score B as well as significantly lower serum levels of protein C and AT III in Child-pugh score B than in Child-pugh score A. Also, there were significantly lower serum levels of PS in Child-pugh score C than in Child-pugh score B and Child-pugh score A. Similarly, another study Tang et al. found that Protein C, Protein S and AT levels were progressively decreased with increasing severity of Child-Pugh class [14].

Table 5. The correlation of the different anticoagulant markers with Child score and MELD score

		Child score	MELD score
Protein C	r-value	-0.728	-0.551
	P-value	<0.001	<0.001
Protein S (PS)	r-value	-0.342	-0.273
	P-value	<0.001	<0.001
Anti-thrombin III (AT III)	r-value	-0.773	-0.612
	P-value	<0.001	<0.001

PS: protein S; AT III: Antithrombin III. Spearman correlation was used

Table 6. Correlation between anticoagulant markers and procoagulant markers

		Protein C	Protein S (PS)	Anti-thrombin III(AT III)
Prothrombin time (PT)	r-value	-0.653	-0.312	-0.670
	P-value	<0.001	<0.001	<0.001
Prothrombin concentration	r-value	0.665	0.298	0.663
	P-value	<0.001	<0.001	<0.001
International randomized	r-value	-0.665	-0.298	-0.665
ratio (INR)	P-value	<0.001	<0.001	<0.001
Activatedpartial	r-value	-0.592	-0.324	-0.673
thromboplastin time(PTT)	P-value	<0.001	<0.001	<0.001

PS: protein S; AT III: Antithrombin III; PT: prothrombin time; INR: International randomized ratio; PTT: Activated Partial thromboplastin time. Spearman correlation was used

Our findings were consistent with previous studies by Saeed et al., who assessed protein C in two groups of patients with early and advanced fibrosis. They reported higher level of protein C in group I (stage 0 - 3.). Mean concentration of protein C was decreased in advanced stage group II patients (stage 4 – 6) [5].

In Saray et al. multivariate analyses, when healthy controls were compared to patients with early and with extensive fibrosis, Protein C levels showed significant decrease in comparison to the healthy control group. In addition, the mean level of AT III showed significant reduction in patients with extensive fibrosis in comparison to patients with mild fibrosis and control [12].

In this study we reported a significant negative correlation between the level of protein C, PS and AT III with Child-pugh score and MELD score. This indicates that the anticoagulant proteins serum levels decrease with increasing liver disease severity.

Similarly, El-Nemr et al. reported that plasma protein C concentrations were found to be decreased significantly with deteriorating liver function, such that both Child Pugh class B and class C patients had significantly lower protein C concentrations than class A. So that protein C activity may be used as a sensitive marker of hepatocellular damage [15].

AL-Dewachi and Kashmoola showed a significant but imperfect correlation of natural anticoagulants (protein and AT III) with INR and MELD score and that AT III and protein C independently predict the MELD score, though this association is only of moderate strengths. Regarding AT III there was progressive reduction in AT III across Child- Pugh grades from A to C and the difference was statistically significant for grade C only when compared with the control and a statistically negative correlation were found between AT III level and Child-Pugh score [16].

Singhal et al. investigated Protein C and S, as well as AT and factor V Leiden mutation in a total of 47 patients with end-stage cirrhosis: 89% had low levels of at least one, and 70% had low levels of all. These deficiencies were greater in those with MELD >15 and also in those with HCV related LC [17].

Recent evidence suggests that changes in the blood levels of natural anticoagulants particularly, PS and Protein C, were found to be more sensitive to hepatocyte dysfunction than the conventional coagulation tests PT and APTT. Depressed levels of PS and Protein C were found even in the mildest forms of liver disease such as chronic viral hepatitis and its carrier state when the other coagulation tests and routine LFT were normal. Therefore, it was concluded that both PS and Protein C are sensitive markers of liver disease; PS is a sensitive marker of liver inflammation, whereas Protein C is sensitive marker for liver fibrosis, as it is least affected by liver inflammation [18].

Our study showed significantly higher PT, INR and PTT in the studied patients than in the controls. Also, there was significantly lower prothrombin concentration in the studied patients than in the controls. PT, INR and PTT were significantly higher in Child C group than Child A and Child B groups and prothrombin concentration was lower in child C group than child A and Child B groups.

Rai et al. found that PT, aPTT in cirrhosis group were significantly higher when compared to chronic hepatitis and control group [1].

On the other hand, a study by researchers confirmed that prolongation of conventional coagulation screening tests appears in advanced liver disease and are not sensitive markers of

liver damage. Further studies have shown that these global tests are not predictive of bleeding in patients with cirrhosis however PT has kept its place as one of the parameters of common prognostic indices in advanced liver disease [1,19,20].

In this study, we also reported significant negative correlation between anticoagulant markers (Protein C, Protein S, AT III) and procoagulant markers (PT, PTT, INR).

Totoki et al. showed that the activity of PS relative to the INR increases in parallel to the model for end-stage liver disease scores [21]

Rashidi-Alavijeh et al. illustrated that INR and protein C are superior in prediction of survival and as classical coagulation parameters reflect well the degree of liver synthesis failure, although their value in predicting bleeding events seems to be negligible due to a rebalanced hemostatic process [22].

5. CONCLUSION

In patients with liver cirrhosis, there is a reduced synthesis of procoagulant proteins. Endogenous anticoagulants such as proteins C, protein S, and AT III serum level were decreased in patients with liver cirrhosis. The degree of decrease in level of protein C, protein S, AT III were correlated to severity of liver disease. The level of protein C, protein S, AT III were negatively correlated to the level of procoagulant markers (PT, PTT and INR).

CONSENT AND ETHICAL APPROVAL

Full consent was obtained from the participants prior to the study. Research participants were not subjected to harm in any ways whatsoever. Protection of the privacy of research participants has was ensured. Adequate level of confidentiality of the research data was ensured. The study was approved by institutional ethics committee number (17100585).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Available:https://doi.org/10.1371/journal.pone.0236528

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/68193