Portal Vein Thrombosis Incidence, Serum AT-III, Protein S, Protein C, Factor II, Factor VII Levels and Platelet Aggregation Function in Patients with Chronic Hepatitis and Liver Cirrhosis

Kronik Hepatit ve Karaciğer Sirozlu Hastalarda; Portal Ven Trombozu Sıklığı, Serum A-III, Protein S, Protein C, Faktör II, Faktör VII Düzeyleri ve Trombosit Kümelenme Fonksiyonu

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ABSTRACT Objective: Liver cirrhosis and chronic hepatitis are a common diseases seen due to several reasons. Acute and chronic liver parenchymal disorders affect platelet and coagulation mechanisms which constitute the steps in haemostasis. In the present study, we aimed to investigate blood levels of Antithrombin III (AT-III), Protein S, Protein C, Factor II, Factor VII, and platelet aggregation function and the frequency of portal vein thrombosis (PVT) in an attempt to reveal the correlation, if any, between them. **Material and Methods:** Factor II, Factor VII, Protein C, Protein S, AT-III and platelets aggregation function were investigated in 25 patients with chronic hepatitis and in 27 patients with liver cirrhosis in this retrospective study. Blood samples of the patients with rapidly delivered to the laboratory and analyzed. Ultrasonographic evaluation was performed in order to assess the hepatic parenchymal structure and dimension, size of the liver patency of the portal vein. Our study was analyzed using Statistical Package for the Social Sciences software; Mann-Whitney U test was implemented to make a comparison between the groups. **Results:** Factor II, Factor VII, Protein C, Protein S, AT-III levels were decreased significantly in patients with liver cirrhosis when compared with the patients with chronic hepatitis. Platelat aggregation function induced by adenosine diphosphate, epinephrine and collagen were statistical significance more destructed in patients, with liver cirrhosis when compared with chronic hepatitis patients. Portal vein thrombosis was observed in two patients. **Conclusion:** As a result haemostatic functions are destroyed in patients with liver cirrhosis. For this reason complications like thrombosis and bleeding are commonly seen in these patients.

Key Words: Portal vein; liver cirrhosis; thrombosis

ÖZET Amaç: Karaciğer sirozu ve kronik hepatit çeşitli nedenlerle sık görülen hastalıklardır. Akut ve kronik karaciğer parankim bozuklukları hemostaz basamaklarını da içine alan trombosit ve koagülasyon mekanizmalarını etkiler. Bu çalışmada Antitrombin III (AT-III), Protein S, Protein C, Faktör II, Faktör VII kan düzeyleri arasında ve varsa trombosit kümelenme fonksiyonu ve portal ven trombozu sıklığı arasındaki ilişki araştırılmıştır. **Gereç ve Yöntemler:** Retrospektif olarak yapılan çalışmamızda 25 kronik hepatitli ve 27 karaciğer sirozlu hastada Faktör II, Faktör VII, Protein C, Protein S, AT-III ve trombosit kümelenme fonksiyonu araştırılmıştır. Hastalardan alınan kanlar laboratuvara hızla ulaştırıldı ve analiz edildi. Portal ven karaciğer açıklığını, hepatik parankim yapısı ve büyüklüğünü değerlendirmek için ultrasonografik inceleme yapıldı. Çalışmamız Statistical Package for the Social Sciences kullanılarak analiz edildi; gruplar arası karşılaştırma için Mann-Whitney U testi uygulandı. **Bulgular:** Kronik hepatitli hastalar ile karşılaştırıldığında Faktör II, Faktör VII, Protein C, Protein S, AT-III düzeyleri karaciğer sirozlu hastalarda önemli ölçüde azalmıştır. Adenozin difosfat tarafından indüklenen platelet kümelenme fonksiyonu, epinefrin ve kollajen karaciğer sirozu olan hastalar kronik hepatitli hastalar ile karşılaştırıldığında önemli ölçüde istatistiksel olarak daha fazla bozuldu. İki hastada portal ven trombozu gözlendi. **Sonuç:** Sonuç olarak karaciğer sirozlu hastalarda hemostatik fonksiyonlar bozulur. Bu nedenle tromboz ve kanama gibi komplikasyonlar sıklıkla bu hastalarda görülür.

Anahtar Kelimeler: Portal ven; karaciğer sirozu; tromboz

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Viral hepatitis constitutes a major cause of chronic hepatitis and liver cirrhosis in our country. The chronicity rate is high, should it be acquired at early ages. Hepatic transaminases have been observed to be elevated in 40% of all patients with incidentally detected positivity for hepatitis B surface antigen (HBsAg). Moreover, chronic hepatitis, cirrhosis and liver cancer can be detected in 22%, 4% and 0.4% of these cases, respectively. Infection with Hepatitis C virus progresses to chronicity in 70-80% of the suffering patients. Chronic hepatitis and cirrhosis have already been evident in 41% and 20% of such cases at the time of diagnosis, respectively.[1] Synthesis of a number of clotting factors is performed in the hepatocytes. Acute and chronic hepatic injuries exert detrimental impact throughout all haemostatic cascades. Both platelets, one of the elements of haemostasis, and the coagulation process itself become severely affected in patients with hepatic diseases (cirrhosis, hepatitis and malignancies).[2] Such blood coagulation tests as Prothrombin time (PT) and partial thromboplastin time (PTT) have been widely accepted to make further contribution to the diagnosis of hepatic diseases. Additionally, thrombocytopenia and platelet dysfunction are likely to emerge in patients with hepatic diseases. The later may also contribute further to evident haemostatic defect in cirrhosis.

Portal vein thrombosis (PVT) is a rare clinical condition of various etiologies which can be seen both in adults and children. In clinical studies reported that hepatic cirrhosis was detected in 24-32% of cases with PVT. The prevalence of PVT in cases with hepatic cirrhosis, on the other hand, varies between 0.6% to 21%.[3,4] Liver also is the production site of such naturally-occurring coagulation inhibitors as Antithrombin III (AT-III), protein C and protein S.[5]

In the present study, we aimed to investigate blood levels of AT-III, Protein S, Protein C, Factor II, Factor VII, and platelet aggregation function and the frequency of PVT in an attempt to reveal the correlation, if any, between them.

MATERIAL AND METHODS

52 consecutive patients who had been admitted to gastroenterology outpatient polyclinic and inpatient service were included in the study. Patients were analyzed retrospectively. The study population was composed of 27 patients suffering from cirrhosis and 25 patients with chronic hepatitis, all diagnosed on the basis of clinical, laboratory and ultrasound examinations. The definitive diagnosis of chronic hepatitis was established through liver biopsy in 20 patients and on the basis of persisting hepatic enzyme elevations for six months in 5 patients positive for HBV DNA and HCV RNA (the liver biopsy procedure was not implemented in these patients owing to patient-related reasons). Ultrasonographic evaluation was performed in order to assess the hepatic parenchymal structure, size of the liver, and whether or not there appeared to be ascites in the abdomen, followed by assessment of patency of the portal vein by alternating to color mode.

During measurement of AT-III, protein C and protein S, 1.8 mL blood was drawn into 0.2 mL of citrate-containing, and then put to centrifugation at 750 *g* for 10 minutes. A certain portion of the supernatant plasma was transferred to a tube containing ice so as to keep it at -30°C in deep freezer until the day of determination of factor II, factor VII levels. The remaining plasma was used to measure the levels of AT-III, protein C and protein S.

1.8 mL blood sample was drawn into the tubes containing 0.2 mL citrate in an attempt for PT determination. The sample taken was then subjected to centrifugation process at 700 *g* for 10 minutes.

As for the blood sample taken for the evaluation of platelet aggregation, it was managed to be transferred to the related laboratory within half an hour. Blood sample of 1.8 mL volume was taken into the tubes containing 0.2 mL citrate and then followed by centrifugation at 350 *g* for 5 minutes. A 450 mL sample was taken from the supernatant portion which was rich in platelets and added on a 3 ml sample from ADP of 1 μM concentration so as

to evaluate the platelet aggregation. Moreover, 450 ml plasma sample was taken again from the same tube and mixed with 3 mL epinephrine of 10 μM concentration, hence assessing the platelet aggregation. Another 450 mL plasma sample was taken and mixed with 1 mL collagen of 1 mg/mL concentration, hence assessing the platelet aggregation in collagen solution. Blood samples taken from the patients were transferred into routine biochemistry tubes, centrifuged at 3500 rpm for 10 minutes. The resultant supernatant plasma portions were used to measure ALT, AST, total bilirubin and albumin levels. The date from our study was analyzed using SPSS (ver=9.05) software; Mann-Whitney U test was implemented to make a comparison between the groups. The related values were given as mean ± standard deviation (SD) in the tables.

RESULTS

A total of 52 patients were included in the study, 27 of whom had been diagnosed with hepatic cirrhosis and 25 of whom with chronic hepatitis. Of the patients with hepatic cirrhosis, 13 (48.1%) were male and 14 (51.9%) were female. The ages of the cases with hepatic cirrhosis were ranging between 46 and 70 years (53.48±0.92 years), with a mean age of 52.61±1.44 years in males and of 54.28±1.18 years in females. As for the patients suffering from hepatic cirrhosis, the underlying etiology in 21 cases was viral hepatitis, whereas it was cryptogenic cirrhosis in the remaining 6 cases. The ages of the patients with chronic hepatitis were ranging between 54.34±0.97 years, with a mean age of 51.13±1.25 years in males and 53.50±1.50 years in females. Of all cases suffering from chronic viral hepatitis, 15 were subjected to chronic B hepatitis, while 10 to chronic C hepatitis. 13 and 14 of all cases comprising the cirrhosis group were male and female, respectively. On the other hand, 14 and 11 of the cases suffering from chronic viral hepatitis were male and female, respectively. PVT was present in our 2 patients with hepatic cirrhosis. All our patients with hepatic cirrhosis were assigned into either Child B or Child A groups according to the Child-Pugh classification. However, we had no patient in Child A group.

AT-III, protein C and protein S levels were measured to be statistically lower in hepatic cirrhosis group compared to chronic hepatitis group ($p<0.05$) (Table 1).

ADP, epinephrine and collagen-induced platelet aggregation ratios were found to be significantly poor in the patients with hepatic cirrhosis compared to those with chronic hepatitis (Table 2).

Albumin levels were observed to be significantly lower in hepatic cirrhotic patients compared to those with chronic hepatitis. Moreover, total bilirubin level in cirrhotic patients were subjected to a statistically significant increase compared to the patients with chronic hepatitis ($p<0.01$) (Table 3).

TABLE 1: AT-III, Protein C and Protein S levels in chronic hepatitis and hepatic cirrhosis groups.

	Hepatic Cirrhosis $\bar{\chi}$±SD (n:27)	Chronic Hepatitis $\bar{\chi}$±SD (n:25)	Result
AT-III (%)	49.13±5.89	89.87±6.99	p<0.05
Protein C (%)	35.67±3.21	69.63±3.94	p<0.05
Protein S (%)	58.60±5.23	82.37±3.60	p<0.05

TABLE 2: Results of platelet aggregation with ADP, Collagen and Epinephrine, together with Platelet counts and PT values.

	Hepatic Cirrhosis $\bar{\chi}$±SD (n:27)	Chronic Hepatitis $\bar{\chi}$±SD (n:25)	Result
ADP (μM)	34.25±2.32	44.32±3.16	p<0.05
Collagen (μg/mL)	31.77±3.03	45.00±2.57	p<0.05
Epinephrin (pg/mL)	31.96±3.21	46.95±2.92	p<0.05
PT (second)	16.11±0.03	12.88±0.25	p<0.05
Platelet (K/mm^3)	122.14±13.62	256.64±11.25	p<0.05

TABLE 3: ALT, AST, total bilirubin and albumin levels in hepatic cirrhosis and chronic hepatitis patient groups.

	Hepatic Cirrhosis $\bar{\chi}$±SD (n:27)	Chronic Hepatitis $\bar{\chi}$±SD (n:25)	Result
ALT (U/L)	32.29±1.97	51.88±2.12	p<0.05
AST (U/L)	34.18±1.83	41.92±2.24	p<0.05
T. Bilirubin (mg/dL)	2.03±0.19	0.78±0.11	p<0.05
Albumin (mg/dL)	3.01±0.10	4.22±0.06	p<0.05

Coagulation factors as factor II and VII are subjected to much more prominent decrease in hepatic cirrhosis ($p<0.05$) (Table 4).

Compared to the patients with chronic hepatitis Upon investigating the hepatic cirrhosis patient group comprising a total of 27 patients, it was seen that 6 and 21 patients were in Child B and Child C levels, respectively. Moreover, the results regarding our study variables were assessed according to the Child classification (Table 5).

When analyzing AT-III levels in hepatic cirrhosis group, the mean level was (58.97±11.69%) in the patients assigned to Child B, whereas it was (46.31±6.81%) for those in Child C. Such difference was not found to be statistically significant ($p>0.05$) (Table 5).

DISCUSSION

Hematological system assumes major changes in hepatic disease states. Changes observed in the process of haemostasis, on the other hand, display close correlation with the prognosis such disease states. The liver is the production site of naturally occurring anticoagulants such as AT-III, protein C and protein S.[6] Decrease in the plasma levels of these proteins can be anticipated. Cucuiano et al. reported significant decrease in protein C levels in patients with decompensated hepatic cirrhosis and suggested that such decrease were likely to stem from impaired or decreased hepatic protein synthesis.[7] Dumantier and the co-workers documented fall in the level of all clotting factors at variable levels, with the most prominent falls in AT-III and protein C levels.[8] Maurizio et al. reported that protein C, AT-III and protein S levels were subjected to a progressive decline as the disease deteriorates, with the most prominent declines in AT-III and protein C levels, and somewhat more moderate decline in protein S level.[9] Kendal and Ayyıldız reported decrease in AT-III, protein C and protein S levels and documented that such decrease were statistically more significant in Child B and Child C compared to Child A. Upon comparing the Child B and Child C groups, however, they showed the decreases in both groups not to reach the statistical level of significance.[10] Kloczko et al. investigated AT-III, protein C and protein S levels in hepatosteatosis, chronic hepatitis and hepatic cirrhosis groups, reporting statistically more significant declines in AT-III, protein C and protein S levels in the hepatic cirrhosis group compared to the chronic hepatitis and hepatosteatosis groups.[11] Gülcan et al. reported a statistically more significant decrease in protein C level in a patient group with hepatic cirrhosis compared to a chronic hepatitis.[12]

In our study, AT-III, protein C and protein S levels were measured to be statistically lower in hepatic cirrhosis group compared to chronic hepatitis group (Table 1). The most prominent decrease in both groups was observed in AT-III and protein C levels, along with the least prominent decline in protein S level. Synthesis capability of the liver is expected to deteriorate across worsening Child class of cirrhosis.

Vukovich and co-workers reported variations in haemostatic activation during progression from Child A to Child B and documented that the most dramatic declines among the indicators of anticoagulation potential especially like AT-III, protein

TABLE 4: Factor II and Factor VII levels in hepatic cirrhosis and chronic hepatitis patient groups.

	Hepatic Cirrhosis $\bar{\chi}$±SD (n:27)	Chronic Hepatitis $\bar{\chi}$±SD (n:25)	Result
Factor II (%)	40.17±3.59	68.05±6.36	p<0.05
Factor VII (%)	52.24±4.49	87.12±4.22	p<0.05

TABLE 5: Comparison of the results within the hepatic cirrhosis group on the basis of child classification.

	Child B $\bar{\chi}$±SD (n:6)	Child C $\bar{\chi}$±SD (n:21)	Result
AT-III (%)	58.97±11.69	46.31±6.81	p>0.05
Protein C (%)	30.07±6.85	37.27±3.69	p>0.05
Protein S (%)	73.85±14.21	54.03±5.10	p>0.05
ADP (μM)	32.16±4.15	34.85±2.77	p>0.05
Collagen (μg/mL)	34.50±2.32	31.00±3.85	p>0.05
Epinephrin (pg/mL)	37.50±6.31	30.30±3.72	p>0.05
Factor II (%)	41.8±8,05	39.71±4.11	p>0.05
Factor VII (%)	53.16±4.89	49.02±11.55	p>0.05

C and protein S occurred when progressing from Child B to Child C.[13] When the hepatic cirrhosis group was assessed within itself, AT-III, protein C and protein S levels were measured to be lower in Child C group compared to Child B group; however, such decrease did not reach statistical level of significance. Our results showed statistically significant decline in such naturally occurring plasma anticoagulants as protein C, protein S and AT-III in the hepatic cirrhosis group compared to the chronic hepatitis group.

PVT can occur for a sizable number of reasons in adults. Hepatic cirrhosis has been regarded for long as the leading cause of PVT in adult population. However, hepatic cirrhosis was detected only in 24-32% of the patients suffering from PVT.[3] The frequency at which PVT develops in hepatic cirrhosis patients is ranging from 0.06% to 21%. In this regard, the lowest PVT frequency (0.06%) was reported in cirrhotic patients by Okuda and the co-workers, while the greatest PVT frequency (21%) was reported by Nonami and the co-workers.[14,15] This great difference is likely to have resulted from distinct diagnostic modalities utilized in the studies and inclusion of cirrhotic patients with different disease levels. As for studies conducted in our country, a study by Öksüzoğlu and the co-workers reported PVT frequency to be 9%, while one other by Sarıçam and the co-workers reported PVT frequency to be 20%.[16,17] Of 27 patients with hepatic cirrhosis, we detected PVT in 2 patients (7.4%). Chen et al. investigated in their study conducted on patients with chronic hepatitis the occurrence of PVT and reported no thrombosis in those patients.[18] Sugimato et al. addressed decrease in portal venous flow velocity and impaired portal venous circulation in patients with hepatic cirrhosis, compared to chronic hepatitis patients.[19] Martinez et al. reported a dramatic increase in such vascular complications as portal vein thrombosis, portal hypertension and porto-systemic shunts in patients with hepatic cirrhosis, compared to those with chronic hepatitis.[20] PVT was not evident in the patient group with chronic hepatitis in our study, which can be ascribed to unimpaired synthesis of naturally occurring anticoagulants thanks to relatively much milder hepatocellular functional deterioration in chronic hepatitis patients compared to those with hepatic cirrhosis.

Platelet dysfunction is likely to develop in patients with hepatic cirrhosis.[21] Calabrese and the co-workers reported a prominent worsening in ADP- and epinephrine-induced platelet aggregation and a decline in platelet count.[22] Giacomo et al. reported a prominent worsening in ADP, epinephrine and collagen-induced platelet aggregation in cirrhotic patients of Child B of Child C classes; however, they also added that such impairment in platelet aggregation did not reach statistical level of significance across the Child classes.[23] Kunihro et al. reported a dramatic impairment in ADP-and collagen-induced platelet aggregation in cirrhotic patients.[21] Rudolf and the co-workers reported a marked decrease in platelet aggregation functions and platelet counts in patients with hepatic cirrhosis compared to these with chronic hepatitis.[24] Mira et al. also reported a decrease in platelet aggregation functions in hepatic cirrhosis compared to the patients with chronic hepatitis.[25]

In our study, ADP, epinephrine and collagen-induced platelet aggregation ratios were found to be significantly poor in the patients with hepatic cirrhosis compared to those with chronic hepatitis (Table 2). When analyzing the cirrhotic patients within their group, we detected a further impairment in platelet aggregation functions in the patient subgroup of Child C class, compared to that of Child B class. This difference, however, did not reach the statistical level of significance ($p>0,05$). Our results implied a frank worsening in platelet aggregation function upon progression from chronic hepatitis into hepatic cirrhosis and from Child B class towards Child C class, which was found to be compatible with the previous studies.

The platelet counts were found to be markedly lower in the patients with hepatic cirrhosis compared to the chronic hepatitis group ($p<0.01$). Such a decline might have been derived from hypersplenism secondary to portal hypertension in hepatic cirrhosis; however, further studies are

required to be conducted in order to elucidate if other factors, if any, can also account for this decline.

Hypoalbuminemia and hypergammaglobulinemia are typical findings in chronic hepatic disease states. Porto-systemic shunts and impairment in the hepatic reticuloendothelial system are held responsible for hypergammaglobulinemia. As for the hypoalbuminemia, it results from reduced hepatic synthesis capacity. Prothrombin time prolongs and did not respond to vitamin K therapy due to insufficient synthesis of the factors playing role in coagulation. Jaundice can also be accepted as a sign for decompensation in such patients, since bilirubin levels are quite well indicators of hepatocellular functions. Increase in serum bilirubin levels is a proxy for the prognosis in hepatic diseases.[26] Van Wersch and the co-workers detected a positive correlation between decreasing albumin level and AT-III and alpha-antiplasmin levels, attributing this result to reduced hepatic synthesis capacity.[27] Karıncalıoğlu et al. reported a marked increase in bilirubin and globulin levels, a marked prolongation in prothrombin time and a marked decrease in albumin level in patients with ascites secondary to hepatic cirrhosis compared to those with ascites secondary to various malignancy conditions. Moreover, they addressed that these parameters proved important parameters in the differential diagnosis of hepatic cirrhosis from other disease states.[28] Rudolf et al. reported a statistically significant decrease in albumin level, a statistically significant prolongation in prothrombin time and a statistically significant increase in bilirubin levels in patients with hepatic cirrhosis.[24] In our study, albumin levels were observed to be significantly lower in hepatic cirrhotic patients compared to those with chronic hepatitis. Moreover, total bilirubin level in cirrhotic patients were subjected to a statistically significant increase compared to the patients with chronic hepatitis ($p<0.01$) (Table 3). Our results again showed a statistically significant prolongation in prothrombin time in hepatic cirrhotic patients compared to those with chronic hepatitis. These findings are compatible with what has been addressed in the literature and can be regarded as a natural of insufficient production of albumin and clotting factors in patients with hepatic cirrhosis. Increase in bilirubin levels were ascribed to the hepatocellular dysfunction evident in these patients. On the other hand, albumin and bilirubin levels, prothrombin time and platelet counts were within normal range in the patients with chronic hepatitis.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the best indicators of acute hepatocyte injury. They also are quite valuable tests both in the differential diagnosis of cholestatic hepatic diseases and in the determination of acute attacks in chronic hepatitis.[1] In our study, AST and ALT levels were found to be statistically more elevated in the group with chronic hepatitis compared to the group with hepatic cirrhosis (Table 3).

Liver parenchymal cells are the cells where clotting factors are synthesized. Işıtan and the coworkers detected an inverse correlation between factor VII level and PT in patients with Child A and Child B cirrhosis, holding decreased hepatic synthesis capacity responsible for this.[29] Rodriquez et al. reported a significant decrease in factor VII level in hepatic cirrhosis compared to chronic hepatitis. The same study also addressed more and more decrease in factor VII level as the degree of fibrosis becomes more and more severe in hepatic cirrhosis.[30] Pagliano et al. reported more significant decrease in factor VII, factor II and factor X levels in patients with hepatic cirrhosis compared to the patients with chronic hepatitis and attributed this to the impairment in hepatic cellular functions.[31] Bick et al. documented cessation in bleeding and restoration of PT back to the normal levels following factor II therapy in patients with esophageal various vein bleeding related to hepatic cirrhosis.[32] Kendal and Ayyıldız documented more dramatic decrease in factor VII, factor VIII and factor IX levels in hepatic cirrhosis upon worsening of Child class from A to C, which also correlated positively with the haemostatic deterioration.[10]

On the basis of aforementioned results, we can suggest that the patients with hepatic cirrhosis are

subjected to much more prominent decrease in such coagulation factor as factor II and VII and such naturally-occurring coagulation inhibitors as protein C, protein S and AT-III, together with increased deterioration in platelet functions compared to the patients with chronic hepatitis. The haemostatic functional parameters subjected to the greatest alteration in chronic hepatic disease states dictate the occurrence of either bleeding diathesis or predisposition to thrombosis. Therefore, we believe that the patients with chronic disease should be followed up more closely with regard to the emergence of bleeding or thrombosis.

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