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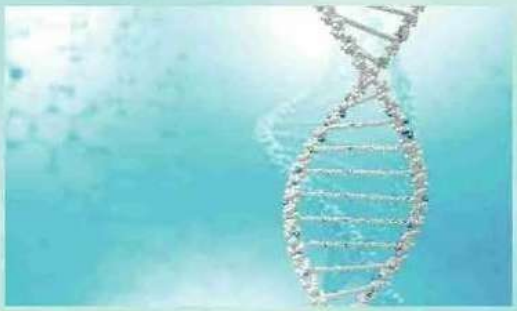

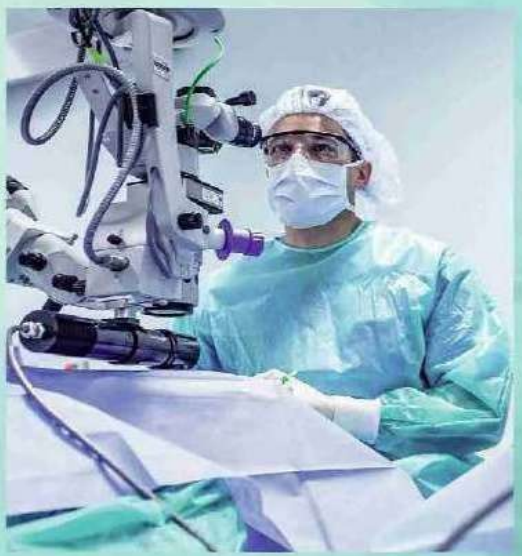

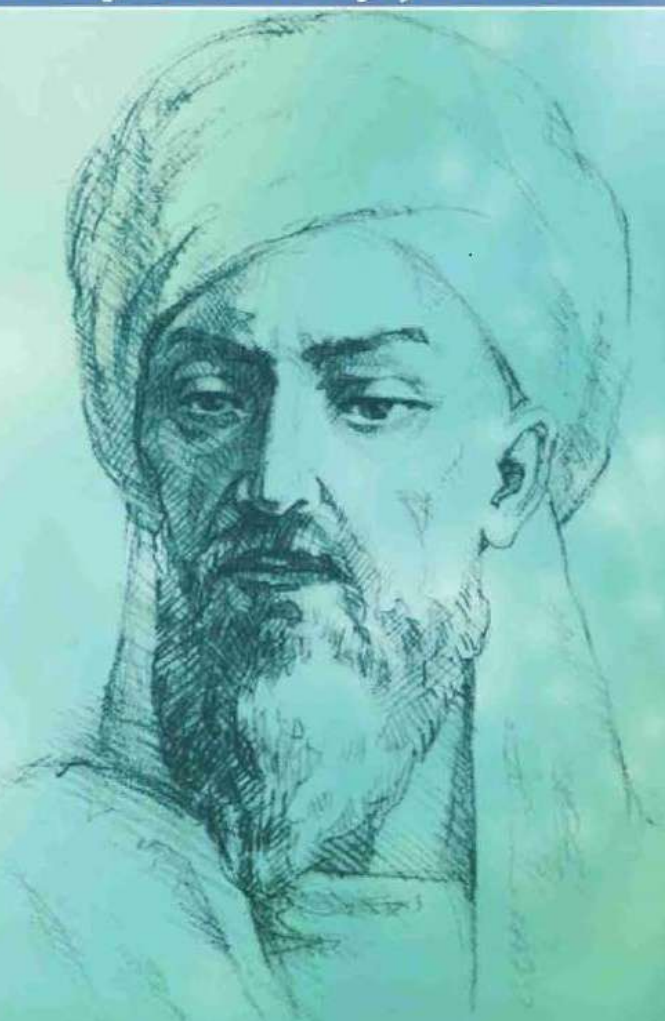

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NEW DAY IN MEDICINE

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VIOLATION OF PLATELET AGGREGATION AND IMBALANCE OF HEMOSTASIS IN PATIENTS WITH CHRONIC VIRAL HEPATITIS C

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✓ ***Resume***

A study investigated the blood clotting and platelet function in patients with chronic hepatitis C (CHC) infection. The study included 82 CHC patients (39 with advanced liver fibrosis and 43 with no or mild liver fibrosis) and 39 healthy individuals. 33 patients were treated and achieved sustained virological response (SVR). Blood samples were collected before and after treatment.

The study found that CHC patients with advanced fibrosis had impaired platelet function and lower levels of antithrombin, platelet count, and coagulation factors II-VII-X compared to healthy individuals. However, thromboelastography (TEG) did not differ between the groups. In patients who achieved SVR, post-treatment platelet count was higher than pre-treatment counts and some measures of platelet function improved, but remained below levels in healthy individuals. The study suggests that CHC-infected patients exhibit rebalanced blood clotting with only partial normalization in patients achieving SVR, which may have implications for the risk of cardiovascular disease and bleeding. Further studies are needed to understand the implications of rebalanced blood clotting.

Keywords: HCV, hemostasis, platelet aggregation

SURUNKALI VIRUSLI GEPATIT C BILAN KASALLANGAN BEMORLARDA TROMBOTSITLAR AGREGATSIYASINING BUZILISHI VA GEMOSTAZNING MUVOZANATLASHISHI

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✓ ***Rezyume***

Tadqiqotimizda surunkali gepatit C (HCV) infeksiyasi bo'lgan bemorlarda qon ivishi va trombotsitlar funksiyasini o'rganib chiqildi. Tadqiqotda 82 HCV bilan kasallangan bemorlar (39 jigar fibrozi rivojlangan va 43 jigar fibrozisiz yoki yengil jigar fibrozisiz) va 39 sog'lom shaxslar o`rganildi. 33 bemor davolandi va barqaror virusga qarshi samaraga (BVQS) erishdi. Qon namunalari davolanishdan oldin va keyin to'plangan.

Tadqiqot davomida fibroz rivojlangan bemorlarda trombotsitlar funksiyasi buzilganligi va antitrombin, trombotsitlar soni va II-VII-X koagulyatsion omillari sog'lom odamlarga nisbatan past bo'lganligi aniqlandi. Biroq, tromboelastografiya (TEG) natijalari guruhlar o'rtasida farq qilmadi. BVQS erishgan bemorlarda davolanishdan keyingi trombotsitlar soni davolanishdan oldingi ko'rsatkichlardan yuqori edi va trombotsitlar funksiyasi yaxshilandi, ammo sog'lom odamlarda normal darajadan past bo'lib qoldi. HCV bilan kasallangan bemorlarda BVQS erishgan bemorlarda faqat qisman normallashtirish bilan muvozanatli qon ivishi namoyon bo'ladi, bu esa yurak-qon tomir kasalliklari va qon ketish xavfiga ta'sir qilishi mumkinligidan dalolat beradi. Balanslangan qon ivishining oqibatlarini tushunish uchun qo'shimcha tadqiqotlar o'tkazish kerak.

Kalit so'zlar: HCV, gemostaz, trombotsitlar agregatsiyasi

НАРУШЕНИЕ АГРЕГАЦИИ ТРОМБОЦИТОВ И ДИСБАЛАНС ГЕМОСТАЗА У БОЛЬНЫХ ХРОНИЧЕСКИМ ВИРУСНЫМ ГЕПАТИТОМ С

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✓ ***Резюме***

В ходе исследования изучались показатели свертываемости крови и функции тромбоцитов у пациентов с хроническим гепатитом С (ХГС). В исследование были включены 82 пациента с ХГС (39 с прогрессирующим фиброзом печени и 43 без фиброза печени или с умеренным фиброзом печени) и 39 здоровых людей. 33 пациента прошли курс лечения и достигли устойчивого вирусологического ответа (УВО). Образцы крови были взяты до и после лечения.

Исследование показало, что у пациентов с ХГС с прогрессирующим фиброзом наблюдались нарушения функции тромбоцитов и более низкие уровни антитромбина, количества тромбоцитов и факторов свертывания II-VII-X по сравнению со здоровыми людьми. Однако результаты тромбоэластографии (ТЭГ) не отличались между группами. У пациентов, достигших УВО, количество тромбоцитов после лечения было выше, чем до лечения, и некоторые показатели функции тромбоцитов улучшились, но оставались ниже показателей здоровых людей. Исследование показывает, что у пациентов, инфицированных ХГС, наблюдается восстановление баланса свертываемости крови, при этом у пациентов, достигших УВО, он нормализуется лишь частично, что может влиять на риск сердечно-сосудистых заболеваний и кровотечений. Необходимы дальнейшие исследования, чтобы понять последствия восстановления баланса свертываемости крови.

Ключевые слова: гепатит С, гемостаз, агрегация тромбоцитов

Relevance

Hepatitis C virus (HCV) is the cause of viral hepatitis, with an estimated 130–150 million persons with chronic hepatitis C infection (CHC) worldwide [1]. Approximately 80% of those infected will develop CHC, and 10–15% of patients with CHC infection will develop advanced liver disease with cirrhosis and increased risk of hepatocellular carcinoma (HCC) [2]. Besides these well-known manifestations of CHC, increased risk of cardiovascular disease (CVD) and thromboembolic events has been documented [3–6]. Vascular inflammation and altered coagulation caused by CHC infection has been hypothesized to contribute to increased CVD risk. In contrast, CHC infection is also associated with thrombocytopenia and lower levels of coagulation factors, contributing to an increased risk of bleeding [7–9]. Evidence thus points towards manifestations of both hypo- and hypercoagulability.

Hemostasis is balanced by pro- and anticoagulant and pro- and antifibrinolytic factors, most of these being synthesized by the liver [10]. Advanced liver disease is thus associated with perturbations in the level of these due to secretory deficiencies [11,12]. Furthermore, lower platelet count, lower concentrations of factor II-VII-X, and anti-fibrinolytic factors are all features of CHC infection, suggesting hypocoagulability [7,10,13]. However, higher concentrations of von-Willebrand factor (vWf) and Factor VIII as well as lower concentrations of anticoagulant factors including Protein C and S have also been reported in CHC infection suggesting hypercoagulability [10,13–15]. The combination of these alterations may lead to a rebalanced hemostasis as a common explanation for the observed increased risk of both thromboembolic events and bleeding in patients with CHC infection [13].

Conventional plasma-based coagulation tests such as activated partial thromboplastin time (APTT) and international normalized ratio (INR) are often used to assess both hemostasis and liver function in CHC-infected patients [16]. However, these tests are poor predictors of bleeding risk and cannot predict thrombotic events [16]. In contrast, the risk of bleeding and thromboembolic events can be assessed by functional hemostatic whole blood tests such as thromboelastography (TEG) and

impedance platelet aggregometry , which are well-established tests reflecting secondary and primary hemostasis, respectively [13,15,17]. To the present authors' knowledge, no previous studies have investigated whole blood hemostatic function in patients with CHC infection.

The primary aim of this study was to investigate hemostasis in patients with CHC infection using functional hemostatic whole blood tests and determine possible associations with liver fibrosis. CHC-infected patients with no or mild and with advanced fibrosis as well as a group of uninfected controls were included in a cross sectional study. To determine possible effects of HCV viral replication on coagulation, a prospective study of patients starting treatment against CHC infection was conducted. It was hypothesized that untreated CHC infection was associated with altered whole blood functional hemostasis tests and that hemostasis would normalize after successful treatment of HCV.

The three groups (CHC with no or mild fibrosis, CHC with advanced fibrosis, and healthy controls) in the cross sectional study differed regarding age. A Spearman correlation test did not reveal any significant correlations between age and TEG or Multiplate data. Furthermore, due to study design, the CHC-infected group with advanced fibrosis had a higher level of fibrosis compared to patients with no or mild fibrosis.

Altered Standard Coagulation Tests in CHC-Infected Patients. Compared to healthy controls, patients with CHC infection, both with no or mild fibrosis and with advanced fibrosis, had lower platelet counts and lower concentration of antithrombin, whereas only patients with advanced fibrosis had lower concentration of coagulation factor II-VII-X. Compared to CHC-infected patients with no or mild fibrosis, CHC-infected patients with advanced fibrosis had lower platelet counts (median 139 × 109/L versus 232 platelets × 109/L, $p < 0.001$) and lower concentration of coagulation factors (0.76 arb.units versus 0.88 arb.units, $p = 0.002$). Furthermore, the concentration of antithrombin was lower in patients with advanced fibrosis compared to patients with only no or mild fibrosis (0.86 IU/L versus 1.01 IU/L ($p < 0.001$)). The proportion of patients with D-dimer above threshold was 21% in the group of CHC-infected patients with advanced fibrosis versus 2% in CHC-infected patients with no or mild fibrosis ($p = 0.009$). APTT and fibrinogen did not differ between CHC-infected patients.

When correcting for platelet count ("multiplate variable"/"platelet count in patient" = multiplate unit per platelet), patients with advanced fibrosis had higher per platelet function than both CHC-infected patients with no or mild fibrosis (TRAP/platelet count = 0.51 versus 0.42 U/109/L $p = 0.008$) and healthy controls (TRAP/platelet count = 0.51 versus 0.46 U/109/L $p = 0.044$). Same pattern was observed for ADPtest but not ASPItest and RISTOhigh test.

Minor Changes in Functional Hemostasis after Treatment. A total of 33 patients were treated for CHC infection and achieved SVR. End of treatment samples were compared with baseline samples. Standard blood coagulation tests, platelet counts, and fibrinogen were partly but not fully restored and remained below the healthy controls . No changes in overall wholeblood coagulation (TEG analysis) were found.

Improvements were observed in the Multiplate analysis with partly normalization of ($p = 0.003$), ASPItest ($p = 0.007$), and RISTOhigh test ($p = 0.003$). No significant differences were observed in the TRAPtest ($p = 0.060$. When correcting for platelet count, the per platelet function did not significantly change post treatment when compared to pretreatment (TRAP/platelet count = 0.51 versus 0.49 U/109/L $p = 0.537$). The same pattern was observed for ADPtest, ASPItest, and RISTOhigh test (data not shown).

Compared to uninfected controls, patients who had been treated for CHC infection and achieved SVR still had lower platelet count ($p = 0.001$) and coagulation factor II-VII-X ($p = 0.001$). In contrast whole blood hemostasis was comparable to uninfected control. Importantly, patients with SVR still had impaired platelet aggregation with lower TRAPtest ($p = 0.001$) ADPtest ($p = 0.001$), ASPItest ($p = 0.001$), and RISTOhigh test ($p = 0.004$) when compared to healthy controls . Patients who achieved SVR continued to have significant lower per platelet activation in TRAP analysis post treatment when compared to healthy controls (TRAP/platelet = 0.49 versus 0.46 U/109/L $p = 0.027$). Same pattern was observed for ADPtest ($p = 0.001$) and RISTOhigh test ($p = 0.036$) but not ASPItest ($p = 0.270$).

Discussion: Patients with CHC infection and advanced fibrosis had decreased platelet count and impaired platelet aggregation when compared to both CHC patients with no or mild fibrosis and healthy controls. However, patients with CHC infection and advanced fibrosis also displayed evidence of no overall impairment in functional hemostasis indicating a rebalanced overall hemostatic capacity Importantly, CHC-infected patients that were treated and achieved SVR only obtained partial

normalization of both platelets count and platelet aggregation, when compared to the healthy controls.

Coagulation in patients with CHC infection has often been evaluated using standard coagulation tests including factor II-VII-X, INR, and APTT. However, the use of these tests in patients with liver disease has been questioned as the tests are poor predictors of both bleeding and cardiovascular comorbidity [5,16]. The accumulating evidence of increased risk of thromboembolic events and CVD in patients with CHC infection warrants application of tests that measure functional hemostatis [16,18]. TEG has been used for a decade to monitor and goal-direct hemostatic therapy in liver transplantation, cardiac surgery, intensive care, and bleeding in trauma patients [19–23]. TEG has also been used to predict cardiovascular events like pulmonary embolism, myocardial infarction, and deep vein thrombosis (DVT) in post-surgical patients [14] and to evaluate risk of bleeding in patients with liver disease [16]. Studies have found an overall normal TEG in patients with liver disease, further suggesting a rebalanced hemostasis [19]. Multiplate has been used in clinical routine to monitor the effect of anti-platelet drugs in surgical settings and platelet dysfunction in critical illness including trauma and sepsis [17] as well as to evaluate risk of cardiovascular events and effect of antithombotic medication [18]. Thus, whole blood functional hemostasis tests may provide additional information about hemostasis and CVD risk in CHC-infected patients. At the University Hospital of Copenhagen, TEG and Multiplate are used to goal-direct transfusion and therapy with pro-hemostatic drugs in bleeding or at risk of bleeding patients and in patients prior to high risk surgical procedure . The present study does not assess the possible benefits of using TEG and/or Multiplate in CHC patients in a surgical setting; further studies are needed to assess this aspect. Using whole blood coagulation test, especially Multiplate, could prove valuable in the clinical assessment of liver disease, especially when complicated with bleeding, but further studies are needed aiming to investigate this CHC patients.

Assessing fibrosis using fibroscan to is feasible, but exact cut-off for fibrosis and cirrhosis are still a matter of debate. According to the European Association for the Study of the Liver (EASL) guidelines, values between 5.2 and 9.5 kPa have been proposed as cut-off for ≥F2 fibrosis and values between 11.9 and 14.8 kPa as cut-off for cirrhosis [34]. Based on these guidelines and guidelines from our clinic, the present study divided patients with CHC infection in two groups. One with Fibroscan <8 kPa termed “CHC patients with no or mild fibrosis level” and one with Fibroscan >8 kPa termed “CHC patients with advanced fibrosis” including cirrhosis.

The prevalence of thrombocytopenia in patients with chronic liver disease, including CHC, has been reported to be between 15–70%, with thrombocytopenia being associated with the severity of disease. In agreement with this, the present study found lower platelet counts in patients with advanced fibrosis as compared to patients with no or mild fibrosis. Furthermore, patients with advanced fibrosis had impaired platelet aggregation compared to patients with no or mild fibrosis and healthy controls. Likewise, previous studies of platelet function in CHC, applying the platelet function analyzer (PFA-100) and quantitative measurements of metabolites from the platelet metabolism, have suggested a dysfunction of platelets in patients with advanced liver disease. Thus, impaired function of platelets in patients with cirrhosis due to impaired inositol lipid and arachidonic acid metabolism has been reported. Furthermore, lower platelet activation in patients with hepatitis B and C was found after stimulated with TRAP but not ADP. Interestingly, the present study found higher per-platelet activation in patients with advanced fibrosis compared to that in healthy controls suggesting a compensatory mechanism in patients with advanced liver disease. The present study, however, does not provide information on the exact mechanism for such a compensation, and further studies are needed to explore this subject.

Previous studies have found impairment of both the pro- and anticoagulant system in patients with chronic liver disease, including CHC infection, and a hypothesis suggesting a rebalanced coagulation has been proposed [9,13–15]. The present study provides support for this hypothesis. Thus, despite having lower platelet count, impaired overall platelet aggregation, and lower concentration of pro-coagulant factors, patients with CHC infection had normal whole blood functional hemostasis when measured with TEG. This suggests that CHC-infected patients have a rebalanced hemostatic system possible partly due to lower levels of antithombin and by higher per-platelet activity found in present study.

The effect of HCV viral replication on coagulation was assessed in a prospective study of 33 patients that were treated for CHC infection and achieved SVR. Only minor changes were observed in standard coagulation parameters post treatment. Thus, although platelet counts and level of coagulation factor II-VII-X increased post treatment, they remained lower compared to healthy controls. A previous study

including 100 patients with SVR showed a slow rise and only gradual normalization in platelet count over 7.5 years of follow up. Likewise, improvement of platelet aggregation was found in post treatment though it did not reach a level comparable with that in healthy controls.

This calls into question whether altered coagulation in CHC infection is merely a direct result of HCV viral replication. An alternative explanation could be damage to the liver as evidenced by the presence of persistent liver fibrosis in patients with SVR. Earlier studies have suggested a slow regression of fibrosis in some but not all patients who achieve SVR. Unfortunately, this study was not able to measure the level of fibrosis post treatment. However, the above suggests a long recovery phase beyond that of achieving SVR, indicating the need to evaluate the functional hemostatic system in studies with longer follow-up.

Conclusion

The present study had some limitations. First, it included a relatively low number of participants especially in the prospective study. The cross-sectional design used in part of the study limits analysis of causality. Treated patients only had one blood sample drawn post treatment, limiting the possible effects of long-term SVR on the coagulation system and unfortunately patients with or without fibrosis differed with regards to age. However, significant correlations between age and the functional hemostasis tests were not found. Finally, all hemostasis tests were performed on blood in vitro, not taking the contribution of the endothelium into account.

LIST OF REFERENCES:

1. Ampuero J. Assessing cardiovascular risk in hepatitis c: An unmet need. //World J. Hepatol. 2015;7:2214.
2. Butt A.A., Wang X., Budoff M., Leaf D., Kuller, L.H., Justice, A.C. Hepatitis c virus infection and the risk of coronary disease. //Clin. Infect. Diseases 2011;49:225-232.
3. Chen S.L.; Morgan T.R. The natural history of hepatitis c virus (HCV) infection. //Int. J. Med. 2006;3:47-52.
4. Clin. Gastroenterol. Hepatol. 2013;11:1064-1074.
5. Fouad Y.M. Chronic hepatitis c-associated thrombocytopenia: Aetiology and management. Trop. //Gastroenterol. 2013;34:58-67.
6. World Health Organization (WHO). Hepatitis C; WHO: Geneva, Switzerland, 2014.
7. Jumayeva M.F., Predictors of The Development Of Hepatorenal Syndrome. //Problems biology and medicine. 2022;6(140):80-82.
8. Jumaeva M.F., Hepatorenal Syndrome. //Asian journal of Pharmaceutical and biological research. SEPT.-DEC. 2022;11(3):72-77.
9. Jumayeva M.F. Hepatocardiorenal syndrome. //Asian journal of Pharmaceutical and biological research. JAN-APR 2022;11(1).
10. Jumaeva M.F., Gepatokardiorenal sindrom. //Farmatsevtika va biologik tadqiqotlar Osiyo jurnali. 2022 YAN-APRAL;11(1):83-97.
11. Jumaeva MF, Gepatorenal sindrom. //Farmatsevtika va biologik tadqiqotlar Osiyo jurnali. SENTYABR-DEK. 2022;11(3):72-77.
12. Jumayeva MF, Gepatorenal sindrom rivojlanishining prognozchilari. //Biologiya va tibbiyot muammolari. 2022;6(140):80-82.
13. Lisman T.; Leebeek F.W.G. Hemostatic alterations in liver disease: A review on pathophysiology, clinical consequences, and treatment. //Dig. Surg. 2007;24:250-258.
14. Lisman T. Hemostatic dysfunction in liver diseases. //Semin. Thromb. Hemost. 2015;445-446.
15. Lisman T., Porte R.J. Rebalanced hemostasis in patients with liver disease: Evidence and clinical consequences. //Blood 2010;116:878-885.
16. Lisman T.; Bongers T.N., Adelmeijer J., Janssen H.L.A., de Maat, M.P.M., de Groot P.G., Leebeek F.W.G. Elevated levels of von willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. //Hepatology 2006;44:53-61.
17. Northup P.G., Caldwel S.H. Coagulation in liver disease: A guide for the clinician.
18. Sherman K.E. Advanced liver disease: What every hepatitis c virus treater should know. //Top. Antivir. Med. 2011;19:121-125.
19. Tripodi A., Mannucci P.M. The coagulopathy of chronic liver disease. //N. Engl. J. Med. 2011;365:147-156.
20. Zampino R., Marrone A., Restivo L., Guerrera B., Sellitto A., Rinaldi L., Romano C., Adinolfi L.E. Chronic HCV infection and inflammation: Clinical impact on hepatic and extra-hepatic manifestations. //World J. Hepatol. 2013;5:528-540.

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