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VIRAL HEPATITIS SOCIETY

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AIM AND SCOPE

Viral Hepatitis Journal (Formerly Viral Hepatit Dergisi) is the regular publishing organ of the Viral Hepatitis Society. This periodical journal covers diagnosis, treatment, epidemiology, prevention and information of hepatitis.

Viral Hepatitis Journal is an open-access journal published 3 times per year (April, August and December). In addition, the special issues are published in some periods. It is a periodic national/international journal, published in English language with abstract and title published also in Turkish language and its editorial policies are based on independent peer-review principles.

The aim of Viral Hepatitis Journal is to continuously publish original research papers of the highest scientific and clinical values specifically on hepatitis, on an international level. Additionally, reviews on basic developments in education, editorial short notes, case reports, original views, letters from a wide range of medical personal containing experiences and comments as well as social subjects are published.

For general practitioners giving first line medical service who are interested in hepatitis, specialists in internal medicine, gastroenterology, microbiology, family physician, public health and hepatology, 'things that must be known' subjects will ensure to involve in Viral Hepatitis Journal.

Efforts are being made to be recognized of Viral Hepatitis Journal by indexes. Online article acceptance through website of the journal and all published volumes can be reached as full text without fee through the web site http://viralhepatitisjournal.org/.

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Viral Hepatitis Journal (Formerly Viral Hepatit Dergisi) is an independent, peer-reviewed international journal published quarterly in April, August, December. The official language of the journal is English.

Viral Hepatitis Journal is a scientific journal that publishes retrospective, prospective or experimental research articles, review articles, case reports, editorial comment/discussion, letter to the editor, surgical technique, differential diagnosis, medical book reviews, questions-answers and also current issues of medical agenda from all fields of medicine and aims to reach all national/international institutions and individuals.

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In the international index and database, the name of the journal has been registered as Viral Hepatitis Journal and abbreviated as Viral Hepat J.

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The content of the submitted manuscripts should conform to the criteria stated in "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" published by International Committee of Medical Journal Editors and updated in 2016 (available at http://www.icmje.org/).

The authors should acknowledge and provide information on grants, contracts or other financial support of the study provided by any foundations and institutions or firms.

The articles sent to be published in the journal shouldn't have been published anywhere else previously or submitted and accepted to be published. However, a complete report that follows publication of a preliminary report, such as an abstract can be submitted. If authors intend to discard any part of the manuscript, a written application should be sent to the Editor.

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PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

STROBE statement—checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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vi. Results (max 400 words)
vii. Discussion (max 700 words)
viii. Referances (should not exceed 15), all words 2000 not exceed.

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• Author number for case report presentations should not exceed four.

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Title Page: Title should be concise and informative (in Turkish and English). The title page should include a list of all contributing authors and all of their affiliations. Positions of authors and names of departments and institutions to which they are attached and the province should be written. Supply full correspondence details for the corresponding author, including phone, mobile phone, fax number and e-mail address.

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The text file should include the title in Turkish, keywords, the title in English, keywords in English, the text of the article, references, tables (only one table for one page) and figure

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Review articles can address any aspect of viral hepatitis Review articles must provide critical analyses of contemporary evidence and provide directions of or future research. Most review articles are commissioned, but other review submissions are also welcome. Before sending a review, discussion with the editor is recommended.

Reviews articles analyze topics in depth, independently and objectively. The first chapter should include the title in Turkish and English, an unstructured summary and keywords. Source of all citations should be indicated. The entire text should not exceed 25 pages (A4, formatted as specified above).

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Letters to the Editor should be short commentaries related to current developments in viral hepatitis and their scientific and social aspects, or may be submitted to ask questions or offer further contributions in response to work that has been published in the Viral Hepatitis Journal. Letters do not include a title or an abstract; they should not exceed 1000 words and can have up to 5 references.

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Journal abbreviations should conform to the style used in the Cumulated Index Medicus. Only list the literature that is published, in press (with the name of the publication known) or with a doi number in references. It is preferred that number of references do not exceed 50 for research articles, 100 for reviews and 10 for case reports.

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Acknowledgment: Only acknowledge persons and institutions who have made substantial contributions to the study, but was not a writer of the paper.

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Seroprevalence Investigation of Hepatitis B and Hepatitis B Core Antigen in Oncology Patients

Onkoloji Hastalarında Hepatit B ve Hepatit B Çekirdek Antijenin Seroprevalansının Araştırılması

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ABSTRACT

Objectives: Hepatitis B virus (HBV) affects a significant part of society and is characterized by high mortality and morbidity. Hepatitis B affects approximately 350 million people worldwide, many of whom are chronic patients. Especially being under immunosuppressive therapy is a risk factor for the reactivation of the disease. The aim of this study was to investigate the seroprevalence of HB in oncology patients.

Materials and Methods: In this study, the seroprevalences of hepatitis B surface antigen (HBsAg), anti-hepatitis C virus, anti-HBs, and anti-hepatitis B core antibody (anti-HBc) immunoglobulin G (IgG) were retrospectively evaluated from the medical records of 84 patients who were diagnosed of cancer, and were admitted to the outpatient clinic of medical oncology in the Batman State Hospital within a period of one year (between January and December 2017).

Results: Anti-HBc IgG was positive in 44 patients (52.2%),16 (36.4%) have received treatment for the prevention of HBV reactivation six of these patients were HBsAg positive No reactivation and no side effects occur in patients who received prophylactic antiretroviral treatment.

Conclusion: In our study, both the proportion of patients with HBsAg positivity and the proportion of patients with natural immunity were found to be slightly higher than those in Turkey and worldwide. No patients with HB reactivation is important evidence of necessity effectiveness of prophylactic antiviral treatment

Keywords: Hepatitis B reactivation, oncology, immunosuppressive treatments, prophylactic antiviral treatments

ÖZ

Amaç: Hepatit B virüsü (HBV) toplumun önemli bir bölümünü etkiler ve yüksek mortalite ve morbidite ile karakterizedir. HB, çoğu kronik hasta olan dünya çapında yaklaşık 350 milyon kişiyi etkilemektedir. Özellikle immünosüpresif tedavi altında olmak, hastalığın yeniden aktivasyonu için bir risk faktörüdür. Bu çalışmanın amacı, onkoloji hastalarında HB seroprevalansını araştırmaktır.

Gereç ve Yöntemler: Bu çalışma retrospektif nitelikte tanımlayıcı bir çalışma olarak gerçekleştirilmiştir. 1 Ocak-2017 ila 31 Aralık 2017 dönemi boyunca Batman Bölge Devlet Hastanesi, Onkoloji Bölümü'ne başvuran 84 hasta çalışmaya dahil edilmiştir. Bu hastaların hepatit serolojileri kayıt altına alınarak hastalar aktif HBV enfeksiyonu, geçirilmiş HBV enfeksiyonu, almış oldukları profilaksiler ve reaktivasyon açısından değerlendirmiştir.

Bulgular: Hastaların 6'sı hepatit B yüzey antijeni (HBsAg) pozitif olarak saptanmış olup, 44 hasta (%52,2) ise anti-HBc immünoglobulin G (IgG) pozitif olarak saptanmıştır. Bu 44 hastadan 28 hasta (63.6%) düşük riskli bir kemoterapotik ajan almaları nedeniyle profilaksi almamıştır, diğer hastalar ise profilaksi almıştır. HBsAg poztif olan hastalardan bir hasta dışında tüm hastalar tedavi almıştır. Tüm pozitif hastalar değerlendirdiğinde takipte hiçbir hastada reaktivasyon gelişmemiştir.

Sonuç: Kapsamlı HB serolojisi onkolojik tedavi planı olan tüm hastalara bilinmeli ve eğer endikasyonu varsa hastalar tedavi veya profilaksi için değerlendirmelidir. Bu değerlendirmelerde kılavuz önerileri esas alınması reaktivasyon gelişme ihtimalini en aza indirecektir.

Anahtar Kelimeler: Hepatit B reaktivasyonu, onkoloji, immünosupresif tedaviler, profilaktik antiviral tedaviler

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Introduction

Hepatitis B virus (HBV) affects a significant part of society and is characterized by a high clinical picture of mortality and morbidity. Hepatitis B affects approximately 250 million people worldwide, many of whom are chronic patients (1).

The current guidelines recommend that patients diagnosed with cancer should be screened for HB immediately after diagnosis (1), and vaccinations should be offered to individuals who have never come in contact with HBV. Patients with anti-HBs positivity should be assessed by anti-hepatitis B core antibody (anti-HBc) immunoglobulin G (IgG) and natural/acquired immunity should be distinguished among all the patients. Those with natural immunity should be assessed for a reactivation prophylaxis requirement by classifying them according to the risk group of the chemotherapy regimen. While patients receiving HB treatment prior to cancer diagnosis and therapy should continue taking their prescribed drugs, patients with hepatitis B surface antigen (HBsAg) positivity who receive no antiviral treatment should be evaluated for reactivation prophylaxis according to oncology treatment regimens (1,2,3).

Hepatitis B virus reactivation (HBVr) can be defined as detectable levels of serum HBV-DNA in patients with a baseline undetectable level ≥2 log10 IU/mL, increase in HBV-DNA in patients with a baseline detectable viral load, or reappearance/reversion of HBsAg (4). Reactivation is more common in HBV than in HVC and occurs more frequently in men than in women (3,4,5).

Furthermore, individuals who come in contact with the HBV on subsequent occasions may develop a natural immunity to the virus (i.e., patients possessed anti-HBs positivity due to their previous history of hepatitis B infection and simultaneously possessed anti-HBc IgG seropositivity. HBVr may develop some symptoms or it may entirely be asymptomatic. Fatigue, nausea, and vomiting are the most common visible symptoms. However, some patients may experience liver failure and some may even die. The risk of HBVr is highest in patients who test positive to HBsAg (up to 50%). Individuals with natural immunity receiving immunosuppressive treatments are also at risk of HBVr (3,6).

In this study, we aim to investigate the frequency of individuals with hepatitis B and naturally acquired immunity against hepatitis B, as well as demonstrate the proportion of patients requiring treatment for the prevention of HBVr by retrospectively screening the hepatitis serological assays of patients who were admitted to and diagnosed with cancer at the Medical Oncology Unit of the Batman Regional State Hospital in 2017.

Materials and Methods

In this study, the seroprevalences of HBsAg, anti-HCV, anti-HBs, anti-HIV, and anti-HBc IgG were retrospectively evaluated from medical records of 84 patients who were diagnosed with cancer and were admitted to the outpatient clinic of Medical Oncology in the Batman Regional State Hospital within a period of one year (between January and December 2017).

In addition, the records of patients that applied to the infectious diseases and gastroenterology departments for oral antiviral treatment to prevent hepatitis B reactivation, according to the examination, were retrospectively examined. The treatments given and the results obtained were subsequently evaluated.

Ethics committee approval for this study was obtained from the Batman Regional State Hospital Non-Invasive Clinical Studies Ethics Committee with the date and number of 01.03.2018/82.

Statistical Analysis

Data from enrolled patients were analyzed using the Statistical Package for the Social Sciences 24 program.

Results

A total of 84 newly diagnosed cancer patients were admitted to the Department of Medical Oncology at the Batman Regional State Hospital in 2017, 43 (51.2%) were women. The mean age of the patients was 55.9 years (range: 17-81 years). Among the 84 patients, 26 (31%) were diagnosed with breast cancer, 15 (14.9%) with lung cancer, 9 (10.7%) with colon cancer, 6 (7.1%) with prostate cancer, 5 (5.9%), other patients diagnosed with other types of cancer.

The seroprevalence of HBsAg positivity was determined in six individuals (7.1%). Anti-HBs negative outcomes were observed in 38 patients (45.9%), while 46 patients (54.1%) showed anti-HBs positivity. Eight patients with anti-HBs positivity (9.5%) were considered as immunized through vaccination. Thirty-eight patients with both anti-HBs and anti-HBc IgG positivity (45.2%) were considered as previously infected with the HBV and as possessing naturally acquired immunity. No anti-HCV or anti-HIV positivity was detected in the patients.

Anti-HBc IgG was positive in 44 patients (52.2%). Six of those patients were positive to HBsAg and 16 (36.4%) received treatment for the prevention of HBVr. One of these HBsAg-positive patients had not been treated for hepatitis B. Among the 16 patients, 7 (43.8%) received entecavir as the treatment regimen, 8 (50%) received tenofovir, and 1 received lamivudine (6.3%). All the patients with HBsAg positivity tested negative to HBeAg. None of these patients had hepatitis B treatment prior to the cancer treatment. The treatments of all the patients were initiated following the serologic screening but preceding the chemotherapy regimens. Twenty-eight patients with natural immunity (63.6%) did not receive the reactivation prophylaxis that was initiated because they had received chemotherapeutic agents in the low-risk group. No reactivation occurred in any of this patients.

Based on the immunosuppressive properties of the chemotherapies initiated, the patients' oral antiviral therapies were scheduled to be discontinued within six months to one year. One (1.2%) of the enrolled patients had isolated anti-HBc IgG positivity

In the one-year follow-up, none of the patients at risk has developed HBVr yet. The follow-up of the patients continuing oral antiviral therapy is still ongoing. None of the patients that were admitted to the outpatient clinics of infectious diseases due to oral antiviral drugs-related adverse events started antiviral treatments.

Discussion

HBV infects close to 350 million individuals annually, while approximately 800 thousand individuals per year die due to hepatitis-related complications. Patients may present with different clinical pictures depending on the HBV types, including acute

infection, chronic infection, hepatic insufficiency, fulminant hepatitis, cirrhosis, and hepatocellular carcinoma (1,2,3).

It is not possible to halt the persistence of this disease because of cccDNA. Hepatitis B affects a large number of individuals worldwide, even though it can be prevented through vaccination. Oral antivirals can also be used to control hepatitis in certain cases, however, the development of hepatocelluler carcinoma cannot be definitively prevented even by this intervention (1,3,7).

Serologic screening for hepatitis B must be performed in oncology patients as well as in all other patients who will receive immunosuppressive treatment for any reason. Also, HBsAg-negative patients should not be considered completely risk-free (3,5). It is important that the HBsAg-negative and anti-HBs-positive patient groups are immunized either naturally or by vaccination. In other words, the HBV exposure status of patients should be clearly determined by serologically testing anti-HBc IgG, particularly in regions where the disease is moderately to highly endemic because the proportion of individuals with natural immunity might be higher (7,8,9).

Turkey is a moderately endemic country for hepatitis B. This implies that some patients in our study require treatment to protect from the risk of reactivation. Such high rates could be because the region where the study was conducted has the highest seroprevalence rates across Turkey (8). However, both the high proportion of individuals with natural immunity and the considerable proportion of patients receiving HBV prophylaxis due to cancer therapy suggest that HBV exposure status must be clearly assessed prior to treatment (in terms of anti-HBc IgG) (1,5).

In the study performed by Kose et al. (10), serological indicators of hepatitis in oncology patients were found as follows: The positivity of HBsAg was determined in 4.2% individuals, anti-HBc total was positive in 38.4% patients,18.1%) patients had isolated anti-HBc total positivity, (10). Compared to this study, HBV exposure rate was higher in our study. The main reason of this difference is thought to be that the disease is more endemic in the South Anatolia region in Turkey. This reveals the importance of investigating the disease with anti-HBc total.

When we compare with world data, Wu et al. (11) HBV reactivation in oncology patients with the meta-analysis study, it was seen that no recoveries were associated in our study with prophylaxis in all patients who needed prophylaxis. The frequency of the disease observed in this study and therefore the different rates of reactivation in different regions seem to be related to the epidemiology of the disease and prophylactic oral antiviral administration at the right time.

The fact that the patients did not develop HBVr during our study was satisfactory; all the patients were fully screened and prophylaxis was administered to all the eligible patients in accordance with the recommended guidelines to formulate these results. Patients' prophylactic regimens, with the exception of one patient who received lamivudine, were administered using drugs with high genetic barriers in accordance with the recommended guidelines (2,3).

Conversely, some patients had low-risk chemotherapy regimens that did not require prophylaxis, and HBVr did not develop among these patients. The lack of treatment for this group of patients is still a controversial subject around the world and the algorithms in this area are often changing.

The patient with isolated anti-HBc IgG positivity didn't receive any treatment aganist HBVr and noticed that this patient was not recommended for an investigation into the occult hepatitis B infection. But in the follow up we have seen that this patient didn't recativate.

Study Limitations

Biggest limitation of our study is it is performed as a retrospective data analysis in a limited cohort of patients. However, the same reason, a certain patient population of patients, minimized data loss.

Conclusion

Hepatitis serology should be evaluated in all patients with an oncologic diagnosis and treatment plan. Prophylactic treatment should be given where necessary. On the other hand, treatment should not be given when not necessary. The risk of HBVr can be minimized with the right approaches according to the guidelines.

Ethics

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Batman Regional State Hospital Non-Invasive Clinical Studies Ethics Committee with the date and number of 01.03.2018/82.

Informed Consent: It wasn't obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.A.K., Design: İ.A.K., Supervision: M.K.Ç., Data Collection or Processing: A.D., Analysis or Interpretation A.D., Literature Search: M.K.Ç., Writing: İ.A.K., G.Ç., M.K.Ç.

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Research Article

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Evaluation of Serum CTNNβ$_1$ and E-cadherin Levels in Hepatitis Patients

Hepatit Hastalarında Serum CTNNβ$_1$ ve E-kadherin Düzeylerinin Değerlendirilmesi

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ABSTRACT

Objectives: Hepatitis B virus (HBV) infection is one of the leading causes of hepatocellular carcinoma, but the underlying molecular mechanisms are quite complex. In this study, the aim was to reveal the relationship of these parameters with HBV-DNA loads by evaluating serum CTNNβ$_1$ (β-catenin) and E-cadherin levels in hepatitis B patients.

Materials and Methods: In this study, between the dates of June 15.06.2018-December 30.12.2019, 75 people who were diagnosed with chronic hepatitis B constituted the patient group (n=75), and 75 people who were not diagnosed with chronic hepatitis B constituted the healthy control group (n=75). In this retrospective study using a random sampling method, the hepatitis B patient group was classified into 3 separate groups among themselves according to HBV-DNA loads; HBV-DNA-1 (x10^6-10^8, n=25), HBV-DNA-2 (x10^3-10^4, n=25) and HBV-DNA-3 (x10^1-10^2, n=25). While the level of serum β-catenin and E-cadherin, the main parameters in the study, were measured using the ELISA method with a commercial kit, the Chemiluminescent Microparticle Immunoassay method was used to evaluate the serological markers in the patients. HBV-DNA level was determined by real-time polymerase chain reaction.

Results: In our study, the average age of individuals was 41.96±13.86 years in the control group and 36.72±16.3, 42.8±10.91 and 46.36 ±12.58 years in the HBV-DNA-1, 2, and 3 groups, respectively. The low age in the HBV-DNA-1 group compared to other groups was statistically significant (p=0.001; p<0.01). The values of E-cadherin

ÖZ

Amaç: Hepatit B virüsü (HBV) enfeksiyonu, hepatosellüler karsinomun önde gelen nedenlerinden biridir, ancak altta yatan moleküler mekanizmalar ise oldukça karmaşıktır. Bu çalışmada hepatit B hastalarında serum CTNNβ$_1$ (β-katenin) ve E-kadherin düzeylerinin değerlendirerek bu parametrelerin HBV-DNA yükleriyle ilişkinin ortaya konması amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmada; 15.06.2018-30.12.2019 tarihleri arasında kronik hepatit B tanısı alan 75 kişi hasta grubunu (n=75), kronik hepatit B tanısı almayan 75 kişi ise sağlıklı konrtol grubunu (n=75) oluşturdu. Rastgele örnekleme yöntemi kullanılan bu retrospektif çalışmada hepatit B hasta grubu HBV-DNA yüklerine göre kendi arasında; HBV-DNA-1 (x10^6-10^8, n=25), HBV-DNA-2 (x10^3-10^4, n=25) ve HBV-DNA-3 (x10^1-10^2, n=25) olmak üzere 3 ayrı gruba ayrıldı. Çalışmanın ana parametresi olan serum β-katenin ve E-kadherin düzeyi, ticari kit kullanılarak ELİSA yöntemi ile ölçülürken, hastaların serolojik belirteçlerin değerlendirilmesinde Kemilüminesan Mikropartikül İmmünoassay yöntemi kullanıldı. HBV-DNA düzeyi ise real-time polimeraz zincir reaksiyonuyla belirlendi.

Bulgular: Çalışmamızda bireylerin yaş ortalaması; kontrol grubunda 41,96±13,86 yıl; HBV-DNA-1, 2 ve 3 grubunda ise sırasıyla; 36,72±16,3; 42,8±10,91; 46,36±12,58 yıl olarak belirlendi. HBV-DNA-1 grubunun yaş değerinin diğer gruplara göre düşük olması istatistiksel olarak anlamlı bulundu (p=0,001; p<0,01). E-kadherin değerleri; kontrol grubunda 44,57±29,61 ng/mL, HBV-DNA-1, 2 ve 3 gruplarında ise sırasıyla; 42,76±23,23; 45,72±27,33; 71,02±31,03

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ABSTRACT

were 44.57±29.61 ng/mL in the control group, and 42.76±23.23, 45.72±27.33 and 71.02±31.03 ng/mL in HBV-DNA-1, 2 and 3 groups, respectively. In addition, E-cadherin values were statistically significant in the HBV-DNA-3 group compared to other groups (p=0.001; p<0.01). The values of β-catenin were 0.75±0.47 ng/mL in the control group and were 1.05±0.63, 0.93±0.4 and 1.58±1.94 ng/mL in the DNA-1, 2, and 3 groups, respectively. The β-catenin value in the control group was found to be statistically significant compared to hepatitis B groups (p=0.001; p<0.01).

Conclusion: E-cadherin values were found to be significantly lower in the HBV-DNA-1 group with the highest viral load. There may be a loss of E-cadherin due to severe inflammation in this group. Monitoring the levels of β-catenin and E-cadherin may be important for evaluating the possible risk and prognosis for liver carcinoma in these patients.

Keywords: Hepatitis B, β-catenin, E-cadherin, viral load

ÖZ

ng/mL olarak belirlendi. Ayrıca E-kadherin değerlerinin HBV-DNA-3 grubunda diğer gruplara göre yüksek olması da istatistiksel olarak anlamlıydı (p=0,001; p<0,01). β-katenin değerleri ise kontrol grubunda 0,75±0,47 ng/mL, HBV-DNA-1, 2 ve 3 gruplarında ise sırasıyla; 1,05±0,63; 0,93±0,4; 1,58±1,94 ng/mL olarak belirlendi. Kontrol grubunun β-katenin değerinin hepatit B gruplarına göre düşük olması istatistiksel olarak anlamlı bulundu (p=0,001; p<0,01).

Sonuç: E-kadherin değerlerinin viral yükü en fazla olan HBV-DNA-1 grubunda anlamlı olarak düşük bulunmuştur. Bu grupta şiddetli enflamasyona bağlı E-kadherin kaybı olabilir. β-katenin ve E-kadherin düzeylerinin takip edilmesi bu hastalarda karaciğer karsinomu yönünden olası riski ve prognozu değerlendirmek açısından önemli olabilir.

Anahtar Kelimeler: Hepatit B, β-katenin, E-kadherin, viral yük

Introduction

Chronic hepatitis B is one of the most common diseases in the world. Hepatitis B is an infectious disease that causes important complications such as cirrhosis and hepatocellular cancer (1). Hepatocellular carcinoma (HCC), the most common primary malignant tumor in the liver, is one of the cancers associated with viral infections in humans, and chronic infection caused by hepatitis B virus (HBV) was stated to be the main etiological factor for HCC (2,3). HCC ranks 5th among cancers in the world (4).

The β-catenin protein is encoded by the *CTNNB*$_1$ gene and was first described as one of the basic molecules involved in intercellular interaction in 1989 (5,6). It acts as a bridge between the part of the E-cadherin located in the cell membrane and functioning in cell adhesion within the cytoplasm and the α-actin in the cytosol (7,8). The Wnt/β-catenin signaling pathway is involved both in the regulation of early embryonic development and in events such as adipogenesis, apoptosis, angiogenesis, and synapse formation in adult tissues. On the other hand, it was thought that disorders occurring on this signal pathway have a role in the etiology of many serious diseases, especially cancer, and in recent years, research about this signal path has increased significantly (7).

While the signal path is inactive and there is no mutation in the biomolecules involved in this signal path, some of the "catenin" is located on the cell membrane to serve in cell connections. The rest is broken down by the effect of the destructive complex that is active in the cytosol. In other words, accumulation of β-catenin in the cytoplasm and nucleus is not observed. However, when the signal path is active or with uncontrolled activation caused by a mutation that occurs in the biomolecules involved in this signal path, β-catenin cannot be broken down. The non-degradable β-catenin first accumulates in the cytoplasm, then it enters the nucleus and provides the transcription of the target genes. Therefore, in this case, accumulation of β-catenin is observed in the cytoplasm and nucleus, as well as the cell membrane (9). Cadherins provide the molecular connection between cells next to each other. The destinies, which are intensely located at the points where the cells are connected, must be connected with the cytoplasmic proteins (e.g., actin) in order to perform their duties. Expression of fate changes dynamically with cell differentiation. Cell-cell relationship is impaired in tumors due to the irregular behavior of tumor cells. The relationship of decreased adhesion and cell relations with neoplastic progression, which occurs with the decrease of e-cadherins on the surface, is becoming more and more apparent (10).

The purpose of this study was to evaluate serum β-catenin and E-cadherin levels in hepatitis B patients and to reveal the correlation of these parameters with HBV-DNA loads.

Materials and Methods

In the study, 75 people who were diagnosed with chronic hepatitis B between the dates of June 15.06.2018-30.12.2019 (n=75), and 75 people who were not diagnosed with chronic hepatitis B constituted the healthy control group (n=75). In this study, which was retrospective and used a random sampling method, the patient group was divided into 3 separate groups (x106-108, x103-104 and x101-102) according to their HBV-DNA loads. The level of serum β-catenin and E-cadherin, the main parameters of the study, were measured using the ELISA method with a commercial kit (elabsscience-catalog no: E-EL-H0014, E-EL-H0666), while the Chemiluminescent Microparticle Immunoassay method was used for the evaluation of serological markers with an Architect i1000 SR (Abbott, USA) device. HBV-DNA level was determined by real-time polymerase chain reaction (COBAS TaqMan High Pure HBV system, Roche Diagnostic, Germany). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) data were obtained from the hospital information system.

This study was approved by Ordu University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2020/69, date: 26.03.2020).

Statistical Analysis

Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, rate, minimum, maximum) as well as

the distribution of the data were evaluated with the Shapiro-Wilk test. The Kruskal-Wallis test was used for comparison of three or more groups that did not show normal distribution of quantitative data, and the Mann-Whitney U test was used for comparison of two groups that did not show normal distribution. The chi-square test was used to examine the relationship between qualitative data. Spearman's correlation analysis was used to determine the relationship between quantitative data. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

Results

The age range of the individuals constituting our study was 18-65 years old and the average age was 41.96±13.86 years in the control group and 36.72±16.3, 42.8±10.91 and 46.36±12.58 years in the HBV-DNA-1, 2, and 3 groups, respectively. The low age in the HBV-DNA-1 group compared to other groups was statistically significant ($p=0.001$; $p<0.01$). No gender difference was found between the groups and no statistically significant relationship was found between the groups and gender ($p>0.05$). Gender characteristics and percentages of the groups are given in Table 1.

There is a statistically significant difference between ALT values according to group ($p=0.001$; $p<0.01$). The high ALT value in the HBV-DNA-1 group compared to other groups was statistically significant ($p=0.001$; $p<0.01$). The ALT values for the HBV-DNA-2 and HBV-DNA-3 groups were found to be higher than the control group ($p=0.001$; $p<0.01$). There was a statistically significant difference between AST values according to group ($p=0.001$; $p<0.01$). The high AST value in the HBV-DNA-1 group compared to other groups was statistically significant ($p=0.001$; $p<0.01$). In addition, the higher ALS values in the HBV-DNA-2 and HBV-DNA-3 groups compared to the control group were statistically significant ($p=0.001$; $p<0.01$).

There was a statistically significant difference between the values for E-cadherin according to the groups ($p=0.003$; $p<0.01$). E-cadherin value in the HBV-DNA-3 group was higher than the other groups and this was statistically significant ($p=0.001$; $p<0.01$).

There was a statistically significant difference between the β-catenin values according to the groups ($p=0.003$; $p<0.01$). The control group β-catenin value was lower than other groups and this was found to be significant ($p=0.001$; $p<0.01$). There was a statistically significant difference between hepatitis B surface antigen (HBsAg) values according to the groups ($p=0.001$; $p<0.01$). The HBsAg value of the control group was found to be statistically significant compared to other groups ($p=0.001$; $p<0.01$). The average values of AST, ALT, HBsAg, E-cadherin and β-catenin belonging to the groups are given in Table 2.

For the correlation analysis of all groups, there were negative and weakly significant relationships between age with ALT and AST ($r=-0.303$, $p<0.01$; $r=-0.362$, $p<0.01$, respectively). There was a positive and very weak relationship between age and E-cadherin ($r=0.184$, $p<0.05$). There was a positive and moderately significant relationship between ALT and AST ($r=0.618$, $p<0.01$). There was no statistically significant relationship between ALT, AST, E-cadherin and β-catenin ($p>0.05$). Correlation analysis is shown in Table 3.

When these profiles are encountered, interpretation of the results should be done meticulously and situations requiring further investigation and evaluation should be taken into consideration.

Discussion

HBV is one of the still infectious factors in our country, as well as in the world, due to the clinical pictures such as acute and chronic hepatitis, serious complications and diagnostic difficulties such as liver cirrhosis and hepatocellular cancer (11,12).

Recently, stabilized mutations of β-catenin, the hallmark of Wnt signaling, were documented in a significant number of primary HCC. Sun et al. (13) reported that HBx, a viral regulatory protein of HBV, plays a role in activating the Wnt/β-catenin signal in hepatoma cells in their work in 2020 about hepatoma cells/β-catenin signal HCC, the primary malignant tumor in the liver, is one of the human cancers that is clearly linked to viral infection. Chronic infection with the HBV was identified as the main etiological agent for HCC (13).

In our study, in parallel with the studies of Sun et al. (13), the β-catenin value of the control group was statistically significantly lower than the hepatitis B groups. High levels of β-catenin in the group of patients exposed to inflammation with hepatitis B may be an important risk factor for activation of the Wnt/β-catenin signal pathway. In addition, in the group comparison of hepatitis B patients separated by HBV-DNA, the lower viral levels in the HVB-DNA-1 group than the other two hepatitis groups and the control group can be interpreted as the loss of E-cadherin due to intense inflammation. This situation can be considered as an important risk factor for HCC. In a similar study conducted by von Olshausen et al. (14) in 2018, parallel to our study, HBV did not alter the overall expression levels of E-cadherin or β-catenin, but decreased the nuclear translocation and activation of target genes of β-catenin.

E-cadherin binds to beta-catenin to form the cadherin/catenin complex required for strong cell adhesion. This complex facilitates inactivation in tumors and invasion into the surrounding tissues.

Table 1. Relationship between wide group and gender

		Gender		p
		Male	Female	
Wide group	**HBV DNA-1 (n=25)**	14 (9.3%)	11 (7.3%)	0.589
	HBV DNA-2 (n=25)	11 (7.3%)	14 (9.3%)	
	HBV DNA-3 (n=25)	11 (7.3%)	14 (9.3%)	
	Control (n=75)	42 (28%)	æ33 (22%)	

Chi-square testi, **p<0.01.
HBV: Hepatitis B virus

Both proteins were reported to change in HCC. Chronic infections with the HBV are seen as the most important cause of HCC. Early diagnosis of HCC is very important for the treatment and prognosis of the disease. For this reason, for early diagnosis of HCC in patients with hepatitis B, evaluation of the fate/catenin complex, especially considering the HBV-DNA loads, will provide extremely important information. Wei et al. (15) conducted a genetic and expression study of E-cadherin and β-catenin in 37 HCC patients, and immunohistochemical analysis of E-cadherin expression in HCC and neighboring non-tumor tissues. Among tumor samples,

Table 2. Comparison of measurements by wide groups

		N	Mean ± SD	Min-max (median)	p
Age, (year)	HBV-DNA-1	25	36.72±16.3	16-91 (32)	**0.001****
	HBV-DNA-2	25	42.8±10.91	28-67 (42)	
	HBV-DNA-3	25	46.36±12.58	23-74 (48)	
	Control	75	57.41±19.08	13-94 (57)	
ALT (IU/L)	HBV-DNA-1	25	43.21±23.66	9-103 (38)	**0.001****
	HBV-DNA-2	25	26.2±24.74	9-137 (20)	
	HBV-DNA-3	25	24.32±11.23	11-55 (21)	
	Control	75	16.39±4.86	10-32 (16)	
AST (IU /L)	HBV-DNA-1	25	51.81±35.97	8-131 (41)	**0.001****
	HBV-DNA-2	25	20.96±13.43	9-77 (18.5)	
	HBV-DNA-3	25	23.36±11.52	12-72 (20)	
	Control	75	16.27±4.86	10-28 (15)	
E-cadherin (ng/mL)	HBV-DNA-1	25	42.76±23.23	2.75-97.36 (39.22)	**0.003****
	HBV-DNA-2	25	45.72±27.33	7.57-97.36 (42.55)	
	HBV-DNA-3	25	71.02±31.03	7.23-110.32 (74.77)	
	Control	75	44.57±29.61	3.21-115.94 (38.76)	
β-catenin (ng/mL)	HBV-DNA-1	25	1.05±0.63	0.29-3.06 (0.98)	**0.003****
	HBV-DNA-2	25	0.93±0.4	0.24-2.23 (0.92)	
	HBV-DNA-3	25	1.58±1.94	0.15-8.31 (0.93)	
	Control	75	0.75±0.47	0.11-2.55 (0.64)	
HBsAg (IU/m)	HBV-DNA-1	25	2568.44±1914.41	166-6342 (2213)	**0.001****
	HBV-DNA-2	25	3749.13±2442.57	0-7838 (3746)	
	HBV-DNA-3	25	3344.32±2189.68	0-6387 (3690)	
	Control	75	428.87±51.97	273-558 (421)	

Kruskall-Wallis testi, *p<0.05, **p<0.001.
HBV: Hepatitis B virus, SD: Standard deviation, Min: Minimum, Max: Maximum, HBsAg: hepatitis B surface antigen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Table 3. Correlation of all groups

		Age	ALT	AST	E-cadherin	β-catenin	HBsAg
Age	r	1.000					
	p	.					
ALT	r	-0.303**	1				
	p	0.000	.x				
AST	r	-0.362**	0.618**	1			
	p	0.000	0.000	.			
E-cadherin	r	0.184*	0.068	0.096	1.000		
	p	0.024	0.416	0.252	.		
β-catenin	r	0	0.123	0.109	0.226**	1	
	p	0.178	0.142	0.191	0.005	.	
HBsAg	r	-0.264**	0.323**	0.249**	0.093	0.151	1
	p	0.001	0	0.003	0.262	0.066	.

Spearman's, **p<0.01, *p<0.05, HBsAg: hepatitis B surface antigen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

40% of tumors had full or heterogeneous downregulation, while 35% of cases reported significant differences up to significant overexpression (15,16). Similar to our study, they reported that there was a statistically significant difference between the values of E-cadherin by group. In our study, the high value of E-cadherin in the HBV-DNA-3 group compared to other groups was statistically significant. The viral load of the HBV-DNA-3 group is less than HBV-DNA-1 and HBV-DNA-2, and the level of E-cadherin lost is lower and this group may be less at risk for HCC than the other two groups. In addition, the fact that the kat-catenin levels in the control group were statistically significantly lower than the HBV-DNA-1, 2 and 3 groups, also supports that the level of β-catenin increases compared to the viral load and that the Wnt/β-catenin signal pathway becomes active, creating a HCC risk.

Study Limitations

The most important limitation of this study is that the levels of β-catenin/E-cadherin observed in serum cannot be matched with liver biopsy taken from patients. This is because some patients needed a liver biopsy, while others did not and were closely followed up. However, we think that the levels of β-catenin/E-cadherin in blood serum should be followed frequently in hepatitis B patients as it is both less risky and gives important information about adhesion molecules in cells.

Conclusion

Hepatitis B still remains an important health problem despite vaccination studies all over the world and in our country. Cirrhosis is among the most important causes of liver failure and liver cancers. Evaluation of the levels of β-catenin/E-cadherin, which is one of the most important molecules considered in evaluating cancer formation and prognosis in a tissue, is very important for early detection of HCC. In these patients, the levels of β-catenin/E-cadherin should be carefully monitored and its correlation with viral load should be evaluated. The data from our study support the idea that the β-catenin/E-cadherin may play a role in HCC from hepatitis B and reflect specific requirements for tumor growth and spread to the liver. Some limitations were encountered while conducting our study.

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Ethics

Ethics Committee Approval: This study was approved by Ordu University Faculty of Medicine, Clinical Research Ethics Committee (approval number: 2020/69, date: 26.03.2020).

Informed Consent: Since our study was retrospective, informed consent was not used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ş., Y.Ç., M.K.Ç., T.N. Consept: A.Ş., Y.Ç., M.K.Ç., Desing: A.Ş., Y.Ç., S.C., Data Collection or Processing: A.Ş., Y.Ç., M.K.Ç., Analysis or İnterpretation: A.Ş., Y.Ç., S.C., T.N., Literature Search: A.Ş., Y.Ç., N.T., Writing: : A.Ş., Y.Ç.

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Research Article

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Influence of Sustained Virological Response on APRI in Chronic Hepatitis C: is APRI a Marker of Only the Stage of Fibrosis?

Kronik Hepatit C'de Sürekli Virolojik Yanıtın APRI Üzerindeki Etkisi: APRI Sadece Fibrozis Evresinin Bir Belirteci mi?

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ABSTRACT

Objectives: Aspartate transaminase (AST) to platelet ratio index (APRI) is widely used to predict the stage of liver fibrosis in patients with chronic hepatit C virus (HCV) infection. In this study, we aimed to evaluate changes in APRI scores in patients with chronic HCV infection who received pegylated interferon (PEG IFN) + ribavirin or direct acting antiviral (DAA) ± ribavirin.

Materials and Methods: We retrospectively reviewed our data of patients with chronic HCV infection who received PEG IFN + ribavirin or DAA ± ribavirin. Patients were classified into 3 groups according to sustained virological response (SVR) by treatment regimens: a) SVR with PEG IFN + ribavirin (PEG IFN-SVR), b) non SVR with PEG IFN + ribavirin (PEG IFN-non SVR), c) SVR with DAA ± ribavirin (DAA-SVR).

Results: The study included 156 patients. APRI scores decreased significantly in PEG IFN-SVR (1.17±1.37 vs 0.38±0.35) and DAA-SVR groups (0.99±0.88 vs 0.31±0.16) (both p=0.001), whereas it did not change in PEG IFN-non SVR group (1.26±1.07 vs 1.33±1.36) (p=0.810) after treatment. In PEG IFN-SVR and DAA-SVR groups, proportions of patients who had APRI scores ≤0.5 and ≤1 increased, while proportions of patients who had APRI scores >1.5 and >2 decreased significantly after treatment (all p<0.05).

Conclusion: APRI score is not indicator of only the stage of fibrosis. Hepatic necroinflammation also influences APRI score by increasing AST levels and decreasing platelet levels.

Keywords: HCV, APRI, fibrosis, necroinflammation

ÖZ

Amaç: Aspartat transaminaz (AST)/trombosit oranı indeksi (APRI), kronik hepatit C virüsü (HCV) enfeksiyonu olan hastalarda karaciğer fibrozisinin evresini tahmin etmek için yaygın olarak kullanılmaktadır. Bu çalışmada, pegile interferon (PEG IFN) + ribavirin veya direkt antiviral ajan (DAA) ± ribavirin tedavisi alan kronik HCV enfeksiyonlu hastalarda APRI skorlarındaki değişiklikleri araştırmayı amaçladık.

Gereç ve Yöntemler: PEG IFN + ribavirin veya DAA + ribavirin tedavisi görmüş kronik HCV enfeksiyonlu hastaların verilerini retrospektif olarak gözden geçirdik. Hastalar tedavi rejimleri ve kalıcı virolojik yanıta (KVY) göre 3 gruba ayrıldı a) PEG IFN + ribavirin ile KVY (PEG IFN-SVR), b) PEG IFN + ribavirin ile KVY elde edemeyen (PEG IFN-non SVR), c) DAA ± ribavirin ile KVY elde edilen (DAA-SVR).

Bulgular: Çalışmaya 156 hasta dahil edildi. APRI skorlarının, PEG IFN-SVR (1,17±1,37'ye karşı 0,38±0,35) ve DAA-SVR gruplarında (0,99±0,88'e karşı 0,31±0,16) önemli ölçüde azaldığı görüldü (her ikisi p=0,001). Buna karşın PEG IFN-non SVR grubunda (1,26±1,07 vs 1,33±1,36) ise tedavi sonrası anlamlı değişim görülmedi (p=0,810). PEG IFN-SVR ve DAA-SVR gruplarında, APRI skorları ≤0,5 ve ≤1 olan hastaların oranı artarken, APRI skorları >1,5 ve >2 olan hastaların oranı tedaviden sonra anlamlı olarak azaldı (tümü p<0,05). PEG IFN-non SVR grubunda ise APRI skorları ≤0,5, >1,5, ≤1 ve >2 olan hastaların oranı değişmedi (p>0,05).

Sonuç: APRI skoru, sadece fibrozisin evresinin göstergesi değildir. Hepatik nekroinflamasyon, AST seviyelerini artırarak ve trombosit seviyelerini düşürerek APRI skorunu da etkiler.

Anahtar Kelimeler: HCV, APRI, fibrozis, nekroinflamasyon

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Introduction

Chronic hepatitis C virus (HCV) infection is one of the most common causes of chronic hepatitis, cirrhosis, liver failure, hepatocellular carcinoma (HCC) and death from liver disease (1). Chronic hepatitis C (CHC) related decompansated cirrhosis and HCC are the leading indications for liver transplantation in developed countries (2). In CHC, the aim of therapy is to achieve sustained virological response (SVR) (3). SVR is associated with regression of liver fibrosis and cirrhosis, and reduction in the risk of HCC development at long term follow-up (4). With the use of direct acting antiviral agents (DAA), >95% of patients achieve SVR (5). In CHC, the stage of liver fibrosis is important for deciding to start antiviral treatment and estimating prognosis. The antiviral therapy may be delayed in patients with no or mild fibrosis, while it should be started in patients with significant fibrosis and cirrhosis (6). Those patients with significant fibrosis and cirrhosis must also be under HCC surveillance.

Although liver biopsy is the gold standard method to define the stage of fibrosis, it has several limitations. The biopsy specimen represents 1/50,000 of the liver which leads to under- or overestimation of the stage of fibrosis (7). Moreover, it is invasive and has serious complications including pain, bleeding and even death. It is also costly (8). In order to overcome these limitations, several non-invasive tests have been developed to predict significant fibrosis and cirrhosis. Since APRI score is based on readily available blood tests and thus is costless, it is the most widely used of these tests (9).

However, APRI may be elevated not only due to advanced stage of fibrosis but also due to high degree of hepatic necroinflammation. APRI score is based on aspartate aminotransferase (AST) and platelet levels. In CHC, hepatic necroinflamation leads to increase in not only alanine aminotransferase (ALT) but also AST levels. This in turn may lead to elevated APRI score and thus overestimation of the stage of fibrosis. On the other hand, AST and ALT levels decrease after SVR due to the resolution of hepatic necroinflammation. However, the same is not true for fibrosis (10). So, increased APRI score may reflect high histological activity index in conjunction the stage of fibrosis.

The aim of the present study is to evaluate changes in APRI score in patients with chronic HCV infection who received pegylated interferon (PEG IFN) + ribavirin and DAA ± ribavirin treatment.

Materials and Methods

We retrospectively reviewed our data of patients with chronic HCV infection who admitted to gastroenterology clinic between 2003 and 2018. The patients were included in the study if they 1) were ≥18 years-old, 2) had anti HCV and HCV RNA positivity for at least 6 months, 3) had liver biopsy result before antiviral treatment, 4) had laboratory test results allowing calculation of APRI score, and serum HCV RNA levels prior to and 24 weeks after treatment, 5) received PEG IFN + ribavirin or DAA ± ribavirin including either sofosbuvir/ledipasvir or ombitasvir/paritaprevir/ritonavir + dasabuvir. Patients were excluded if they 1) were <18 years-old, 2) had coinfection with hepatitis B virus and/or human immunodeficiency virus, 3) had other etiology for chronic liver diseases, 4) had history of liver transplantation and HCC. One hundred and fifty six patients who met the inclusion criteria were included in the study.

The laboratory test results including AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and upper limit of normal (ULN) values of each test, and platelet values prior to and 24 weeks after treatment were recorded. We calculated APRI scores at corresponding time points according to the following formula: (AST/ULN)/platelet x100. The thresholds of APRI were ≤0.5 and >1.5 for the exclusion and prediction of significant fibrosis, and ≤1 and >2 for the exclusion and prediction of cirrhosis (11).

All biopsy specimens were analyzed by a single pathologist experienced in hepatopathology. The stage of fibrosis was scored according to the ISHAK system (12). Significant fibrosis was defined as F3-6 and cirhosis as F5-6.

SVR was defined as negative HCV RNA at 24th week after the end of treatment in patients who received PEG IFN + ribavirin or DAA ± ribavirin. Non SVR was defined as any treatment outcome other than SVR. Patients were classified into 3 groups according to SVR by treatment regimens: a) SVR with PEG IFN + ribavirin (PEG IFN-SVR), b) non-SVR with PEG IFN + ribavirin (PEG IFN-non SVR), c) SVR with DAA (DAA-SVR).

Local Ethic Committee approval was taken from the University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospaital (approval number: 771/12/2018-14).

Statistical Analysis

We compared APRI scores at baseline and at the 24th week after treatment in each group. We also compared proportions of patients who had APRI scores ≤0.5, >1.5, ≤1 and >2 at baseline and at week 24 after treatment in each group.

Continuous variables were presented as means ± standard deviation, and categorical variables as number (%). Means of metric variables were assessed by using paired Sample test. McNemar's test was used for two groups with paired data. ANOVA test was applied for all group comparisons. Level of significance was defined as $p<0.05$. Statistical analyses were performed by using SPSS v.23.0 (SPSS, Inc, Chicago, IL, USA) for Windows.

Results

In total, 156 patients were included in the study. All patients were Caucasian. Of them, 108 received PEG IFN + ribavirin and 48 received DAA ± ribavirin treatment. Of the patients who received PEG IFN + ribavirin, 59 achieved SVR and 49 did not achieve SVR. All patients who received DAA ± ribavirin achieved SVR.

The mean ages of patients in groups PEG IFN-SVR, PEG IFN-non SVR and DAA-SVR were 52.64±9.89, 56.29±9.06 and 58.65±10.92 years, respectively ($p=0.008$). The groups were similar in terms of gender ($p=0.170$). The proportions of patients with significant fibrosis and cirrhosis in each group were 25.4%, 59.2% and 81.2% ($p=0.001$), and 11.9%, 42.9% and 22.9% ($p=0.002$), respectively. Baseline characteristics of patients are shown in (Table 1).

There were significant decreases in AST/ULN and ALT/ULN at the 24th week after treatment in comparison to pretreatment values in all 3 groups (all $p<0.05$). The platelet levels did not change in PEG

IFN-SVR group (p=0.800), decreased in PEG IFN-non SVR group (p=0.010) and increased in DAA-SVR group (p=0.005) at the 24th week after treatment in comparison to baseline. APRI decreased significantly in PEG IFN-SVR and DAA-SVR groups (both p=0.001), while it did not change in PEG IFN-non SVR group (p=0.810) at the 24th week after treatment in comparison to baseline (Table 2).

In group PEG IFN-SVR, proportions of patients who had APRI scores ≤0.5 (from 35.6% to 84.7%) and ≤1 (from 69.5% to 96.6%) increased, while proportions of patients who had APRI scores >1.5 (from 22.0% to 3.4%) and >2 (from 13.6% to 1.7%) decreased significantly at the 24th after treatment in comparison to baseline (all p<0.05). In group DAA-SVR, proportions of patients who had APRI scores ≤0.5 (from 35.4% to 87.5%) and ≤1 (from 66.7% to 100.0%) increased, while proportions of patients who had APRI scores >1.5 (from 18.7% to 0.0%) and >2 (from 12.5% to 0.0%) decreased significantly at week 24 after treatment in comparison to baseline (all p<0.05). In group PEG IFN-non SVR, proportions of patients who had APRI scores ≤0.5, >1.5, ≤1 and >2 did not change (all p>0.05) (Table 3).

Discussion

In the present study, we evaluated changes in APRI scores in CHC patients after treatment. In the patients who achieved SVR with either PEG IFN + ribavirin or DAA ± ribavirin, APRI scores decreased significantly at the 24th week after treatment. On the other hand, APRI scores did not change in those patients who did not achieve SVR. Moreover, proportions of those who had APRI scores ≤0.5 and ≤1 increased, while proportion of patients who had APRI scores >1.5 and >2 decreased significantly after achieving SVR with either PEG IFN + ribavirin or DAA ± ribavirin. In contrast, they did not change in patients who did not achieve SVR. Our findings were consistent with the existing literature which evaluated changes in several noninvasive tests in CHC patients after treatment.

Bachofner et al. (13) assessed changes in APRI scores in 392 patients with chronic HCV infection who received DAA treatment. They reported that APRI scores decreased significantly from 1.07 to 0.41 in patients with SVR. Moreover, all the patients with SVR had APRI scores below the cut off values for the prediction of significant fibrosis. Similar to our study, APRI scores in SVR

Table 1. Baseline characteristics of patients

	PEG IFN-SVR (n=59)	PEG IFN-non-SVR (n=49)	DAA-SVR (n=48)	p
Age (mean ± SD)	52.64±9.89	56.29±9.06	58.65±10.92	0.008
Gender (male, %)	34 (57.6)	23 (46.9)	19 (39.6)	0.170
HCV RNA (mean ± SD, IU/mL)	4.865.062±10.450.502	3.406.105±4.769.597	7.672.239±7.503.896	0.030
Genotype, n (%)				
G1	44 (74.6)	47 (95.9)	41 (85.4)	0.001
Non-G1	3 (5.1)	0 (0)	7 (14.6)	0.001
Unknown	12 (20.3)	2 (4.1)	0 (0)	0.001
Fibrosis, n (%)				
F0-2	44 (74.6)	20 (40.8)	9 (18.8)	0.001
F3-6	15 (25.4)	29 (59.2)	39 (81.2)	0.001
F0-4	52(88.1)	28 (57.1)	37 (77.1)	0.030
F5-6	7(11.9)	21 (42.9)	11 (22.9)	0.002

SD: Standard deviation, PEG IFN: Pegylated interferon, SVR: Sustained virological response, DAA: Direct acting antivirals

Table 2. Changes in laboratory parameters and APRI scores at week 24 after treatment in comparison to baseline

	PEG IFN-SVR (n=59)			PEG IFN-non SVR (n=49)			DAA-SVR (n=48)		
	Baseline Mean ± SD	Post-Tx Mean ± SD	p	Baseline Mean ± SD	Post-Tx Mean ± SD	p	Baseline Mean ± SD	Post-Tx Mean ± SD	p
AST/ULN	1.91±1.53	0.69±0.41	0.001	1.79±1.20	1.61±0.80	0.010	1.59±1.04	0.59±0.17	0.001
ALT/ULN	2.03±1.66	0.53±0.48	0.001	1.56±0.86	1.46±0.73	0.010	1.82±1.54	0.48±0.26	0.001
ALP/ULN	0.63±0.24	0.56±0.24	0.001	0.62±0.21	0.58±0.26	0.300	0.62±0.29	0.56±0.26	0.080
GGT/ULN	1.01±1.04	0.50±0.45	0.001	1.65±1.36	1.14±0.97	0.520	1.57±1.77	0.67±0.83	0.001
Platelet ($x10^9$/L)	207.75±70.18	210.81±63.42	0.800	170.59±57.51	164.88±63.17	0.010	194.90±63.08	215.23±76.07	0.005
APRI	1.17±1.37	0.38±0.35	0.001	1.26±1.07	1.33±1.36	0.810	0.99±0.88	0.31±0.16	0.001

PEG IFN: Pegylated interferon, SVR: Sustained virological response, DAA: Direct acting antivirals, Post-Tx: Post-treatment, ULN: Upper limit of normal, AST: Aspartate transferase, ALT: Alanine transferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, APRI: AST to platelet ratio index, SD: Standard deviation

Table 3. Changes in APRI scores at week 24 after treatment in comparison to baseline according to cut off values

	PEG IFN-SVR (n=59)			PEG IFN-non-SVR (n=49)			DAA-SVR (n=48)		
APRI	**Pre tx**	**Post tx**	**p**	**Pre tx**	**Post tx**	**p**	**Pre tx**	**Post tx**	**p**
≤0.5	21 (35.6)	50 (84.7)		11 (22.4)	12 (24.5)		17 (35.4)	42 (87.5)	
>0,5	28 (64.4)	9 (15.3)	0.010	38 (77.6)	37 (75.5)	0.890	31 (64.6)	6 (12.5)	0.001
≤1,5	46 (78.0)	57 (96.6)		37 (75.5)	36 (73.5)		39 (81.3)	48 (100.0)	
>1.5	13 (22.0)	2 (3.4)	0.003	12 (24.5)	13 (26.5)	0.310	9 (18.7)	0 (0)	0.004
≤1	41 (69.5)	57 (96.6)		28 (57.1)	28 (57.1)		32 (66.7)	48 (100.0)	
>1	18 (30.5)	2 (3.4)	0.001	21 (42.9)	21 (42.9)	0.920	16 (33.3)	0 (0)	0.001
≤2	51 (86.4)	58 (98.3)		42 (85.7)	41 (83.7)		42 (87.5)	48 (100.0)	
>2	8 (13.6)	1 (1.7)	0.040	7 (14.3)	8 (16.3)	0.170	6 (12.5)	0 (0)	0.030

PEG IFN: Pegylated interferon, SVR: Sustained viral response, DAA: Direct acting antivirals, Post-Tx: Post-treatment, APRI: AST to platelet ratio index

patients were significantly decreased, while they remained high in non SVR patients. They evaluated changes in transient elastograpy (TE) and FIB-4 scores as well. Not only APRI scores, but also TE and FIB-4 scores decreased in SVR patients. They concluded that suppression of viral replication might cause decreases in non-invasive tests without fibrosis regression. Similarly, Chekuri et al. (14) assessed changes in TE in patients who achieved SVR with either IFN-containing and IFN-free regimens. In both groups, liver stiffness decreased significantly 24 weeks after treatment. Decrease in LS was more significant in patients with cirrhosis than non-cirrhotics. However, 60% of LS-proven cirrhotic patients still had cirrhosis after therapy and LS remained unchanged beyond 24 weeks.

It is known that stage of fibrosis regresses after achieving SVR. However, it does not regress as rapidly as hepatic necroinflammation after successful treatment. Petrenkiene et al. (15) performed liver biopsy before and 24 weeks after treatment in patients who received IFN and ribavirin. In that study, histological activity index decreased significantly in both SVR and non-SVR groups after treatment. However, the stage of fibrosis remained unchanged even in patients who achieved SVR. Huang et al. (16) assessed changes in several non-invasive fibrosis scores in 40 CHC patients who achieved SVR with DAA. They assessed changes in histological changes in paired liver biopsy specimens 24 weeks after treatment as well. In that study, the degree inflammation improved and the stage fibrosis regressed in 83% and 38% of patients, respectively after achieving SVR. Decrease in APRI scores were similar in both patients with or without fibrosis regression (16). Briefly, 24 weeks after treatment is too short for fibrosis scores to improve and it occurs several years after treatment (17). So, rapid decrease in APRI and other non-invasive scores can not be the result of fibrosis regression. Rather, it can be due to rapid resolution of hepatic necroinflammation after SVR.

The effect of hepatic necroinflammation on non-invasive fibrosis scores was shown in several studies. Fujita et al. evaluated the effect of hepatic necroinflammation on various noninvasive scores including APRI in 122 patients with CHC (18). In that study, non-invasive scores were shown to be influenced by the grade of histological activity. This is also true for serum ALT levels, since ALT levels were higher in patients with high grade of histological activity than those with low grade of histological activity in the same stage of fibrosis. The depending on histopathological examination, they indicated that ALT level might be a significant predictor for necroinflammatory activity. Huang et al. (16) showed that APRI scores were higher in patients with more severe inflamation and advanced fibrosis.

Similarly, liver stiffness was shown to be increased significantly in patients with more severe inflammation than in those with less severe inflammation especially in more advanced stages. In a study by Vispo et al. (19), patients with ALT >100 IU/L had higher liver stiffness measurements than those with ALT <100 IU/L regardless of the stage of fibrosis. This indicates that intense hepatic necroinflammation leads to overestimation of the stage of fibrosis with using TE (19).

It is clear that decrease in AST levels is the result of resolution of hepatic necroinflammation after achieving SVR. In the present study, AST and ALT levels decreased in all 3 patient groups. However, the decrease in AST and ALT levels were more significant in patients who achieved SVR. Besides the decrease in AST levels, increased platelet levels also contribute to the decrease in APRI scores in patients who achieved SVR (14). The main reason for increased platelet levels after SVR seems to be decrease in portal venous pressure. Despite the persistence of liver fibrosis, resolution of hepatic oedema associated with hepatic necroinflammation might lead to decrease in portal venous pressure and increase in platelet levels (20). In the present study, platelet levels increased in patients who achieved SVR with DAA + ribavirin and did not change in those who achieved SVR with PEG IFN + ribavirin. In contrast, platelet levels decreased in patients who did not achieve SVR. The decrease in APRI in patients who achieved SVR can be attributed to decreased AST levels along with increased or stable platelet levels.

According to the aforementioned studies and our study, it is clear that not only fibrosis but also hepatic necroinflammation influence APRI and the other noninvasive scores in CHC. All of these scores can overestimate the stage of fibrosis in patients with high necroinflammatory activity, while they can underestimate in those with low histological necroinflammatory activity in any given stage. If high APRI scores had indicated only the stage of liver fibrosis, the decrease in APRI scores would have indicated the regression of fibrosis and even cirrhosis immediately after SVR.

Study Limitations

Our study has some limitations. The study included small number of patients and was retrospective. Moreover, patients did not have paired liver biopsy samples after treatment. Therefore, correlation between APRI and the stage of liver fibrosis after treatment can not be assessed. However, the stage of liver fibrosis is not expected to change as early as 24 weeks after treatment.

Conclusion

In conclusion, non-invasive fibrosis scores including APRI should not be the indicator of only the stage of fibrosis. Hepatic necroinflammation also influences APRI score by increasing AST levels and decreasing platelet levels. After successfull treatment of CHC, APRI scores decrease significantly; however, this can not correspond to regression of significant fibrosis and cirrhosis.

Ethics

Ethics Committee Approval: Local Ethic Committee approval was taken from the University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospaital (approval number: 771/12/2018-14).

Informed Consent: It wasn't obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.B., F.G., Design: Ö.B., F.G., Supervision: F.G., Materials: C.S., Data Collection or Processing: S.Ö., H.Ş., M.K., E.K., A.G.D.S., Analysis or Interpretation: S.Ö., H.Ş., M.K., E.K., A.G.D.S., Literature Search: C.S., Writing: Ö.B., C.S.

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Research Article

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Consideration Whether Hepatitis B Exists in Children Whose Mothers Suffer from Chronic Hepatitis B and These Mothers in Gestational Age

Kronik Hepatit B Enfeksiyonu Olan Annelerin Gebeliklerinde ve Çocuklarında Hepatit B Enfeksiyonun Değerlendirilmesi

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ABSTRACT

Objectives: Perinatal and intrauterine transmission of the hepatitis B virus (HBV) represents a major factor, leading to the development of chronic infection. This study aimed to explore the status of mothers and their children for hepatitis B (HB) infection during pregnancy and childhood, and whether active and passive immunoprophylaxis was administered to infants shortly after birth.

Materials and Methods: We performed multicenter, retrospective research on voluntary hepatitis B surface antigen (HBsAg)-positive mothers admitted to infectious diseases polyclinics was performed. Mothers and their children were queried by a questionnaire about their HB infection status. Data from the electronic data recording system was scanned retrospectively.

Results: Three hundred-one mothers and 616 children were included in the study. HBsAg was examined in 354 (57.4%) of pregnancies. Of 91 children with HBsAg positivity, 83 were not applied active and passive immunoprophylaxis after birth. Eight 276 babies received both immune prophylaxes after birth were then detected as HBsAg positive. On HBV examination, 148 children

ÖZ

Amaç: Hepatit B virüsünün (HBV) perinatal ve intrauterin bulaşı, kronik enfeksiyonun gelişmesine yol açan önemli bir faktörü temsil etmektedir. Bu çalışmada, annelerin ve çocuklarının hamilelik ve çocukluk döneminde hepatit B (HB) enfeksiyonu için değerlendirilme durumlarını ve doğumdan hemen sonra bebeklere aktif ve pasif immünoprofilaksi uygulanıp uygulanmadığının araştırılması amaçlandı.

Gereç ve Yöntemler: Enfeksiyon hastalıkları polikliniğine başvuran gönüllü hepatit B yüzey antijeni (HBsAg)-pozitif annelere yönelik çok merkezli, retrospektif araştırma yaptık. Annelere ve çocuklarına HB enfeksiyonu durumları hakkında bir anket uygulandı. Elektronik veri kayıt sistemindeki verileri geriye dönük olarak tarandı.

Bulgular: Üç yüz bir anne ve 616 çocuk çalışmaya dahil edildi. HBsAg gebeliklerin 354'ünde (%57,4) tetkik edildi. HBsAg pozitifliği olan 91 çocuğun 83'üne doğumdan sonra aktif ve pasif immünoprofilaksi uygulanmadığı saptandı. Doğumdan sonra her iki immün profilaksiyi de alan 276 bebekten 8'i HBsAg pozitif olarak tespit edildi. HBV incelemesinde, 148 çocuğun HBV ile karşılaştığı bulundu. HBsAg

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ABSTRACT

were found to encounter the HBV. HBsAg positivity rate was significantly higher in children born before 1997.
Conclusion: The remarkable decrease in HBsAg positivity of children reveals the efficacy of national vaccination. By informing both healthcare workers and society, awareness about examining pregnants for HBsAg during pregnancy should be increased.
Keywords: Pregnant, HBsAg, immune prophylaxis

ÖZ

pozitiflik oranı 1997'den önce doğan çocuklarda anlamlı olarak daha yüksek olarak belirlendi.
Sonuç: Çocukların HBsAg pozitifliğindeki dikkat çekici azalma, ulusal aşılamanın etkinliğini ortaya koymaktadır. Hem sağlık çalışanlarını hem de toplumu bilgilendirerek, hamilelik sırasında HBsAg için gebelerin tetkik edilmesi konusunda farkındalık artırılmalıdır.
Anahtar Kelimeler: Gebe, HBsAg, immün proflaksisi

Introduction

Hepatitis B virus (HBV) infection remains to be a significant global public health issue affecting more than 257 million people in the whole world (1,2,3). By the World Health Organization (WHO), it was reported that one million people for reasons related to viral hepatitis have been dying every year, and there has been a 22% increase in deaths since 2000. WHO, for 2030, aims to reduce the number of hepatitis infections by 90% and mortality by 65%, also suggests essential strategies (2,3). One of these strategies is the prevention of transmission from mothers with hepatitis infection to the baby, which is one of the main ways to reduce the incidence of HBV in the community (2,4,5). The perinatal or vertical transmission of the virus in pregnancy, birth, early infancy to babies of hepatitis B surface antigen (HBsAg) positive mothers plays a vital role in endemic infection and to develop chronic infection (3,6). The administration of active and passive immunoprophylaxis [hepatitis B hyperimmune globulin (HBIG) with HBV vaccine] within the first 12-24 hours immediately after birth to infants of mothers with HBsAg positivity prevents 90-95% transmission of the HBV to the baby (1,2). This application is, therefore, crucial to prevent both becoming chronic of the infection and complications of the infection by not being taken the virus at an early age (2,4,6). Screening mothers for hepatitis B (HB) infection in pregnancy and administering active and passive immune prophylaxis to their babies in the presence of HB is one of the most critical viral hepatitis prevention strategies of WHO to reduce the incidence of HB infection in the community (3,5,7,8,9). Also, after examining and following up the pregnant for HB, the initiation of antiviral therapy or prophylaxis, if necessary, and monitoring of exacerbations that may develop due to HB infection during and after pregnancy, are essential for the prevention of transmission. Perinatal transmission all over the world and in our country is one of the most common transmission ways of HBV infection (3,8). The perinatal transition rate of 5-15% could be seen in babies of hepatitis B e antigen (HBeAg) positive or high viral loaded pregnant women, in whom HBsAg positivity was detected despite appropriate active and passive immune prophylaxis (10,11,12). The risk of transition from mother to baby is tried to be reduced further even in high viral loaded (200000 IU/mL) pregnant women in recent years by using antiviral medication in addition to active and passive immune prophylaxis (13,14,15,16,17).

We aimed in our study to determine the status of evaluating the pregnants for HB infection during pregnancy, whether active and passive immunoprophylaxis was administered to infants immediately after delivery and then, whether HBV examination was made and immunity was developed in children of mothers against current HB infection, and to reveal the related deficiencies.

Materials And Methods

Our study was planned as a multicenter, retrospective, descriptive cross-sectional research, and it was held in five different provinces (Rize, İzmir, Gaziantep, Manisa, İstanbul) from five different regions of Turkey. The mothers with HBsAg positivity who were followed by infectious diseases and clinical microbiology clinics of tertiary universities or educational research hospitals or referred by obstetrics and gynaecology clinics were included in the study. Ethical permission: A multicenter study permit from the Ethics Committee University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (appoval number: 27.10.2015/2) and permission from the Republic of Turkey Public Health Agency (appoval number: 45202601) were obtained for the study.

Collection of Data

The study was conducted on HBsAg positive mothers admitted to infectious diseases polyclinics between 2015 and 2017 after obtaining their consent, by performing a questionnaire through the face-to-face interviews. Mothers whose children were born after 1991, and their children were included in the study. We also scanned files and evaluated the electronic registration data system of the study participants retrospectively.

Data Collection Tools

Besides the demographic data of mothers and their children, examinations performed and treatments administered during and after their pregnancy, and the follow-up status of their children was questioned. For this purpose, we asked the mothers whether they were examined for HBsAg during their pregnancy and whether vaccine and HB immunoglobulin was administered to their babies within the first 12-24 hours immediately after delivery. The questions regarding the screening of mothers for HBV were asked; besides, children too, were questioned about the immune status of them after the completion of three doses of HB vaccines. The current situation of their children for HBV acquisition was also re-examined. Relevant information that could not be obtained from subjects were tried to be reached from the patient files.

Statistical Analysis

SPSS for Windows 21.0 program was used for statistical analyses. Descriptive statistics and frequency distributions were

calculated in line with the characteristics of the variables in the study. According to whether the data obtained were categorical or not and were independent or not, and the number of groups of the obtained data, the Pearson chi-square test, Student's t-test, and Mann-Whitney U test was performed. For the comparison of more than two groups, we used ANOVA for parametric data and the Kruskal-Wallis test for non-parametric data. The statistical significance level was accepted as $p<0.05$.

Results

In our study, 301 mothers and 616 children were evaluated. The mean age of mothers was 38.6±7.5 (19-64), and the mean age at diagnosis was detected to be 24.3±10.6 (6-54). In 262 of 616 pregnancies, mothers were found to be not examined for hepatitis infection. The sociodemographic characteristics of mothers (data) were summarized in Table 1. The mean age of children was 12.8±6.6 (2-28) years, and the female to male ratio was identified to be 295/321 (47.8%, 52.2%). The socio-demographic characteristics (data) of children were given in Table 2.

When we questioned mothers, we learned that HBsAg had been examined in 57.4% of pregnancies. Furthermore, the HBV examination was done to only 294 (47.7%) children at any time, while 96 (15.6%) had no HBV examination until now. Of those children undergoing HBV examinations, 91 (20%) were with HBsAg positivity, and 57 (14.5%) had natural immunity. The status of being examined for HBV, the HBV examination results, and the status of vaccine and HBIG administration after birth in children were summarized in Table 3.

Despite the administration of active and passive immunoprophylaxis within the first 12-24 hours immediately after delivery, 8 (2.9%) of 276 infants had HBsAg positivity. Based on the electronic registration data, we found the mothers of these children to be with HBeAg positivity and high HBV-DNA levels in their pregnancies. It was also determined that they had used medication, too, in their follow-up after their pregnancies. In the current study, HBsAg positivity was found to be significantly higher in children born before 1997 (n=34 and %37.2) (p=<0.001). We observed the mothers of the majority of children who have HBsAg

Table 1. Socio-demographic data of mothers (n=301)

	Characteristic	n	%		Characteristic	n	%
Age	19-25 years	7	2.3	How was HBV infection diagnosed?	During pregnancy	86	27.7
	25-29 years	17	5,6		Due to another HBV in the family	47	15.2
	30-39 years	154	51.2		In the preoperative period	17	5.5
	40-49 years	104	34.6		While getting married	60	19.4
	50-59 years	14	4.7		At the time of blood donation	4	1.3
	60 years and older	5	1.7		While starting a job	4	1.3
Educationstatus	Not literate	24	8.0	HBV status in pregnancy*	Coincidentally, in the examination	41	13.2
	Literate	14	4.7		Others	42	13.5
	Primary school graduate	157	52.2		Inactive carrier	304	49.4
	Secondary school graduate	41	13.6		Previously treated	19	3.1
	High school graduate	46	15.3		Currently under treatment	28	4.5
	Graduated from a university	19	6.3		Cirrhosis	3	0.5
					Unknown	262	42.5

*A total of 616 pregnancies were taken as the number of birth, HBV: Hepatitis B virus

Table 2. Socio-demographic data of the children (n=616)

	Feature	n	%		Feature	n	%
Age	1-6 years	156	25.9	State of having received vaccination or HBIG at birth	Vaccination	154	25.0
	6-12 years	197	32.8		Vaccination + HBIG	276	44.8
	13-18 years	149	24.8		Unknown	84	13.6
	19-23 years	41	6.8		None	102	16.6
	24-28 years	73	12.1	State of having been given vaccination card	Given	420	68.2
Mode of delivery	Spontaneous vaginal delivery	420	68.2		Not given	68	11.1
	C/S	196	31.8		Not remembered	128	20.1
Place of delivery	Hospital	467	75.8	State of having received HBVexamination	At age one	294	47.7
	Home	18	2.9		After age one	197	31.8
	Community clinic	131	21.3		Never	96	15.6
-	-	-	-		Not remembered	29	4.7

HBIG: Hepatitis B hyperimmune globulin, HBV: Hepatitis B virus, C/S:

positivity, not to be examined for HBsAg during pregnancy (46.2% not examined, 16.4% examined, 39.4% unknown). Again, the vast majority of these children have not received vaccines and immunoglobulin (n=83 and 91.2%). The comparison of the clinical status of children, whose mother was positive for HBsAg during pregnancy by age in terms of hepatitis infection was summarized in Table 4.

Discussion

It is reported in various studies that the administration of active and passive immune prophylaxis to babies of mothers with HBsAg positivity in the first 12-24 hours of life immediately after birth prevents 90-95% transmission of the HBV to the infant (1,2,18,19).

In our country, despite all efforts, in general, routine screening of HBsAg in pregnant women, administration of active or passive immune prophylaxis to the babies of mothers with HB infections, and then monitoring the immune status of those is not at the desired level (20). It is seen that the awareness and application of the "Prenatal Care Guide" created by the Ministry of Health and updated in 2014 in the field are quite low and that the HBsAg test is not requested enough for pregnant women in many institutions (20,21). With this aim, by the Ministry of Health in 2018, Viral

Table 3. Children's states of having received HBV examination, examination results and states of having received vaccination + hyper immunoglobulin

	State of having received HBV examination					State of having received vaccination and HBIG after delivery				
	At age one	After age one	Does not know	Never	Total	Vaccinated	Vaccine + HBIG	Does not know	None	Total
Anti-Hbs positive	167	105	1	0	273	39	165	23	46	273
Immune	48	9	0	0	57	21	26	5	5	57
HBsAg positive	57	34	0	0	91	28	8	19	36	91
Anti-HBc IgG positive	2	1	0	0	3	1	1	0	1	3
Kr HBV on treatment	1	2	0	0	3	1	0	0	2	3
Ex	0	1	0	0	1	0	0	0	1	1
Not remembered	8	29	28	96	161	64	62	31	4	161
HBV negative	11	16	0	0	27	0	14	6	7	27
Total	294	197	29	96	616	154	276	84	102	616

HBV: Hepatitis B virus, HBIG: Hepatitis B hyperimmune globulin

Table 4. Comparison of the clinical states of children born from HBsAg positive mothers in terms of birth year

		1991-1997	1998-1999	2000-2005	2006-2011	2012-2017	Total	p
HBV state	Anti-HBs positive	10	16	70	98	79	273	<0.001
	Immune	13	2	8	20	14	57	
	HBsAg positive	34	12	29	14	2	91	
	Isolated anti-HBc IgG	0	0	1	1	1	3	
	Chronic HBV treatment	3	0	0	0	0	3	
	Ex	0	0	0	1	0	1	
	Not examined	9	11	31	54	56	161	
	HBV negative	4	0	10	9	4	27	
	Total	73	41	149	197	156	616	
State of having received vaccination-HBIG at delivery	Not vaccinated	17	7	34	62	34	154	<0.001
	Vaccine + HBIG	5	9	47	102	113	276	
	None	35	15	36	16	0	102	
	Unknown	16	10	32	17	9	84	
	Total	73	41	149	197	156	616	
State of having received HBV examination	At age one	41	15	61	102	75	294	0.01
	After age one	25	17	61	49	44	196	
	Unknown	1	2	5	8	13	29	
	Never	6	7	22	38	24	97	
	Total	73	41	149	197	156	616	

HB: Hepatitis B, HPV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, HBIG: hepatitis B hyperimmune globulin

Hepatitis Prevention and Control Program was put into effect, and performing the HBsAg test for pregnant women has been made compulsory by no longer being a recommendation (5,8).

No studies are examining whether the HB vaccine and HBIG prophylaxis could be administered together or separately. In our study, the rates of administering alone HB vaccine to babies after birth were 25% (n=154). In contrast, the rate of administering vaccine and immune globulin was found at 44% (n=276). In 55.6% (n= 340) of pregnancies, no immunoglobulin was applied, or whether applied or not of those were identified to be unknown. Some of the mothers even stated that they heard this expression for the first time. This situation suggests the insufficiencies in efforts leading pregnant women to be followed up and informed. In this context, a multidisciplinary joint action by all healthcare professionals, primarily including the clinicians working at Family Medicine, Obstetrics and Gynecology, and Infectious Diseases Clinics, is thought to be going to increase awareness. First, informative training for HBV examination during pregnancy should be given to pregnant women. Second, the control of the mother and child monitoring and the support of hospital administrations in eliminating the related deficiencies need to be increased. Third, intervention commissions should be established, and audits and feedback should be conducted. In this way, we think that both the rates of making the diagnosis of HB infection and the rates of administration of active and passive immunoprophylaxis to newborns could be increased. In Koruk et al.'s (22) intervention research from our country to prevent HB infection, the informative education, the identification of the deficiencies and taking the relevant measures, and acting together of all healthcare professionals, of hospital management, and public cooperation have been seen to yield successful results. The rate of immunoglobulin administration, which was 28.2% before that study, increased 5.8 times after the intervention, whereas that of vaccine administration increased two times (22,23). Such practices need to be increased nationwide.

Vaccines protecting the health of the entire society, especially children, is the most effective method of preventing diseases in terms of cost and reliability (2,3,12,20,22,24,25,26). Thanks to widespread vaccination campaigns, with vaccination studies carried out in one of the poorest countries in the world, 6.4 billion people survived between 2011-2020, and treatment costs seemed to decrease (9). HB infection is one of the primary vaccine-preventable diseases. Co-administration of active and passive immunoprophylaxis enhance immune protection. In our study, the determination of HBsAg positivity in only %2,9 (n=8) of infants who received the vaccine and hyper immunoglobulin prophylaxis proved such co-administration to be quite effective in preventing HBV transmission. The relationship between anti-HBS positivity in infants and increased postpartum immunoprophylaxis over the years was found to be statistically significant. Other studies, too, described the efficacy of the application of HB immunoglobulin with the vaccine to increase protection (18,23,27,28,29). In Lee et al.'s (18) research, HB infection has been shown to develop much less frequently in vaccine or vaccine plus hyper immunoglobulin prophylaxis administered group compared to the placebo or untreated group. Again, Yi et al. (28) reported in their study that HBIG and vaccine combination reduced the rate of viral transmission from mother with HBeAg positivity to baby from 90% to 3-7%. HBsAg incidence with universal vaccination of infants was, moreover, noted to fall from 9-12% to less than 1%; besides, the protective efficacy of the HB vaccine with HBIG administration was shown to increase to 90-95% (30). In the research of Pande et al. (25), six babies from 259 babies born from HBeAg positive mothers had hepatitis infection, and they observed those babies be in the group without active and passive immunoprophylaxis (24). In our country, after the HB vaccine has been available and entered the calendar, although the incidence of HBV has been declared to decrease, no studies have been encountered in literature, documenting the rate of passive immune prophylaxis (24). At the same time, proper and effective administration of active and passive immunoprophylaxis remarkably prevents to get the HBV in infancy or early childhood and reduces becoming infection chronic and the deaths associated with HB that may develop in advanced ages (12,25,31).

The vaccine and HBIG immunoprophylaxis in the prevention of transmission of HBV are 90-95% effective; however, especially in pregnant women with high viral load and HBeAg positivity, there is a 5-10% viral transmission (4,11,12). In the study of Farmer et al. (10), despite vaccination and HBIG immune prophylaxis, protection was accounted for 81%. Whereas occult HB infection in Pande et al.'s (25) study developed at 64%, the majority of these patients were in the group receiving active and passive immunoprophylaxis. Those results of several studies mentioned above support the requirement for giving antiviral medication to pregnant women, particularly with HBeAg positive and viral load >107-8. Many other guides and studies today recommend, too, the use of oral antivirals, especially in subjects with HBeAg positivity and high viral load (HBV-DNA >107-8) and in subjects, whom liver damage begins (13,14,15,16,17).

Follow-up of babies after birth is important in terms of HB infection and immunization. In our country, few studies are examining immune prophylaxis and then the immune status of the baby against HB infection, and our research is one of them (24). In our trial, both the follow-up of the babies who were given immune prophylaxis could not be done enough, and their immune controls could not be screened adequately in the first year. HB infection has been detected in 34 of 197 children who were examined in later ages, but not being examined in the first year of infancy. Moreover, it has been stated that 17 of the children examined have not developed immunity, and booster doses have been made. This situation on the field suggests that there are deficiencies in the monitoring of mothers and children with HB infection. In our study, under the influence of National Viral Hepatitis Vaccination Programs, although the number of babies with HBsAg positivity has decreased over the years, the status of being examined mothers for the presence of HB infection during pregnancy and the follow-up of their babies' immune status one year after birth was determined to be not enough. Also, awareness of whether hyperimmune globulin prophylaxis was applied to infants or not was insufficient, and we saw troubles in the storage of documents or cards indicated immune prophylaxis had been done. The consciousness levels of mothers about the presence, follow-up, treatment, and prevention of HB infection are required to be

increased to be monitored themselves and their babies. Providing controllability and increasing the sensitivity may help increase awareness in terms of informing mothers for the importance of conducting HB tests and monitoring their results, of automatizing the hepatitis-related examinations as being visible in all centers, of arranging documents showing that immune prophylaxis has been done, and of following the cards about the vaccination. The application of the following recommendations could, therefore, reduce the frequency of HB infection among mothers and babies: 1- acting all together of family physicians, pediatricians, gynecology and infection clinics, and all healthcare professionals, especially hospital management, 2- the identification of deficiencies and the establishment of intervention commissions, 3- organizing training and ensuring continuity of that to increase the level of knowledge of the entire society.

Strength of the Study

Our study is is the first multicenter study conducted in our country, examining the follow up of mothers with HB infection, whether babies are given both hepatitis vaccine and HBIG at birth, and the current status of children in terms of HB infection. The identification of deficiencies and making new arrangements even partially in the monitoring of HB infection in mothers and their babies could shed light on and contribute to future studies.

Study Limitations

Based on information from file scans and electronic data records, mothers evaluated for HB in their pregnancies were observed to be examined only in terms of HBsAg. Although the results were positive for HBsAg in most of them, deficiencies were found in requesting and examining for HBeAg and HBV-DNA. This was one of the limitations of our study and caused babies born from HBeAg positive mothers not to be compared with babies born from HBeAg negative mothers. Also, since HBV-DNA data are not available in most pregnancies, no comparison could be made in terms of viral load in children. Moreover, the study is limited to five centers and does not reflect the country. The number of data needs to be supported by reflecting the whole country and with patient information, where all HB examinations are regularly monitored.

Conclusion

The follow-up of mothers and babies is not at the desired level in terms of preventing HB infection. Awareness should, therefore, be raised by eliminating related deficiencies.

Ethics

Ethics Committee Approval: A multicenter study permit from the Ethics Committee University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (appoval number: 27.10.2015/2) and permission from the Republic of Turkey Public Health Agency (appoval number: 45202601) were obtained for the study.

Informed Consent: The study was conducted on HBsAg positive mothers admitted to infectious diseases polyclinics between 2015 and 2017 after obtaining their consent, by performing a questionnaire through the face-to-face interviews.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Design: S.T., Data Collection or Processing: İ.E.Y., S.T., S.Ş., L.N.A., K.U., A.B., Analysis or Interpretation: İ.E.Y., Literature Search: S.T., Writing: İ.E.Y.

Conflict of Interest: Authors declare no conflict of interest.

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Research Article

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How Aware are We of the Immune Status of Hepatitis B and Hepatitis A in Chronic Hepatitis C Patients? A Multicenter Retrospective Study from Turkey

Kronik Hepatit C Hastalarında Hepatit B ve Hepatit A'nın Bağışıklık Durumunun Ne Kadar Farkındayız? Türkiye'den Çok Merkezli Retrospektif Bir Çalışma

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ABSTRACT

Objectives: Patients with chronic hepatitis C virus (HCV) infection and superinfection by hepatitis A or hepatitis B virus have higher morbidity and mortality when compared with those without HCV infection. The aim of this study was to determine hepatitis A and B seroprevalence rates and immunity in patients with chronic HCV in different regions of Turkey.

ÖZ

Amaç: Kronik HCV enfeksiyonu olan ve hepatit A veya hepatit B virüsü ile süperenfeksiyonu olan hastalar, HCV enfeksiyonu olmayanlara göre daha yüksek morbidite ve mortaliteye sahiptir. Bu çalışmanın amacı, Türkiye'nin farklı bölgelerindeki kronik HCV hastalarında hepatit A ve B seroprevalans oranlarını ve bağışıklığı belirlemektir.

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ABSTRACT

Materials and Methods: This multi-center study involving HCV-infected chronic cases was conducted between July 2016 and October 2017. Serological tests of Hepatitis B surface antigen, anti-HBs, hepatitis B core antibody (anti-HBc) immunoglobulin G (IgG) and anti-HAV IgG were evaluated by ELISA, and the files of HCV infected patients at the age of 18 or over who applied to 15 hospitals in 13 different cities of our country were screened.

Results: Three hundred sixty-two of the 828 patients were men and 466 were women. The prevalence of HBV/HCV coinfection was 2.4%, while the anti-HBs positivity rate was 46.9%. Of the 610 patients evaluated in terms of anti-HAV IgG serology, 88.8% were anti-HAV IgG positive, while 11.1% were anti-HAV IgG negative. Isolated anti-HBc IgG positivity was detected in 5.8% of patients.

Conclusion: Revealing the serological status of other hepatitis agents, such as hepatitis A and B, in patients with chronic hepatitis C is important in terms of providing the opportunity to immunize or treat when required.

Keywords: Chronic hepatitis C, hepatitis A, hepatitis B, seroprevalence

ÖZ

Gereç ve Yöntemler: HCV ile enfekte kronik olguları içeren çok merkezli bu çalışma Temmuz 2016-Ekim 2017 tarihleri arasında yapıldı. Hepatit B yüzey antijeni (HBsAg, antiHBs, antiHBcIgG ve antiHAVIgG'nin serolojik testleri ELISA ve 18 yaşında HCV ile enfekte hastaların dosyaları veya Ülkemizin 13 farklı ilinde 15 hastaneye başvuranlar tarandı. Ülkemizin 13 farklı ilindeki 15 hastanenin HCV ile enfekte hastalarının dosyaları tarandı ve ELISA yöntemi ile değerlendirilen HBsAg, anti-HBs, anti-HBc IgG ve anti-HAV IgG bakıldı.

Bulgular: Sekiz yüz yirmi sekiz hastanın üç yüz altmış ikisi erkek, 466 kadındı. HBV/HCV koenfeksiyon prevalansı %2,4 iken anti-HBs pozitiflik oranı %46,9 idi. Anti-HAV IgG serolojisi açısından değerlendirilen 610 hastanın %88,8'i anti-HAV IgG pozitif, %11,1'i anti-HAV IgG negatif idi. Hastaların %5,8'inde izole anti-HBc IgG pozitifliği saptandı.

Sonuç: Kronik hepatit C'li hastalarda hepatit A ve B gibi diğer hepatit ajanlarının serolojik durumunun ortaya konması, gerektiğinde aşılama veya tedavi fırsatı sağlama açısından önemlidir.

Anahtar Kelimeler: Kronik hepatit C, hepatit A, hepatit B, seroprevalans

Introduction

Hepatitis C virus (HCV) infection is a global public health problem. More than 170 million people worldwide are believed to be infected with HCV, the prevalence of which is approximately 3% (1,2). In Turkey, HCV seroprevalence ranges between 0.4% and 1.15% in the general population (3). Improved understanding of the molecular biology of HCV in recent years has led to improvements in the effectiveness and tolerability of HCV treatment, and to the development of numerous direct-acting antiviral agents (4). Despite this success achieved in treatment, however, there is still no vaccine for the HCV. Protection against other hepatitis viruses such as hepatitis A and hepatitis B that cause inflammation in the liver can be provided through immunization. Of these viruses, the HAV is asymptomatic in childhood, but manifests as a self-limiting infection with mortality rates between 0.01% and 0.5% in adults (5). In addition, HAV superinfection in patients with chronic liver disease, including patients with chronic hepatitis caused by HCV, is associated with a risk of fulminant hepatitis and associated mortality (6).

The number of people worldwide infected with chronic HBV infection, which is capable of causing cirrhosis and hepatocellular cancer by leading to liver damage, similarly to chronic hepatitis C, is approximately 240 million, and every year some one million people die from the disease (7). The prevalence of hepatitis B positivity in Turkey varies between regions, but generally ranges between 2% and 12% (8). Several studies have shown accelerated progression of liver fibrosis in patients with chronic HCV infection and co-infection with HBV, with a higher risk of hepatocellular carcinoma (HCC) compared to chronic HCV infection alone (9,10). For that reason, Centers for Disease Control and Prevention and the World Health Organization Advisory Committee of Immunization Practices recommend that patients with chronic liver disease, including chronic hepatitis C, be immunized against both HAV and HBV (11).

The aim of this study was to determine hepatitis A and B seroprevalence rates and immunity in patients with chronic hepatitis C in different regions of Turkey.

Materials and Methods

The research was planned as a multi-center observational study. Physicians working in infectious diseases and gastroenterology clinics in 13 different provinces in Turkey between July 2016 and October 2017 were contacted. Three centers were university hospitals, seven were education-research hospitals, four were public hospitals, and one was a private hospital. The files of patients over 18 under follow-up with diagnoses of chronic hepatitis C were screened retrospectively. The demographic data and HBsAg, anti-HBs, anti-HBc IgG and anti-HAV IgG results investigated using the ELISA method of 828 chronic hepatitis C patients whose records were available were recorded onto an Excel file.

Statistical Analysis

Statistical analysis was performed on SPSS (Version 13.0) software. Numerical variables such as age were expressed as mean ± standard deviation and median, while categorical data were expressed as number and percentage.

Results

Three hundred sixty-two (43.8%) of the 828 patients were men and 466 (56.2%) were women. The patients' mean age was 57.85±14.75 years (18-86). The genotype rates of the hepatitis C patients and the names of the regions where the data were collected are shown in Table 1. The prevalence of HBV/HCV coinfection was 2.4% (n=20), while the anti-HBs positivity rate was 46.9% (n=389). Of the 610 patients evaluated in terms of anti-HAV IgG serology, 88.8% (n=542) were anti-HAV IgG positive, while 11.1% (n=68) were anti-HAV IgG negative. Isolated anti HBc

IgG positivity was detected in 5.8% (n=611) of patients (Table 2). Approximately half the HCV-positive patients (47.8%, n=396) were anti-HBs negative. In addition, a significant proportion of the patients (26.3%, n=218) were not examined in terms of hepatitis A serology. The proportions of patients not examined in terms of HBsAg and anti-HBs were 1.9% (n=16) and 1.8% (n=15), respectively.

Discussion

The epidemiology of HAV and HBV varies depending on the geographical area involved. The situation in each country therefore needs to be examined to determine the immunological status of the population against these viruses. Knowledge of the serological profile against HAV and HBV, that can be prevented through immunization, especially in patients with underlying chronic hepatitis C, is important in order to reduce the risk of superinfection (9,10,11).

Rates of anti-HAV IgG seropositivity in patients with chronic hepatitis vary considerably in studies from different countries. Differing results have even been obtained among different regions of the same country. In a study from Italy, the rate of anti-HAV IgG seropositivity was 53.5% among 2830 patients with chronic hepatitis, the rate being higher in the southern and central provinces of the country than in the north (12). Anti-HAV IgG seropositivity of 55% was determined in chronic hepatitis patients in the USA, another developed country (13). Three different studies from Italy have reported anti-HAV IgG seropositivity rates of 79.3% (12) and 85.7% (14) in chronic hepatitis patients, and as high as 97.6% (15) in patients with chronic hepatitis C. This situation, associated with the higher mean age among HCV patients and increased seropositivity with age, was revealed in a study by da Silva et al. (16). The results of the present study indicated a high prevalence (88.8%) of anti-HAV IgG, a serological marker that indicates previous contact with HAV, among adult patients with chronic HCV infection. However, we also found that the anti-HAV IgG test was not requested or the results were not known in one in four patients with chronic hepatitis C (26.3%). This suggests that rather more care is required on the subject of serological screening among chronic hepatitis patients.

Table 1. HCV patients' demographic characteristics and genotype rates

Characteristics	
Male/female n (%)	362 (43.8)/466 (56.2)
Mean age, years	57.85±14.75
Genotype (n=465)	
1	88
1b	336
2	12
3	19
4	8
5	2

HCV: Hepatitis C virus

Table 2. HCV-positive patients' serological status

Serological marker	**%**
Anti-HAV IgG (n=542/610)	88.8%
HBsAg (n=20)	2.4%
Anti-HBs (n=389)	46.9%
Isolated anti-HBc IgG positivity (n=611)	5.8%

HCV: Hepatitis C virus, HAV: hepatitis A virus, IgG: Immunoglobulin, HBsAg: Hepatitis B surface antigen,

One study showing that HAV superinfection in patients with chronic HCV infection can be fatal reported that HAV superinfection developed in 17 out of 432 chronic hepatitis C patients followed-up over seven years, and that six of these died from fulminant hepatitis (6). Another study showed low effectiveness when hepatitis A or B immunization was administered to patients who were decompensated due to chronic hepatitis or in the immunosuppressed period following liver transplantation (17). Both studies are noteworthy in showing the importance of screening of chronic hepatitis patients and of early immunization of seronegative patients in the early period.

Patients coinfected with HBV and HCV experience more rapid fibrosis, higher progression rates, and more severe liver disease. The risk of developing HCC is also higher in coinfected patients compared to those with HBV or HCV monoinfection (18,19). Due to the lack of extensive research into HBV/HCV coinfection worldwide, the prevalence is not exactly known. Marot et al. (10) study from the Far East showed HBV positivity in 2-10% of chronic hepatitis C patients. A study from the USA emphasized the higher likelihood of encountering HBV in chronic hepatitis C due to similar modes of transmission, such as intravenous drug use, in both (20). The number of studies investigating HBV seroprevalence in patients with HCV infection in Turkey is limited. In one multi-center study from Turkey, 10,167 patients were screened, and HBV/HCV coinfection was detected in 99 (974/100,000) (21). Demirtürk et al. (22) determined an HBV positivity rate of 1.9% in patients infected with chronic hepatitis C, while Akça et al. (23) reported a figure of 4.4%. Studies show that anti-HBs seropositivity in patients with chronic hepatitis C varies between 29.3% and 39.1% (24,25). According to the results of the present study, HBV/HCV coinfection (2.4%) was similar to the rates in previous studies, while anti-HBs seropositivity (46.9%) was higher. Isolated anti-HBc IgG positivity is common in HBsAg and anti-HBs negative cases. Although the prevalence of this serological profile varies according to societies, it is between 0.1-20% (26,27). In a study conducted by Tahmaz et al. (28) from our country, anti-HBc IgG seropositivity was found to be 12.5%, and in our study it was found to be 5.8% similar to the literature.

Study Limitations

One limitation of this study is that due to its retrospective design and multicenter nature not all patients' data could be retrieved. No distinction between immunization and natural immunity was therefore possible.

Conclusion

Revealing the serological status of other hepatitis agents, such as hepatitis A and B, in patients with chronic hepatitis C is important in terms of providing the opportunity to immunize or treat when

required. The fact that the serological profile of hepatitis A virus was not examined to a significant extent in our study showed the lack of screening. Further more extensive studies are now needed to reveal the true picture in Turkey.

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Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: N.İ., S.T., Design: S.T., Data Collection or Processing: A.B., M.U., N.Ö.Ç., İ.E.Y., T.Y., K.U., N.Ç., G.D., G.İ., S.A.C., M.D., Analysis or Interpretation: P.E., R.G., M.B., Literature Search: N.İ., Writing: N.İ., S.T.,

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Research Article

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Investigating the Prevalence of Hepatitis Delta and Assessment of Treatment Response

Delta Hepatit Sıklığının Araştırılması ve Tedavi Yanıtının Değerlendirilmesi

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ABSTRACT

Objectives: The purpose of this study was to investigate the seroprevalence of delta virus, assess the treatment outcomes of patients receiving treatment.

Materials and Methods: The files of patients diagnosed with chronic hepatitis B followed up between 01.01.2015 and 31.12.2019 were examined. For the patients positive for delta antibody, demographic information, hepatitis delta virus (HDV)-RNA levels, treatment information and treatment outcomes were recorded from the files. Undetectable HDV-RNA levels after treatment was considered as total virologic response.

Results: There was a delta antibody positivity in 2.9% (n=74) of the 2,548 patients positive for hepatitis B surface antigen (HBsAg). The HDV-RNA tests of 60 patients found to be positive for delta antibody could be accessed. HDV-RNA was positive in 33.3% (n=20/60) of these patients, while 60% among the positive ones (n=12) received treatment. Among the patients who received treatment, 58.3% (n=7) were male, 41.7% (n=5) were female, and their median age was 53 (31-69) years. There was virologic response in 50% of the patients who received treatment, while no patient displayed HBsAg seroclearance.

Conclusion: At similar rates to those in other studies conducted in Turkey, hepatitis delta seroprevalence, virologic response rate were found to be low.

Keywords: Hepatitis delta, prevalence, treatment

ÖZ

Amaç: Bu çalışmanın amacı kronik hepatit B tanılı hastalarda delta virüs seroprevalansını araştırmak, tedavi alan hastaların tedavi sonuçlarını değerlendirmekti.

Gereç ve Yöntemler: 01.01.2015-31.12.2019 tarihleri arasında takip edilen kronik hepatit B tanılı hastaların dosyaları incelendi. Delta antikor pozitif olan hastaların demografik bilgileri, hepatit delta virüsü (HDV)-RNA düzeyleri, tedavi bilgileri ve tedavi sonuçları dosyalardan kayıt edildi. Tedavi sonrası HDV-RNA saptanamaz düzeyde olması virolojik tam yanıt olarak değerlendirildi.

Bulgular: Hepatit B yüzey antijeni (HBsAg) pozitif 2.548 hastanın %2,9'unda (n=74) delta antikor pozitifliği saptandı. Delta antikor pozitif tespit edilen 60 hastanın HDV-RNA testine ulaşıldı. Hastaların %33,3'ünde (n=20/60) HDV-RNA pozitif tespit edilmiş olup bu hastaların %60'ına (n=12) tedavi uygulanmıştı. Tedavi uygulanan hastaların %58,3'ü erkek (n=7), %41,7'si (n=5) kadın olup yaş ortanca 53 yıl (31-69) yıldı. Tedavi gören hastaların %50'sinde virolojik yanıt gözlenirken hiçbir hastada HBsAg seroklirensi gözlenmedi.

Sonuç: Türkiye'de yapılan diğer çalışmalara benzer oranda delta hepatit seroprevalansı, virolojik yanıt oranı düşük saptanmıştır.

Anahtar Kelimeler: Delta hepatit, prevalans, tedavi

Ergen P, Yılmaz Karadağ F, Aydın Ö. Investigating the Prevalence of Hepatitis Delta and Assessment of Treatment Response. Viral Hepat J. 2020;26:135-140.

Introduction

The hepatitis delta virus (HDV) is an RNA virus, which causes a hepatitis delta infection in only hepatitis B surface antigen (HBsAg)-positive individuals. The virus was detected for the first time in Italy in 1977 by Rizzetto et al. (1), (2). While delta virus infection prevalence changes from country to country, it is estimated that 15 million people around the world are infected with HDV (3). Although HDV infections are endemic in Turkey, their seroprevalence varies from region to region (4,5).

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Its form of contagiousness is similar to that of the hepatitis B virus (HBV) infection, and it is transmitted by contaminated blood and blood products, infected body fluids, vertically from the mother to the infant and horizontally. Hepatitis delta progresses with two different clinical pictures as coinfection and superinfection. When someone is infected by HDV and HBV at the same time, a co-infection develops, and the clinical condition is more severe. Superinfection develops when an individual already infected with HBV receives HDV later and the clinical picture is milder. The only agent that is still used in treatment is alpha interferon (6).

Our purpose in this study was to investigate the seroprevalence of hepatitis delta in patients diagnosed with hepatitis B who had been followed up at our polyclinic for the last five years and to assess the treatment responses among the patients who were treated.

Materials and Methods

The data of 2548 HBsAg-positive patients who visited our polyclinic between 01.01.2015 and 31.12.2019 were retrospectively examined. In addition to delta antibody positivity, the treatment responses of the patients who received treatment due to hepatitis delta infection were investigated. HBsAg, anti-HDV studied with the ELISA method and HDV-RNA values measured by the polymerase chain reaction method. In addition to IV drug user, men who have sex with men (MSM), human immmunodeficiency virus (HIV)/HCV co-infection, whether their partners had HDV infection or not, the patients were also evaluated in terms of co-infection, superinfection, fulminant hepatitis, cirrhosis and hepatocellular carcinoma. Assessment of the treatment response was performed based on the Turkey 2017 Clinical Practice Guidelines on Hepatitis Delta Virus Infection Diagnosis, Monitoring, Management and Treatment (7). Total virologic response was accepted as undetectable levels of HDV-RNA. Hepatitis B e antigen (HBeAg)/anti-HBe, alanine aminotransferase (ALT), HBV-DNA, alpha-fetoprotein, abdominal imaging and liver pathology tested at the beginning of the treatment and HDV-RNA, HBV-DNA, ALT, HBsAg/anti-Hbs tested after the treatment were examined.

The study was approved by the Ethics Board of the İstanbul Medeniyet University, Göztepe Training and Research Hospital (decision no: 2020/0032, date: 21.01.2020). The study was carried out in compliance with the principles of the Declaration of Helsinki.

Statistical Analysis

Utilizing the SPSS IBM 22.0 (SPSS Inc., Chicago Il) software, the data was processed. The distribution of the data was evaluated by Kolmogorov-Smirnov test. The descriptive variables are presented as frequency, percentages, mean and standard deviation, while non-normally distributed variables are expressed as median (minimum-maximum). Using chi-squared test and Fischer's exact test, comparisons were made. A p-value of smaller than 0.05 was accepted as statistically significant.

Results

Delta antibody positivity was determined in 2.9% (n=74) of the 2548 HBsAg-positive patients. 50% of the patients (n=37) were male, 50% (n=37) were female, and their median age was 51 (23-80) years. The HDV-RNA tests of 60 patients with positive delta antibody could be accessed. HDV-RNA was positive in 33.3% (n=20/60) of these patients, while 60% among the positive ones (n=12) received treatment. Eight patients had not received treatment due to reasons such as pregnancy, being of foreign nationality and not being able to receive treatment or not coming for follow-up. Among the patients who received treatment, 58.3% (n=7) were male, 41.7% (n=5) were female, and their median age was 53 (31-69) years. The patients received at least 48 weeks of pegylated interferon (Peg-IFN) treatment. 66.7% (n=8) of these patients received interferon only the treatment by itself, while 33.3% (n=4) received a nucleoside/nucleotide analogue alongside with interferon. There was virologic response in 50% of the patients who received treatment, while no patient displayed HBsAg seroclearance or seroconversion. Fulminant hepatitis was not observed in this study, but hepatocellular carcinoma developed in one patient who received treatment and was being monitored for a long time with negative HDV-RNA. The pre-treatment and post-treatment data of the patients who received treatment, the treatment that they received and treatment durations are shown in Table 1.

Discussion

In HBsAg-positive individuals, delta infection is a condition that always needs to be kept in mind and monitored. Especially individuals born in places with high HDV endemicity, those using intravenous drugs, MSM, HCV- or HIV-infected individuals, those with multiple partners or previous history of sexually transmitted disease and individuals with high ALT values alongside low or undetectable HBV-DNA are under the risk of HDV infection (8). While none of our patients had intravenous drug use, MSM history or HIV and/or HCV positivity but the spouse of one patient had a diagnosis of hepatitis delta. Also one of our patient came from a foreign country.

In the course of HDV infection, acute hepatitis, chronic hepatitis, fulminant hepatitis, cirrhosis and hepatocellular carcinoma may appear (2,9). Fulminant hepatitis was not observed in any of our patients examined in this study, while it was determined that hepatocellular carcinoma developed in one patient who received treatment and was being monitored for a long time with negative HDV-RNA (Table 1, patient no: 10). Rates of becoming chronic following superinfection are 70-90%, while there are much higher in comparison to rates after coinfection (7,10,11). None of our patients had acute coinfection, in all patients delta positivity was determined during their monitoring.

Turkey is a moderately endemic region in terms of delta infection, while the positivity rates show differences between the east and the west of the country (12). In the meta-analysis by Değertekin et al. (4), when the data of studies conducted after 1995 were examined, it was shown that the anti-HDV positivity rate in the west of Turkey was 4.8%, while it was 27.1% in the east. In their study conducted in 2019 in İstanbul, Yolcu et al. (13) reported the anti-HDV positivity rate as 4.1%. The delta positivity rate in this study was 2.9%, and it was lower than those in eastern provinces and similar to those in western ones.

Studies have shown a decrease in the HDV prevalence in Turkey throughout the years. Ayaz and Sarı (14), in their study covering the period of 2012-2017, determined anti-delta positivity as 4.4%, and

Table 1. Data of treated patients before and after treatment

Patient no	Gender	Age	Before treatment HBV-DNA (IU/mL)	Before treatment HBeAg/anti-HBe	Before treatment ALT	Before treatment Alfa Feto Protein	Before treatment imaging	Before treatment (HAI*, Fibrozis)	Treatment	Treatment duration (week)	After treatment HDV-RNA	After treatment HBV-DNA	After treatment ALT	After treatment HBsAg/anti-HBs
1	Male	1969	3.109.096	-/+	249	1.81	Hepatosteatosis	7/2	Pegile interferon alfa 2b, 100 mcg	48	Negative	88	23	+/-
2	Male	1969	12.098	-/+	63	4.21	Hepatosteatosis	Did not performed	Pegile interferon alfa 2b, 150 mcg	48	Positive	106	145	+/-
3	Female	1979	6.017	-/+	26	1.62	Within normal range	6/0	Pegile interferon alfa 2a, 180 mcg + entekavir 0.5 mg	48	Negative	Negative	20	+/-
4	Male	1959	3.778	-/+	36	2.06	Hepatosteatosis	11/4	Pegile interferon alfa 2b, 100 mcg	48	Negative	7.091	6	+/-
5	Female	1972	32	-/+	46	6.14	Fine granular pattern	13/2	Pegile interferon alfa 2b, 120 mcg	96	Positive	Negative	19	+/-
6	Female	1962	4.729.680	+/-	96	3.23	Fine granular pattern	Did not performed	Pegile interferon alfa 2b, 120 mcg + entekavir 0.5 mg	48	Positive	Negative	86	+/-
7	Female	1989	51.161	-/+	121	2.69	Fine granular pattern	6/1	Pegile interferon alfa 2a, 180 mcg	48	Positive	14.000	71	+/-
8	Male	1965	1.931.073	+/-	56	1.57	Minimal granular appearance	6/3	Pegile interferon alfa 2b + tenofovir disoproksil fumarat 245 mg	96	Positive	Negative	76	+/-

Table 1 contiuned

9	Male	1954	Negative	-/+	28	4.3	Within normal range	Did not performed	Pegile interferon alfa 2a, 180 mcg	48	Positive	Negative	23	+/-
10	Male	1951	Negative	-/+	102	6.04	Hepatomegaly granular pattern	12/3	Pegile interferon alfa 2a, 180 mcg	96	Negative	38	25	+/-
11	Male	1985	Negative	-/+	49	2.39	Within normal range	Did not performed	Pegile interferon alfa 2b, 80 mcg	96	Negative	38	25	+/-
12	Female	1957	70.240	-/+	46	2.85	Hemangioma in the liver	Could not be performed	Pegile interferon alfa 2a 180 mcg + tenofovir disoproksil fumarat 245 mg	48	Negative	Negative	45	+/-

*HAI: Histological activity index, HBV: Hepatitis B virüs, HBeAg: Hepatitis B e antigen, ALT: Alanine aminotransferase, HBsAg: Hepatitis B surface antigen

they reported that this rate was 8.52% in their study covering the period of 2002-2004 (14,15). Eser-Karlıdağ (16) found the delta positivity in Elazığ in eastern Turkey as 8.8% and reported that this ratio was lower in comparison to those reported in previous studies in the region. It is an ordinary outcome that, with the addition of hepatitis B vaccination to the national vaccination program in 1998, there has been a decrease in the prevalence of chronic hepatitis B, therefore, the prevalence of hepatitis delta, among young adults. Despite this, as hepatitis B infections have not been eradicated, HDV still continues to be a public health problem.

While studies are going on regarding new agents including the hepatocyte entry inhibitor myrcludex B, farnesyl transferase inhibitor lonafarnib, nucleic acid polymers and Peg-IFN-λ, the only option in treatment today is still Peg-IFN-α (17,18). The primary target in treatment is to lower the HDV-RNA value to an undetectable level. HBsAg clearance and seroconversion are the ultimate goal, while it is highly difficult to reach this goal. Without regards to treatment response, PEG-IFN treatment must continue for 48 weeks. While reaching undetectable levels of HDV-RNA and continuation of these 6 months after the end of the treatment are desired, low rates of sustainable HDV suppression are reached after treatments of 48-96 weeks (19). For this reason, the HDV-RNA negativity we obtained 6 months after the end of the treatment cannot be considered as permanent virologic response, but biochemical and virologic monitoring is recommended. In the 5-year follow-up study of HIDIT-1 by Heidrich et al. (20), at least one positivity was determined in the follow-ups of 9 of 16 patients whose HDV-RNA was determined as negative 24 weeks after the end of the treatment. Rather than IFN monotherapy, combined treatment studies are also conducted to increase the success of treatment. In the randomized controlled HIDIT-1 and HIDIT-2 studies conducted by Wedemeyer et al. (21) , (22), no significant difference could be found in the treatment responses between patients receiving IFN treatment and those receiving IFN and tenofovir disoproxil treatment. There are also other studies showing that usage of nucleoside/nucleotide analogues as monotherapy or in combination with PEG-IFN does not have an additional benefit (23,24,25). Combined treatment may be recommended in patients with diagnosis of chronic hepatitis B needing treatment in addition to HDV infection. While HBV-DNA was negative after treatment in all 4 patients we gave combined therapy, only 2 patients were found to have negative HDV-RNA values.

In the review by Yurdaydin and Idilman (26), virologic success was reported as 14-50% in controlled studies conducted on patients using IFN and 17-47% in studies conducted with PEG-IFN. In our study, virologic response was determined at a rate of 50%, which was similar to those reported in studies conducted in Turkey and around the world.

As eradication is out of the question as long as the presence of HBsAg continues, the necessity of HDV-RNA monitoring is clear. During the treatment of HDV which is generally dominant in HDV coinfection, HBV-DNA monitoring of patients should also be conducted (27).

Study Limitations

The limitation of the study is that it is a retrospective study, so all patient datas were not available.

Conclusion

The primary way of preventing delta infection development is to achieve protection of under-risk individuals by applying effective vaccination programs and eradicating hepatitis B infection by raising awareness in all parts of the society. All patients positive for HBsAg should be screened in terms of HDV, and patients with HDV viremia should be treated. While IFN is still the only preferred option in treatment, a more effective antiviral agent is needed.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Board of the İstanbul Medeniyet University, Göztepe Training and Research Hospital (decision no: 2020/0032, date: 21.01.2020).

Informed Consent: Since our study was retrospective, informed consent was not used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.E., F.Y.K., Ö.A., Design: P.E., Ö.A., Data Collection or Processing: P.E., Analysis or Interpretation: F.Y.K., Literature Search: Ö.A., Writing: P.E., F.Y.K.,

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Research Article

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Examination of Mutations in the HBsAg and Polymerase Genes Induced by Pegylated Interferon Alpha and Oral Antivirals Used in the Treatment of Chronic Hepatitis B

Kronik Hepatit B Tedavisinde Kullanılan Pegile İnterferon Alfa ve Oral Antivirallerin HBsAg Geni ve Polimeraz Geni Üzerinde Yaptığı Mutasyonların Araştırılması

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ABSTRACT

Objectives: The Hepatitis B Virus is a virus having high mutation frequency due to having a high replication capacity and not having error correction capability in reverse transcription.It is aimed to examine the mutations created by the oral antivirals used in CHB treatment on pol gene and S gene, to determine the clinical and epidemiological significance of these mutations, and to specify the development of drug resistance in long terms and the results it may cause. Secondly, it is aimed to determine whether the quantitative HBsAg titers are early markers for detecting drug resistance or not.
Materials and Methods: Correlation analyses were performed with monitoring qHBsAg levels and HBsAg (S/Co) and HBV-DNA levels of the patients.
Results: It was seen in the correlation analysis, a statistically significant middle level correlation existed between the initial qHBsAg and HBV-DNA levels. It was concluded that the efficiency of qHBsAg levels on making diagnosis is at a good degree to distinguish inactive HBsAg carriers and HBeAg negative CHB patients, and the cutoff value was determined as 2188 IU/mL.
Conclusions: In order to understand the usability of HBsAg titres as a marker in early diagnosis of these mutations more comprehensive studies are required.
Keywords: Chronic hepatitis B, quantitative HBsAg, mutatition, nucleos(t)ide analogs, polymerase gene

ÖZ

Amaç: Hepatit B Virusu (HBV), yüksek replikasyon kapasitesinin olması ve ters transkripsiyon işleminde hata düzeltme yeteneğinin olmaması nedeniyle, yüksek mutasyon sıklığına sahip bir virustur. Bu çalışmada KHB tedavisinde kullanılan oral antivirallerin pol geni ve S geni üzerinde yaptığı mutasyonların araştırılması ve bu mutasyonların klinik ve epidemiyolojik öneminin saptanması, uzun dönemde ilaç direnci gelişiminin ve bunun yol açacağı sonuçların belirlenmesi amaçlanmıştır. İkincil olarak, kantitatif HBsAg (qHBsAg) titrelerinin ilaç direncini belirlemede erken bir marker olup olmadığının saptanması amaçlanmıştır.
Gereç ve Yöntemler: Hastaların qHBsAg düzeyleri ile HBsAg (S/Co) ve HBV-DNA düzeyleri takip edilerek korelasyon analizleri yapıldı.
Bulgular: Tedavi alan hastaların tamamı ele alınarak yapılan korelasyon analizlerinde başlangıç qHBsAg ve HBV-DNA seviyeleri arasında istatistiksel olarak anlamlı orta düzeyde bir korelasyon olduğu görüldü. İnaktif HBsAg taşıyıcıları ile HBeAg negatif KHB hastalarını ayırmada qHBsAg düzeylerinin tanı koymadaki etkinliğinin iyi derecede olduğu sonucuna varıldı, cut off değeri ise 2188 IU/mL olarak belirlendi.
Sonuç: Bu mutasyonların erken tanısında HBsAg titrelerinin bir belirteç olarak kullanılabilirliğini anlamak için daha kapsamlı çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Kronik hepatit B, kantitatif HBsAg, mutasyon, nükleoz(t)ide analogları, polimeraz geni

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Introduction

Despite recent developments in chronic hepatitis B (CHB) treatment, complete eradication of this disease does not seem possible due to the persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes. The primary goal of treatment is the effective repression of hepatitis B virus (HBV)-DNA, and if possible, hepatitis B surface antigen (HBsAg) loss and seroconversion, and prevention of complications such as cirrhosis and hepatocellular carcinoma (HCC). Today, interferons (IFN) and nucleoside/nucleotide analogues (NA) are used for the treatment of CHB. IFNs are immunomodulating drugs, which have specific expiration dates, and do not facilitate the development of resistance. NA should be used for at least 1 year to effectively repress HBV-DNA. The most significant problem associated with NA treatment is the development of drug resistance and cross-resistance in the long term (1,2). Telbivudine (LdT) is a L-nucleoside analogue with more potent antiviral activity against HBV than Lamivudine (LAM). However, 2-5% of the patients develop resistance after 1 year of treatment (3). Entecavir (ETV) and tenofovir (TDF) are oral antiviral NA agents that exhibit potent viral suppressive effects and lower resistance rates due to their high genetic barriers (1).

Currently, HBV-DNA level determination, an expensive method requiring experience, is used to make the decision whether to begin antiviral therapy or not, to determine the follow-up response to the treatment, and to determine if there is resistance to the antiviral. Recent studies suggest that predictions about the prognosis of the disease can be made through the use of serum HBsAg quantification (qHBsAg), which is a less costly method. There is a relationship between the HBsAg quantitative values and clinical stage, fibrosis score, and treatment response of the disease. Since serum HBsAg levels correlate with intrahepatic cccDNA levels, quantification reflects the level of infection. Therefore, qHBsAg can be helpful in differentiating HBeAg negative patients, who have low HBV-DNA levels, from inactive carriers (4).

Due to its high replication capacity (>10^{12} virions/day) and the lack of an ability to correct errors, HBV has a high mutation frequency (5). While NA resistance-associated mutations may occur prior to treatment, mutations responsible for resistance to antiviral agents may also occur during long-term treatment of CHB with NA (6,7). Additionally, due to the polymerase (pol) and surface (S) genes existing in an overlapping position in the HBV genome, NA drug resistance mutations may lead to amino acid changes in the structure of the HBsAg. In recent years, due to the overlapping of the HBV pol/S genes, the term, Antiviral Drug-Associated Potential Vaccine-Escape Mutant (ADAPVEM), has been utilised (8,9).

The goal of this study was to determine the mutations in the pol and S genes induced by oral antivirals used in the treatment of CHB, to establish the clinical and epidemiological significance of these mutations, and to track the long-term development of drug resistance and determine its consequences. Secondly, we aimed to determine if quantitative HBsAg titres could be utilised as an early marker of drug resistance.

Materials and Methods

Patients and Study Design

The study was conducted between 2009 and 2014. This study was approved by the Kocaeli University Faculty of Medicine Ethics Committee of Clinical Research (approval number: 2009/97, date: June 26.06.2009) and written consent was obtained from each patient. Patients for the study were selected from volunteers that were seen in the Infectious Diseases and Clinical Microbiology polyclinic diagnosed with CHB infection but had not previously undergone treatment. Before inclusion in the study were all patients gave informed consent. Patients with decompensated cirrhosis, hepatocellular carcinoma, alcoholic hepatitis, autoimmune hepatitis, patients with co-infections, pregnant females, lactating females, and minors under 18 years of age were excluded from the study.

Peg-IFN treatment was administered to the first patient group, whereas TDF 245 mg/day, ETV 0.5-1 mg/day, LdT 600 mg/day were used as treatments in the second, third, and fourth patient groups, respectively. A fifth group consisted of only inactive HBsAg carriers who received follow-up treatment. As the treatment response criteria, an HBV-DNA viral load <2000 IU/mL in the sixth month was used for Peg-IFN-treated patients, while HBV-DNA viral loads determined in the 12th month were used for NA-treated patients.

Prior to treatment, a liver biopsy was obtained from all patients. Histological activity index (HAI) and degree of fibrosis were reported with the values within the ranges 0-18 and 0-6, respectively, using the Ishak modified Knodell system.

Serum HBsAg Quantification

For patients in the treatment group, the qHBsAg titres were checked prior to, in the third month, and after the first year of treatment; while the qHBsAg titres of inactive HBsAg carriers were measured once every other year, twice in total. Serum qHBsAg was examined using the Electrochemiluminescence Immunoassay method, using the HBsAg II Quant Kit (Roche Diagnostics, Indianapolis, USA) in the Cobas e601 system. The measurement range of the test was determined to be 0.05-130 IU/mL for undiluted samples and 20-52000 IU/mL for 400-fold diluted samples according to Clinical Laboratory Standards Institute EP17-A requirements.

HBV-DNA Measurements

HBV-DNA was isolated using the QIAsymphony SP magnetic particle isolation platform (QIAGEN GmbH, Hilden, Germany). HBV-DNA was assayed using the Rotor-GENE platform (QIAGEN GmbH, Hilden, Germany), using the real-time PCR technique with the Artus HBV-DNA RGQ kit.

HBV-DNA Sequencing

HBV genotype/subgenotype determination was analysed by sequencing all known primary/compensatory NA resistance mutations and mutations of the S gene overlapping with the pol gene (HBsAg protein; amino acids 111-227), HBV pol gene (reverse transcriptase; RT region, amino acids 80-250) (10). For this purpose, HBV-DNA was isolated from serum samples (Anatolia Geneworks, Bosphore® Viral DNA Extraction Spin Kit and Magnesia® 16 Magnetic Bead Extraction System, Istanbul,

Turkey). For HBV pol gene amplification (742 bp), forward (F:5'-TCGTGGTGGACTTCTCTCAATT-3') and reverse (R:5'-CGTTGACAGACTTTCCAATCAAT-3') primers were used. For PCR conditions, the following temperature/time cycle was applied: an initial 10-minute pre-denaturation at 95°C, 35 cycles at 95°C for 45 seconds, at 60°C for 45 seconds and at 72°C for 45 seconds. All PCR products were purified with the High Pure PCR Product Purification Kit (Roche Diagnostics, Germany). In the sequencing protocol, the Phire Hot Start DNA polymerase (Finnzymes Oy, Finland) enzyme was used. Sequencing was performed using the BigDye Terminator v3.1 Cycle Sequencing Kit (Amersham Pharmacia Biotech Inc., USA), 36-cm capillary and POP-7 TM polymer (Applied Biosystems Inc., USA), according to the manufacturer's recommendations, in the ABI PRISM 3130 (Applied Biosystems Inc., USA) platform. The PCR protocol used for direct sequencing was 35 cycles at 95°C for 20 seconds, at 50°C for 25 seconds and finally at 60°C for 2 minutes. Electropherograms were obtained using the Vector NTI v5.1 (InforMax, Invitrogen, Life Science Software, USA) software. The resulting sequences were analysed in the Geno2pheno Drug Resistance (Center of Advanced European Studies and Research, Germany) software. The Geno2pheno software compares the unknown nucleic acid sequences in fasta format with the reference sequences in its database. After the comparison, amino acids at positions 80, 84, 85, 91, 169, 173, 180, 181, 184, 191, 194, 202, 204, 214, 215, 233, 236- 238 and 250 of the HBV pol gene RT loop were analysed for primary drug resistance and compensatory mutations (10). Additionally, amino acids at positions 121, 135, 137, 139-149, 151-153, 155-157, 161, 164, 172, 173, 175, 176, 182, 193-196 of the S gene region that overlaps with the HBV RT loop were also analysed for the presence of mutations (11).

Patients in the treatment group had their serum HBV-DNA levels checked prior to, in the third month, and after first year of the treatment, while inactive HBsAg carriers were measured once every other year, twice in total. DNA sequence analysis was performed for all patients and again for the inactive HBsAg carriers whose HBV-DNA level was >100 IU/mL. DNA sequence analysis was also performed on serum taken when a breakthrough occurred during the follow-up of NA-treated groups.

Statistical Analyses

The SPSS (SPSS, Inc., Chicago, IL, version 17.0) software package was used to perform the statistical analysis. Qualitative values were expressed as numbers and percentages. Since the measurable values did not conform to a normal distribution, they were given as median values (25-75 percentiles). For comparison of dependent groups, the Wilcoxon and Friedman tests were used, while Mann-Whitney U and Kruska-Wallis tests were performed for comparisons of independent groups. Nominal values were analysed with chi-squared and Fisher's tests. During the statistical assessment, values of $p<0.05$ were considered to indicate significance. For correlation analysis, Spearman's rho test was used. receiver operating characteristic (ROC) analysis was performed using Medcalc version 13.0.6.0. With regard to the correlation coefficients; ranges of 0.70-1.00; 0.70-0.30; and 0.30-0 were respectively interpreted as high correlation, moderate correlation, and low correlation, and were accepted as significant at $p<0.01$.

Results

Fifty-five active CHB-diagnosed but untreated patients and 39 inactive HBsAg carriers, 94 patients in total, were enrolled in our study. Four groups of active CHB-diagnosed patients, containing 15, 17, 15, and 8 members, were treated with peg-IFN, TDF, ETV, and LdT, respectively. Thirty-nine patients, who were inactive HBsAg carriers, constituted the control group. Fifty-six of the patients involved in the study were male, while the remaining 38 were female.

Demographic characteristics of the groups, the initial laboratory conditions, HBV-DNA levels, qHBsAg titres, and the histopathological liver characteristics are shown in Table 1. When the initial and first year aspartate aminotransferase (AST), alanine aminotransferase (ALT), qHBsAg, and HBV-DNA levels of active CHB-diagnosed patients (n=55) were compared with those of the control group (n=39), a statistically significant difference was observed. In the first year, the treatment group showed no reduction in HBsAg (S/CO) levels in response to the treatment; however, AST, ALT, qHBsAg, and HBV-DNA levels decreased (Table 2).

In the histopathological examination of 53 active CHB patients that underwent liver biopsy, 24 patients (45.3%) had a HAI ≥6, while 29 patients (54.7%) had a score <6. Due to cirrhosis-associated thrombocytopenia, a liver biopsy could not be taken from two patients, who were treated with ETV (Table 3).

Thirty-four of the fifty-three active CHB patients from whom a liver biopsy was taken were HBeAg-negative, and 19 patients were HBeAg-positive. The HBeAg-negative patients were compared to fibrosis scores. The ALT, HBsAg (S/Co), qHBsAg, HBeAg (S/Co), and HBV-DNA viral load values exhibited a significant difference at the beginning of treatment, but not at 12 weeks or after the first year of treatment (Table 4). Regarding the biopsy results of the 19 HBeAg-positive patients, 13 had a fibrosis score less than four, while 6 patients had a fibrosis score equal to or greater than four. The initial ALT values of the group with a fibrosis score equal to or greater than four were significantly higher than those of the group with a fibrosis score of less than four. The qHBsAg level of the group with a fibrosis score less than four was significantly higher at all three time points (Table 5).

The health status of the patients undergoing treatment was evaluated, and their levels of ALT, qHBsAg, HBsAg (S/Co), HBeAg (S/Co), and HBV-DNA viral loads prior to and after 1 year of treatment were compared. Since one of the patients receiving peg-IFN did not respond to the treatment, this patient was omitted from the first year data analysis. Following 1 year of treatment, a statistically significant decrease was observed in ALT, qHBsAg, and HBV-DNA viral load (Table 6).

In the current study, when the patients were grouped according to the phase of CHB infection, the median qHBsAg values were 25.405 IU/mL in HBeAg-positive patients (n=20), 964.6 IU/mL in inactive HBsAg carriers (n=39), and 4,797 IU/mL in HBeAg-negative patients. During the course of treatment, while the ALT, qHBsAg, and HBV-DNA viral load levels decreased in both HBeAg-positive and HBeAg-negative patients in the first year, no decrease in HBsAg (S/Co) levels was detected in both groups in response to the treatment (Table 7).

Table 1. Demographic, histopathological and baseline characteristics of the patients

	Peg-IFN	TDF	ETV	LdT	Control group	p*
	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	
Age	36 (18-70)	33 (24-74)	36 (22-55)	34.5 (18-68)	40 (21-70)	0.392
HAI	5 (2-7)	6 (4-16)	6 (2-12)	4.5 (4-9)	.	0.038
Fibrosis score	3 (2-4)	4 (1-6)	4 (2-5)	3 (2-4)	.	0.148
AST, U/L	67 (26-126)	53 (17-130)	40 (17-218)	27.5 (16-113)	22 (12-78)	0.000
ALT, U/L	125 (37-284)	82 (21-248)	70 (17-815)	45 (19-317)	20 (13-108)	0.000
Albumin, g/dL	4.1 (3.8-4.6)	4.3 (3.5-4.9)	4.1 (3.2-4.5)	4.1 (3.8-4.7)	4.4 (3.1-5.1)	0.006
Globulin, g/dL	3.6 (2.5-4.3)	3.1 (2.5-4.7)	3.1 (2.1-3.9)	3.25 (2.8-4.1)	2.9 (2.1-4.3)	0.054
PTT	13.9 (12.6-14.9)	13.6 (12.5-15.9)	13.4 (12.1-16)	12.7 (12.3-13.3)	13 (11.9-14.3)	0.000
INR	1.1 (1-1.2)	1.1 (0.9-1.3)	1 (0.9-1.3)	0.95 (0.9-1)	1 (0.9-1.1)	0.000
Platelet, x10^3/µL	206 (114-333)	207 (106-271)	164 (58.1-268)	226.5 (179-327)	262 (153-357)	0.000
HBsAg (S/Co)	1843 (335.5-5057)	2514 (270-6227)	3202 (192.1-4351)	3673 (1273-6125)	3827 (12.9-6869)	0.125
qHBsAg (IU/mL)	9599 (213.4-52000)	9776 (1781-33406)	5235 (2439-10294)	5002.5 (455.3-33562)	964.6 (0.05-19994)	0.000
HBeAg (S/Co)	0.341 (0.076-1384)	160.6 (0.069-1667)	0.383 (0.076-2032.9)	0.3565 (0.146-140,9)	0.381 (0.226-0.533)	0.441
HBV-DNA x10^3 IU/mL	154 (7.64-149000)	11300 (0.195-178000)	4260 (2.37-484000)	30.15 (5.61-10500)	0.068 (0-1.21)	0.000

*Kruskal Wallis test.
HAI: Histologic activity index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PTT: Prothrombin tim, INR: International normalized ratio, HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, qHBsAg: Quantitative hepatitis B surface antigen, HBeAg: Hepatitis B e antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, peg-IFN: Pegylated interferon, TDF: Tenofovir, ETV: Entecavir, LdT: Telbivudine, min: Minimum, max: Maximum

Table 2. Baseline and first year characteristics of the patients.

	Treatment group (n=55)	Control group (n=39)	
	Median (25-75% persentil)	Median (25-75% persentil)	p*
Baseline AST	46 (32-74)	22 (18-25)	0.000
Baseline ALT	80 (52-137)	20 (16-33)	0.000
Baseline HBsAg (S/CO)	2923 (1671-4070)	3827 (2290-5032)	0.035
Baseline qHBsAg	5882 (3232-21298)	964.6 (143.2-3092)	0.000
Baseline HBV-DNA	346000 (18800-33200000)	68 (30-425)	0.000
1st year AST	24 (20-32)	20 (15-24)	0.002
1st year ALT	27.5 (23-36)	21 (15-31)	0.006
1st year HBsAg (S/CO)	3257 (1652-4405)	3651 (2150-4454)	0.503
1st year qHBsAg	5487 (2226-16445)	835.1 (174.9-2975)	0.000
1st year HBV-DNA	0 (0-42)	44 (0-276)	0.002

*Mann-Whitney U test.
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBsAg: Hepatitis B surface antigen, qHBsAg: Quantitative hepatitis B surface antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acid

Table 3. Comparison of liver histopathological characteristics of patients in the treatment group.

	Fibrosis <4 n (%)	Fibrosis ≥4 n (%)	HAI <6 n (%)	HAI ≥6 n (%)
Peg-IFN (n=15)	11 (73.3%)	4 (26.7%)	11 (73.3%)	4 (26.7%)
TDF (n=17)	5 (29.4%)	12 (70.6%)	6 (35.3%)	11 (64.7%)
ETV (n=13)	6 (46.2%)	7 (53.8%)	6 (46.2%)	7 (53.8%)
LdT (n=8)	7 (87.5%)	1 (12.5%)	6 (75%)	2 (25%)
Total (n=53)	29 (54.7%)	24 (45.3%)	29 (54.7%)	24 (45.3%)

HAI: Histologic activity index, peg-IFN: Pegylated interferon, TDF: Tenofovir, ETV: Entecavir, LdT: Telbivudine

The diagnostic efficacy of serum qHBsAg levels to differentiate between inactive HBsAg carriers and CHB patients was tested by ROC analysis. The area under curve (AUC) was 0.833 (good), sensitivity 80%, specificity 76.92% and p<0.0001. According to this analysis, the cut-off value for qHBsAg was 3.092 IU/mL (Figure 1).

The diagnostic efficacy of serum qHBsAg levels for differentiating between inactive HBsAg carriers and HBeAg-negative CHB patients was tested by ROC analysis. The AUC was 0.733 (good), sensitivity 80%, specificity 69.2% and p<0.0001. According to this analysis, the cut-off value for qHBsAg was 2.188 IU/mL (Figure 2).

Results of Correlation Analyses

In the correlation analyses of pre-treatment values, a statistically significant negative correlation (r=-0.754/-0.590; p=0.000) was determined between HBsAg (S/Co) and both the qHBsAg and HBV-DNA values of treated patients (n=55). Between the initial

Table 4. Comparing baseline, 12th week and first year results of HBeAg negative patients, who are treated, in accordance with fibrosis position

	Fibrosis <4 (n=16)	Fibrosis >4 (n=18)	
	Median (25-75% persentil)	Median (25-75% persentil)	p*
Baseline ALT	85 (40-148.5)	86 (37-137)	0.959
Baseline HBsAg (S/Co)	3001 (1897-4652)	3633 (3202-4565)	0.384
Baseline qHBsAg (IU/mL)	5217 (1990.5-16190.5)	4252 (2439-5567)	0.443
Baseline HBeAg (S/Co)	0.28 (0.095-0.42)	0,31 (0,12-0,4)	0.958
Baseline HBV-DNA, x10³ IU/mL	30.15 (15.05-129.6)	74,85 (8,9-473)	0.646
12th week ALT	35.5 (21-46)	35 (23-56)	0.878
12th week HBsAg (S/Co)	3728 (2728.5-4540.5)	3434 (2103-4082)	0.33
12th week qHBsAg (IU/mL)	4907.5 (1715-13627.5)	3818 (1870-4407)	0.164
12th week HBeAg (S/Co)	0.34 (0.3-0.4)	0.32 (0.27-0.34)	0.237
12th week HBV-DNA	30 (0-40.5)	0 (0-30)	0.365
1st year ALT	31 (25.5-51)	25 (20-34)	0.109
1st year HBsAg (S/Co)	3359 (2196-4260)	4391.5 (3682-4857)	0.109
1st year qHBsAg (IU/mL)	4953.5 (635.75-10113)	3124 (1511-5210)	0.528
1st year HBeAg (S/Co)	0.37 (0.28-0.4)	0.35 (0.28-0.43)	1
1st year HBV-DNA	0 (0-15)	0 (0-0)	0.33

*Mann-Whitney U test.
ALT: Alanine aminotransferase, HBsAg: Hepatitis B surface antigen, qHBsAg: Quantitative hepatitis B surface antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acid

Table 5. Comparing baseline, 12th week and first year results of HBeAg-positive patients, who are treated, in accordance with fibrosis position

	Fibrosis <4 (n=13)	Fibrosis =>4 (n=6)	
	Median (25-75 % persentil)	Median (25-75% persentil)	p*
Baseline ALT	76 (60-82)	161 (74-214)	0.036
Baseline HBsAg (S/Co)	1385 (335.5-1816)	2065.5 (1671-2514)	0.087
Baseline qHBsAg (IU/mL)	33505 (25831-52000)	10729 (7698-13555)	0.005
Baseline HBeAg (S/Co)	717.1 (183.4-1077)	806.4 (684-809)	0.924
Baseline HBV-DNA, x10³ IU/mL	35100 (10500-140000)	55500 (27700-110000)	0.765
12th week ALT	37 (28-63)	43 (28-65)	0.701
12th week HBsAg (S/Co)	1738 (553.3-2251)	2310 (1643-3220)	0.072
12th week qHBsAg (IU/mL)	30753 (22736-52000)	9188 (8269-12031)	0.009
12th week HBeAg (S/Co)	171.6 (30.9-1129)	15.93 (1-304.3)	0.087
12th week HBV-DNA	1730 (331-24500)	161.5 (30-8750)	0.179
1st year ALT	34.5 (26-37)	25.5 (24-32)	0.385
1st year HBsAg (S/Co)	1457.5 (1112.35-2238)	2232.5 (1652-2749)	0.083
1st year qHBsAg (IU/mL)	32289 (20225.5-46758)	10230 (8293-16445)	0.013
1st year HBeAg (S/Co)	32.45 (10.23-439.55)	11.23 (1.3-51.9)	0.291
1st year HBV-DNA	849.5 (38-7910)	0 (0-30)	0.005

*Mann Whitney U test.
ALT: Alanine aminotransferase, HBsAg: Hepatitis B surface antigen, qHBsAg: Quantitative hepatitis B surface antigen, HBeAg: Hepatitis B e antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acid

Table 6. Comparison of baseline and first year characteristics of patients in the treatment group

	n	Median	25-75% persentil	Min-max	p*
Baseline ALT	55	80.00	52-137	17-815	<0.0001
1st year ALT	54	27.50	22.75-36	11-101	
HBsAg (S/Co)	55	2923.00	1671-4070	192.1-6227	0.106
1st year HBsAg (S/Co)	54	3257.00	1635-4407	2.7-5463	
qHBsAg (IU/mL)	55	5882.00	3232-21298	213.4-171800	0.004
1st year qHBsAg (IU/mL)	54	5487.00	2136-16860.25	0.08-52000	
HBV-DNA, x 10^3 IU/ml	55	346	18.8-33200	0.195-484000	<0.0001
1st year HBV-DNA	54	0.00	0-43	0-56700	

*Wilcoxon test.
ALT: Alanine aminotransferase, HBsAg: Hepatitis B surface antigen, qHBsAg: Quantitative hepatitis B surface antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acidi min: Minimum, max: Maximum

Table 7. Comparing the chronic hepatitis B infection of patients by their phases

	HBeAg-positive patients (n=20)	Inactive HBsAg carriers (n=39)	HbeAg-negative patients (n=35)
	Median (25-75% persentil)	Median (25-75% persentil)	Median (25-75% persentil)
Baseline AST	49.5 (32/88)	22 (18/25)	46 (32/74)
Baseline ALT	79 (61.5/143)	20 (16/33)	83 (37/137)
Baseline HBsAg (S/Co)	1681.5 (840.5/2305.5)	3827 (2290/5032)	3539 (2839/4565)
Baseline qHBsAg (IU/MI)	25405 (10071/42781)	964.6 (143.2/3092)	4797 (2333/7431)
Baseline HBeAg (S/Co)	790 (183.4/11929)	0.381 (0.35/0.41)	0.2945 (0.10/0.40)
Baseline HBV-DNA	41350000 (14100000/128000000)	68 (30/425)	49100 (13400/251000)
1st year AST	22 (20/28)	20 (15/24)	25 (21/36)
1st year ALT	32 (24/36)	21 (15/31)	27 (22/36)
1st year HBsAg (S/Co)	1652 (1320/2658)	3651 (2150/4454)	3979 (3088/4513)
1st year qHBsAg (IU/mL)	18970 (8293/38678)	835.1 (174/2975)	3789 (946.8/5623)
1st year HBeAg (S/Co)	23.06 (2.64/139.1)	0.433 (0.40/0.49)	0.355 (0.28/0.42)
1st year HBV-DNA	42 (0/2130)	44 (0/276)	0 (0/0)

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBsAg: Hepatitis B surface antigen, qHBsAg: Quantitative hepatitis B surface antigen, HBeAg: Hepatitis B e antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acid

qHBsAg and HBV-DNA values of the treated patients (n=55), a statistically significant moderate correlation (r=0.619, p=0.000) was detected. When a correlation analysis was performed for the initial HBsAg (S/Co), qHBsAg, and HBV-DNA values of the control group (n=39), no statistically significant correlation was determined.

When the treated patients were grouped according to their fibrosis status, a statistically significant negative correlation was observed between the initial HBsAg (S/Co) with both qHBsAg and HBV-DNA values in both groups, one with a fibrosis score <4 (n=29) and the other having a fibrosis score ≥4 (n=24) (in the group with a fibrosis score <4: r=-0.804/-0.611, p=0.000; in the group with a fibrosis score ≥4: r=-0.533/-0.553, p=0.007/0.005). Between the initial qHBsAg and HBV-DNA values of the group with a fibrosis score <4, a statistically significant high correlation (r=0.759, p=0.000) was identified; whereas a statistically significant moderate correlation (r=0.661, p=0.000) was observed between the initial qHBsAg and HBV-DNA values of the group with a fibrosis score ≥4.

When the treated patients were divided into the peg-IFN treated group (n=15), and the NA-treated group (n=40), and analysed in terms of correlations of initial values; no statistically significant correlation was observed between HBsAg (S/Co), qHBsAg, and HBV-DNA values of the peg-IFN treated group. However, in the NA-treated group, a statistically significant negative correlation (r=-0.886/-0.712, p=0.000) was identified between HBsAg (S/Co) with both qHBsAg and HBV-DNA.

After the treated patients were grouped into HBeAg-positive (n=20) and HBeAg (n=35) negative groups, no correlation was detected between the initial qHBsAg and HBV-DNA values of the groups. However, following the first year of treatment a statistically significant high correlation (r=0.736, p=0.000) was identified between the qHBsAg and HBV-DNA values of the HBeAg-positive patient group.

Correlation analyses performed after 1 year of treatment demonstrated a statistically significant negative correlation (r=-0.588/-0.432; p=0.000/0.001) between HBsAg (S/Co) and both

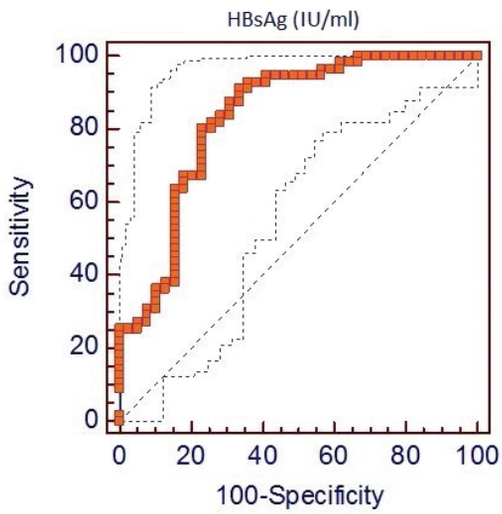

Figure 1. Effectiveness of qHBsAg in establishing diagnosis in distinguishing between inactive HBsAg carriers and chronic hepatitis B patients. When tested by ROC analysis AUC: 0.833, 80% sensitivity, specificity 76.92%, a cut-off value for HBsAg 3092 IU/mL, p<0.0001.

qHBsAg: Quantitative hepatitis B surface antigen, HBsAg: Hepatitis B surface antigen, ROC: Receiver operating characteristic, AUC: Area under curve

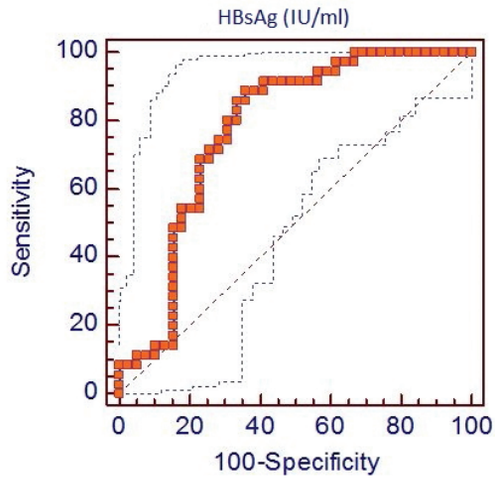

Figure 2: Effectiveness of qHBsAg in establishing diagnosis in distinguishing between inactive HBsAg carriers and HBeAg-negative chronic hepatitis B patients. When tested by ROC analysis AUC: 0.733, 80% sensitivity, 69.2% specificity, cut-off value for HBsAg 2188 IU/mL, p<0.0001.

qHBsAg: Quantitative hepatitis B surface antigen, HBsAg: Hepatitis B surface antigen, ROC: Receiver operating characteristic, AUC: Area under curve

qHBsAg and HBV-DNA in all treated patients. After the first year, a statistically significant moderate correlation (r=0.512, p=0.000) was observed between the qHBsAg and HBV-DNA values of the treated patients. In the first year results of the control group (n=39), while no statistically significant correlation between HBsAg (S/Co) and qHBsAg and HBV-DNA values was observed, a statistically significant low correlation (r=0.418, p=0.008) was detected between the qHBsAg and HBV-DNA values.

Treatment Responses

When a qHBsAg value <1500 IU/mL was accepted as the treatment response criterion, the number of patients that responded in the third month was four (26.7%) in the peg-IFN group, one in the TDF group (5.9%), one in the ETV group (6.7%), and two in the LdT group (25%). After the first year of treatment, six patients (42.9%) in the peg-IFN group responded to the treatment, and one patient from the TDF group (5.9%), two patients from the ETV group (13.3%), and two patients from the LdT group (25%) showed responses.

HBV-DNA Sequencing Analyses

HBV-DNA sequencing was performed using serum collected prior to treatment from 71 of the total of 94 naïve patients in the study. All patients were infected with genotype D. According to the HBV subgenotyping results, 65 of 71 patients were infected with D1, 4 with D2, and 2 patients were infected with D3. The HBV pol gene region was analysed for drug resistance mutations in all patients (Table 8). The HBsAg escape mutations detected are shown in Table 9. In addition, ADAPVEM analysis was performed on the patients that underwent HBV-DNA sequencing analysis. In these patients, two naturally developing ADAPVEM patterns-W196*/L/S (treated with peg-IFN) and S193L (treated with LdT)-were detected.

In one patient in the peg-IFN-treated group, 1 year after completing 48 weeks of IFN treatment, the development of HBsAg loss was observed. Comparisons of the HBV-DNA sequences prior to and after treatment indicated that an I110L leakage in the immune system mutation occurred in the S gene.

Following a breakthrough in 3 of the total of 17 TDF-treated patients, HBV-DNA sequencing analysis was performed. Two of these three patients exhibited no mutations in any of the analyses performed (analysis of one patients was performed in the first, and the other in the second, year) either in the pre-treatment period or during the period when the breakthrough developed. When treatment of the patient who experienced breakthrough in the second year of his treatment was continued, it was determined that his viral load became negative and HBeAg seroconversion developed at the end of the third year. While the third patient from the TDF group also had a breakthrough, a N236T mutation was detected in the D2 subtype and pol gene prior to receiving treatment; however, a L126I mutation was detected in the S gene after the first year, when the breakthrough developed. In another patient from the TDF group, HBeAg seroconversion developed during the first year of the treatment, although HBV-DNA remained positive.

One of the patients from the ETV group demonstrated no mutations in the pre-treatment analyses, or a response to treatment after the first year, so the treatment was ended. In the second year of treatments in 2 of the 15 ETV-treated patients, loss of HBeAg was determined, but no mutation was detected in the pre-treatment analyses of both patients.

Discussion

HBsAg is produced from the integration of the HBV-DNA molecule into the host genome through the use of host enzymes

or through the translation of transcriptionally active cccDNA molecules. It is thought that serum HBsAg levels are correlated with intrahepatic cccDNA levels, and quantification can be used as a marker of the level of liver cell infection (12). Chan and Wong (13) reported that the relationship between qHBsAg levels with HBV-DNA and cccDNA changes depends on the phase of the disease. In the same study, it was reported that there was no correlation in the HBeAg-negative group, while in the HBeAg-positive patient group a positive correlation was observed between HBsAg titre and HBV-DNA and cccDNA levels (13). Lee et al. (14) reported that if the HBsAg level in HBeAg-positive patients was <3,000 IU/mL in the third month of treatment, qHBsAg can be accepted as an independent predictive factor for HBV-DNA negativity and HBeAg seroconversion in the first year of treatment. However, since the HBsAg titre was continuously increasing during treatment in the HBeAg-negative group, it was concluded that the qHBsAg level was not suitable for use in the follow-up of treatment (14). Correlation analyses including all of the patients treated in our study demonstrated a statistically significant moderate correlation between the initial qHBsAg and HBV-DNA levels. However, no significant correlation was observed between the initial qHBsAg and HBV-DNA levels of inactive HBsAg carriers.

Brunetto et al. (15) concluded that qHBsAg level, when considered in combination with the HBV-DNA level, could be used specifically to distinguish the HBeAg-negative CHB group from the inactive HBsAg-carrier group. When the diagnostic efficacy of serum qHBsAg levels to distinguish inactive HBsAg carriers from CHB patients was tested using ROC analysis in our study, the diagnostic efficacy, sensitivity, and specificity of qHBsAg were determined to be good, 80%, and 76.92% ($p<0.0001$), respectively. According to this analysis, the cut-off value for qHBsAg was 3,092 IU/mL (Figure 1). Similarly, to distinguish inactive HBsAg carriers from HBeAg-negative CHB patients, the diagnostic efficacy, sensitivity and specificity of serum qHBsAg levels were determined to be good, 80%, and 69.2% ($p<0.0001$), respectively. The cut-off value for qHBsAg was 2,188 IU/mL according to this analysis (Figure 2).

NA used in CHB treatment can cause the development of point mutations in the pol gene. When a point mutation occurs, drug resistance can also develop (16). These mutations are mainly divided into two groups: primary drug resistance mutations that cause unresponsiveness to the drugs used and compensatory mutations affecting viral fitness (viral load increasing and replication capacity reparative). In our study, we detected primary drug resistance mutations during the naïve period of two patients: the

Table 8. HBV polymerase gene mutations and drug resistance status in patients who may be subject to HBV-DNA Sequence analysis

HBV polymerase gene mutations character	Patients who underwent analysis (n=71) The pattern of mutation, (n)	Clinical significance	Treatment given
Primary drug resistance mutation	M204I (1)	LdT and LAM resistance	Peg-IFN
	N236T (1)	ADV resistance, mutations reducing the susceptibility to TDF	TDF
Partial drug resistance mutation	M204I (1)	ETV resistance	Peg-IFN
Compensatory mutation	L91I (3)	Associated with LdT	TDF
	Q149K (1)	Associated with LAM and ADV	TDF
	N139K (1)	-	TDF
	V214A (2)	Associated with LAM and ADV	TDF/control group
	Q215S (3)	Associated with LAM and ADV	TDF/LdT/control group
	Q215H (1)	Associated with LAM and ADV	Control group
	N238D (1)	Associated with ADV	Control group

Peg-IFN: Pegylated interferon, TDF: Tenofovir, ETV: Entecavir, LdT: Telbivudine, LAM: Lamivudine, ADV: Adefovir

Table 9. Typical HBsAg escaping mutations in HBV S gene in patients who may be subject to HBV-DNA sequence analysis

HBV S gene mutation character	Patients who underwent analysis (n=71) The pattern of mutation, (n)
HBIg escape	T123N (1), P142S (1), G145R (1), P120T (1), G119R (2), T126I (1), C124 (1), C139S (1), K141I (1), Q129H (1), L126I* (1).
Vaccine escape	P142S (1), G130R (1), S143L (1), G145R (1), Q129H (1), L109R (1), Q129R (1), T126I (1), P120T (1), L126I* (1).
Diagnostic test escape	R122K (1), T123N (1), P142S (1), G130R (1), M133T (1), S143L (1), G145R (1), P120T (1), G145L (1), Q129R (1), T131N (2).
Immune response escape	I110L (1), S132F (1), I110L (1), P120R (1).

*Mutation detected in analysis when a breakthrough develops.
HBV: Hepatitis B virus, S: Surface, HBIg: Hepatitis B immunoglobulin

M204I mutation causing LdT and LAM resistance, and the N236T mutation causing ADV resistance and decreasing sensitivity to TDF (Table 8). When HBV-DNA sequencing analysis was redone in a TDF-treated patient who had a naturally occurring N236T mutation after a breakthrough developed in the first year of treatment, an L126I mutation was detected in the S gene. The detection of a naturally occurring N236T mutation, which reduces susceptibility to TDF, in this D2 subgenotype patient explains the breakthrough that developed in the first year of treatment, and indicates the importance of a pre-treatment mutation analysis.

Some studies have demonstrated that primary drug resistance, which develops in CHB infection in response to NA treatment, also increases the HCC risk. In one study, it was reported that HCC developed due to sL21*, sW156* and sW172* mutations in 8 of 141 HCC patients with CHB (17). In another prospective study, the cumulative risk of HCC development (30.6%) in patients displaying primary drug resistance (n=36), among 198 patients that had decompensated cirrhosis, were treated with NA, and followed-up for 2 years, was higher than in patients who developed virological responses (18). In the current study, we did not detect any mutation that increased the risk of progression to HCC.

Due to the circular organisation of the HBV genome, NA used in the treatment of CHB can lead to the formation of typical HBsAg escape mutations in the S gene. sP120T, sM133I, sS143L, sD144A/E, sG145R, sE164D, sW172* and sW182* are examples of such mutations, which are of clinical and epidemiological significance (10,19,20). Typical HBsAg escape mutations can also lead to a failure to detect HBsAg using diagnostic tests, the protection generated by HBIg, and deficiency of anti-HBs antibodies following vaccination (21). It has been reported that G145R and P120T, which are examples of hepatitis B vaccine/HBIg escape mutations, can be present in combination with LAM-associated resistance mutations (22). In addition, a sT143* mutation causing HBV vaccine leak in a child with CHB, sM125T and sT127P mutations causing HBsAg escape mutations in the child's family, and a sS143L mutation resulting in escape from an HBsAg diagnostic test in one patient that was not vaccinated against HCV, have been reported in Turkey (23,24,25). A breakthrough developed in three patients treated with NA in our study, and no mutations were detected in two of these patients. As a result of the analyses performed after a breakthrough developed in one patient at the end of the first year of treatment, a L126I mutation, a hepatitis B vaccine/HBIg leak mutation, was detected (Table 9).

In a wide-ranging study conducted on NA-treated (n=185) patients and patients with treatment-naïve CHB (n=142) in Turkey, 15 HBsAg escape mutations (sY100C, sL109I, sI110V, sS117INST, sP120T, sP127T, sG130R, sS132A, sM133I, sY134N, sC137L, sC137G, sD144E, sG145X and sG145R) were detected. Typical HBsAg escape mutations were detected in patients with CHB, cumulatively at a ratio of 27/327 (8.3%), but no difference in typical HBsAg escape mutation prevalence was observed between the NA-treated and treatment-naïve patients (10). These data suggest that typical HBsAg escape mutations can also develop naturally. In another study conducted in Turkish patients undergoing haemodialysis, it was reported that typical HBsAg escape mutations were detected in 43/94 (46%) treatment-naive CHB patients. Among these patients, HBIg escape mutations (sT118A/R, sP120K/Q/T, sT123A, sC124G, sQ129R, sM133L, sY134N, sD144E, sG145E/K/R) were present at an 18/43 (18%) ratio; HBV vaccine escape mutations (sP120S, sT126I, sM133L, sS143L, sD144E, sG145R, sS193L) at a 15/43 (16%) ratio; HBsAg diagnostic test escape mutations (sP120S/T, sT131I, sM133T, sS143L) at a 8/43 (8.5%) ratio; and immune response escape mutations (sY100C/S, sQ101H/R, sP105A/R, sL109R, sI110L, sS114A/T, sS117G/N, sG119I/R/V, sP120T, sT123A/D/N, sP127T, sA128V, sG130E/K/R, sT131N, sS132C/P, sY134F, sT140I, sS143T, sD144E, sG145R) at a 31/43 (33%) (26). As a result of the pre-treatment analyses performed in our study, typical HBsAg escape mutations were detected in 17/71 (24%) of the patients (Table 9). The detected pattern is consistent with previous studies conducted in Turkey (21,27,28). Detection of typical HBsAg escape mutations in CHB patients that were not treated with NA, despite the differences in the patterns defined, suggests that these mutations can result from both NA-treatment and HBV's natural kinetics.

Due to the circular structure of the HBV genome, the pol gene (encodes reverse transcriptase) and the S gene (encodes HBsAg protein) are in overlapping positions (20). Overlapping of these genes (pol/S) leads to changes in the region encoding the HBsAg protein because of primer/compensatory drug resistance mutations. This situation leads to the formation of ADAPVEM according to recent findings. Additionally, the overlap of the pol and S genes can cause problems that can directly affect public health. For example, the formation of escape mutations from anti HBs antibodies in people with HBV vaccine-induced immunity, the formation of HBsAg diagnostic test escape variants, and the formation of HB Ig protection escape variants (19). In a study conducted in CHB patients in Turkey, six types of ADAPVEM (sE164D, sI195M, sW196L, sW172L, sL175F, s176V) mutation motifs were defined in 10/94 (10.6%) patients (25). In another comprehensive study conducted in Turkey on CHB patients who were followed-up for approximately 3 years, seven types of ADAPVEM (rtM204V/sI195M, rtM204I/sW196S, rtM204I/sW196L, rtV173L/sE164D, rtA181T/sW172*, rtA181T/sW172L and rtA181V/sL173F) mutation motifs were detected in 46/442 (24%) patients. The ADAPVEM ratios of NA-treated and treatment-naive patients were determined to be 44/186 (24%), and 2/256 (0.79%), respectively, and this difference was statistically significant (29).

In our study, a total of two ADAPVEM mutation motifs (W196*/L/S and S193L) were detected in two patients during the naïve period. These findings indicate that NA treatment can cause ADAPVEM mutations, and these mutations can also occur in naïve patients.

Conclusion

A number of mutations can occur in the pol and S genes, depending on which oral antivirals are used for the treatment of a CHB infection. To understand the utility of HBsAg titres as a marker for the early diagnosis of these mutations, which is of clinical importance, further, more comprehensive studies are required.

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Ethics

Ethics Committee Approval: This study was approved by the Kocaeli University Faculty of Medicine Ethics Committee of Clinical Research (approval number: 2009/97, date: June 26.06.2009).

Informed Consent: The written consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Concept: E.S.A., S.A., Design: E.S.A., S.A., Data Collection or Processing: E.S.A., S.A., M.S., Analysis or Interpretation: E.S.A., S.A., Literature Search: E.S.A., S.A., M.S., Writing: E.S.A., S.A., M.S.

Conflict of Interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Research Article

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Evaluation of Health-Related Life Quality of Patients with Chronic Hepatitis Admitted to a Medical Faculty Hospital

Tıp Fakültesi Hastanesine Başvuran Kronik Hepatitli Hastaların Sağlıkla İlişkili Yaşam Kalitesinin Değerlendirilmesi

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ABSTRACT

Objectives: The aim of this study was to determine the life quality and related factors of patients with chronic hepatitis B and C who admitted to the Infectious Diseases Clinic of Erciyes University Medical Faculty Hospital.
Materials and Methods: In this cross-sectional study, a total of 234 patients with chronic hepatitis B and C between December 2016 and June 2017 were included. The questionnaire consisted of 16 sociodemographic questions and SF-36 life quality form.
Results: The average age of 234 participants was 53.4±13.2 (minimum: 19, maximum: 84) years. 19.7% of the participants were hepatitis B carriers, 44.0% were chronic hepatitis B and 36.3% were chronic hepatitis C patients. Life quality scores were found to be significantly lower in patients with hepatitis C, in women, the elderly, those with low educational and economic status, and those who did not work, who had an additional disease and who did not perform regular physical activity.
Conclusion: Social arrangements to improve life quality especially for women, the elderly, individuals with lower education and economic status, some economic improvements in the treatment process and encouraging patients to physical activity may be beneficial.
Keywords: Patients with hepatitis, life quality, SF-36

ÖZ

Amaç: Bu çalışmanın amacı, Erciyes Üniversitesi Tıp Fakültesi Hastanesi Enfeksiyon Hastalıkları Kliniğine başvuran kronik hepatit B ve C'li hastaların yaşam kalitesini ve ilişkili bazı faktörleri belirlemektir.
Gereç ve Yöntemler: Kesitsel nitelikteki bu çalışmaya Aralık 2016 ile Haziran 2017 ayları arasındaki kronik hepatit B ve C'li toplam 234 hasta dahil edilmiştir. Anket 16 sorudan oluşan sosyo-demografik anket formundan ve SF-36 yaşam kalitesi ölçeğinden oluşmaktadır.
Bulgular: Toplamda 234 katılımcının ortalama yaşı 53,4±13,2 (minimum: 19, maximum: 84) yıldır. Katılımcıların %19,7'si hepatit B taşıyıcısı, %44,0'ı kronik hepatit B ve %36,3'ü ise kronik hepatit C hastasıydı. Çalışmamızda yaşam kalitesi puanları kadınlarda, yaşlılarda, eğitim durumu ve ekonomik durumu düşük olanlarda, çalışmayan, ek bir hastalığı olan ve düzenli fiziksel aktivite yapmayan gruplarda, hepatit türüne göre ise hepatit C'li hastalarda anlamlı olarak düşük bulunmuştur.
Sonuç: Özellikle kadınlar, yaşlılar, eğitim düzeyi ve ekonomik durumu düşük olan bireyler için yaşam kalitesini artırmaya yönelik sosyal düzenlemeler, tedavi sürecinde ekonomik bazı iyileştirmelerin yapılması ve hastaların fiziksel aktiviteye teşvik edilmesi faydalı olabilir.
Anahtar Kelimeler: Hepatitli hastalar, yaşam kalitesi, SF-36

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Introduction

Hepatitis is an infectious disease which has an important place in liver diseases. It is an important public health issue related to individual health that has social dimensions. It can be passed as an acute infection, some of these infections become chronic and sometimes these infections continue until the end of life. Hepatitis B and C, which tend to be chronic, are the most common types of hepatitis. Furthermore, inactive hepatitis B carriage may become chronic and cause serious liver diseases in the following years (1). It is known that viral hepatitis can become chronic and lead to the development of liver failure, cirrhosis, and liver cancer and cause serious morbidity and mortality (2).

In the Global Hepatitis Report published in 2017, the World Health Organization stated that 257 million people lived with chronic hepatitis B and 71 million people lived with chronic hepatitis C and 1.34 million deaths were caused by hepatitis in 2015 (3). Chronic hepatitis B and C are caused by 96% of these deaths. The burden of hepatitis infection is not evenly distributed throughout the world but is more concentrated in West Africa and East-South Asia. Almost half of all deaths due to hepatitis occur in these regions (4). In Turkey, the prevalence of hepatitis B is reported as 4% and hepatitis C as 1% and it is reported that one out of every three adults encountered hepatitis B (2,5).

The survival of this two hepatitis which became chronic requires regular follow-up and treatment, affects the patients as well as the national economy and brings a serious burden of disease. The chronicity of the disease affects the quality of life of hepatitis patients as in all other chronic diseases. Life quality is a concept that evaluates the individual's well-being in many aspects. Although life quality coincides with terms such as "well-being", "social determinants of health" and "way of life", they are not synonymous (6). Similar to the definition of health as physical, mental and social well-being, life quality is also related to the level of perception of the aims, expectations, standards, and concerns of individuals in the socio-cultural environment in which they live. It can be defined as the individual's own level of perception about how much social wishes and needs can be met (7,8).

While life quality evaluates physical, mental and social functioning, it also refers to the reflections of individuals' health perceptions in daily life. It is possible that chronic hepatitis patients may suffer from impaired life quality, reduced functionality in daily activities and their physical, mental and social life may be affected negatively. Determining the life quality levels and perceptions of patients at regular intervals in every stage of the disease is a very important issue in coping with stress in the management of the disease. In the literature, there is a limited number of studies evaluating the life quality of hepatitis patients. This situation reveals that this issue should be examined.

Our aim in this study is to examine the life quality of chronic hepatitis patients and some factors that may affect this and to contribute to the improvement of conditions that may adversely affect the life quality of hepatitis patients with similar studies.

Materials and Methods

This cross-sectional study was conducted in Erciyes University Medical Faculty Hospital between December 2016 and June 2017. All chronic Hepatitis B and Hepatitis C patients who were admitted to Infectious Diseases and Clinical Microbiology clinic of Erciyes University Medical Faculty Hospital were interviewed. Information was given to all patients about the study. Identity information was not wanted from the participants and a face-to-face interview was conducted with those who decided to participate. The interview period lasted approximately 15 minutes for each participant. The questionnaire interviews were conducted by a single researcher. A total of 312 patients with hepatitis B carriers, chronic hepatitis B and C outpatients who were diagnosed as chronic hepatitis B and C were interviewed and 234 patients who agreed to participate in the study were included in the study.

The survey form composed of SF-36 Life Quality Scale and 16 questions that questioning socio-demographic characteristics of the participants such as age, gender, marital status, educational status, regular medicine use status, social security and whether they accompanied by any other chronic disease (9). Life quality scale was developed by Ware and Sherbourne and its reliability and validity in Turkish were performed by Koçyiğit et al. (10). In addition, the validity and reliability of the scale were tested by Pınar (11) in cancer patients and it was shown to be used for the patients who has chronic diseases. The scale consists of 36 items and has 8 sub-dimensions. These sub-dimensions were physical functionality (10 items), physical role difficulties (4 items), emotional role difficulties (3 items), energy-vitality (4 items), mental health (5 items), social functionality (2 items), pain (2 items) and general health perception (5 items). The fourth and fifth questions of the scale are yes/no type and the other questions are the Likert type (9,10,12). While physical functionality is related to the ability to perform all physical activities, such as bathing and dressing, physical role difficulty is related to problems encountered at work or other daily activities as a result of deterioration of physical health. Emotional role difficulty refers to problems experienced at work or other daily activities due to emotional problems. Social functionality; excessive and frequent interruptions in social activities due to physical and emotional problems, energy-vitality; continuous tired and tired or lively and energetic feelings, mental health, constant irritability or depression or constant calm, relaxed and happy feeling, pain is severe and restrictive pain, general health perception is related to believing that their health is good, bad or perfect. The scores of the subscales ranged from 0 to 100, and higher scores indicate a good life quality, while lower scores indicate poor life quality. Only the second question of the scale evaluates the health status in the last one year, while the other questions are aimed to evaluate the last four weeks (9,10,12).

This study was approved by the Erciyes University Clinical Research Ethics Committee. Permission was obtained from the Erciyes University Faculty of Medicine Hospital Head Department and the department headship of the related department. All participants were informed about the study before the study and their verbal consent was obtained.

Statistical Analysis

At the end of the study, the data obtained through the questionnaire form was entered in to SPSS version 21.0. The controls and analysis of the data were performed in the same program. Frequency and percentage, mean value, standard deviation, highest and lowest values were used for descriptive

statistics. Pearson chi-square test was used for statistical analysis of categorical data, and Shapiro-Wilk and Kolmogorov-Smirnov tests were used for statistical analysis of quantitative data to determine the compatibility of normal distribution. Mann-Whitney U and Kruskall-Wallis (post hoc Dunn's test) were used because the dependent variables did not fit the normal distribution. Spearman Correlation Coefficient was used to show the relationship between the variables. Statistical significance was considered as $p<0.05$.

Results

The average age of 234 participants was 53.4±13.2 (min: 19, max: 84) years. The rate of participants under the age of 40 is 15.0%, those between the ages of 41-59 are 47.4% and those over the age of 60 are 37.6%. While the average age of women was 54.4 years, the average age of men was 52.0 years. 65.4% of the participants were women, 88.9% were married and 74.4% lived in the city centre and 17.5% lived in the district centre. When education status was evaluated, 73.1% of participants were secondary and below, 12.4% of those were high school and 14.5% of those were university, graduates. Only 2 of the participants do not have social security. According to their statements, 81.6% of hepatitis patients had moderate economic status and 75.6% did not have a job. Only 3.8% of the participants lived alone.

While the hepatitis B carrier was 19.7%, 44.0% of the participants were chronic hepatitis B and 36.3% of the patients were chronic hepatitis C. 81.2% of the patients stated that they have been living with hepatitis for more than 5 years. About half of them had an additional chronic disease and took regular medication. Until the study period 14.5% of the participants stated that they received any psychological support and 23.5% of those stated that they exercised regularly. Among the participants, smoking rate is 12.4% and alcohol is 7.3%, according to their own statements.

When the age distribution of the groups was examined according to the status of hepatitis, hepatitis carriers and patients with chronic hepatitis B were mostly in the 41-59 age range, and majority of hepatitis C patients were 60 years or above. There was a significant difference between the groups (X^2: 54,779, ($p<0.001$). In addition, 52.2% of hepatitis B carriers were male and 80% of hepatitis C patients were female. There was a significant difference between the groups in terms of gender (X^2: 15,098, $p=0.001$). When the existing hepatitis types in the patients were evaluated according to their education status, 86.5% of them had secondary and lower education graduates and they were chronic B and C patients. 38.2% of university graduates hepatitis carriers (X^2: 23,183, $p<0.001$). 52.2% of hepatitis carriers were working, and the majority of chronic hepatitis B and C patients (73.8% and 92.9%, respectively) were not working (X^2: 33.315, $p<0.001$). There was no statistically significant difference was found between the types of hepatitis and the duration of their diseases, whether there was an additional disease, psychological support, smoking and their economic status ($p>0.05$). When the mean scores obtained from the SF-36 life quality scale were compared according to the hepatitis type in the patients, a significant difference was found between the groups in the physical functionality and pain subscale ($p<0.05$). This difference was lower in patients with chronic hepatitis C (Table 1). The scale scores of all hepatitis patients were found to be significantly lower than the standard scores of the Turkish population excluding pain sub-dimension (Table 1).

Table 1. Type of hepatitis and life quality scale scores in patients

Life quality scale subdimensions	Hepatitis type				
	Carrier	Chronic HB	Chronic HC	Average of all patients	Turkish population average
Physical functionality	81.7±19.5[a]	78.3±21.1[a]	64.4±24.0[b]	73.91±23.0	86.6±25.2
	***p<0.001**			****p<0.001**	
Physical role difficulty	64.7±47.0	67.0±46.3	53.9±48.6	61.75±47.5	89.5±29.6
	*p=0.135			****p<0.001**	
Emotional role difficulty	67.4±46.3	67.3±46.0	52.5±49.4	62.0±47.7	94.7±20.9
	*p=0.088			****p<0.001**	
Energy vitality	61.2±23.0	57.8±13.1	52.2±26.1	56.5±24.4	67.0±13.8
	*p=0.121			****p<0.001**	
Mental health	64.2±23.0	57.8±23.1	52.2±26.2	65.3±20.2	73.5±11.6
	*p=0.969			****p<0.001**	
Social functionality	87.0±20.6	90.8±18.4	85.3±21.7	88.0±20.2	94.8±14.2
	*p=0.169			****p<0.001**	
Pain	85.0±17.4[a]	89.2±16.2[b]	80.7±20.7[a]	85.3±18.5	86.1±20.6
	***p=0.009**			**p=0.508	
General health	64.7±24.6	58.6±22.6	60.1±23.2	60.3±23.2	73.9±17.5
	*p=0.231			****p<0.001**	

*Kruskal-Wallis (post hoc Dunn's test) (Kruskal-Wallis was performed because the data did not fit the normal distribution, but average values were given to compare with the Turkish population average), a, b, The difference between groups that do not carry the same letter in each row is significant ($p<0.05$). **OneSample t test
HB: Hepatitis B, HC: Hepatitis C

When the scale scores were evaluated in terms of gender, although not significant in social functioning the scale scores were found to be significantly higher in men in all other sub-dimensions ($p < 0.05$). Scale scores of patients according to age groups; physical functionality, physical role difficulties, emotional role difficulties, and energy-vitality subscales were lower in the 61years old and above groups. A significant difference was found between the groups with these values being higher in the group with age 40 and below ($p<0.05$). There was a negative and poor correlation with the value 0.05 between all other dimension scores except mental health and general health perception with age. In other words, as age increases, scale scores decrease (Table 2).

There was a significant difference between the groups in all sub-dimensions except social functioning. This value was lower in the group having secondary education and lower education level ($p<0.05$) (Table 2). A positive weak correlation was found between education status and all other subscale scores except the social functioning subscale. In other words, the higher the level of education, the higher the scale scores. According to their economic status, physical functionality, energy-vitality, pain and mental health sub-dimensions of the scale scores were found to be significant and high in the groups who stated their economic status high compared to the other groups ($p<0.05$) (Table 2). Scale scores were found to be significantly lower in patients with an additional disease, in regular medication use, in those who did not exercise regularly, and in those who did not work ($p<0.05$). The subscale scores of energy-vitality, mental health, social functioning, pain, and general health perception were found significantly lower in those receiving psychological support ($p<0.05$) (Table 2).

Discussion

Hepatitis is an important infectious agent in liver diseases. The chronicity of some of hepatitis, their lifelong survival, the need for regular follow-up and treatment affect the daily life of the patients. It brings some limitations, both physically and spiritually. These limitations and adversities directly affect life quality and cause life quality to be lower than expected. The decrease in life quality also affects the disease process. The life quality decreases in patients who are in a vicious circle and problems may arise in the management of the disease. For this purpose, the determination of physical, mental and social changes of patients becomes an important issue (13,14,15,16).

In our study, the life quality scores of the participants were found to be well below the society average. When the scores evaluated according to hepatitis type, physical functionality and pain subscale scores were significantly lower in hepatitis C patients (Table 1). As in our study, life quality scores were significantly lower in patients with hepatitis C in other studies (13,14). This may be related to the fact that hepatitis C patients are more females and that they are in a more advanced age group. In a study performed by Taşbakan et al. (15) in another center for hepatitis carriers and chronic hepatitis B patients, overall scale scores were found to be higher than our study scores. Whereas, the scale scores were found to be lower than our study scores in a study performed by Yiğit et al (16). Such differences between studies may be due to differences among participants' age, gender, and educational background. As a matter of fact, the work of Taşbakan et al. (15) was conducted on a younger and higher education group. This study may have caused the mean age of our study group to be higher than this study. In support of this finding, in our study, physical functionality, physical role difficulty, emotional role difficulty and energy-vitality subscale scores of the patients in the age group of 61 years and above were significantly lower. Scale scores decreased with age. In a study conducted by Bilir et al. (17) in men aged 15 years and over in Van, they demonstrated a decreasing life quality with age. In the general population of Malaysia, Azman et al. (18) and Jayasinghe et al. (19) in adults with chronic disease in Australia showed the decreased life quality scores with increasing age as in our study (17). Many factors such as increase in health problems with age, the presence of multiple chronic diseases and being away from working life may demonstrate themselves with a decrease in life quality.

In our study, all sub-dimension scores of males except social functioning were found to be higher than females. In the studies conducted in patients with hepatitis, in general, scale scores were found to be higher in males as in our study (20-22). At the same time, in other studies on life quality other than hepatitis also it was found that life quality was significantly lower in women (18,23-27). In addition to the difficulties posed by chronic illness, women's domestic responsibilities, lower level of education may lead to difficulty in accessing health services and taking social support and therefore this negatively affects their life quality.

In our study, the relationship between the participants' educational status and scale scores was positive and the scale scores were found to be high in the group with high educational status. Other studies in the literature were shown a positive relationship between education level and quality of life (15,18,22,28-30). An increase in the level of education brings also an increase in health awareness, ease of use of health services and an increase in health perception together with an increase in life quality. In addition, job opportunities provided to individuals by education, which is one of the influential factors on life quality, positively affect life quality by enabling both the economic level to increase and individuals to socialize with work life. In our study, physical functionality, energy-vitality, and mental health sub-dimensions and life quality in the working group were found to be significantly higher in the group that stated their economic status as high. When the literature is examined, there are studies that do not have a significant relationship between economic status and quality of life, for example, Abdo's study in Saudi Arabia. However, there are also studies showing a significant relationship. For example, Jayasinghe et al. (19) found a higher life quality in employees according to the unemployed and retired in Australia. Similarly, Karacaer et al. (22) also found higher life quality in participants with regular income. Preto et al. (29) found the life quality of the unemployed to be lower in their study (19,20,22). In order to meet the physical needs of human beings, it is likely that they need an income. Based on the data of all these studies and our research, the high economic situation is related to better life quality. In addition, working in any job provides a regular income. It helps the person to be away from financial problems and to meet the physical needs which are the first step in realizing himself/herself. In this way, it provides the individual with status and gives him/her feelings of respect and belonging. It helps the individual to socialize and achieve a better life quality.

Table 2. Life quality scale scores of patients according to some variables

Variables		n PF Mean ± SS	Life quality scale subdimensions							
			PRD	ERD	E-V	MF	SF	P	GH	
			Mean ± SS	Mean ± SS	Mean ± SS	Mean ± SS	Mean ± SS	Mean ± SS	Mean ± SS	
Gender	Female	153	68.3±22.6	52.9±48.9	53.2±49.5	50.7±24.1	62.6±20.5	87.1±21.2	81.9±19.9	55.4±23.6
	Male	81	84.4±20.0	78.4±39.9	78.6±39.2	67.4±21.1	70.5±18.6	89.8±18.0	91.6±13.5	69.7±19.3
	p*		<0.001	<0.001	<0.001	<0.001	**0.004**	0.456	<0.001	**<0.001**
Age	≤40	35	86.3±17.6[a]	80.0±39.2[a]	80.0±38.9[a]	66.4±20.8[a]	70.3±18.0	93.9±15.3	91.4±13.8	62.7±24.7
	41-59	111	77.4±21.2[a]	60.6±47.5[a.b]	59.8±48.2[a.b]	55.1±24.4[b]	64.8±21.3	86.6±22.2	84.7±18.9	60.9±22.9
	60≤	88	64.5±23.7[b]	56.0±49.1[b]	57.6±48.9[b]	54.1±25.1[b]	64.0±19.4	87.5±19.0	83.6±19.3	58.8±23.2
	p**		<0.001	0.043	0.049	**0.034**	0.324	0.120	0.117	0.605
Education status	Secondary school and below	171	68.8±22.8[a]	56.1±48.7[a]	56.7±49.0[a]	52.5±23.8[a]	63.2±19.9[a]	87.3±20.9	82.6±19.5[a]	56.6±23.2[a]
	High school	29	83.4±18.6[b]	64.7±48.0[a.b]	65.5±48.4[a.b]	69.5±21.4[b]	72.7±17.6[b]	92.2±14.3	94.1±10.0[b]	70.0±17.8[b]
	Üniversity	34	91.5±14.9[b]	87.5±29.7[b]	85.3±30.9[b]	65.3±24.3[b]	69.8±21.7[a.b]	88.2±20.4	91.2±15.0[b]	71.0±22.2[b]
	p**		<0.001	0.002	0.013	<0.001	**0.018**	0.695	0.001	**<0.001**
Economic status	High	30	86.3±18.3[a]	79.2±40.5	77.8±40.4	71.0±20.0[a]	74.8±15.6[a]	91.7±17.5	91.5±12.2[a]	67.8±18.5
	Moderate	191	72.7±22.3[b]	59.0±47.9	59.5±48.3	55.5±23.6[b]	64.6±20.1[b]	88.0±20.0	85.1±18.5[a.b]	59.3±23.8
	Low	13	63.1±32.0[b]	61.5±50.6	61.5±50.6	36.5±24.9[c]	53.8±23.6[b]	79.8±26.8	74.4±25.5[b]	57.7±23.1
	p**		0.003	0.120	0.183	<0.001	**0.006**	0.265	0.019	0.197
Working status	Working	177	89.1±18.6	87.3±31.4	84.2±34.0	67.7±21.0	71.8±20.1	91.6±17.6	92.9±13.2	69.4±21.1
	Not working	57	69.0±22.2	53.5±48.9	54.8±49.3	52.8±24.4	63.2±19.8	86.9±20.8	82.7±19.3	57.4±23.2
	p*		<0.001	<0.001	<0.001	<0.001	**0.003**	0.090	<0.001	**<0.001**
Additional disease	Yes	130	64.9±23.4	52.1±48.9	51.3±49.5	48.5±23.9	59.5±20.6	85.0±22.5	80.1±20.7	54.4±24.1
	No	104	85.1±16.9	73.8±42.9	75.3±41.8	66.3±21.3	72.6±17.1	91.8±16.1	91.8±12.6	67.7±19.8
	p*		<0.001	0.001	<0.001	<0.001	<0.001	0.030	<0.001	**<0.001**
Regular medication	Yes	116	63.6±23.2	52.4±49.0	50.9±49.0	48.8±23.9	59.4±19.8	83.5±23.5	80.0±20.6	54.1±24.0
	No	118	84.0±17.8	71.0±44.2	72.9±43.8	63.9±22.7	71.1±18.9	92.5±15.1	90.5±14.4	66.5±20.8
	p*		<0.001	0.002	<0.001	<0.001	<0.001	0.003	<0.001	**<0.001**
Regular exercise	Yes	55	85.2±17.4	75.0±43.3	73.3±42.7	70.7±20.6	73.6±15.0	95.2±12.8	92.2±14.5	69.5±22.7
	No	179	70.4±23.4	57.7±48.1	58.5±48.7	52.1±23.8	62.7±20.9	85.8±21.5	83.2±19.1	57.5±22.7
	p*		<0.001	0.015	0.043	<0.001	0.001	0.003	<0.001	**<0.001**
Psychological support status	Yes	34	66.3±28.6	50.7±47.5	49.0±48.7	46.2±25.3	53.8±23.0	76.1±27.9	72.4±24.6	50.0±20.4
	No	200	75.2±21.7	63.6±47.3	64.1±47.3	58.2±23.9	67.3±19.0	90.1±17.8	87.5±16.3	62.1±23.2
	p*		0.087	0.119	0.074	0.010	0.001	0.003	<0.001	**0.003**

*Mann-Whitney U, **Kruskall-Wallis (post hoc Dunn's test), a, b, c: The difference between groups that do not carry the same letter in each column is significant (p<0.05) PF: Physical functionality, PRD: Physical role difficulty, ERD: Emotional role difficulty, EV: Energy vitality, MF: Mental functionality, SF: Social functionality, P: Pain, GH: General health

In our study, all scale scores were found to be significantly lower in patients with the additional disease and in regular medication use ($p<0.05$). The majority of participants have been living with hepatitis for more than five years. In addition to the burden of disease caused by hepatitis, the presence of another disease may cause serious disruptions in the management of the disease. Karacaer et al. (22) found that all scale scores were significantly lower in patients with hepatitis with an additional chronic disease as in our study. In addition, in another study conducted in Australia with chronic disease, it was stated that the life quality scores of those with two or more chronic diseases significantly lower than those without additional diseases. Similarly, those with chronic pain in France stated that significantly lower life quality scores than those without pain (19,26). In our study, scale scores were found to be significantly lower in those who did not perform physical activity regularly. Regular physical activity is an indication of the importance that individuals attach to healthy living. It can be said that individuals who do physical activity pay more attention to their health. It is an important fact that physical activity contributes positively to the management of the disease and coping with stress.

Conclusion

As a result, in our study, life quality scores were found to be significantly lower in women, the elderly, those with low educational and economic status, in those who did not work, who had an additional disease and who did not perform regular physical activity, and in patients with hepatitis C compared to the type of hepatitis. The presence of diseases with increasing age, limitation of movement and distancing from work-life adversely affect life quality. Supporting patients in the management of multiple diseases and regular physical activity will benefit the treatment period during the control of the disease. Patients should be encouraged to engage in physical activity. If they do not have any income-generating work for them to feel more active in, social activities, especially for women and the elderly, will be beneficial to create a safe environment where hepatitis patients can share their coexistence experiences. At the same time, psychological counseling should be given to patients with mental problems. Studies related to the subject in different disease periods of hepatitis patients and supporting these studies by the management will help to improve the life quality of the patients with hepatitis. It may also be useful to make some economic improvements in the treatment process.

Ethics

Ethics Committee Approval: This study was approved by the Erciyes University Clinical Research Ethics Committee.

Informed Consent: All participants were informed about the study before the study and their verbal consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.Ç., Design: F.Ç., Data Collection or Processing: B.O., Analysis or Interpretation: B.O., İ.G., F.Ç., Literature Search: B.O., İ.G., F.Ç., Writing: B.O., İ.G., F.Ç.

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An Evaluation of Health Personnel Exposed to Occupational Injuries in Terms of HBV, HCV, and HIV Infections

Mesleki Yaralanmalara Maruz Kalan Sağlık Personellerinin HBV, HCV, HIV Enfeksiyonları Açısından Değerlendirilmesi

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ABSTRACT

Objectives: This study aims to determine the rates, distribution and risk factors of needle-stick and sharps injuries that cause diseases spread through blood and body fluids, to discuss relevant precautions, and to monitor seroconversion conditions of viral hepatitis and human immunodeficiency virus (HIV) in injured health personnel in our hospital.

Materials and Methods: The data recorded by the Infection Control Committee about health personnel who were exposed to blood or body fluids as a result of needle-stick and sharps injuries between January 2018 and May 2020 were analyzed retrospectively. The results were presented as percentages.

Results: A total of 187 health workers were included in the study. The injuries were most common among nurses 48.66%. The most common instrument causing needle-stick and sharps injuries was needle tip 80.8%. In addition, 89.85% of them were vaccinated for hepatitis B. According to the serological status of infected sources, 8.02% were infected with hepatitis B, 10.16% with hepatitis C and 2.67% with HIV. No seroconversion was observed in the injured personnel.

Conclusion: Although health workers are given regular training on occupational hazards during recruitment and employment, they still face risky injuries. Therefore, all health personnel should be informed to raise their awareness of blood-borne infections, undergo medical screening regularly, and have up-to-date vaccines.

Keywords: Health personnel, sharp injuries, viral hepatitis

ÖZ

Amaç: Bu çalışmada hastanemizde kan ve vücut sıvıları ile bulaşan hastalıklara yol açan kesici delici alet yaralanma oranlarını, dağılımlarını, risk faktörlerini tespit etmek, alınacak önlemleri irdelemek, bu kazalardan sonra yaralanan personelin viral hepatitler ve insan immun yetmezlik virüsü (HIV) serokonversiyon durumlarını takip etmeyi amaçladık.

Gereç ve Yöntemler: Ocak 2018-Mayıs 2020 yılları arasında kesici delici alet yaralanması sonucu kan veya vücut sıvısıyla temas eden sağlık personelinin Enfeksiyon Kontrol Komitesi tarafından kayıt altına alınan verileri retrospektif olarak irdelendi. Sonuçlar yüzdelik birim olarak ifade edildi.

Bulgular: Çalışmamıza mesleki yaralanmaya maruz kalan 187 personel dahil edildi. Yaralanmalar en sık hemşire grubundaydı %48,66. Yaralanma aleti en fazla iğne ucuyla %80,8 gerçekleşmekteydi. Personelin %89,85'inin hepatit B aşısı vardı. Kaynağın serolojik durumu incelendiğinde %8,02 hepatit B, %10,16 hepatit C, %2,67 HIV ile enfekte idi. Yaralanan personellerin hiçbirinde serokonversiyon saptanmadı.

Sonuç: Sağlık çalışanlarına işe girişte ve çalışma süreleri boyunca düzenli eğitim verilmesine rağmen halen riskli yaralanmalarla karşı karşıya kalınmaktadır. Tüm personel kanla bulaşan enfeksiyonlar konusunda bilinçlendirilmeli, taramaları yapılmalı, aşıları tamamlanmalıdır.

Anahtar Kelimeler: Sağlık personeli, kesici ve delici alet yaralanmaları, viral hepatit

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Introduction

Health workers are at risk for blood-borne infections due to procedures performed during health care services. This risk varies depending on gender of the agent, viral load of the source, type of the exposure, and prevalence of the disease (1). Studies have reported that more than 20 pathogens can be causative agents for needle-stick and sharps injuries (2,3). The most common of these pathogens are hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV), which can cause mortality and morbidity (4,5).

Infection can occur mainly via percutaneous route due to injector or sharp object injuries or disruption of skin integrity as a result of damage to the skin, or via mucosal route due to splashing/spraying of blood or body fluids into mucosal surfaces (eyes, nose, mouth). HIV, HBV and HCV cannot penetrate intact skin and are not transmitted through air. Since the prevalence of HBV, HCV and HIV infections are high in developing countries, health workers in these countries are at higher risk for blood-borne infections (6).

Risky injuries most commonly occur in medical personnel due to sharp objects (7). The risk of infection in needle-stick and sharps injuries varies between 0.2-0.5% for HIV and increases up to 3-10% for HCV and 40% for HBV (8). Occupational exposures cause anxiety and stress in health workers. Personnel injuries create a huge burden on society in terms of treatment costs and loss of labor (9).

In 1987, the Centers for Disease Control and Prevention published universal measures on awareness, immunization, waste control and post-contact prophylaxis to protect employees, emphasizing that being careful and taking necessary actions would reduce injuries (10). The World Health Organization has published a guidance intended to reduce the risk of infection to health personnel through safe injection (11).

The rate of reporting needle-stick and sharps injuries is low, which may endanger occupational hazard assessments and prophylaxis measures for HIV and HBV (12). This study aimed to evaluate, prevent and reduce the injuries associated with blood and body fluids in our hospital.

Materials and Methods

This study retrospectively analyzed the data recorded by the Infection Control Committee about health personnel who were exposed to blood or body fluids as a result of needle-stick and sharps injuries between January 2018 and May 2020 in İstanbul Medeniyet University, Göztepe Training and Research Hospital. Data on gender, profession, place of injury, tool of injury, immune status, use of protective equipment, cause of injury, infection status of injured organ and source, and prophylaxis and follow-up for injured health workers were recorded.

This study was approved by İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology (approval number: 2020/0149, date: 24.06.2020).

Statistical Analysis

The results were presented as percentages.

Results

A total of 187 health workers exposed to injury were included in the study. Of them, 126 (67.38%) were female and 61 (32.62%) were male; 165 (88.23%) were injured by needle-stick and sharp objects and 22 (11.77%) were injured by mucosal contact. Most of the needle-stick and sharps injuries were superficial (n=106, 64.24%), and the most common sites of injury were the hands/arms (n=161, 97.57%). The most frequent cause for injury was reported as the personnel's own fault (n=136, 72.72%), and the most common sharp instrument causing needle-stick and sharps injuries was needle tip (n=133, 80.8%), followed by suture needle (n=8, 4.8%), and branule (n=6, 3.6%). Mucosal contacts occurred most frequently due to blood splashes (n=19, 86.36%). Most of the health personnel (n=147, 78.61%) were using personal protective equipment during the injury (Table 1). The injuries were most common among nurses (n=91, 48.66%), followed by interns (n=41, 21.92%), doctors (n=23, 12.29%) and cleaning/support staff (n=23, 12.29%) (Figure 1). The injuries were most frequently occurred in internal and surgical clinics (n=83, %44.38), followed by intensive care units (n=33, 17.64%), emergency room (n=27, 14.43%), and operating rooms (n=18, 9.62%). Of those in

Table 1. Distribution of the injured health personnel by gender, type of injury, tool of injury, severity of injury, site of injury, use of protective equipment, and cause of exposure

Features	Number	%
Gender	187	-
Female	126	67.38
Male	61	32.62
Type of injury	187	-
Percutaneous	165	88.23
Mucosal	22	11.77
Tool of injury	165	-
Needle tip	133	80.8
Suture needle	8	4.8
Branule	6	3.6
Bisturi	5	3
Lancet	2	1.2
Other	11	6.6
Severity of injury	165	-
Superficial	106	64.24
Deep	59	35.76
Site of injury	165	-
Hand-arm	161	97.57
Foot-leg	4	2.43
Use of protective equipment	187	-
Yes	147	78.61
No	40	21.39
Cause of exposure	187	-
One's own fault	136	72.72
Someone else's fault	51	27.28

the clinics, 43 (51.81%) were in internal clinics and 40 (48.19%) were in surgical clinics. In addition, 168 (89.85%) of the injured health personnel were vaccinated for HBV, 16 (8.56%) had natural immunity, 2 (1.06%) were unvaccinated, and 1 (0.53%) was a hepatitis B carrier. Moreover, 86 (52.12%) of them were vaccinated, whereas 79 (47.88%) were unvaccinated for tetanus. According to the serological status of infected sources, 15 (8.02%) were infected with hepatitis B, 19 (10.16%) with hepatitis C, and 5 (2.67%) with HIV (Table 2). Both immunization and prophylaxis were applied to the injured personnel. No seroconversion was observed in these personnel during six-month follow-up period.

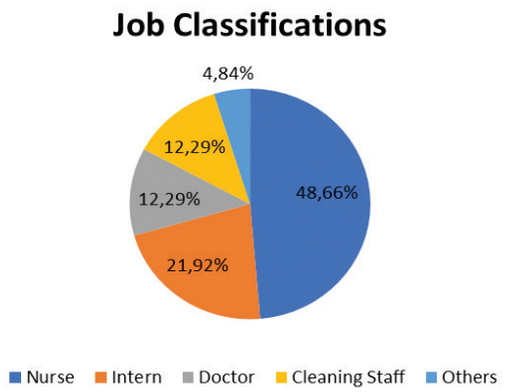

Figure 1. Distribution of health personnel by profession

Table 2. Distribution of the injured health personnel by place of injury, HBV and Tetanus vaccine status, and source

Features	Number	%
Place of injury	187	-
Clinic	83	44.38
Intensive care unit	33	17.64
Emergency room	27	14.43
Operating room	18	9.62
Blood collection unit	9	4.81
Other	17	9.12
HBV vaccine status	187	-
Vaccinated	168	89.85
Natural immune	16	8.56
Carrier	1	0.53
Unvaccinated	2	1.06
Tetanus vaccine status	165	-
Vaccinated	86	52.12
Unvaccinated	79	47.88
Source	187	-
HBV	15	8.02
HCV	19	10.16
HIV	5	2.67
Unknown	148	79.14

HBV: Hepatitis B virus, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Discussion

Healthcare-related injuries in health workers can be prevented, but they are a frequently encountered problem in medical field. In this study, the injuries were most common among nurses (48.66%), which is consisted with those of studies previously conducted in both Turkey and across the world. Nurses were reported as the healthcare professional group most exposed to injuries with a percentage of 54.8% by Yılmaz et al. (13), 39.1% by Satılmış and Şahin (14), 60.8% by Karadeniz et al. (15), and 42.2% by Çağlar-Özer et al. (16) Badiee-aval et al. (17) stated that the most common occupational injuries were observed in nurse groups in their multicentric researches, also Motaarefi et al. (18) reviewed 11 articles and archived same result. This may be because nurses are the main healthcare personnel who most administer intravenous treatments to patients and involve in blood collection and care services, therefore they may not be careful enough and may not wear protective equipment by acting hastily during these procedures due to intense work shifts and heavy workload. In this study, 78.61% of the health personnel exposed to injuries used protective equipment during the injury, and 72.72% of them were injured because of their own fault.

Over 75% of occupational injuries in health workers are considered percutaneous (19). In this study, 88.23% of the injured health personnel had percutaneous injuries and 11.77% were injured by mucosal contact. In particular, 64.24% of the percutaneous injuries were superficial tissue injuries, and 86.36% of the mucosal injuries occurred due to blood splashes. Similar to this study, Tao et al. (20) retrospectively examined a total of 155 occupational exposures in China and found that most of the injuries (89.03%) were percutaneous. Needle tip was found as the most common instrument causing needle-stick and sharps injuries with a percentage of 80.8% by the present study, 86.1% by Karacaer et al. (21), 52.2% by a survey study involving 8645 health workers in Taiwan (22), and 74.2% by Kesmez-Can and Sezen (23). This study found that the most common sites of injury were the hands/arms (97.57%), which is consistent with those reported by previous studies (14,16,23).

In this study, the injuries were most frequently occurred in clinics (44.38%), followed by intensive care units (17.64%) and emergency room (14.43%). In addition, 51.81% and 48.19% of the injuries in clinics occurred in internal and surgical clinics, respectively. The most common injury occurred during blood glucose measurement processes, especially when the needle was reclosed with the cap. Similarly, medical injuries were most observed in internal clinics by Çağlar-Özer et al. (16), in surgical clinics by Özakar-Akça and Aydın (24), and in emergency rooms by Dizili-Yelgin et al. (25).

In Turkey, the positivity rates of hepatitis B surface antigen and anti-HCV antibody for healthy population were reported as 6.8% and 0.5%, respectively; and the rates for health workers as 4.8% and 0.7%, respectively (26). Hepatitis B vaccine, one of the preventive measures, has been available since 1982, and was started to administer on health workers since 1987 (27). In this study, 89.85% of the injured health personnel were vaccinated for hepatitis B, 8.56% had natural immunity, 1.06% were unvaccinated and 0.53% were hepatitis B carriers. When the injuries were examined according to the source, 8.02% were

infected with HBV, 10.16% with HCV and 2.67% with HIV. In injuries caused by instruments contaminated with hepatitis B, the injured personnel whose anti-HBs antibody level is below <10 mIU/mL are administered hepatitis B immunoglobulin and three doses of vaccination. In this study, as the personnel injured by instruments contaminated with hepatitis B had anti-HBs titer above 10mIU/mL, they were not administered hepatitis B prophylaxis. The personnel injured by HIV-infected sources were administered Tenofovir disoproxil fumarate/Emtricitabine (300 mg/200 mg) once a day and Raltegravir (400 mg) twice a day for four weeks. Those injured by instruments infected with hepatitis C were monitored only, because there was no prophylaxis option. During their six-month follow-up, none of them had seroconversion in terms of HBV, HCV and HIV infections, which was pleasing. Tetanus vaccine was administered to 52.12% of the injured health personnel.

Occupational injuries pose a risk of infection, causing anxiety in both health workers and their families during the six-month follow-up period. This can decrease their work efficiency, affecting health system financially in a direct or indirect way. Preventing the spread of infectious diseases costs only one third of the post-exposure expenses to the health system (28). By assuming that all patients are infected, it is extremely important to provide patients with medical intervention, treatment and care services by taking standard protection measures.

Study Limitation

The most important limitation of the study was that it was retrospective. Another was the inadequacy of the notification of the personnel exposed to the injury. Despite these limitations, our study increases awareness about the risks of occupational injury.

Conclusion

Health workers are exposed to occupational injuries and infection risks despite all precautions today. Occupational injuries still continue in our hospital and all of the personnel are not fully vaccinated. Therefore, relevant training activities to prevent infections and personnel screening tests should be performed during recruitment process and then repeated regularly, and health personnel who are not fully vaccinated should complete the vaccine series, whereby especially getting vaccinated for hepatitis B should be set a target for all personnel.

Ethics

Ethics Committee Approval: This study was approved by İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology (approval number: 2020/0149, date: 24.06.2020).

Informed Consent: Since our study was retrospective, informed consent was not used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.A., Design: Ö.A., Data Collection or Processing: Ö.A., P.E., H.Ç., Analysis or Interpretation: P.E.,

Literature Search: Ö.A., P.E., Writing: P.E.

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Research Article

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Genotype Distribution of Hepatitis C Virus and Demographic Features of The Patients in The Province of Karabük

Karabük İlinde Hepatit C Virüsünün Genotip Dağılımı ve Olguların Demografik Özellikleri

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ABSTRACT

Objectives: It was aimed to determine the distribution of hepatitis C virus (HCV) genotypes among patients who had HCV infection, and to identify the demographic characteristics of these patients.
Materials and Methods: Adult patients who underwent HCV genotyping between January 2016 and December 2019 in the microbiological laboratory of our hospital were included in the research. The age and gender of the patients were investigated retrospectively from the hospital registry.
Results: 63% of the 169 patients who were included in the study were female and the mean age was 63.4±16.1. It was found out that of the patients, 85.8% were with genotype 1b, 4.2% with genotype 1a and 0.62% with genotype 2, while 3% of them had genotype 3 and 11% of them had genotype 4. It was determined that the mean age (62.2±14.6) and rate of female gender of patients who had genotype 1 was significantly higher than other patients. Whereas genotype 1b did not decline over the years, a slight increase was determined in genotype 4.
Conclusion: It was found out that genotype 1b, was to be the most frequent genotype. The fact that most of the patients were female as well as they were elderly is epidemiologically remarkable.
Keywords: Genotype, hepatitis C virus, viral infection

ÖZ

Amaç: Hepatit C virüsü (HCV) infeksiyonu olan olgularda HCV genotip dağılımının belirlenmesi ve hastaların demografik bilgilerin saptanması amaçlanmıştır.
Gereç ve Yöntemler: Hastanemiz mikrobiyoloji laboratuvarında Ocak 2016-Aralık 2019 tarihleri arasında HCV genotiplendirmesi yapılan erişkin hastalar çalışmaya dahil edilmiştir. Olguların yaş ve cinsiyeti geriye dönük olarak hastane kayıtlarından incelenmiştir.
Bulgular: Çalışmaya alınan 169 olgunun %63'ü kadın olup yaş ortalaması 63,4±16,1 idi. Olguların %85,8'inde genotip1b, %4,2'inde genotip 1a, %0,6 2'inde genotip 2, %3'ünde genotip 3 ve %11'inde genotip 4 sapanmıştır. Genotip 1 olgularında yaş ortalaması (62,2±14,6) ve kadın cinsiyeti genotip 1 dışı olgulara göre belirgin olarak yüksek bulunmuştur. Yıllar içinde genotip 1b'de azalma saptanmazken genotip 4'te hafif bir artış belirlenmiştir.
Sonuç: Genotip 1b en yaygın genotip olarak saptanmıştır. Hastaların ileri yaşta olup kadın cinsiyetinin daha fazla olması epidemiyolojik açıdan dikkati çekmektedir.
Anahtar Kelimeler: Genotip, hepatit C virüsü, viral infeksiyon

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Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus from the Flaviviridae virus family and is a crucial public health problem across the world. It is the cause of chronic liver disease, and cirrhosis as well as hepatocellular carcinoma (1,2). It is estimated that around one million people have been infected with HCV in Turkey (3). Hitherto, 7 distinct genotypes and over 90 sub-types of HCV have been identified. It has been found that specific genotypes have prevalence in various geographical regions of the world. While genotype 1 (46.2%) is the most prevalent genotype across the world, it is followed by genotype 3, 2, 4, and 6, respectively. Whereas, genotype 5 (0.8%) is the least prevalent HCV genotype. Genotype 1 is the most prevalent HCV genotype in Turkey (4,5,6). It was found in the researches, which was performed in our country, that majority of the patients had genotype/sub-type1b, whereas few of them had genotype/sub-type 1a (7,8).

Knowing the distribution of HCV genotype is crucial for determining the epidemiological characteristics of infection, as well as for the selection of direct-acting antiviral therapies. Direct-acting antiviral agents have specific efficiencies in different genotypes. Hence, treatment guidelines recommend treatment regimens and duration of treatment based on HCV genotypes (9,10).

In this study, it was intended to find out the genotype distribution among patients who had chronic HCV infection in our hospital and to investigate the demographic findings of these patients.

Materials and Methods

HCV genotyping was conducted among patients whose HCV-RNA was detected as positive from serum samples that were tested in the Microbiology Laboratory of Karabük University, Training and Research Hospital between January 2016 and December 2019. Magnesia Viral DNA/RNA Extraction Kit EP and Magnesia16 Nucleic Acid Extraction Instrument (Anatolia Geneworks) were utilized for the extraction of viral RNA. Subsequently, extracted samples were studied following the instructions of the manufacturer by using Bosphore HCV Genotyping Kit v3 on Montania 4896 Real-Time PCR device (Anatolia Geneworks), and genotyping was accomplished.

The data including age, gender, and nationality of the patients were obtained from the registry and database system of the hospital. Restudied samples and patients who were under 18 years old were excluded from the research.

Thereafter, the distribution of HCV genotypes was analyzed regarding the age, gender, and years. The patients were sub-classified as 18-25, 26-35, 36-45, 46-55, 56-65, and over 65 based on their age range.

Statistical Analysis

The software of Statistical Package (SPSS Inc.; Chicago, IL, USA) 15.0 Windows was used for the statistical analysis of data. Chi-square test was used for descriptive statistical variables that include the mean values, and standard deviation as well as for the categorical variables, while the Student t-test was used for normally distributed variables. Alpha significance level was considered as <0.05.

Results

HCV-genotyping of 169 patients was performed with the blood samples that had been given to the microbiology laboratory of our hospital throughout the study. The mean age of the patients was 63.4±16.1, while 107 (63%) of them were female, and 62 (37%) were male. The rate of female patients was found to be significantly higher ($p<0.05$). Genotype 1b was detected in 145 patients (85.8%). Also, it was determined that 62.7% (106) of the patients were over 65 years old. In addition to that, 98% (104) of these patients had genotype 1b. Besides, of these patients who had genotype 1b 66% (70) were female (Table 1). Genotype 3 was detected in two female patients who had the nationality of Afghanistan. Apart from these two female patients, all of the patients were citizens of the Republic of Turkey.

A moderate rise has been determined in the number of genotype 4 per year in our hospital. However, genotype 1b was found to be significantly higher in all years (Table 2).

Upon comparing the patients with and without genotype 1, it was demonstrated that the mean age of patients with genotype 1 was 62.2±14.6, while the mean age of all other patients was 50.8±18.7. The mean age was significantly higher in genotype 1 patients ($p<0.001$). The rate of women among patients with genotype 1 was 68% (103), while the rate of women among patients who had not genotype 1 was 30% (5). Thus, it was identified that the female ratio among patients who had genotype 1 was significantly higher ($p<0.002$).

Table 1. Age and gender distribution of HCV genotypes between 2016 and 2019

Age	Female		Male		Total		G.1a		G.1b		G.1		G.2		G.3		G.4	
	n	%	n	%	N	%	N	%	n	%	n	%	n	%	n	%	n	%
18-25	-	-	5		5	3	3	43	-	-	3	2	-	-	1	10	1	17
26-35	1	11	8	89	9	5	3	43	-	-	3	2	-	-	4	40	2	33
36-45	5	83	1	17	6	4	-	-	4	2	4	3	-	-	2	20	-	-
46-55	5	83	1	17	6	4	-	-	4	2	4	3	-	-	2	20	-	-
56-65	26	70	11	30	37	21	1	14	33	23	34	22	-	-	1	10	2	33
>65	70	66	36	34	106	63	-	-	104	73	104	68	1	100	-	-	1	17
Total	107	63	62	37	169	100	7	100	145	100	152	100	1	100	10	100	6	100

HCV: Hepatitis C virus, G.1a: Genotip 1a, G.1b: Genotip 1b, G.1: Genotip 1, G.2: Genotip 2, G.3: Genotip 3, G.4: Genotip 4

Table 2. The distribution of HCV genotypes per year

Year	Genotip 1a n (%)	Genotip 1b n (%)	Genotip 1 n (%)	Genotip 2 n (%)	Genotip 3 n (%)	Genotip 4 n (%)	Total
2016	-	28 (100)	28 (100)	-	-	-	28
2017	1 (1.5)	57 (90.5)	58 (92.0)	1 (1.5)	1 (1.5)	3 (5.0)	63
2018	5 (13.2)	26 (68.3)	31 (81.5)	-	4 (10.5)	3 (8.0)	38
2019	1 (2.5)	34 (85.0)	35 (87.5)	-	-	5 (12.5)	40
Total	7 (4.2)	145 (85.7)	152 (90)	1 (0.6)	5 (3.0)	11 (6.5)	169

HCV: Hepatitis C virus

Discussion

It has been determined that the genotype 1 was the most prevalent (90%) among the population of the research over four years. Genotype 1 is the most common genotype across the world (5,11). Similar to our findings, it was found out in the researches, which were performed previously in Turkey, that the genotype 1 was the most frequent genotype (8,12,13,14). In recent years, the rate of genotype 1 (79.8%) was found to be lower in the research, which was conducted in İzmir by Kaya et al. (12), compared to our results, while this rate was found to be 89.5% in the research, which was performed in Aydın by Tiryaki et al. (8), that was analogous to our findings. The mean age of patients in previous studies conducted in Turkey was 41-56, and it was lower compared to our findings (15,16,17,18). In the study, which was performed by Kaya et al. (12), 30.7% of the patients were identified as 65 years and over. Unlike the study of Kaya et al. (12), the mean age of the patients was higher (63.4) in our study, while 60.7% of the patients were over 65 years old. Genotype 1b (98%) was determined to be the most dominant genotype among the patients over 65 years old. In another study conducted by Altuglu et al. (19), iatrogenic risks such as dental procedures and surgeries were found to be the most prevalent risk factors for HCV. Determination of the higher mean age in our research compared to previous studies points out to a decline in the incidence rate of new infections among younger people. Hence, this finding reveals that measures, which diminish iatrogenic contamination, such as safe blood transfusion, are efficient. No variation was detected between the ratios of males and females in studies, by which risk factors for HCV infection were investigated (19,20). However, the number of female patients was found significantly (63%) higher in our study. Moreover, when compared with patients who had not genotype 1, it was determined that the rate of elderly and female patients was significantly higher among our patients with genotype 1.

Upon examining the distribution of genotypes per year, it was found out that there was a moderate increase in genotype 4, while the rate of genotype 1b was higher among our patients in all years. It was revealed in the study of Tiryaki et al. (8) that 11 patients were foreign nationals, and genotype 4 was most prevalent among Syrian patients. Apart from 2 Afghan patients (genotype 3), all of the patients who had been included in our research were citizens of the Republic of Turkey and had lived in the province of Karabük.

Study Limitations

Our study does not provide adequate data related to risk factors and modes of transmission for patients since the study investigates records of hospital retrospectively. Thus, it is unable to clarify why the female gender is dominant.

Conclusion

It has been found out that the female gender was most common among HCV cases in our province, genotype 1b was the most prevalent genotype, and our patients had applied to hospital at advanced ages. We are of the opinion that our research might be a guideline in terms of epidemiological knowledge and for the selection of treatment.

Ethics

Ethics Committee Approval: The research was performed following the approval, which is numbered with 77192459-050.99-E.21430 and dated to 11.06.2020, of Karabük University Non-invasive Clinical Research Ethics Committee.

Informed Consent: It wasn't obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.K., A.A.H, Design: A.A.H, Data Collection or Processing: C.K., Analysis: C.K., A.A.H, Literature Search: C.K., A.A.H, Writing: C.K., A.A.H.

Conflict of Interest: All authors declare to have no conflict of interest.

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Research Article

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Effect of Hepatitis C Infection and Its Clearance on the Frequency of Coronary Artery Disease in Diabetics

Hepatit C Enfeksiyonunun ve Klirensinin Diyabetik Hastalarda Koroner Arter Hastalığı Sıklığına Etkisi

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ABSTRACT

Objectives: Chronic hepatitis C (CHC) infection considered to be associated with an increased risk of coronary artery disease (CAD). However, there is not enough data concerning this association in diabetics. Thus, this study investigated the effect of chronic HCV infection and its clearance on the CAD risk in diabetics.

Materials and Methods: This was a retrospective case-control study conducted at the Mustafa Kemal University, Department of Infectious Diseases and Clinical Microbiology, Hatay, between January 2010 and January 2015. The presence of CAD and its main risk factors such as age, sex, hypertension (HT), hyperlipidaemia (HL), chronic obstructive pulmonary disease and chronic renal failure were compared between 100 HCV infected diabetic patients and 100 uninfected diabetic controls. The HCV-infected patients were further divided into a viral clearance group and a persistence group, and the CAD prevalence was also compared between these two groups.

Results: Patients with CHC were predominantly male (55% vs 39%) and predominantly older than 60 years of age (68% vs 51%) in comparison with controls. The HCV-infected group had a significantly lower prevalence of CAD, HT and HL compared with controls (p<0.001). Furthermore, no significant differences were found between groups with viral clearance and persistent viremia for the prevalence of CAD (p=0.80).

Conclusion: Our data suggested that chronic HCV infection might be a protective factor against CAD and successful HCV eradication may not increase the risk of CAD in diabetics. These findings indicate a need for additional studies to clarify the effects of HCV infection and its clearance on the risk of CAD in diabetics.

Keywords: Chronic HCV infection, coronary artery disease, diabetes mellitus

ÖZ

Amaç: Kronik hepatit C (KHC) enfeksiyonunun artmış koroner arter hastalığı (KAH) riski ile ilişkili olduğu kabul edilmektedir. Bununla birlikte diyabetik hastalarda bu ilişki ile ilgili yeterli veri bulunmamaktadır. Bu nedenle bu çalışma ile kronik HCV enfeksiyonunun ve klirensinin, diyabetik hastalardaki KAH riski üzerine etkisi araştırılmıştır.

Gereç ve Yöntemler: Bu çalışma; Mustafa Kemal Üniversitesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilimdalı, Hatay'da, Ocak 2010-2015 tarihleri arasında yapılan retrospektif bir olgu kontrol çalışmasıdır. HCV ile enfekte diyabetik olgular (n=100) ile HCV ile enfekte olmamış diyabetik kontrol grubu (n=100) arasında KAH varlığı ve yaş, cinsiyet, hipertansiyon (HT), hiperlipidemi (HL), kronik obstrüktif akciğer hastalığı ve kronik böbrek yetmezliği gibi KAH için risk faktörleri açısından karşılaştırıldı. Buna ek olarak, HCV ile enfekte diyabetik olgular viral klirens gelişen ve persistan viremisi olan olgular olarak iki alt gruba ayrıldı ve bu iki grup arasında da KAH prevalansı karşılaştırıldı.

Bulgular: CHC olguları kontrol grubuna göre çoğunluğu erkekti (%55'e karşı %39) ve ağırlıklı olarak 60 yaşından büyüktü (%68'e karşı %51). HCV ile enfekte olan grupta, kontrol grubuna kıyasla KAH, HT, HL prevalansı anlamlı olarak daha düşüktü (p<0.001). Ayrıca, viral klirens gelişen ve persistan viremisi olan olgular arasında KAH prevalansı açısından anlamlı fark bulunmadı (p=0.80).

Sonuç: Verilerimiz kronik HCV enfeksiyonunun KAH'a karşı koruyucu bir faktör olabileceğini ve başarılı HCV eradikasyonunun diyabetik hastalarda KAH riskini arttırabileceğini düşündürmektedir. Bu bulgular HCV enfeksiyonunun ve klirensinin diyabetik hastalarda KAH riski üzerindeki etkilerini açıklığa kavuşturmak için ek çalışmalara ihtiyaç olduğunu göstermektedir.

Anahtar Kelimeler: Kronik hepatit C enfeksiyonu, koroner arter hastalığı, diabetes mellitus

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Introduction

Some studies have suggested that chronic infections including chronic active hepatitis C plays a role in the pathogenesis of atherosclerosis and coronary artery disease (CAD) (1,2). However, the effect of hepatitis C virus (HCV) infection on the risk of CAD is still unclear. Even though most studies have declared that HCV increases the risk of CAD (3,4), some studies have shown no association (5,6), while others have reported that HCV could be protective against CAD (7). As diabetic patients, have higher mortality rates from CAD than non-diabetics (8), this association gains more importance in diabetics. The presence of HCV infection is known to accelerate the occurrence of both metabolic syndrome and diabetes mellitus (DM) (9). This seems to support the studies that have reported an increased risk for CAD with HCV infection. On the other hand, lower serum lipid levels have been observed in patients infected with HCV (4). HCV-related hypolipidemia could be associated with decreases in atherosclerosis (10), which may then decrease the risk of CAD. This study aimed to investigate the effect of HCV infection and its clearance on CAD risk in diabetics. To our knowledge this is the first study performed in diabetic patients concerning this issue.

Materials and Methods

Study population

We conducted a retrospective case-control study that included 200 diabetics with and without chronic hepatitis C (CHC) infection who were admitted to our clinic between January 2010 and January 2015. Of the 200 patients, 47% were male and 53% were female. The mean age of the patients was 62.8±9.8 (range: 37-88) years. Patients were classified into two groups. Group A was comprised of 100 diabetic patients with chronic HCV infection and group B had 100 uninfected diabetic patients as a control group. Among CHC patients, 90% of cases were infected with genotype 1b, while the remaining 10% were infected with genotype 4. The presence of CAD and its main risk factors such as age, sex, hypertension (HT), hyperlipidaemia (HL), chronic obstructive pulmonary disease (COPD) and chronic renal failure (CRF) were compared between the two groups.

According to the treatment results, the patients in Group A also were divided into subgroup A1 (47 patients) for those who achieved viral clearance and subgroup A2 (53 patients) for those with persistent viremia (who failed therapy or were untreated). The prevalence of CAD was also compared between these two subgroups (subgroup A1 and A2). Patients coinfected with hepatitis B were excluded from the study as well as patients who were diagnosed as having CAD before the diagnosis of the HCV infection.

Definitions

CHC was defined by the presence of the HCV antibody and the persistence of detectable HCV-RNA for at least six months. Patients who were negative for HCV antibodies were considered as HCV-uninfected. Subjects were considered diabetic if they had plasma glucose levels of ≥200 mg/dL and if they were under treatment for DM. CAD was defined as 50% or more stenosis in at least one major coronary artery as determined with anjiography. HT was defined by the presence of diagnostic codes (ICD-10 codes) for HT and the use of antihypertensive drugs. HL was defined by the presence of elevated serum cholesterol levels (total cholesterol >200 mg/dL; LDL-C >130 mg/dL) and a current prescription of cholesterol-lowering medication. CRF was defined as an estimated glomerular filtration rate less than 30 mL/min for at least three months. COPD was defined by the presence of the diagnostic code (ICD-10 code) for COPD and the use of nebulizer therapy.

Statistical Snalysis

Statistical analyses were performed using the SPSS version 23. The chi-square test (or Fisher's exact test, where appropriate) and the Student's t-test were used for statistical comparisons. A p-value <0.05 was considered significant.

Results

CHC patients were predominantly male (55% vs 39%) and were predominantly older than 60 years (68% vs 51%) in comparison with the controls. However, there were no statistically significant differences in age between the HCV-infected patients and controls (p=0.075). The HCV-infected group had a significantly lower prevalence of CAD compared with controls (p<0.001). The prevalence of HT and HL were also significantly lower in the HCV-infected group (p<0.001 for both). The HCV group had a higher prevalence of COPD and CRF, but these differences were not statistically significant (p=0.45 and p=0.47 respectively).

There were no statistically significant differences in the CAD prevalence between subjects with viral clearance (group A1) and subjects with persistent viremia (group A2) (p=0.80).

Comparisons of the characteristics of HCV negative and positive diabetic patients are shown in Table 1.

Discussion

There is much evidence that HCV infection have been associated with an increased risk of CAD (11,12,13). However, in our study we observed that HCV-infected diabetic patients had a lower prevalence of CAD in comparison with the uninfected controls. This difference that we found in our study may be due to the different study population, which, in this study, consisted entirely of diabetics.

There are two possible explanations for this difference in diabetic patients in the present study. The first is that lower sustained virologic response (SVR) rates have been reported in diabetic patients compared with non-diabetics (14). This suggests that diabetics may have higher viral load levels than non-diabetics. This hypothesis also was supported by findings of one study conducted by Hsu et al. (15), who found a relationship between high viral load levels and insulin resistance. Furthermore, one study has indicated a relationship between high viral load and lower lipid levels in patients with HCV infection (16). As a result, possible higher viral load levels and related lower lipid levels in the present study, compared with similar studies, may explain the decreased CAD risk in diabetics, which was observed in this study.

Another explanation stems from a previous report indicating that genetic polymorphisms in IL28B may influence the risk of developing DM and related complications like CAD in patients with genotype 1 CHC infection (17). Different genetic variants of IL28B

Table 1. Comparisons of the characteristics of HCV negative and positive diabetic patients

Characteristics	HCV (+) diabetics (n=100)	HCV (-) diabetics (n=100)	p
Age (years)	63.9±8.9	61.4±10.5	0.075
Age			
37-60	32	49	-
≥60	68	51	-
Males (n)	55	39	0.023
CAD (n)	14	36	<0.001
COPD (n)	5	2	0.45
CRF (n)	11	8	0.47
HL (n)	17	56	<0.001
HT (n)	26	50	<0.001

CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, HL: Hyperlipidaemia, HT: Hypertension, HCV: hepatitis C virus

may explain the difference in the impact of HCV on the prevalence of CAD in diabetics.

In the present study, we also observed that the HCV-infected group had a lower prevalence of HT and HL, which is consistent with other studies (4,18). Although lower lipid levels were described in HCV-infected patients, achieving SVR has been found to be associated with a rebound increase in lipid levels (4,19). As high lipid levels are considered a risk factor for CAD, rebound increases in lipid levels may also be associated with an increased risk of CAD. Therefore, we also analysed the effect of viral clearance on the development of CAD in diabetics. However, we did not see a significant association between viral clearance of HCV and the development of CAD in diabetics.

Study Limitations

Our study has some limitations due to its retrospective nature. First, we had no information on body mass index, family history of CAD and smoking history in our study population. These are important risk factors for developing CAD. Second, we did not have information about the degree of liver fibrosis, which is a condition that may influence the risk of CAD. Finally, we could not examine IL28 B genotypes in patients.

Despite these limitations, this is the first study to investigate the effects of HCV infection on the risk of CAD in diabetics. This is also the first study to look at the effect of successful HCV eradication on the development of CAD in diabetics.

Conclusion

The results of this study have important ramifications for future research. Our findings suggest that the presence of HCV infection may reduce the risk of CAD in diabetics. Our findings also suggest that successful HCV eradication may not increase the risk of CAD in diabetics. Further prospective studies are necessary to clarify the roles of HCV and HCV eradication in the development of CAD in diabetics.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Mustafa Kemal University Hospital (approval number: 07, date: 11/06/2020).

Informed Consent: Due to the restrospective design of the study informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Authors contributions

Concept: T.B., C.K., Design: T.B., C.K., M.C., Y.O., Data Collection or Processing: T.B., C.K., Analysis: T.B., C.K., M.C., Y.O., Literature Search: T.B., C.K., Writing: T.B., C.K.

Conflict of Interest: The authors declare no conflict of interest.

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HBV Flare Under Tenofovir Treatment in Chronic Hepatitis B: Case Report

Kronik Hepatit B'de Tenofovir Tedavisi Altında HBV Alevlenmesi: Olgu Sunumu

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ABSTRACT

The purpose of chronic hepatitis B treatment is to stop the progression of the disease and prevent cirrhosis and liver cancer that may occur with the progression of the disease. In the current treatment, one of the nucleosis (t) id analogs, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate and entecavir (ETV), is preferred due to its high genetic barriers. In this study; HBV flare was detected in a patient who received TDF treatment and rtN236T, sP120T and sC124R mutations were identified as a result of the resistance analysis. A logarithmic reduction in HBV-DNA level was achieved by adding ETV to the current treatment. As a result, acyclic phosphonate mutations can reduce the clinical response in the treatment of CHB with TDF. HBV drug resistance analysis should definitely be used in rational use of TDF, a potent drug, and in determining the direction in KHB treatments.
Keywords: Chronic hepatitis B, hepatitis B virus, tenofovir, treatment failure, drug resistance

ÖZ

Kronik hepatit B tedavisinin amacı, hastalığın ilerlemesini durdurmak ve hastalığın ilerlemesi ile oluşabilecek siroz ve karaciğer kanserini önlemektir. Mevcut tedavide, yüksek genetik bariyerleri nedeniyle nükleoz (t) id analoglarından biri olan tenofovir disoproksil fumarat (TDF) veya tenofovir alafenamid fumarat ve entekavir (ETV) tercih edilmektedir. Olgumuzda; TDF tedavisi almakta iken HBV alevlenmesi tespit edilmiştir ve direnç analizi sonucunda rtN236T, sP120T ve sC124R mutasyonları tespit edilmiştir. Mevcut tedaviye ETV eklenerek HBV-DNA seviyesinde logaritmik azalma sağlanmıştır. Sonuç olarak, asiklik fosfonat mutasyonları, CHB'nin TDF ile tedavisinde klinik yanıtı azaltabilir. HBV ilaç direnç analizi, güçlü bir ilaç olan TDF'nin akılcı kullanımında ve KHB tedavilerinde yön belirlemede mutlaka kullanılmalıdır.
Anahtar Kelimeler: Kronik hepatit B, hepatit B virus, tenofovir, tedavi başarısızlığı, ilaç direnci

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Introduction

Chronic hepatitis (CHB) remains a global public health problem in changing epidemiology due to various factors such as vaccination policies and migration. It is estimated that 2 billion people worldwide are infected with the hepatitis B virus (HBV) and approximately 248 million people live with CHB (1,2). According to the global hepatitis B surveillance of the World Health Organization, our country is among the middle endemic regions (2-7%). Although the prevalence of hepatitis B surface antigen (HBsAg) positivity is 4% in people over the age of 18, this rate can be up to 10% in the Southeastern Anatolia region of Turkey (3).

The purpose of CHB treatment is to increase the life quality and duration of the patient by preventing complications such as cirrhosis, liver failure and hepatocellular carcinoma that may occur with the progression of the disease (4). Although this goal can be achieved by permanently suppressing HBV replication, eradication of the virus is not possible due to the persistence of cccDNA in the hepatocyte nucleus. Therefore, the achievable goal is the suppression of HBV-DNA in the bloodstream and normalization

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of alanine aminotransferate (ALT). With or without anti-HBs seroconversion, HBsAg negativity is defined as optimal treatment success (5). Many agents such as recombinant interferons (IFN) (conventional and pegylated IFN), nucleos(t)ide analogs [lamivudine, telbivudine, adefovir, entecavir (ETV), and tenofovir] can be used in the treatment of CHB (5). Even though rare cases with sustained virologic responses were been, pegylated IFN was abandoned due to side effects and lamivudine due to drug resistance issues (6). Likewise, adefovir has limited use because of its low genetic barrier and nephrotoxicity. The use of telbivudine is also limited due to its slow effectiveness (7). Today, drugs with high resistance barrier like TDF, ETV, and tenofovir alafenamide fumarate (TAF) is preferred according to the patients' comorbid conditions. In our country, 1,206,000 boxes of NA were used from 2018 to 2019. 15% of this distribution is original TDF drug, 43% is generic TDF drugs, 12% is original (ETV) drug and 19% is generic ETV drugs. TAF, which is new to use, seems to have been used at 3% (8). On the other hand, HBsAg negativity can be achieved at a low rate (0.6-4.6) and the duration of the treatment can be lifelong in hepatitis B e antigen (HBeAg) negative patients with NA treatments (5). Therefore, the long-term side effects of NA treatments and drug resistance that may develop should be managed well (9).

The main cause of drug resistance in NA treatments is mutations in the HBV polymerase (pol) gene. This mutation may occur in individuals naive to treatment because of the natural viral kinetics of HBV and may cause drug unresponsiveness (primary drug resistance mutations) or repair the replication capacity of HBV variants (compensatory mutations) (10). Due to the circular and double- stranded genome organization of HBV, the pol gene overlaps the envelope (S) gene (11). Therefore, pol gene mutations in NA treatments of CHB can also lead to changes in the "a" determinant (between 124th-149th aminoacids) encoding the HBsAg protein (12,13). This problem can lead to the emergence of variants that can escape from anti-HBs antibodies after HBV vaccination, inactivation of passive immunization with HBIg and pseudo-HBsAg negativity in diagnostic tests (14).

In this study, we aimed to present the management of HBV flare in an HBeAg positive and TDF treated CHB patient.

Case Report

Twenty-eight-years-old male patient was admitted to our outpatient clinic upon detection of HBV-DNA level 1.70+E8 IU/mL while being examined for infertility at the urology clinic. The patients HBsAg and HBeAg test results were positive. Anti-HBs, anti HBc IgM, anti HBe, anti HCV, anti-HIV, and HDV-RNA results were negative. Although the patient with normal ALT level was evaluated in the immune tolerant phase, a liver biopsy was performed because of family history. The biopsy result was classified as grade: 4, stage: 3 according to modified Knadell scoring. In the monthly follow-ups of the patient whose TDF treatment was started, regular logarithmic HBV DNA decrease was observed. However, the 7th month of treatment (October 2018), HBV-DNA level was defined as above 1.70+E8 IU/mL. Thereupon, HBV drug resistance analysis was requested. HBV-DNA and ALT levels and drug resistance analysis results over time are shown in Figure 1.

HBV drug resistance analysis was done by Sanger dideoxy sequencing method. Pol gene in HBV-DNA isolated from patient plasma sample (forward primer: 5'-TCGTGGTGGACTTCTCTC AAT T-3' - reverse primer: 5'-CGTTGACAGACTTTCCAATCA AT-3') was amplified with primers. Genafor/Arevir (http://coreceptor.bioinf.mpi-inf.mpg.de/) program was used to identify mutations responsible for drug resistance. Eleven months after ETV was added to the treatment, the patient's HBV-DNA level decreased to 3.52+E3 IU/mL. AST and ALT levels returned to normal.

Discussion

In our case, rtN236T mutation was detected in the pol gene of HBV isolated from the plasma sample which could explain NA non-response or suboptimal response. The rtN236T mutation is associated with acyclic phosphonate drugs but also reduces TDF sensitivity (15). Various mutations have been identified in TDF clinical applications leading to decreased sensitivity in vitro conditions (16,17). To manage viral flare in TDF treatment of CHB, HBV drug resistance analysis must be performed and drug class can be changed or combined according to the nature of the

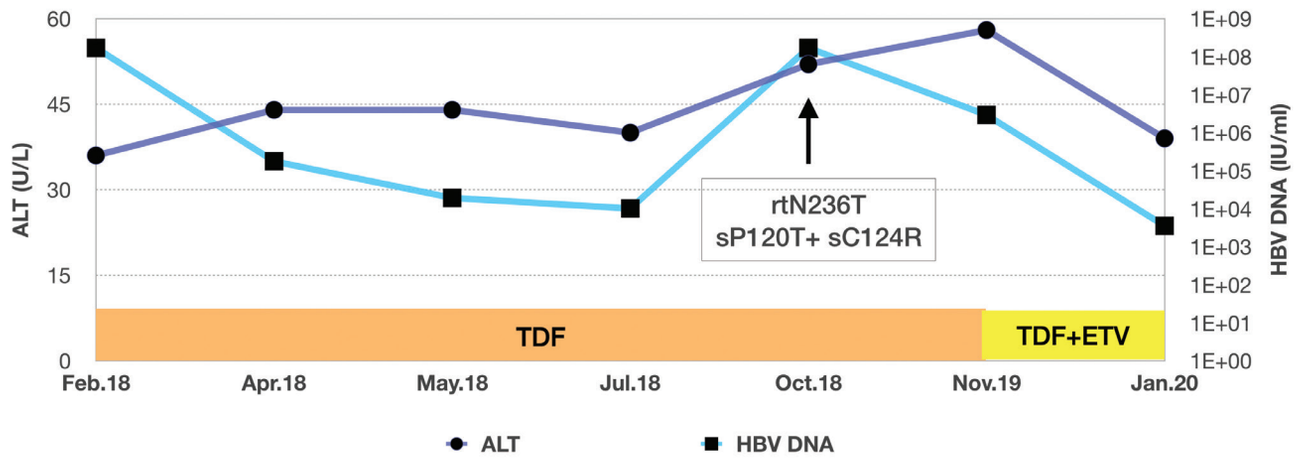

Figure 1. HBV-DNA, ALT levels and clinically important mutations detected in the patient over time
HBV: Hepatitis B virus, ALT: Alanine aminotransferate, TDF: Tenofovir disoproxil fumarate, ETV: Entecavir

detected mutation. In our case, the sP120T and sC124R mutations detected in the HBV-S gene indicates variant characteristics that can escape from the vaccine, HBIg treatment, and HBs Ag diagnostic tests. Carefully monitoring of HBV variants in CHB treatment with NA and analyzing S gene as well as the pol gene for treatment failure will be beneficial for public health (13,18).

As a result, acyclic phosphonate mutations reduce the clinical response. HBV drug resistance analysis should definitely be used in the national use of TDF, a potent drug, and in determining the direction in the treatment of CHB.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.D.T., M.S., S.A., Design: M.D.T., M.S., S.A., Data Collection or Processing: M.D.T., M.S., S.A., Analysis or Interpretation: M.D.T., M.S., S.A., Literature Search: N.Z., N.E., Writing: M.D.T., M.S., S.A.

Conflict of Interest: The authors declare no conflict of interest.

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Letter to the Editor

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Relationship Between Viral Load and Prohepcidin Levels in Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında Viral Yük ve Prohepsidin Düzeyi Arasındaki İlişki

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Dear Editor;

Viral hepatitis represents a major cause of chronic liver disease leading to cirrhosis and hepatocellular carcinoma (HCC), worldwide. Increased iron storage has an important role in the diseases associated with Hepatitis B virus (HBV). This may be associated with the iron's ability to produce oxidative stress and cause tissue damage and chronic inflammation in the liver. Hepcidin is a hormone which functions as a key regulator in iron homeostasis and is produced in the liver. Understanding the regulation of hepcidin in chronic viral hepatitis (CVD) associated diseases may explain the relation among viral hepatitis, iron accumulation and HCC to a great extent (1,2). In this study, serum prohepcidin levels were assessed in four different groups of patients followed up with the diagnosis of chronic hepatitis B (CHB). The aim of this study was to evaluate prohepcidin levels with HBV-DNA levels in HBV infected patients and healthy volunteers.

The study included the serum samples, which were sent to Sakarya University, Sakarya Training and Research Hospital, Medical Microbiology Laboratory and routinely tested and then stored at -80 °C, from patients who were followed up with CHB infection and healthy population. Patients with chronic hepatic or hematologic conditions were excluded. The participants were divided into four groups according to their status of using medication and level of viral load ($\geq 10^5$ IU/mL was accepted as high). The serum prohepcidin levels in the samples of the study were investigated with the method of ELISA test (Boster, Pleasanton CA).

A total of 60 patients with CHB (33 male, mean age 42.4±6.3 years) and 20 healthy volunteers were included in the study. The prohepcidin levels of the control group were found to be higher than patient groups. Also, it was detected to be higher in those with the viral load $<10^5$ IU/mL compared to those with the viral load $\geq 10^5$ IU/mL. The prohepcidin levels of the control group and patient groups are illustrated in the Table 1.

Hepcidin is a circulating peptide hormone that is synthesized mainly from the liver and is the main regulator of systemic iron balance. As it is produced mainly by hepatocytes, liver diseases may affect hepcidin production. There are a few studies evaluating hepcidin expression in CVD but remains controversial. Understanding the regulation of hepcidin in HBV-associated diseases may increase our knowledge on the relationship among

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Table 1. Prohepcidin levels of the patient groups and control group

Prohepcidin-level (pg/mL)	Patients on medication and with HBV-DNA $<10^5$ IU/mL, (n=15)	Patients on medication and with HBV-DNA $>10^5$ IU/mL, (n=15)	Patients who were not on medication and with HBV-DNA $<10^5$ IU/mL, (n=15)	Patients who were not on medication and with HBV-DNA $>10^5$ IU/mL, (n=15)	Control group, (n=20)
Minimum	133	131	70	216	629
Maximum	1272	851	1132	1117	1819
Mean value	644.06	619.57	742.88	695.55	1185.1

P<0.05 between group 1 and 2, p>0.05 between group 3 and 4, p<0.05 between control group and all patient groups.
HBV: Hepatitis B virus,

viral hepatitis, iron storage and HCC. Although the determination of hepcidin levels by immunoassays and mass spectrometry has begun to be used more, accurate and easy hepcidin quantitation remains as a problem.

The elevated serum iron level has been described in chronic liver diseases, including CHC, nonalcoholic steatohepatitis and alcoholic liver disease (3,4). However, some other studies show that hepcidin was down-regulated in HCV and liver cirrhosis, and ferritin levels being negatively correlated (5). There are few reports of hepcidin levels in patients with HBV infections, and the results are inconsistent. Wang et al. (2) showed that serum ferritin and hepcidin levels were significantly higher in patients with hepatitis B than in controls, and positive correlations were found between log (hepcidin) and log (HBV-DNA) (2). However; Armitage et al. (4) found that there was no evidence of hepcidin up-regulation during the primary viremia phases of HCV or HBV infection.

We found that prohepcidin levels are significantly lower in patients with CHB, in our study. Since our study had cross-sectional design, the prognostic value of low prohepcidin in chronic HBV could not be assessed. There is still need for further research on physiological and pathological changes of hepcidin during HBV infection for better understanding clinical monitorization and management of HBV-associated diseases.

Ethics

Peer-review:

Authorship Contributions

Concept: M.A. Design: M.A., M.K., F.G.A., Data Collection or Processing: M.A., T.D., K.Y., F.G.A., Analysis or Interpretation: M.A., T.D., B.T., F.G.A., Literature Search: M.A., M.K., B.T. Writing: M.A., B.T.

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