

**Original article / Araştırma****The relationship between duration, stage and, treatment of illness and depression or anxiety in patients with chronic hepatitis B****Gülden ESER KARLIDAĞ,<sup>1</sup> Murad ATMACA<sup>2</sup>****ABSTRACT**

**Objective:** This study aims to establish in chronic HBV patients the frequency of depression and anxiety, independently from drug side effects, among the antiviral-treated group and the untreated follow-up group and accordingly, to evaluate relationship between the treatment and the factors affecting prevalence of depression and anxiety in these patients. **Methods:** Included in our study are patients aged between 18 and 60 followed-up and treated for chronic hepatitis B. Three groups were formed in our study: chronic hepatitis group treated with oral antiviral agents (n=103 patients), untreated chronic infection group (n=94 patients) and healthy control group with the same age as treatment group patients (n=50). Factors such as age, sex, education, marital status of the patient, duration of the illness, whether or not the patient is treated, treatment type if treated, history of a prior hepatitis and cirrhosis in family are examined. All participants are scored using Hamilton Anxiety and Hamilton Depression Scales. **Results:** Two hundred and forty-seven people consisting of 169 males (68.4%) and 78 females (31.6%) were included in this study. No difference was observed in terms of demographical characteristics of all groups. In comparison there among, a statistically significant anxiety and depression score was detected between the chronic infection group on one side and the chronic hepatitis and the control groups on the other side. For participants with a family history of cirrhosis due to chronic HBV, not only anxiety, but also depression scores were detected to be significantly high. Compared to participants with higher education levels, anxiety and depression scores of participants with lower education levels were determined to be significantly high. **Conclusion:** This study, the depression and anxiety scores being lower in antiviral treatment group as regards the group treated for chronic infection may be construed as a result of therapeutic effect of antiviral agents on hepatitis, but beyond that, it may also be a reflection of direct effect of known immunological impacts of inflammation on depression and anxiety in the etiology of which inflammation is known to play a significant role. This finding requires further studies on wider sampling groups. (*Anatolian Journal of Psychiatry* 2019; 20(5):515-521)

**Keywords:** chronic hepatitis B, depression, anxiety, treatment

## **Kronik hepatit B hastalarında hastalık süresi, evresi ve tedavisinin depresyon ve anksiyete ilişkisi**

**ÖZ**

**Amaç:** Kronik HBV hastalarında, antiviral tedavi gören grupla tedavisiz izlenen grup arasında ilaç yan etkilerinden bağımsız olarak depresyon ve anksiyete sıklığını ortaya koymak ve beraberinde bu hastalarındaki depresyon ve anksiyete sıklığını etkileyen etkenlerle ilişkisinin değerlendirilmesi amaçlanmıştır. **Yöntem:** Bu çalışmaya, kronik hepatit B tanısı ile tedavi edilen ve izlenen 18-60 yaşları arasındaki hastalar alındı. Çalışmamızda oral antiviral ajan alan kronik hepatit B grubu (n=103 hasta), tedavi almayan kronik enfeksiyon grubu (n=94 hasta) ve çalışma hastaları ile aynı yaş grubunda sağlıklı bireylerden oluşan kontrol grubu (n=50) olmak üzere üç grup oluşturuldu. Hastaların

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yaş, cinsiyet, eğitim düzeyi, medeni durumu, hastalık süresi, tedavi alıp/almadığı, aldığı tedavi, ailede hepatit ve siroz öyküsü sorgulandı. Tüm katılımcılara Hamilton Anksiyete ve Hamilton Depresyon Ölçekleri uygulandı. **Bulgular:** Çalışmaya 169 (%68.4) erkek, 78 (%31.6) kadından oluşan toplam 247 kişi alındı. Tüm grupların demografik özellikleri arasında farklılık gözlenmedi. Gruplar arasında yapılan karşılaştırmada kronik enfeksiyon grubu ile kronik hepatit ve kontrol grubu arasında anksiyete ve depresyon puanı açısından istatistiksel olarak anlamlı düzeyde fark saptandı. Ailede kronik HBV hastalığına bağlı siroz öyküsü olanlarda, hem anksiyete hem de depresyon puanları anlamlı düzeyde daha yüksekti. Eğitim düzeyi düşük olanlarda yüksek olanlara göre anksiyete ve depresyon puanlarında anlamlı yükseklik saptandı. **Tartışma:** Çalışmamızda antiviral tedavi gören grupta kronik enfeksiyonu olanlara göre depresyon ve anksiyete puanlarının daha düşük bulunması antiviral tedavinin hepatiti tedavi edici etkisine bağlı olabileceği gibi, inflamasyonun, etiyolojisinde önemli rol oynadığı depresyon ve anksiyete üzerine immünolojik açıdan etkilerinin doğrudan bir etkisi de olabilir. Bu durum daha geniş örneklemede araştırılmalıdır. (*Anadolu Psikiyatri Derg* 2019; 20(5):515-521)

**Anahtar sözcükler:** Kronik hepatit B, depresyon, anksiyete, tedavi

## INTRODUCTION

Chronic hepatitis B virus (HBV) infection globally affects more than 240 million of people.<sup>1</sup> In our country, hepatitis B prevalence in general population has been reported to be 4% despite variance according to region.<sup>2</sup> In general, although hepatitis B prevalence globally decreases, according to a recent analysis, death rate from liver complications due to hepatitis B from 1990 to 2013 has increased by 33%.<sup>3</sup> More than one million death cases resulting from hepatocellular carcinoma and end-stage liver disease complications such as chronic HBV infection and cirrhosis have been reported worldwide.<sup>4</sup>

According to European Association for the Study of Liver Diseases (EASL) guide, patients are categorized as chronic infection and chronic hepatitis patients as not every patient has chronic hepatitis. Patients with HBsAg positive, normal ALT levels and an undamaged or slightly damaged liver histology are categorized as patients with chronic infection. Patients with HBsAg positive, a value over HBV-DNA 2000 IU/ml, high ALT levels and moderately or severely damaged liver histology are categorized as patients with chronic hepatitis. In this guide, chronic infection term is used instead of the previously used inactive carrier and immunotolerant terms. Diagnosis, treatment and follow-up processes of patients are based on these categories. Preferred treatment options for chronic hepatitis treatments are entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), peginterferon (PegIFN).<sup>5</sup>

The term 'chronic diseases' expresses diseases that are not self-recovering and generally cannot be treated completely and as a result, patients have to live therewith for their lifetimes and said diseases affect patients' mental and social lives significantly, as well as their bodies with physical symptoms thereof.<sup>6</sup> Therefore, it is also quite

important to evaluate life quality of patients in addition to disease symptoms in order to gain a clear understanding about their health status. It is known that chronic somatic diseases are often accompanied by psychiatric comorbidities. It has been shown that these psychiatric comorbidities, particularly depression and anxiety significantly and adversely affect life qualities of patients.<sup>7,8</sup>

Previous studies showed that psychiatric disorders are seen in HBsAg-positive patients more often than the community in general.<sup>9,10</sup> Kunkel et al.<sup>11</sup> reported that 46% of the chronic hepatitis patients have depressive signs. In another study where 43 asymptomatic hepatitis B carriers and 43 healthy controls were compared, it was reported that psychiatric disorders were found to be more common in carriers than controls (30.2% vs. 11.6%). Based on these results, authors concluded that follow-up of asymptomatic hepatitis B virus carriers should cover a psychiatric visit as well.<sup>12</sup> However, effects of oral antiviral treatments commonly used nowadays on depression and anxiety levels of such patients have never been studied so far.

In recent years, investigations on the effects of inflammatory and immunologic pathways in the pathogenesis of depression are growing.<sup>13</sup> In the depression, alterations in the values of cytokines, stress hormones, brain-derived neurotrophic factor (BDNF) implicate the relationship between depression and inflammatory pathways.<sup>14</sup> On the other hand, the fact that pro-inflammatory cytokines were found to be increased in BOS of depressive patients is another support for this relationship.<sup>15,16</sup>

Accordingly, this study firstly aims to establish, independently from drug side effects, depression and anxiety prevalence among untreated group on one side. In addition, treatment group administered with oral antiviral agents which are in no case reported in the medical literature to have

caused or triggered depression and anxiety in chronic HBV patients, as well as to evaluate relationship between the treatment and the factors affecting prevalence of depression and anxiety (mental stress due to having a chronic disease, necroinflammatory activity in liver or direct effect of hepatitis viruses on central nervous system) in these patients.

## METHODS

Included in this study were patients from Fethi Sekin City Hospital who were those with chronic hepatitis B diagnosis aged between 18 and 60 followed-up and treated in accordance with EASL guides. The study was performed prospectively and between April 2018 and December 2018. Approval of Firat University Ethics Committee (Decision Number: 01, Date: 05.04.2018) was obtained for this study. The study was designed pursuant to ethical principles of World Medical Association Declaration of Helsinki about medical studies on human volunteers. An informed written consent was obtained from all participants.

According to EASL 2017 guide, our patients were divided into two groups: chronic infection and chronic hepatitis. These categories were formed based on HBV-DNA levels, HBe Ag positivity/negativity, ALT levels and liver histology of the patients.<sup>3</sup> Patients in chronic infection group were followed-up without a treatment thereinfor. With regard to EASL guide, all patients in the chronic hepatitis group were given entecavir (ETV) and tenofovir disoproxil fumarate (TDF). HBV-DNA levels of the patients determined to be not given any treatment were followed-up at intervals of 3-6 months (ALT), for periods of 6 months to 3 years according to their categories.

In the end, three groups were formed in our study: the chronic hepatitis group treated with oral antiviral (Group 1, n=103 patients), the untreated chronic infection group (Group 2, n=94 patients) and the control group consisting of healthy individuals at the same age as treatment group patients (Group 3, n=50). A semi-structured data form was used for recording information such as age, sex, education, marital status of the patient, duration of the illness, whether or not the patient is treated, treatment type if treated, a family history of a prior hepatitis and cirrhosis.

Excluded from this study were patients suffering from any chronic disease other than hepatitis B (diabetes, chronic liver disease, transplantation

history, liver cirrhosis, chronic rheumatic disease, malignancy etc.), who were illiterate and probable targets of an antiviral treatment for any reason whatsoever, and had high ALT levels and a psychiatric diagnosis, and have previously received or are currently receiving an interferon treatment. These criteria, together with hepatitis B presence exclusion criteria, were used for individuals in the control group.

All participants were examined by the same doctor and rated using Hamilton Depression (HAM-D) and Hamilton Anxiety (HAM-A) Scales. HAM-D is a rating scale consisting of 17 items examining depression signs. The highest score is 53. A score of 0-7 shows non-existence of depression, a score of 8-16 slight depression, a score of 17-23 moderate depression, and scores of and over 24 severe depression.<sup>17</sup> HAM-A measures anxiety level and severity level change in patients by asking 14 questions examining mental and physical signs. A score of 0-7 shows non-existence of anxiety, a score of 8-14 slight anxiety, 15-23 moderate anxiety, and scores of and over 23 severe anxiety.<sup>18</sup>

Data were entered to SPSS 22.0 package program. During data analysis, chi-square test was used for categorical variables, t test and Mann-Whitney U test for continuous variables and ANOVA test for inter-group comparisons. Pearson's correlation test was used to evaluate correlation of Hamilton depression and anxiety scores with other various data.  $p < 0.05$  value was regarded as limit of significance.

## RESULTS

Two hundred forty-seven individuals consisting of 169 males (68.4%) and 78 females (31.6%) were included in this study. Average age of the patients was  $39.01 \pm 11.38$  for the chronic hepatitis group,  $38.46 \pm 12.06$  for the chronic infection group and  $36.60 \pm 8.16$  for the control group. No significant difference was detected among these groups in terms of age, sex, marital status, education levels, as well as having a family history of a chronic HBV disease and a family history of cirrhosis due to hepatitis, and duration of disease. Their demographic characteristics were presented in Table 1.

When anxiety score was evaluated for patient groups, it was determined to be  $11.24 \pm 7.11$  in total and  $8.00 \pm 4.24$  for the control group with a statistically significant difference ( $p = 0.007$ ). It was  $13.68 \pm 7.03$  for the chronic infection group,  $9.01 \pm 6.45$  for the chronic hepatitis group and

**Table 1.** Sociodemographic features of the groups

|                      | Chronic hepatitis<br>% (n=103) | Chronic infection<br>% (n=94) | Control groups<br>% (n=50) | p     |
|----------------------|--------------------------------|-------------------------------|----------------------------|-------|
| Age                  | 39.01±11.38                    | 38.46±12.06                   | 36.60±8.16                 | 0.581 |
| Gender               |                                |                               |                            |       |
| Male                 | 72.8                           | 70.2                          | 56.0                       |       |
| Female               | 27.2                           | 29.8                          | 44.0                       |       |
| Marital status       |                                |                               |                            | 0.523 |
| Married              | 71.8                           | 72.3                          | 80.0                       |       |
| Single               | 28.2                           | 27.7                          | 20.0                       |       |
| Education            |                                |                               |                            | 0.099 |
| Primary school       | 29.1                           | 34.0                          | 14.0                       |       |
| Middle school        | 29.1                           | 19.1                          | 22.0                       |       |
| Collage              | 21.4                           | 25.5                          | 36.0                       |       |
| University           | 20.4                           | 21.3                          | 28.0                       |       |
| Family HBV history   |                                |                               |                            | 0.744 |
| Positive             | 57.3                           | 59.6                          |                            |       |
| Negative             | 42.7                           | 43.4                          |                            |       |
| Family HBV cirrhosis |                                |                               |                            | 0.452 |
| Positive             | 17.5                           | 19.1                          |                            |       |
| Negative             | 82.5                           | 80.9                          |                            |       |
| Duration of disease  | 10.59±6.10                     | 10.40±7.02                    |                            | 0.841 |

8.00±4.24 for the control group. Intergroup comparison revealed a statistically significant increase in HAM-A score between the chronic infection group on one side and the chronic hepatitis and the control groups on the other side ( $p<0.001$ ) (Table 2).

When depression score was evaluated for patient groups, it was determined to be 6.88±5.06 in total and 5.16±3.51 for the control group with a non-significant difference ( $p=0.060$ ). It was

8.46±5.44 for the chronic infection group, 5.28±4.16 for the chronic hepatitis group and 5.16±3.51 for the control group. Intergroup comparison revealed a statistically significant increase in depression score between the chronic infection group on one side and the chronic hepatitis and the control groups on the other side ( $p<0.001$ ). No statistically significant difference was detected among other groups for anxiety and depression scores ( $p>0.05$ ) (Table 2).

**Table 2.** The comparisons of HAM-A, HAM-D scores of the groups

|                     | Chronic hepatitis<br>Mean±SD | Chronic infection<br>Mean±SD | Control groups<br>Mean±SD | p      |
|---------------------|------------------------------|------------------------------|---------------------------|--------|
| Hamilton Anxiety    | 9.01±6.45                    | 13.68±7.03                   | 8.00±4.24                 | <0.001 |
| Hamilton Depression | 5.28±4.16                    | 8.46±5.44                    | 5.16±3.51                 | <0.001 |
| Hamilton Anxiety    | 11.24±7.11                   |                              | 8.00±4.24                 | 0.007  |
| Hamilton Depression | 6.88±5.06                    |                              | 5.16±3.51                 | 0.060  |

Anxiety and depression scores of women were found to be significantly higher than men (respectively,  $p=0.007$ ,  $p=0.001$ ). It was found that as education level decreases, both anxiety and depression scores increase significantly (respectively,  $p<0.001$ ,  $p=0.002$ ). For participants with a family history of chronic HBV disease due to cirrhosis, anxiety and depression scores were determined to be significantly high (respectively, **Anatolian Journal of Psychiatry 2019; 20(5):515-521**

$p=0.001$ ,  $p=0.023$ ). No significant relation was detected between marital status, family history of chronic HBV and duration of disease, and scores of anxiety and depression ( $p>0.05$ ).

When groups were compared as to anxiety and depression incidences and severity, it was found that incidence and severity thereof were significantly high in the chronic HBV infection group

**Table 3.** The comparisons of HAM-A, HAM-D severity of the groups

|                     | Chronic hepatitis<br>% (n=103) | Chronic infection<br>% (n=94) | Control groups<br>% (n=50) | p      |
|---------------------|--------------------------------|-------------------------------|----------------------------|--------|
| Hamilton Anxiety    |                                |                               |                            | <0.001 |
| None                | 50.5                           | 17.0                          | 56.0                       |        |
| Mild                | 33.0                           | 44.7                          | 40.0                       |        |
| Moderate            | 11.7                           | 25.5                          | 4.0                        |        |
| Severity            | 4.9                            | 12.8                          | 0.0                        |        |
| Hamilton Depression |                                |                               |                            | <0.001 |
| None                | 85.4                           | 46.8                          | 80.0                       |        |
| Mild                | 11.7                           | 42.6                          | 20.0                       |        |
| Moderate            | 1.9                            | 10.6                          | 0.0                        |        |
| Severity            | 1.0                            | 0.0                           | 0.0                        |        |

(respectively,  $p < 0.001$ ,  $p < 0.001$ ) (Table 3).

## DISCUSSION

Our study is the first of its kind comparing the patient group treated with oral antivirals against the untreated hepatitis group and the healthy control group. With respect thereto, it would be advantageous to re-emphasize some important results. Anxiety scores of the general patient group were significantly higher than the healthy control group. However, compared to the untreated group, both anxiety and depression scores of the chronic hepatitis group, i.e. the treatment group were significantly lower and close to the level measured for the healthy controls.

In a study conducted by Yigit et al.<sup>19</sup> in accordance with presence/absence of anxiety and depression through HAD scale, whereas no difference was detected for anxiety prevalence between chronic hepatitis B patient group and control group, but a significant difference was detected for depression. A population-based cohort study by Lee et al.<sup>20</sup> evaluated the relationship between chronic liver diseases and depression and compared data obtained from 46 of HBV patients against general population data of 9178 individuals and accordingly, reported that there was no significant relationship there between. In our study where the total patient group was compared to the control group in terms of anxiety and depression scores, anxiety score of the patient group was determined to be significantly higher; on the other hand, no significant difference was detected in depression score.

Altındağ et al.<sup>21</sup> compared life quality and depression levels of 30 individuals with chronic

hepatitis B and 30 hepatitis B carriers and 30 healthy controls. Authors found that in comparison to the controls, life quality of not only the chronic hepatitis patients, but also the carriers without any disease finding decreased and depression score measured according to Beck Depression Inventory increased. In this study, no difference was detected between the carriers and the patients; however, authors associated this finding with the small number of cases studied thereat. In a study conducted by Demir et al.<sup>22</sup> on 249 chronic hepatitis infection cases and 195 chronic hepatitis cases, it was found that depression and anxiety prevalences were significantly higher in the treatment group, i.e. the chronic hepatitis group. Authors reported that 65 of the participants of this study had an additional chronic disease, and 56 individuals in all groups previously received psychiatric treatment and also, in the chronic hepatitis group, 44 patients received interferon and 115 patients received oral antiviral treatment. In this study, the fact that some of the patients received psychiatric or interferon treatment, and had an accompanying additional chronic disease may have affected prevalences of anxiety and depression in the chronic hepatitis group. In the study conducted by Yigit et al.<sup>19</sup> on 100 hepatitis patients, 100 carriers and 100 healthy individuals serving as controls, no significant difference was detected between the hepatitis patients and carrier groups.

Distinction between chronic hepatitis and chronic HBV infection is important to determine whether the patient is a candidate for treatment or just a follow-up patient not requiring treatment. All kinds of treatments mainly aim to regulate necro-inflammation in liver by assuring long term suppression of HBV-DNA level and inhibit progress

of fibrosis and also, decrease hepatocellular carcinoma risk. Different drugs are used in treatment of chronic HBV infection. The main object of such treatment is to improve life quality and lifespan of patients.<sup>5</sup> Neuropsychiatric complications associated with interferon alpha are being known since 1980. These complications frequently lead to termination of treatment. Interferon alpha causes cognitive, behavioral and effective disorders, resulting in major depressive disorder, impairment in memory, difficulty in concentration, decreased attention and anxiety.<sup>23,24</sup> No side effects are reported in literature evidencing that use of entecavir (ETV) and tenofovir disoproxil fumarate (TDF) in treatment causes anxiety and depression. On the contrary, in our study, the depression and anxiety scores being lower in antiviral treatment group as regards the group treated for chronic infection may be construed as a result of therapeutic effect of antiviral agents on hepatitis. But beyond that, it may also be a reflection of direct effect of known immunological impacts of inflammation on depression and anxiety in the etiology of which inflammation is known to play a significant role, and that is why this finding requires further studies on wider sampling groups.

In our study, when the chronic hepatitis and chronic infection groups categorized as patient group herein were compared among themselves and individually against the control group in terms of anxiety and depression scores, no significant difference was detected between the chronic hepatitis group and the control group. On the other hand, a significantly increased score both for anxiety and for depression in favor of the infection group was detected between the chronic infection and the control groups and also, between the chronic hepatitis and chronic infection groups. This finding was different from the results of previous studies performed up to this point of time. In two previous studies, prevalence of anxiety and depression was determined to be high in the chronic hepatitis group compared to the carrier group. This may be a result of inclusion in the patient groups thereof individuals with an additional chronic disease other than hepatitis and the fact that some patients of the treatment group previously received or continued to receive interferon during the course of study may have increased anxiety and depression ratios in the chronic hepatitis group. Since education level of the participants of our study is not very high in general, patients may tend to experience anxiety and depression as they are followed-up without any treatment despite having a serious

and potentially life-threatening disease. In a study conducted in Australia, it was found that lower academic education level among participants significantly increased their anxiety and worry about hepatitis B and this finding supports the meaningful correlation in our study between decreased education level and increased scores of anxiety and depression.<sup>25</sup> In addition, chronic viral infection may produce changes causing depressive symptoms in immune system and accordingly, antiviral treatment may suppress such symptoms.

With respect to the relationship between sex and depression in patients with hepatitis, it was seen that depression is high in women independently of other factors.<sup>20</sup> Çelik et al.<sup>26</sup> reported that anxiety and depression scores were high in women. In accordance with literature, anxiety and depression scores of women were significantly higher than men in our study (respectively,  $p=0.001$  and  $p=0.007$ ).

Losses due to hepatitis and other chronic diseases within family significantly decrease the life quality of individuals and increase their tendency to psychiatric disorders.<sup>27</sup> As a result of a study conducted on chronic hepatitis C patients, Evon et al.<sup>9</sup> reported that incidences of accompanying diseases increase the risk of depression. In our study, anxiety and depression scores of patients without a family history of cirrhosis due to hepatitis were determined to be lower than those with a family history, and this difference was considered to be statistically significant not only for anxiety score, but also for depression score (respectively,  $p=0.001$  and  $p=0.023$ ).

Included in this study were patients receiving antiviral treatment (entecavir and tenofovir) and patients unfit for treatment and healthy volunteers (control group). The fact that there was no patient receiving pegileinterferon causing anxiety and depression side effects, and that depression and anxiety were not indicated as side effects of entecavir and tenofovir molecules suggests that results of this study are not the side effects of a drug. Thus, it may be considered that the study results are suggestive of both the nature of underlying disease, and the positive reflections of being cognizant of treatment.

Consequently, in our study, the depression and anxiety scores being lower in antiviral treatment group as regards the group treated for chronic infection may be construed as a result of therapeutic effect of antiviral agents on hepatitis. But beyond that, it may also be a reflection of direct

effect of known immunological impacts of inflammation on depression and anxiety in the etiology of which inflammation is known to play a significant role, and that is why this finding requires further studies on wider sampling groups.

**Authors' contributions:** G.E.K.: concept, design, materials, data collection and/or processing, analysis and/or interpretation, writing, critical reviews; M.A.: design, analysis and/or interpretation, critical reviews.

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