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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