International Journal of Medical Science and Clinical Invention 10(11): 6951-6955, 2023
DOI:10.18535/ijmsci/v10i11.01
https://valleyinternational.net/index.php/ijmsci

Original Article,

The Analysis of the Correlations between Quantitative HBsAG Level, Virological Markers, and Histopathological Findings in Patients with Chronic Hepatitis B

Özcan Deveci[1] Çiğdem Mermutluoğlu[2], Muhammed Bekcibaşı[3], Serkan Cerrah[4], Alicem Tekin[5], Mustafa Kemal Çelen[2]

[1] Genesis Hospital, Department of Infectious Diseases and Clinical Microbiology, Diyarbakır, Turkey
[2]Dicle University Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, Diyarbakir, Turkey
[3]Health SciencesUniversity, Gazi Yaşargil Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Diyarbakir, Turkey
[4]Health Sciences University, Erzurum Regional Training and Research Hospital, Department of Gastroenterology, Erzurum, Turkey
[5] Health SciencesUniversity, Gazi Yaşargil Training and Research Hospital, Department of Medical Microbiology, Diyarbakir, Turkey
E-mailAddress: ozcandeveci1@hotmail.com

Abstract:

Introduction: We aimedto analyze the correlations between serum HBsAg quantification (qHBsAg) level and virological properties in chronic hepatitis B (CHB) patients.
Materials and Methods: The study was conducted with 53 CHB patients who underwent liver biopsy. Demographic characteristics of patients, biochemical parameters, serum qHBsAg levels, liver biopsy, and histopathology were assessed retrospectively.
Results: A total of 53 patients were included in the study the mean patient age was 28,7 ± 8.1 and 34 (64.2%) were male. The mean patient qHBsAg was 631.4 ± 431.5, fibrosis score was 1,35 ± 0.87, ALT index score was 67.1 ± 53.4, and histologic activity index (HAI) score was 4,54 ± 1.55. In the statistical analysis, it was determined that there were negative correlations between the serum qHBsAg level and the HBV DNA level (r: -0,618, P<0.001), fibrosis score (r: -0,273, P: 0.048), ALT (rho: -0,489, P<0.001), and HAI index scores (r: -363, P: 0.008), while there was a positive correlation with the HBeAg positivity (rho: 0.445, p: 0.001).
Conclusion: There were negative correlations between the qHBsAg level and virological (HBV DNA level), histopathological (fibrosis score, HAI index) findings, and a positive correlation with serological (HBeAg positivity) findings.

Keywords: Quantitative, qHBsAg, Hepatitis B, Chronic hepatitis.

Introduction:

In the clinical prognosis in Chronic hepatitis B (CHB) patients, the follow-up of hepatitis B surface antigen (HBsAg), hepatitis B envelop antigen (HBeAg)seroconversion, Hepatitis B virus (HBV) DNA, and aminotransferase levels guide the physicians[1]. Early diagnosis of serious liver disease may improve the status of the disease even in patients who develop decompensation with treatment [2]. However, noninvasive tests are insufficient to determine liver disease to a certain level [3]. Thus, new diagnostic methods are required to diagnose liver fibrosis in the early period. Among these methods, there is a rising interest in the clinical determination of serum HBsAg quantification (qHBsAg) inrecent years due to the standardization of automatic systems [4,

[5]. A correlation was reported between the qHBsAg serum level and livercovalentlyclosedcircular (ccc) DNA [6]. As the understanding of the molecular virology of HBsAg has improved, it was suggested that serum HBsA gconcentration reflected the cccDNA content, which serves as the transcription pattern for the integrated viral genes in liver hepatocytes. It was reported that the measurement of the HBsAg concentration could be a beneficial marker in addition to HBV DNA level and HBeAg in HBV patients under Peginterferon or Nucleotide analog treatment [7, 8]. Thus, it was argued that it allows the prediction of the viral replication levels of circulation HBsAgconcentrations to determine disease activity and response to antiviral treatment[9]. In recent studies, it was reported that serum qHBsAg levels may be a good indicator in the evaluation of patient disease activity and response to interferon-based treatment in CHB, and there was a strong correlation between serum qHBsAgandHBV DNA levels [10, 11]In a study conducted by Tuaillon et al.,it was observed that there was a weak correlation between qHBsAg and HBV DNA levels [12].

The present study aimed to analyze the correlations between serum qHBsAglevel and virological properties in CHB patients.

Material and method:

CHB patients who underwent liver biopsy at xxxxxxUniversity Faculty of Medicine, Infectious Diseases and Clinical Microbiology Clinicin 2011-2013were included in this retrospective study.

Inclusion criteria

1) Presence of serum HBsAg for more than 6 months
2) Alanine aminotransferase (ALT) values greater than 1.5 times the normal value (normally, the ALT value is below 40 IU/mL)
3) HBV-DNA value ≥100,000 copies/mL (20,000 IU/mL) in those positive for the HBeAg(HBeAg-positive)
4) In those who are HBeAg-negative ≥10,000 copies/mL (2,000 IU/mL)

Exclusion criteria

1) Patients younger than 18 years of age
2) Patients with diabetes mellitus, liver cirrhosis, hepatocellular carcinoma, hypertension, coronary arterial disease, chronic obstructive pulmonary disease, malignancy, morbid obesity, liver and kidney failure, and pregnancy

The age, gender, HBsAg, HBeAg status, ALT, aspartate aminotransferase (AST), HBV-DNA, qHBsAgvalues, histologic activity index (HAI), and fibrosis scores of the patients were recorded.

xxxxxxUniversity Medical Faculty Ethics CommitteeforNoninterventional Studies approved this study. (Date: 2016, Decision No:243)

Hepatitis serological markers (HBsAg, Anti-HBs, HBeAg, Anti-HBe, anti-HDV), complete blood count, biochemical tests (ALT, AST, alkaline phosphatase, gamma-glutamyltransferase, albumin, globulin, total bilirubin, prothrombin time and alpha-fetoprotein), HBV DNA and qHBsAg were studied in samples taken during routine outpatient follow-up.

The patient serums were obtained and stored at -80^0C. After the DNAs were isolated with AmplipPrep Total Nucleic Acid Isolation Kit, the DNA level was determined with the COBAS® Amplip / Cobas® Taqman® HBV test V2.0 for HBV. The patient's HBV DNA levels were recorded as IU / ml. HBsAg quantitation was studied with the Modular E170 assay which is a two-step sandwich chemiluminescentmicroparticle immunoassay (Roche Diagnostics, Meylan, France).

Statistical analyses were performedusingthe SPSS version24.0 (Statistical Package for Social Science, Chicago, IL, USA).Inthecomparison of independentgroups, ifthenumericalvariablesshow normal distribution, theindependent t test; If normal distributioncould not be achieved, the Mann-Whitney U test wasused. In the correlation analysis, the Pearson correlation test (r) wasused for normally distributednumericalparameters, and Spearman'sRho test (rho) wasused for the analysis of categoricalandnon-normally distributed data.

Table 1. Baseline Characteristics of the 53 Patients Included in the Study

Characteristics	Total patients (n=53)
Age (years)	**28.7 ± 8.1**
Sex, male (%)	**19 (35.8 %)**
ALT (U/L)	**67.1 ± 53.4**
AST (U/L)	**41.3 ± 32.3**
HBeAg (+)	**23 (43.4 %)**
Anti-Hbe (+)	**30 (56.6 %)**
qHBsAg (U/L)	**631.4 ± 431.5**

Results:

The study was conducted with 53 patients. Most of the patients were men 34 (64.2%), and the mean patient age was 28,7 ± 8.1 years. The mean patient qHBsAgwas631.4 ± 431.5, fibrosis score was 1,35 ± 0.87, ALT index score was 67.1 ± 53.4, and HAI index score was 4,54 ± 1.55. The baseline characteristics of the study patients are listed in Table 1.

In the statistical analysis, it was determined that there were negative correlations between the serum qHBsAg level and the HBV DNA level (r: -0,618, P<0.001), fibrosis score (r: -0,273, P: 0.048), ALT (rho: -0,489, P<0.001), and HAI index scores (r: -363, P: 0.008), while there was a positive correlation with the HBeAg positivity (rho: 0.445, p: 0.001). Serum qHBsAg levels were found to be significantly high in HBeAg‑negative CHB patients compared with the HBeAg‑positive CHB patients (P: 0.001)

Discussion:

HBsAg is secreted from hepatocytes in the HBeAg-positive and HBeAg-negative phases of disease and can be copied and translated from different sources of the viral genome. Therefore, the quantification of serum HBsAg has gained wide interest in the last decades [13].

qHBsAg levels were recently used to monitor the prognosis or treatment of CHB infection [14]. However, molecular tests are more important in monitoring HBV-DNA-positive patients with no identifiable qHBsAg levels [15].In a previous study; it was observed that the qHBsAg level was effective in the evaluation of different CHB phases. It was reported that it could help the differentiation of immune tolerance and immune scavenging in HBeAg-positive patients. In HBeAg-negative patients, it was reported that there was a statistically significant correlation between qHBsAg and HBV DNA in CHB patients and spontaneous serum HBsAglosing and inactive disease could be estimated[8]. A statistically significant correlation was reported between quantitative qHBsAg and HBV DNA levels in a study conducted on elderly CHB carriers followed up for five years.[7].

In a limited number of population studies, it has been shown that qHBsAg measurement correlates with HBV DNA and may be a suitable marker for monitoring the effectiveness of HBV treatment [16].Studies with a larger number of patients, it has been shown that the qHBsAg level could be used to differentiate inactive and active hepatitis B patientsandsince the use of qHBsAg tests are less costly in laboratories where molecular tests cannot be applied, it has been suggested as a more appropriate approach in CHB treatment monitoring[17, 18]. In the present study, a negative correlation was determined between qHBsAg and HBV DNA levels and a significant positive correlation between HBeAg positivity and qHBsAg level.

There are certain studies where a stronger negative correlation was reported between qHBsAg level and fibrosis stage in HBeAg-positive and CHB patients[19, 20].Our study confirms the negative correlation between qHBsAg levels and the fibrosis stage from previously reported studies. On the contrary, some studies reported that a positive correlation was found between qHBsAg and HBV DNA, ALT, HAI score, fibrosis score[21, 22].

In conclusion, we found negative correlations between the qHBsAg level and HBV DNA level, fibrosis score, and HAI, and a positive correlation with HBeAg positivity. Most of the studies reported different results about the correlations between qHBsAg level and virological markers and histopathological findings.However, these potential benefits of HBsAg quantification are suitable for only limited populations. Larger-scale studies are required to standardize these findings.

References:

[1] Valsamakis A. Molecular testing in the diagnosis and management of chronic hepatitis B. Clin Microbiol Rev. 2007: 426 [PMID: 17630333 10.1128/CMR.00009-07: 10.1128/CMR.00009-07]

[2] Srivastava M, Rungta S, Dixit VK, Shukla SK, Singh TB, Jain AK. Predictors of survival in hepatitis B virus related decompensated cirrhosis on tenofovir therapy: an Indian perspective. Antiviral Res. 2013: 300 [PMID: 24012998 10.1016/j.antiviral.2013.08.020: 10.1016/j.antiviral.2013.08.020]

[3] Sanai FM, Babatin MA, Bzeizi KI, Alsohaibani F, Al-Hamoudi W, Alsaad KO, et al. Accuracy of international guidelines for identifying significant fibrosis in hepatitis B e antigen--negative patients with chronic hepatitis. Clin Gastroenterol Hepatol. 2013: 1493 [PMID: 23811251 10.1016/j.cgh.2013.05.038: 10.1016/j.cgh.2013.05.038]

[4] Chan HL, Thompson A, Martinot-Peignoux M, Piratvisuth T, Cornberg M, Brunetto MR, et al. Hepatitis B surface antigen quantification: why and how to use it in 2011 - a core group report. J Hepatol. 2011: 1121 [PMID: 21718667 10.1016/j.jhep.2011.06.006: 10.1016/j.jhep.2011.06.006]

[5] Nguyen T, Desmond P, Locarnini S. The role of quantitative hepatitis B serology in the natural history and management of chronic hepatitis B. Hepatol Int. 2009: 5 [PMID: 19763714 10.1007/s12072-009-9149-7: 10.1007/s12072-009-9149-7]

[6] Chan HL, Wong VW, Tse AM, Tse CH, Chim AM, Chan HY, et al. Serum hepatitis B surface antigen quantitation can reflect hepatitis B virus in the liver and predict treatment response. Clin Gastroenterol Hepatol. 2007: 1462 [PMID: 18054753 10.1016/j.cgh.2007.09.005: 10.1016/j.cgh.2007.09.005]

[7] Kuo YH, Chang KC, Wang JH, Tsai PS, Hung SF, Hung CH, et al. Changing serum levels of quantitative hepatitis B surface antigen and hepatitis B virus DNA in hepatitis B virus surface antigen carriers: a follow-up study of an elderly cohort. Kaohsiung J Med Sci. 2015: 102 [PMID: 25645989 10.1016/j.kjms.2014.11.002: 10.1016/j.kjms.2014.11.002]

[8] Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HLA, Chan HL. The role of quantitative hepatitis B surface antigen revisited. J Hepatol. 2017: 398 [PMID: 27575311 10.1016/j.jhep.2016.08.009: 10.1016/j.jhep.2016.08.009]

[9] Wong GL, Chan HL. Use of quantitative hepatitis B surface antigen with hepatitis B virus DNA in clinical practice. Clin Liver Dis (Hoboken). 2013: 8 [PMID: 30992811 10.1002/cld.165: 10.1002/cld.165]

[10] Rijckborst V, Hansen BE, Cakaloglu Y, Ferenci P, Tabak F, Akdogan M, et al. Early on-treatment prediction of response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B using HBsAg and HBV DNA levels. Hepatology. 2010: 454 [PMID: 20683945 10.1002/hep.23722: 10.1002/hep.23722]

[11] Sonneveld MJ, Rijckborst V, Boucher CA, Hansen BE, Janssen HL. Prediction of sustained response to peginterferon alfa-2b for hepatitis B e antigen-positive chronic hepatitis B using on-treatment hepatitis B surface antigen decline. Hepatology. 2010: 1251 [PMID: 20830787 10.1002/hep.23844: 10.1002/hep.23844]

[12] 12. Tuaillon E, Mondain AM, Nagot N, Ottomani L, Kania D, Nogue E, et al. Comparison of serum HBsAg quantitation by four immunoassays, and relationships of HBsAg level with HBV replication and HBV genotypes. PLoS One. 2012: e32143 [PMID: 22403628 10.1371/journal.pone.0032143: 10.1371/journal.pone.0032143]

[13] Mak LY, Seto WK, Fung J, Yuen MF. Use of HBsAg quantification in the natural history and treatment of chronic hepatitis B. Hepatol Int. 2020: 35 [PMID: 31745711 10.1007/s12072-019-09998-5: 10.1007/s12072-019-09998-5]

[14] 14. Zeng DW, Zhu YY, Huang Q, Zhang JM, Wu YL, Dong J, et al. Hepatitis B surface antigen in late hepatitis B infection. J Med Virol. 2015: 380 [PMID: 25604455 10.1002/jmv.24078: 10.1002/jmv.24078]

[15] Liu YP, Yao CY. Rapid and quantitative detection of hepatitis B virus. World J Gastroenterol. 2015: 11954 [PMID:

26576084 10.3748/wjg.v21.i42.11954: 10.3748/wjg.v21.i42.11954]

[16] Ozaras R, Tabak F, Tahan V, Ozturk R, Akin H, Mert A, et al. Correlation of quantitative assay of HBsAg and HBV DNA levels during chronic HBV treatment. Dig Dis Sci. 2008: 2995 [PMID: 18409002 10.1007/s10620-008-0263-5: 10.1007/s10620-008-0263-5]

[17] Ülger Tezcan S, Delialioğlu N, Kandemir Ö, Ovla Çelikcan H. Quantitative Determination of HBsAg Levels in Chronically Infected Patients with Hepatitis B Virus. Türk Mikrobiyol Cem Derg. 2018: 60

[18] Gunal O, Barut S, Etikan I, Duygu F, Tuncel U, Sunbul M. Relation between serum quantitative HBsAg, ALT and HBV DNA levels in HBeAg negative chronic HBV infection. Turk J Gastroenterol. 2014: 142 [PMID: 25910293 10.5152/tjg.2014.5711: 10.5152/tjg.2014.5711]

[19] Martinot-Peignoux M, Carvalho-Filho R, Lapalus M, Netto-Cardoso AC, Lada O, Batrla R, et al. Hepatitis B surface antigen serum level is associated with fibrosis severity in treatment-naive, e antigen-positive patients. J Hepatol. 2013: 1089 [PMID: 23369792 10.1016/j.jhep.2013.01.028: 10.1016/j.jhep.2013.01.028]

[20] Marcellin P, Martinot-Peignoux M, Asselah T, Batrla R, Messinger D, Rothe V, et al.Serum Levels of Hepatitis B Surface Antigen Predict Severity of Fibrosis in Patients With E Antigen-Positive Chronic Hepatitis B. Clin Gastroenterol Hepatol. 2015: 1532 [PMID: 25542306 10.1016/j.cgh.2014.12.017: 10.1016/j.cgh.2014.12.017]

[21] Balkan A, Namiduru M, Balkan Y, Mete AO, Karaoglan I, Bosnak VK. Are serum quantitative hepatitis b surface antigen levels, liver histopathology and viral loads related in chronic hepatitis b-infected patients? Saudi J Gastroenterol. 2016: 208 [PMID: 27184639 10.4103/1319-3767.182454: 10.4103/1319-3767.182454]

[22] Yildiz Kaya S, Mete B, Kaya A, Balkan, II, Saltoglu N, Tabak OF. The role of quantitative HBsAg in patients with HBV DNA between 2000-20,000 IU/ml. Wien Klin Wochenschr. 2021: 647 [PMID: 33914152 10.1007/s00508-021-01854-7: 10.1007/s00508-021-01854-7]