ORIGINAL ARTICLE VIROLOGY

Quantitative hepatitis B core antibody levels in the natural history of hepatitis B virus infection

L.-W. Song[1], P.-G. Liu[3], C.-J. Liu[4], T.-Y. Zhang[1], X.-D. Cheng[5], H.-L. Wu[4], H.-C. Yang[4], X.-K. Hao[5], Q. Yuan[1,2], J. Zhang[1,2], J.-H. Kao[4], D.-S. Chen[4], P.-J. Chen[4] and N.-S. Xia[1,2]

1) *National Institute of Diagnostics and Vaccine Development in Infectious Diseases, State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Life Sciences,* 2) *School of Public Health, Xiamen University,* 3) *Zhongshan Hospital, Medical College of Xiamen University, Xiamen, China,* 4) *National Taiwan University College of Medicine, National Taiwan University, Taipei, Taiwan and* 5) *Center of Clinical Laboratory Medicine of PLA, Xijing Hospital, Fourth Military Medical University, Xi'an, China*

Abstract

We previously demonstrated that pretreatment quantitative anti–hepatitis B core protein (qAnti-HBc) levels can predict the treatment response for both interferon and nucleoside analogue therapy, but the characteristics of qAnti-HBc during chronic hepatitis B virus (HBV) infection remain poorly understood. To understand this issue, the qAnti-HBc levels were evaluated in individuals with past HBV infection, occult HBV infection and chronic HBV infection in the immune tolerance phase, immune clearance phase, low-replicative phase and hepatitis B e antigen (HBeAg)-negative hepatitis phase. Individuals with hepatitis B surface antigen (n = 598, 3.74 ± 0.90 $\log_{10}$ IU/mL) had significantly higher ($p < 0.001$, approximately 1000-fold) serum qAnti-HBc levels than those who had occult HBV, and serum qAnti-HBc levels were significantly higher in the occult HBV group than in the past HBV infection group ($p < 0.001$). qAnti-HBc levels were positively correlated with alanine aminotransferase levels ($R = 0.663$, $p < 0.001$), and subjects with an abnormal alanine aminotransferase level had a higher qAnti-HBc level ($p < 0.001$). Serum qAnti-HBc level varied in different phases of HBV infection, as determined by host immune status. Serum qAnti-HBc level is strongly associated with hepatitis activity in subjects with chronic HBV infection.

Keywords: Chronic hepatitis B (CHB), hepatitis activity, host immune status, natural history of CHB, quantitative anti-HBc
Original Submission: 4 May 2014; **Revised Submission:** 17 July 2014; **Accepted:** 5 October 2014
Editor: G. Antonelli
Article published online: 29 October 2014

Corresponding authors: Q. Yuan and N.-S. Xia, National Institute of Diagnostics and Vaccine Development in Infectious Diseases, Xiamen University, China
Corresponding author: P.-J. Chen, Graduate Institute of Clinical Medicine and Department of Internal Medicine, National Taiwan University College of Medicine, Taiwan
E-mails: yuanquan@xmu.edu.cn **(Q. Yuan),** peijerchen@ntu.edu.tw **(P.-J. Chen),** nsxia@xmu.edu.cn **(N.-S. Xia)**
The first two authors contributed equally to this article, and both should be considered first author

Introduction

The natural history of hepatitis B virus (HBV) infection is variable and complex. Chronic HBV infection (CHB) can typically be divided into four phases on the basis of the characteristics of the host immune response and the virus: the immune tolerance phase (IT), the immune clearance phase (IC), the low-replicative phase (LR) and the hepatitis B e antigen (HBeAg)-negative hepatitis (ENH) phase [1,2]. Knowledge of the natural history of HBV infection is essential for the improvement of the clinical management of HBV-related liver disease and for a better understanding of the underlying pathogenic mechanisms of HBV infection. Several studies have examined the use of

http://dx.doi.org/10.1016/j.cmi.2014.10.002

novel quantitative assays for classical serologic HBV markers as tools for the prediction of treatment response and disease progression, such as quantitative hepatitis B surface antigen (HBsAg) and HBeAg [3–7]. However, practical biomarkers and assays that can be used to characterize host immune readiness against HBV remain lacking.

Hepatitis B core protein antibody (Anti-HBc) is a classical serologic HBV marker that has been clinically used for more than 35 years [8]. However, the clinical significance of quantitative anti-HBc (qAnti-HBc) measurements has not been carefully investigated. With a novel double-sandwich anti-HBc quantitative immunoassay [9], we recently demonstrated that the pretreatment anti-HBc level is a potential new predictor for treatment response in both adefovir dipivoxil and peginterferon therapy [10], and it is the strongest predictor for 2-year HBeAg seroconversion in HBeAg-positive subjects treated with telbivudine alone or in combination with adefovir [11]. This new finding highlights the prognostic value of the qAnti-HBc level in CHB subjects. However, the profiles and the dynamics of the anti-HBc level during the natural course of HBV infection are still largely unknown.

Methods

Subjects and cohorts

A cross-sectional cohort consisting of three groups was studied. The first group included samples from 535 healthy individuals with serologic evidence of past HBV infection (PBI) collected from the Xiamen Blood Service. All PBI individuals were HBsAg negative, HBV DNA negative and Anti-HBc positive, and had alanine aminotransferase (ALT) values less than the upper limit of normal. The second group included 56 blood donors with occult HBV infection (OBI) who were anti-HBc positive, HBsAg negative and HBV DNA positive, and who were part of a previously described OBI cohort (n = 61) identified from 38 499 blood donors by nucleic acid testing [12]. The third group included a total of 598 subjects with CHB, 316 of whom were from Zhongshan Hospital (Xiamen, China) and 282 of whom were from Xijing Hospital (Xi'an, China). All subjects were positive for HBsAg over a 6-month period; were negative for anti–human immunodeficiency virus, anti–hepatitis C virus, anti–hepatitis D virus and other markers of coexistent autoimmune or metabolic liver disease; and were treatment naïve or had a treatment-free interval of >1 year at the time of enrollment. All the subjects with evidence of liver cirrhosis were excluded. Enrolled subjects were categorized by phase of CHB infection on the basis of the guidelines for the management of CHB [1]: 108 subjects were in the IT phase (HBeAg-positive with a high virus load (>5 × 10^7 IU/mL) and persistently normal ALT); 209 were in the IC phase (HBeAg positive with an elevated ALT and a virus load >2000 IU/mL); 148 were in the LR phase (HBeAg-negative with inactive viral replication (virus load <2000 IU/mL) and persistently normal ALT); and 133 were in the ENH phase (HBeAg negative with active viral replication (virus load >2000 IU/mL) and elevated ALT).

The upper limit of normal of ALT was 40 U/L in this study. Subjects in the IT group or the LR group had persistently normal ALT for 6 months before enrollment. Forty-eight subjects in the IC and ENH phases underwent liver biopsy, and none presented evidence of liver cirrhosis. Plasma samples were stored at −20°C until tested. The study was approved by the institutional review board of Xijing Hospital of PLA and Zhongshan Hospital in accordance with the Declaration of Helsinki.

Laboratory measurements

The serum qAnti-HBc level was measured using a newly developed double-sandwich immunoassay (dynamic range 0.08–2.5 IU/mL; Wantai, China), which was calibrated using the World Health Organisation (WHO) standard (NIBSC, UK) [13] (Supplementary Fig. S1). The samples were tested at dilutions of 1:10 to 1:100 000 (10-fold increase) if the Anti-HBc level was >2.5 IU/mL. The HBsAg level was measured using a microplate chemiluminescent assay (WTultra; dynamic range 0.02–100 IU/mL; Wantai, China) calibrated using the WHO HBsAg standard. The samples were tested at dilutions of 1:500 and 1:5000 if the HBsAg was >100 IU/mL. HBeAg, anti-HBe and anti-HBs were detected by Architect assays (Abbott Laboratories). The serum HBV DNA level and the virus genotype were determined as previously described [14].

Statistical analysis

The unpaired t test and a Kruskal-Wallis analysis of variance were used to compare continuous variables, and the Mantel-Haenszel χ^2 test or Fisher's exact test was used for categorical variables. Linear regression models and Spearman's rho tests were used for correlation analyses. Receiver operating characteristic (ROC) curves and areas under the ROC (AUROC) curves were used to determine diagnostic accuracy. Differences were considered significant at a two-tailed $p < 0.05$. SPSS software, v17.0, was used for all statistical analyses.

Results

Anti-HBc levels in subjects during different phases of HBV infection

The characteristics of the individuals in the cross-sectional cohort according to the phases of HBV infection are

presented in Table 1. As shown in Fig. 1(a), HBsAg-positive individuals (CHB group, n = 598, 3.74 ± 0.90 $\log_{10}$ IU/mL) had significantly higher (p < 0.001, approximately 1000-fold) serum qAnti-HBc levels than those who were HBsAg negative in both the OBI and PBI groups. ROC analysis was performed to discriminate HBsAg status by anti-HBc level among all cases (AUROC = 0.991, 95% confidence interval 0.986–0.995, p < 0.001, Fig. 1(b)), and the optimal cutoff was 89 IU/mL, with a sensitivity of 95.8% and a specificity of 98.0%. Interestingly, the OBI group (1.02 ± 0.76 $\log_{10}$ IU/mL) presented a significantly higher (p < 0.0001, Fig. 1(a)) average qAnti-HBc than the PBI group (0.40 ± 0.62 $\log_{10}$ IU/mL). The AUROC of qAnti-HBc for the diagnosis of OBI among HBsAg-negative individuals was 0.723 (95% confidence interval 0.651–0.795, p < 0.001), and the optimal cutoff was 6.6 IU/mL, with a sensitivity of 60.7% and a specificity of 75.3% (Fig. 1(c)).

Among CHB subjects, the qAnti-HBc levels varied significantly and were widely distributed among different phases of infection (Fig. 1(a)). The mean levels of qAnti-HBc were 3.03 ± 1.04 $\log_{10}$ IU/mL for IT subjects (median 1996 IU/mL, range 1–26 980 IU/mL), 4.19 ± 0.62 $\log_{10}$ IU/mL for IC subjects (median 20 553 IU/mL, range 131–177 680 IU/mL), 3.17 ± 0.70 $\log_{10}$ IU/mL for LR subjects (median 1997 IU/mL, range 8–34 744 IU/mL) and 4.27 ± 0.54 $\log_{10}$ IU/mL for ENH subjects (median 21 852 IU/mL, range 96–174 960 IU/mL). The mean Anti-HBc levels in the IC and ENH subjects were approximately 10-fold higher (p < 0.001) than those in both the IT and LR subjects, whereas there was no significant difference in the anti-HBc level between IT and LR subjects (p 0.20) or between IC and ENH subjects (p 0.22).

No significant difference (p > 0.05) was observed between men and women in each phase (Supplementary Fig. S2). Upon virus genotyping (Supplementary Fig. S3), subjects infected with HBV genotype B had significantly higher qAnti-HBc levels than genotype C in the IT (p 0.02) and IC (p < 0.001) phases, while it is significantly lower in LR phase (p < 0.001). However, there was no significant difference (p 0.66) in ENH subjects. Among HBsAg-negative subjects (Supplementary Fig. S4), the qAnti-HBc levels seems to be higher in Anti-HBsAg-positive individuals in the PBI (n = 381) and OBI (n = 16) groups, but no statistical significance was observed (PBI p 0.06; OBI p 0.19). In 31 subjects, we observed S-region mutants in the OBI group (Supplementary Table 1), whereas no significant difference was presented in qAnti-HBc levels between individuals with or without mutation (p 0.35, Supplementary Fig. S4).

Correlation of qAnti-HBc with ALT in CHB subjects

Among all CHB subjects, univariate analysis (Table 2) revealed that the qAnti-HBc level was strongly correlated with the levels of ALT (R = 0.663, p < 0.001), aspartate aminotransferase (AST) (R = 0.687, p < 0.001) and total bilirubin (R = 0.439, p < 0.001); slightly correlated with age (R = 0.097, p 0.017) and HBV DNA (R = 0.139, p 0.001); and not correlated with HBsAg levels (R = −0.058, p 0.155). Multivariate regression analysis (Table 2) revealed that the only independent factors associated with qAnti-HBc were subjects' ALT (β = 0.557, p < 0.001) and AST (β = 0.286, p < 0.001). The correlation between the qAnti-HBc level and the ALT level was significant in both men (R = 0.654, p < 0.001) and women (R = 0.628, p < 0.001), in both genotype B (R = 0.675, p < 0.001) and genotype C (R = 0.606, p < 0.001), and in both HBeAg-positive (R = 0.623, p < 0.001) and HBeAg-negative subjects (R = 0.679, p < 0.001).

The correlation between qAnti-HBc and ALT was further analysed (Fig. 2(a)). The average anti-HBc level successively

TABLE 1. Baseline characteristics of the cross-sectional cohort according to CHB phase

Characteristic	HBsAg negative individuals		HBsAg positive (CHB)				p
	Past HBV infection (n = 535)	Occult HBV infection (n = 56)	Immune tolerance (n = 108)	Immune clearance (n = 209)	Low replicative (n = 148)	HBeAg-negative hepatitis (n = 133)	
Age, years, median (range)	36 (1–55)	31 (19–54)	22 (4–54)	30 (10–68)	37 (4–75)	41 (14–82)	<0.001
Sex, M/F	204/331	40/16	59/49	170/38	86/62	103/30	<0.001
Genotype, B/C[a]	UD	20/36	52/56	93/115	53/60	63/66	0.53
HBeAg positive, n (%)	0	0	108 (100)	209 (100)	0	0	<0.001
Anti-HBe positive, n (%)	160 (29.9)	30 (53.5)	0	19 (9.0)	132 (89.2)	107 (80.5)	<0.001
ALT, U/L, median (range)	14 (6–40)	21 (6–46)	26 (12–39)	152 (40–3525)	21 (8–39)	238 (41–4093)	<0.001
AST, U/L, median (range)	ND	ND	22 (12–37)	94 (22–2261)	21 (9–46)	143 (27–2693)	<0.001
TBIL, μM, median (range)	ND	ND	12 (5–21)	19 (4–646)	12 (3–21)	23 (5–586)	<0.001
HBV DNA, Log_{10} IU/mL, mean ± SD[b]	UD	1.70 ± 0.84	8.42 ± 0.58	6.92 ± 1.52	2.67 ± 0.60	5.32 ± 1.57	<0.001
HBsAg, Log_{10} IU/mL, mean ± SD	UD	UD	4.85 ± 0.46	4.14 ± 0.95	2.88 ± 1.10	3.31 ± 1.04	<0.001
Anti-HBc, Log_{10} IU/mL, mean ± SD	0.40 ± 0.62	1.02 ± 0.76	3.03 ± 1.04	4.19 ± 0.62	3.17 ± 0.70	4.27 ± 0.54	<0.001

CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; ND, no data; UD, undetectable; AST, aspartate aminotransferase; TBIL, total bilirubin; HBc, hepatitis B core protein; IC, immune clearance phase; LR, low-replicative phase; ENH, HBeAg-negative hepatitis phase.
[a]Due to the limit of low virus load, the virus genotype was unable to be determined in 1 IC subject, 35 LR subjects and 3 ENH subjects. Only 1 ENH subject was determined to be infected with HBV genotype D; no other genotype was observed.
[b]Two subjects had a virus load of $<10^7$ but $>10^6$ IU/mL with normal ALT was included in the IT group when the subjects had no subsequent DNA decrease or ALT elevation within the next 3 months. Four subjects with a virus load of >2000 IU/mL but <3000 IU/mL with persistent normal ALT were included in the LR group. Four subjects with a virus load of <2000 IU/mL but >1000 IU/mL with persistent ALT elevation were included in the IC (n = 1) or ENH (n = 3) group according to their HBeAg status.

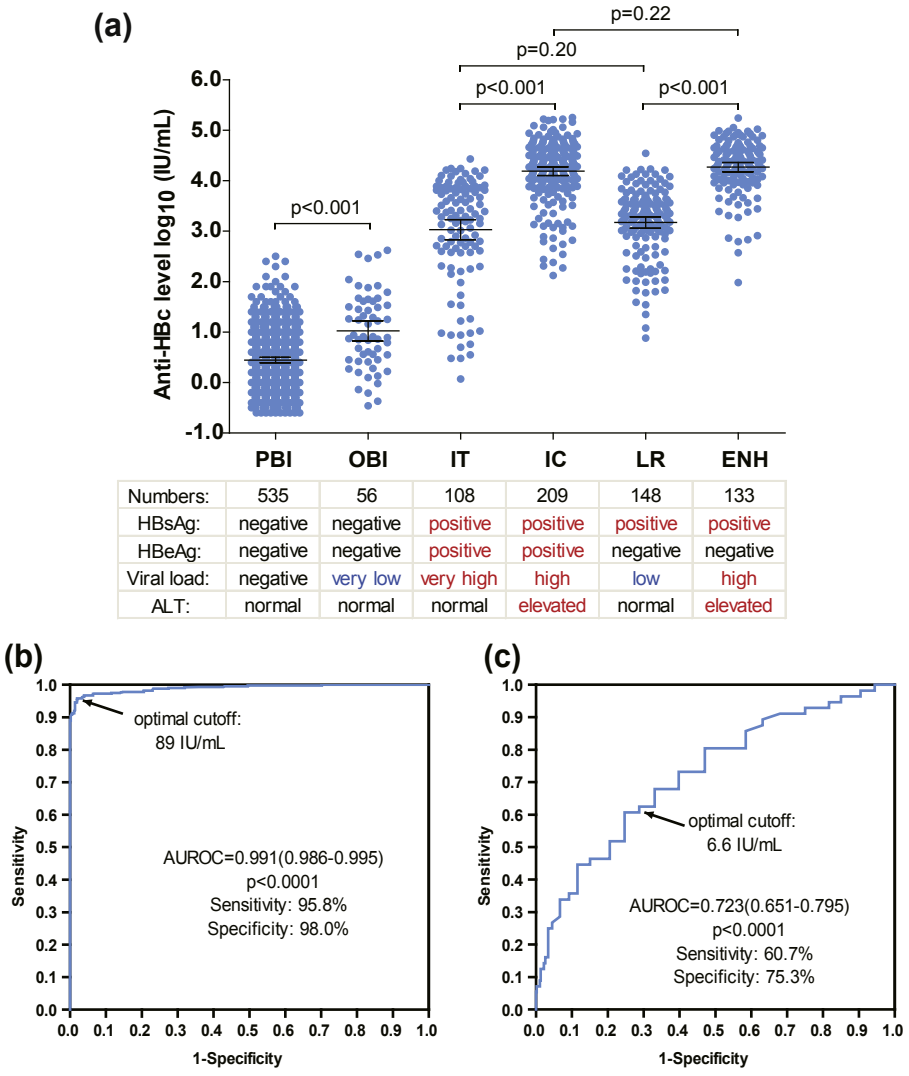

FIG. 1. Distribution of serum anti-HBc levels during different phases of HBV infection. (a) Distribution of serum anti-HBc levels during different phases of HBV infection. Bars represent the mean with a 95% confidence interval. PBI, past hepatitis B virus infection (n = 535); OBI, occult HBV infection (n = 56); IT, immune tolerance phase (n = 108); IC, immune clearance phase (n = 209); LR, low-replicative phase (n = 148); ENH, HBeAg-negative hepatitis phase (n = 133). Receiver operating characteristic analyses of the qAnti-HBc to differentiate (b) HBsAg-positive individuals among all anti-HBc-positive subjects and (c) OBI individuals among HBsAg subjects.

increased (p_{trend} <0.001) with increasing ALT level among the subjects in the first 5 ALT strata (≤5 × the upper limit of normal (ULN)), and it reached a plateau (p 0.95) in the subjects with ALT >5 × ULN. When an ROC analysis was performed to discriminate the immunoactive phases (IC and ENH) on the basis of qAnti-HBc level (Fig. 2)(b), the AUROC was 0.887 (95% confidence interval 0.861–0.913, p < 0.001), and the optimal cutoff was 7820 IU/mL, with a sensitivity of 79.8% and a specificity of 85.2%.

TABLE 2. Correlation between anti-HBc levels of other quantitative parameters in CHB subjects

	Univariate analysis		Multivariate analysis	
Anti-HBc vs.:	***R***	**p**	**β**	**p**
Age (years)	0.097	0.017	0.047	0.169
HBsAg (log_{10} IU/mL)	−0.058	0.155	0.016	0.638
HBV DNA (log_{10} IU/mL)	0.139	0.001	−0.015	0.662
ALT, log_2 (U/L)	0.663	<0.001	0.557	<0.001
AST, log_2 (U/L)	0.687	<0.001	0.286	0.006
TBIL, log_2 (μM)	0.439	<0.001	0.013	0.766

HBc, hepatitis B core protein; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.

Correlations between the qAnti-HBc level and other clinical parameters in different CHB phases

As shown in Fig. 3, the qAnti-HBc level was positively associated with ALT and AST levels in all phases. The correlation of the qAnti-HBc level and AST was statistically significant in all phases (R value 0.212–0.381, p < 0.01), and the correlation with ALT was significant in the IT, IC and ENH phases (R value 0.277–0.314, p < 0.01) but not in the LR phase (R = 0.149, p 0.071). The correlation between qAnti-HBc and HBsAg was significantly inverse in both the IT (R = −0.268, p < 0.001) and IC (R = −0.297, p < 0.001) phases. Interestingly, it was positively

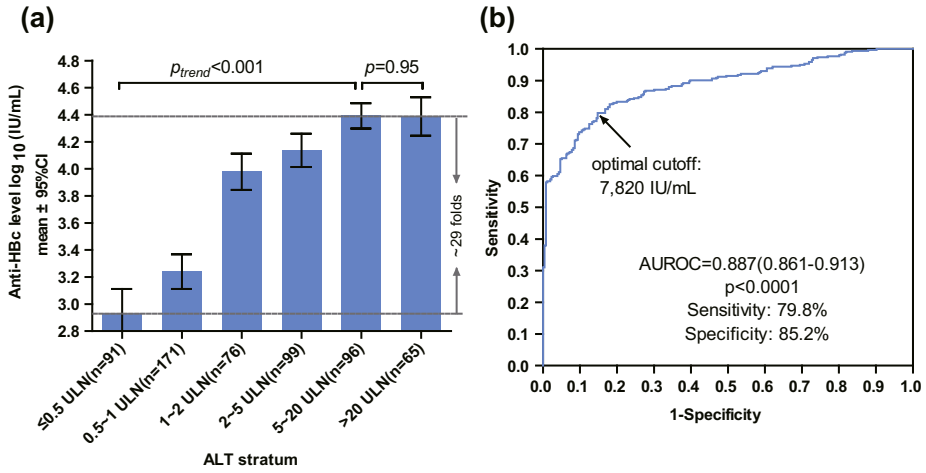

FIG. 2. Association between the levels of anti-HBc and ALT in CHB subjects. (a) Average serum anti-HBc levels of CHB subjects according to the ALT stratum. (b) ROC analysis of the anti-HBc level to discriminate ALT elevation (greater than the upper limit of normal) in CHB subjects. HBc, hepatitis B core protein; ALT, alanine aminotransferase; CHB, chronic hepatitis B; ROC, receiver operating characteristic curve; AUROC, area under the ROC curve.

in the LR phase (R = 0.324, p < 0.001), whereas no association was observed in the ENH phase (R = 0.047, p 0.588). Moreover, no significant correlation was observed between the qAnti-HBc level and the HBV DNA level.

Discussion

Hepatitis B core protein is the most immunogenic HBV antigen, and its antibody can persist for a long time, irrespective of an ongoing infection or virus clearance in an HBV-infected host. Therefore, anti-HBc is well accepted as the most sensitive marker of a history of HBV infection. Anti-HBc can be found in serum shortly after the appearance of HBsAg in the initial phase of HBV infection [15,16]. Nearly 100% of CHB subjects and more than 90% of individuals with OBI are anti-HBc seropositive [1]. Even in subjects who have completely recovered from HBV infection after HBsAg loss, the persistence of anti-HBc typically continues for 10 to 20 years or is lifelong. However, little is known about the quantitative levels of anti-HBc during the natural course of HBV infection. In this report, on the basis of a cross-sectional study, we demonstrated that serum anti-HBc quantification was closely related to the HBsAg status and hepatic inflammatory activities.

Significant differences in serum qAnti-HBc levels were observed across the different phases of HBV infection. Among HBsAg-negative healthy individuals who had detectable anti-HBc (>0.25 IU/mL), either with (OBI group) or without (PBI group) a low level of serum HBV DNA, the qAnti-HBc levels were dramatically lower (approximately 1000-fold) than in those who were persistently HBsAg positive (CHB group). In addition, the average qAnti-HBc level in the OBI group was significantly higher (approximately 4-fold) than that in the PBI group. These findings suggest that virus antigens are the essential factors that stimulate and maintain qAnti-HBc levels. Hence, the qAnti-HBc measurement can be considered a sentinel marker to trace the virus in the host in either overt (HBsAg positive) or occult infections (HBsAg negative).

Immune-activated CHB subjects (IC or ENH) had significantly higher qAnti-HBc levels than immunotolerant and/or inactive subjects, which suggests that the qAnti-HBc levels of HBsAg-positive individuals are primarily determined by the host immune status and hepatitis activities, and not by the levels of HBV DNA or virus antigen. Theoretically, the circulatory HBV core antigen (HBcAg) should affect the qAnti-HBc level. Although HBcAg can be secreted into the blood as a component of the virions, it is typically contained within the virus envelope and is not readily accessible by B cells. This containment of HBcAg may provide a mechanistic explanation for the low levels of anti-HBc but high levels of HBV DNA and HBsAg in IT subjects with normal ALT levels. However, HBcAg can be released from damaged infected hepatocytes and provide potent antigenic stimulation to B cells to raise the qAnti-HBc level. This assumption is supported by the observation of a simultaneous increase in qAnti-HBc, ALT and AST in CHB subjects. However, we cannot exclude the possibility that excess qAnti-HBc antibodies may have direct cytolytic effects, such as antibody-dependent cell-mediated cytotoxicity. Consistent with this possibility, we observed that the peak anti-HBc level might anticipate the ALT peak in some subjects

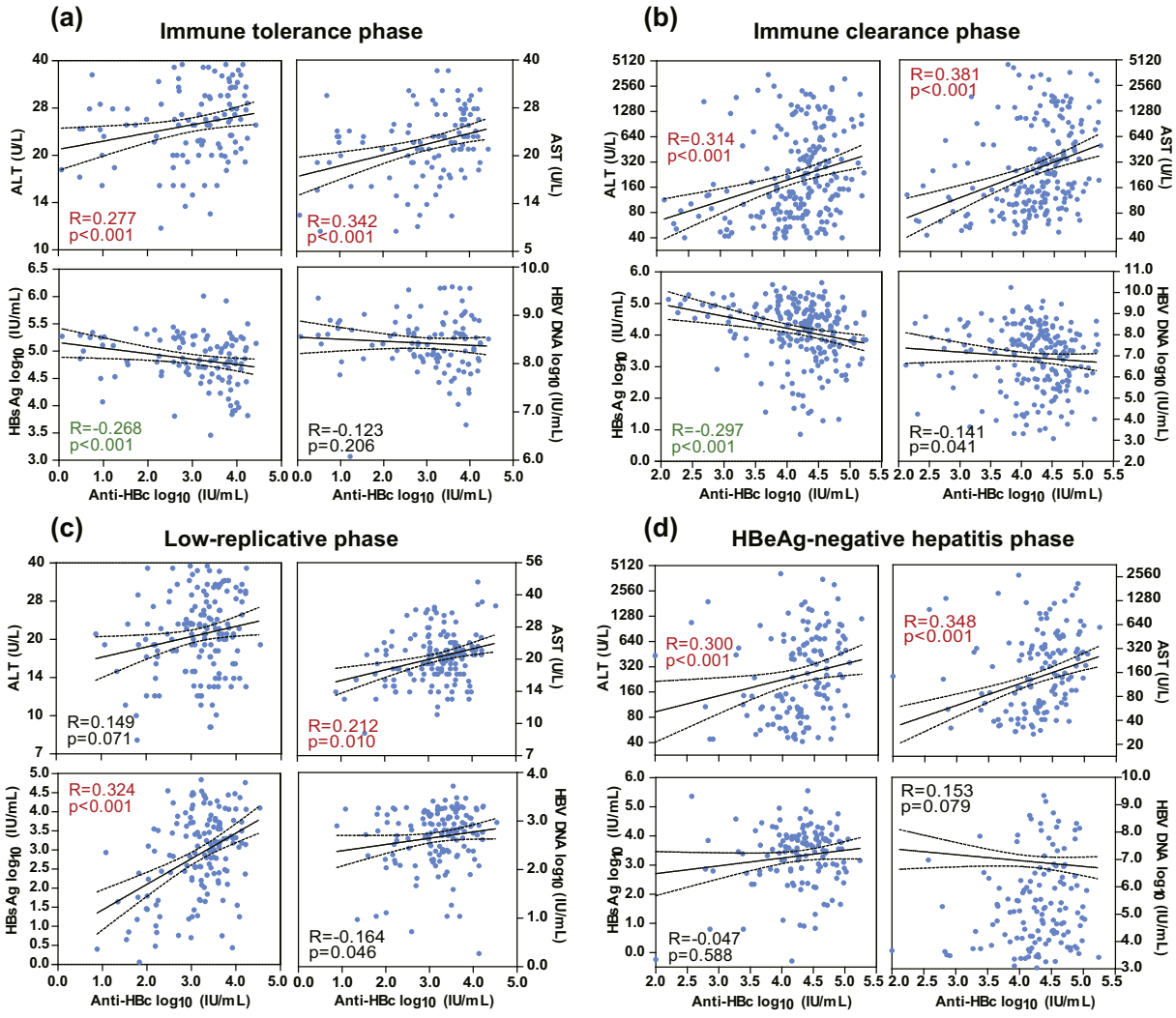

FIG. 3. Correlation between the qAnti-HBc level and ALT, AST and HBV DNA, and HBsAg in subjects in various infection phases. (a) IT phase. (b) IC phase. (c) LR phase. (d) ENH phase. qAnti-HBc, quantitative anti–hepatitis B core protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; IT, immune tolerance phase; IC, immune clearance phase; LR, low-replicative phase; ENH, HBeAg-negative hepatitis phase.

during exacerbation of hepatitis. HBV appeared to induce certain naïve B cells to rapidly proliferate and produce large amounts of anti-HBc during the initial immune encounter. Although these hypotheses both appear reasonable, the underlying mechanisms that regulate the qAnti-HBc level in CHB subjects require further exploration.

In CHB, ALT is a surrogate marker for the host immune response against HBV because elevated ALT levels in CHB subjects often result from cytolytic T cell–mediated hepatocytolysis. A high pretreatment ALT level, particularly when more than 5 × ULN, is a strong predictor of HBeAg seroconversion in both interferon and nucleos(t)ide analogue therapy [17,18]. In CHB subjects, the anti-HBc level was positively correlated with the ALT level from 0.5 × ULN to 5 × ULN and reached a plateau at ALT levels greater than 5 × ULN, the cutoff value for treatment response prediction. It may not be possible for the immune system to be overactivated without limitation; therefore, ALT may be influenced by factors in basic hepatic disease other than the anti-HBV cytotoxic T cell response when ALT is higher than 5 × ULN. In that particular scenario, qAnti-HBc may be a better marker of the host immune response than ALT.

Our analyses established an anti-HBc level of >7820 IU/mL as an optimal cutoff value for distinguishing subjects with or without hepatitis activation. Although the ALT level is a generally accepted surrogate marker to measure host immune

strength in CHB subjects, the half-life of serum ALT is shorter than that of serum immunoglobulin antibodies. Therefore, in clinical scenarios in which ALT levels return to normal, such as during or at the end of treatment, the measurement of the serum qAnti-HBc titre may provide additional information about the host immune status.

In conclusion, the serum qAnti-HBc level is determined by the host immune status and is strongly associated with hepatitis activity in subjects with CHB. These findings suggest that monitoring the dynamic changes in the qAnti-HBc level could serve as a useful marker for clinicians to characterize the disease phase of subjects as well as their immune readiness against HBV.

Transparency declaration

This project was supported by grants from the National Science Fund (81371819 and 30925030), and the National Scientific and Technological Major Project (2012ZX10002-005 and 2012ZX10004503-005). All authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2014.10.002.

References

[1] EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–85.
[2] McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009;49:S45–55.
[3] 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;52:454–61.
[4] Moucari R, Mackiewicz V, Lada O, Ripault MP, Castelnau C, Martinot-Peignoux M, et al. Early serum HBsAg drop: a strong predictor of sustained virological response to pegylated interferon alfa-2a in HBeAg-negative patients. Hepatology 2009;49:1151–7.
[5] Lee JM, Ahn SH, Kim HS, Park H, Chang HY, Kim do Y, et al. Quantitative hepatitis B surface antigen and hepatitis B e antigen titers in prediction of treatment response to entecavir. Hepatology 2011;53:1486–93.
[6] Tseng TC, Liu CJ, Su TH, Wang CC, Chen CL, Chen PJ, et al. Serum hepatitis B surface antigen levels predict surface antigen loss in hepatitis B e antigen seroconverters. Gastroenterology 2011;141:517–25. e1–2.
[7] Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, et al. Determinants of spontaneous surface antigen loss in hepatitis B e antigen-negative patients with a low viral load. Hepatology 2012;55:68–76.
[8] Hoofnagle JH, Seeff LB, Bales ZB, Zimmerman HJ. Type B hepatitis after transfusion with blood containing antibody to hepatitis B core antigen. N Engl J Med 1978;298:1379–83.
[9] Li A, Yuan Q, Huang Z, Fan J, Guo R, Lou B, et al. Novel double-antigen sandwich immunoassay for human hepatitis B core antibody. Clin Vaccine Immunol 2010;17:464–9.
[10] Yuan Q, Song LW, Liu CJ, Li Z, Liu PG, Huang CH, et al. Quantitative hepatitis B core antibody level may help predict treatment response in chronic hepatitis B patients. Gut 2013;62:182–4.
[11] Sun J, Yuan Q, Xie Q, Fan R, Tan D, Ning Q, et al. Baseline quantitative hepatitis B core antibody is the strongest predictor for 2-year HBeAg seroconversion in HBeAg positive CHB patients treated with telbivudine alone or combined with adefovir. In: American Association for the Study of Liver Diseases Abstracts; 2013. Hepatology 2013:701A.
[12] Huang CH, Yuan Q, Chen PJ, Zhang YL, Chen CR, Zheng QB, et al. Influence of mutations in hepatitis B virus surface protein on viral antigenicity and phenotype in occult HBV strains from blood donors. J Hepatol 2012;57:720–9.
[13] World Health Organization. WHO international standard: first international standard for anti–hepatitis B core antigen. Available from: http://www.nibsc.ac.uk/documents/ifu/95-522.pdf [accessed 10.11.08].
[14] Yeh SH, Tsai CY, Kao JH, Liu CJ, Kuo TJ, Lin MW, et al. Quantification and genotyping of hepatitis B virus in a single reaction by real-time PCR and melting curve analysis. J Hepatol 2004;41:659–66.
[15] Marc G, Ghany TJL. Acute viral hepatitis. In: Yamada Tadataka, editor. Atlas of gastroenterology. New York: J. Wiley; 2009. pp. 623–35 [Chapter 56].
[16] Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. Nat Rev Immunol 2005;5:215–29.
[17] Chien RN, Liaw YF, Atkins M. Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. Asian Hepatitis Lamivudine Trial Group. Hepatology 1999;30:770–4.
[18] Yuen MF, Yuan HJ, Hui CK, Wong DK, Wong WM, Chan AO, et al. A large population study of spontaneous HBeAg seroconversion and acute exacerbation of chronic hepatitis B infection: implications for antiviral therapy. Gut 2003;52:416–9.