High serum adiponectin correlates with advanced liver disease in patients with chronic hepatitis B virus infection

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Received: 11 July 2008 / Accepted: 30 October 2008 / Published online: 2 December 2008
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Abstract

Purpose Adiponectin possesses anti-inflammatory and insulin-sensitizing properties. Little is known about the role of adiponectin in hepatitis B-related liver disease.

Methods Serum adiponectin and hepatitis B viral factors were cross-sectionally assayed in 280 patients with chronic hepatitis B virus (HBV) infection including 120 patients with chronic HBV infection, 40 patients with cirrhosis, and 120 patients with hepatocellular carcinoma (HCC); 116 healthy adults were used as controls. The dynamics of serum adiponectin level was also studied longitudinally in 25 patients with hepatitis B e antigen (HBeAg) seroconversion (SC).

Results We found that serum adiponectin level in patients with chronic HBV infection was similar to that in healthy controls and was significantly lower than patients with cirrhosis and HCC. In univariate analysis, high serum adiponectin level significantly correlated with the presence of HBV-related cirrhosis or HCC, abnormal serum ALT level, and HBV genotype C. Multivariate analysis revealed that high serum adiponectin level significantly correlated with the development of HCC. Serum adiponectin levels remained stationary in patients experiencing HBeAg SC.

Conclusions Our findings suggest that HBV infection itself does not affect adiponectin levels. Serum adiponectin level correlates with the progression of HBV-related liver diseases but not with the development of HBeAg SC.

Keywords Hepatitis B virus · Adiponectin · ALT · HBeAg seroconversion · Genotype

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Introduction

Chronic hepatitis B virus (HBV) infection is an important cause of liver disease-related morbidity and mortality worldwide [1]. The pathogenesis of HBV infection involves repeated necroinflammation and regeneration, as well as the

interplay among the virus, host immunity, and hepatocytes [2]. Therefore, both host and viral factors are known to contribute to the clinical outcomes of chronic hepatitis B [3].

Apart from host factors, such as age and gender, adiponectin is a potential candidate that needs further evaluation. This protein possesses anti-inflammatory and insulin-sensitizing properties [4]. In humans, circulating adiponectin levels are positively correlated with insulin sensitivity and decreased in obese and type 2 diabetic patients [5–9]. Adiponectin has also been found to antagonize tumor necrosis factor (TNF) α [10] and plays a central role in the attenuation of carbon tetrachloride-induced liver fibrosis in mice [11]. Because adiponectin appears to induce insulin sensitivity and modulate inflammatory responses, its level in both healthy subjects and patients with different stages of liver diseases, particularly in those with nonalcoholic fatty liver disease (NAFLD) and chronic hepatitis C virus (HCV) infection, has been partly unraveled [4–25]. Consistently, serum adiponectin levels tend to be lower in patients with elevated serum alanine aminotransferase (ALT) values and those with fibrosis [23, 26, 27]. Paradoxically, serum adiponectin level seemed higher in patients with impaired liver function such as those with advanced fibrosis or cirrhosis, possibly because of decreased hepatic extraction of adiponectin [28–30].

Although adiponectin may have implications in the pathogenesis of NAFLD and HCV infection, little is known about the role of adiponectin in hepatitis B-related liver diseases [28, 31]. We thus hypothesized that in patients with chronic HBV infection, the anti-inflammatory actions of adiponectin may ameliorate severity of liver diseases. To investigate this hypothesis, we first assayed and compared serum adiponectin level between 280 HBV carriers with different stages of liver diseases and 116 healthy controls. Second, to clarify the role of adiponectin in the seroconversion (SC) from hepatitis B e antigen (HBeAg) to anti-HBe, which usually indicates decline of HBV replication and remission of hepatitis activity, as well as confers favorable long-term outcomes in the natural history of chronic HBV infection [32], we studied the dynamics of serum adiponectin level in 25 patients with chronic hepatitis who experienced sustained HBeAg SC during follow-up. In addition, the association of serum adiponectin with host and hepatitis B viral factors was also analyzed.

Materials and methods

Patients

From January 2002 to December 2005, we cross-sectionally evaluated 280 patients, including 120 patients with chronic HBV infection, 40 patients with cirrhosis, and 120 HCC

patients. In addition, 116 healthy adults were used as controls. Chronic HBV carriage was defined as positivity for HBsAg for at least 6 months and without evidence of cirrhosis or hepatocellular carcinoma (HCC). The diagnosis of cirrhosis and HCC was based on histologic examinations of the biopsied or resected specimens. None had serologic evidence suggestive of autoimmune liver disease or inheritable disorders such as hemochromatosis or Wilson's disease, as well as history of alcoholism or drug abuse. None had concomitant hepatitis C or D virus infection.

Of chronic hepatitis B cohort, 25 patients (17 men and 8 women; median age 25 years, range 21–52 years) with sustained HBeAg SC (loss of HBeAg and appearance of anti-HBe) were collected by the following criteria: (1) follow-up for at least 1 year before SC and at least 1 year thereafter; and (2) available serum samples at several time points before, during, and after SC for testing. The time of SC was defined as the date when HBeAg was tested negative and anti-HBe first became positive.

Baseline serum samples from each subject were stored at -70°C until use. For patients with histologically verified HCC, serum samples were collected at the time when surgical resection of HCC was performed. In the 25 selected patients who experienced sustained HBeAg SC, we determined the serum adiponectin level in serum samples obtained 1 year before, both 6 and 3 months before, at the time of, 6 months after, and 1 year after SC.

Hepatitis virus markers and virologic studies

HBsAg, antibody to HBsAg (anti-HBs), HBeAg, anti-HBe, and anti-HDV were assayed with commercial kits (AxSYM System[®], Abbott Laboratories, North Chicago, IL). Anti-HCV was tested by a second-generation enzyme-linked immunoassay (Abbott Laboratories).

Quantification and genotyping of HBV

We developed a 1-tube assay for both quantification and genotyping of HBV at the same time as previously described [33]. The HBV DNA concentrations obtained from this quantification assay showed satisfactory consistency with Roche Amplicor assay and NGI SuperQuant assay (Pearson $\rho > 0.99$) in the linear range from 10^2 to 10^{11} copies/ml. The low detection limit of HBV DNA is 10^2 copies/ml. The genotypes of HBV were determined by using melting curve analysis with genotype-specific probes.

Strict precautions were taken to avoid possible contaminations. In addition, reagents were stored in small aliquots. All the pipet tips and Eppendorf tubes were disposable and the pipet tips were filtered. Only those data that revealed no false-positive results in the negative controls and those that were reproducible were used.

Quantification of serum adiponectin level

Serum adiponectin level was determined by a commercial ELISA assay (Human Adiponectin ELISA Kit, B-Bridge International, Inc., Mountain View, CA, USA) according to the manufacturer's instructions [16].

Ethical considerations

This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki in a priori approval by the institutional review board of the National Taiwan University Hospital (NTUH9461701235) and all patients gave their written informed consent.

Statistical analysis

Continuous data were expressed as mean $\pm$ standard deviation (SD) or median (range) and the categorical data as number (percentage). The differences in demographic and clinical features between patients with HBV-related liver diseases and healthy controls were evaluated by Pearson chi-square test, Fisher's exact test, and Student *t* test where appropriate. Univariate and multivariate analyses were used to assess the influence of viral and host factors on the risk of HCC development or the level of serum adiponectin. All tests were 2-sided and a *P* value < 0.05 was considered statistically significant.

Results

Clinical and virologic characteristics of patients

The mean ages of 280 HBV-infected Taiwanese patients and 116 healthy controls were 41.7 years and 53.8 years, respectively (Table 1). Male gender predominated in both patients and controls. Patients with cirrhosis and HCC were significantly older than those with chronic HBV infection

(50.3 ± 8.8 vs. 50.7 ± 13.8 vs. 29.9 ± 9.1 , $P < 0.05$). Patients with HCC also had a higher percentage of male gender than those with chronic HBV infection (83% vs. 53%, $P < 0.05$).

Genotyping and quantification of HBV were performed in all patients with chronic HBV infection. HBV could be genotyped in all patients with chronic HBV infection, 36 (90%) patients with cirrhosis, and 113 (94.2%) HCC patients. The most prevalent genotypes were B (70.6%) and C (29.4%). Serum HBV DNA was detected in all patients with chronic HBV infection, as well as patients with cirrhosis, and 109 (90.9%) HCC patients. The distributions of HBV genotype and serum HBV DNA level in each category of liver disease are shown in Table 1.

High serum adiponectin level correlated with the presence of advanced liver diseases and abnormal serum ALT levels

The distribution of serum adiponectin level in patients with different stages of liver disease and healthy controls is shown in Tables 2, 3, 4 and 5. Overall, serum adiponectin level in patients with chronic HBV infection was similar to that in healthy controls but was significantly lower than patients with cirrhosis or HCC patients (Table 2).

In univariate analysis, high serum adiponectin levels significantly correlated with the presence of HBV-related cirrhosis or HCC (vs. chronic hepatitis stage), abnormal serum ALT level (vs. normal ALT), and HBV genotype C (vs. genotype B) (Table 2).

Influence of body mass index (BMI) and gender on the profile of serum adiponectin was performed by linear regression analysis in a subset of 120 patients with chronic hepatitis whose data were available. We found that BMI but not gender or age negatively correlated with serum adiponectin level ($P = 0.022$) (Table 6).

After adjustment for age and gender, advanced liver diseases and abnormal serum ALT level remained significantly associated with high serum adiponectin level (Table 7).

Table 1 Baseline characteristics of patients and controls

	Patients with CHB (<i>n</i> = 120)	Patients with cirrhosis (<i>n</i> = 40)	Patients with HCC (<i>n</i> = 120)	Healthy controls (<i>n</i> = 116)
Age, year	29.9 $\pm$ 9.1*	50.3 $\pm$ 8.8*	50.7 $\pm$ 13.8*	53.8 $\pm$ 10.5*
Gender, male/female	63 (53%)/57 (47%)*	29 (73%)/11 (27%)	100 (83%)/20 (17%)*	67 (58%)/49 (42%)
ALT, IU/L	23.8 $\pm$ 40.8*	144.2 $\pm$ 304.2*	49.1 $\pm$ 43.3*	24.6 $\pm$ 14.6
HBV DNA, copies/mL	$1.26 \times 10^8 \pm 3.65 \times 10^8$ *	$1.02 \times 10^8 \pm 2.78 \times 10^8$ *	$2.67 \times 10^6 \pm 1.10 \times 10^7$ *	–
Genotype, B/C	104 (87%)/16 (13%)*	19 (53%)/17 (47%)*	77 (68%)/36 (32%)*	–

Values expressed as mean $\pm$ SD or number (%). Genotype could not be determined in 4 patients with cirrhosis and 7 HCC patients

CHB chronic hepatitis B, HCC hepatocellular carcinoma, ND not determined

* $P < 0.05$

Table 2 Distribution of serum adiponectin levels in healthy controls and HBV carriers with different liver disease stages

Overall	Adiponectin, $\mu\text{g/ml}$		<i>P</i>
	Case number	Mean $\pm$ SD	
Healthy controls	116	9.4 $\pm$ 2.2	<0.0001
Patients with CHB	120	9.6 $\pm$ 4.5	
Patients with cirrhosis	40	18.5 $\pm$ 12.3	
Patients with HCC	120	18.6 $\pm$ 11.5	0.91
Gender	Female	137	
	Male	259	
ALT, IU/L	<40	287	<0.0001
	≥ 40	99	
HBV DNA, ^a copies/ml	<10 ⁴	91	0.41
	$\geq 10^4$	178	
HBV DNA, ^a copies/ml	<10 ⁵	132	0.52
	$\geq 10^5$	137	
Genotype ^b	B	200	0.03
	C	69	

^a Serum HBV DNA could not be determined in 11 patients with HCC

^b Serum HBV genotype could not be determined in 4 patients with cirrhosis and 7 HCC patients

CHB chronic hepatitis B, HCC hepatocellular carcinoma

Subgroup analysis

Healthy controls and patients with chronic HBV infection

Serum adiponectin level was not related with gender (male vs. female: 9.1 $\pm$ 2.2 vs. 9.7 $\pm$ 2.3 $\mu\text{g/ml}$, $P = 0.16$) and serum ALT level (normal versus abnormal serum ALT level: 9.4 $\pm$ 2.3 vs. 9.6 $\pm$ 2.1 $\mu\text{g/ml}$, $P = 0.73$) in healthy controls. The distribution of serum adiponectin level was also similar in patients with chronic HBV infection

Table 3 Distribution of serum adiponectin levels in 120 patients with chronic HBV infection

	Adiponectin, $\mu\text{g/ml}$		<i>P</i>
	Case number	Mean $\pm$ SD	
Gender	Female	57	0.95
	Male	63	
ALT, IU/L	<40	108	0.85
	≥ 40	12	
HBV DNA, copies/ml	<10 ⁴	47	0.61
	$\geq 10^4$	73	
HBV DNA, copies/ml	<10 ⁵	58	0.97
	$\geq 10^5$	62	
Genotype	B	104	0.93
	C	16	

regardless of gender, serum ALT level, serum HBV DNA level, and HBV genotype (Table 3).

Patients with cirrhosis and HCC

In patients with cirrhosis, female gender correlated with a high serum adiponectin level (Table 4). In HCC patients, female gender and abnormal serum ALT level correlated with a high serum adiponectin level (Table 5). In addition to older age, male gender, HBV genotype C, and abnormal serum ALT, high serum adiponectin level independently correlated with the presence of HCC in multivariate analysis (Table 8).

Dynamics of serum adiponectin in chronic hepatitis B patients with hepatitis B e antigen SC

The baseline features of the 25 patients who developed HBeAg SC during follow-up are shown in Table 9.

Table 4 Distribution of serum adiponectin levels in 40 patients with cirrhosis

	Adiponectin, $\mu\text{g/ml}$		<i>P</i>
	Case number	Mean $\pm$ SD	
Gender	Female	11	0.0085
	Male	29	
ALT, IU/L	<40	9	0.82
	≥ 40	31	
HBV DNA, copies/ml	<10 ⁴	6	0.51
	$\geq 10^4$	34	
HBV DNA, copies/ml	<10 ⁵	13	0.51
	$\geq 10^5$	27	
Genotype	B	19	0.36
	C	17	

Table 5 Distribution of serum adiponectin levels in 120 patients with HCC

	Adiponectin, $\mu\text{g/ml}$		<i>P</i>
	Case number	Mean $\pm$ SD	
Gender	Female	20	0.02
	Male	100	
ALT, IU/L	<40	66	0.048
	≥ 40	44	
HBV DNA, copies/ml	<10 ⁴	38	0.94
	$\geq 10^4$	71	
HBV DNA, copies/ml	<10 ⁵	61	0.79
	$\geq 10^5$	48	
Genotype	B	77	0.85
	C	36	

Table 6 Multivariate analysis of factors associated with the level of serum adiponectin in 120 patients with chronic HBV infection

	Coefficient	95% confidence interval	P
Age (per year)	0.0001	−0.007 to 0.007	0.97
Male vs. female	0.098	−0.083 to 0.28	0.29
Body mass index, kg/m ²	−0.029	−0.053 to −0.004	0.022

Concomitantly, serum adiponectin level tended to increase right before the SC event (Fig. 1). However, this increase in serum adiponectin level was not statistically significant when compared with baseline level ($P > 0.05$). When hepatitis activities were taken into consideration in these patients, abnormal serum ALT level was noted in 60.9%, 76.5%, 71.4%, and 56.5% at 1 year, 6 months before, 3 months before, and at the time of HBeAg SC, respectively. When all serum adiponectin levels of these 25 patients were correlated with serum ALT levels obtained at the same time, a positive parallel relationship was found as well, although not reaching statistical significance ($P = 0.09$).

Discussion

The implications of adiponectin have been investigated extensively in patients with NAFLD [5, 6, 8] and limitedly in patients with chronic HVC infection [16]. However, the role of adiponectin in the development of HBV-related liver cirrhosis and HCC remains largely unknown. In this study, we demonstrated that serum adiponectin correlated well with the presence of advanced liver diseases but not with the development of HBeAg SC.

Table 8 Multivariate analysis of factors associated with the development of hepatocellular carcinoma in patients with chronic HBV infection

	Odds ratio	95% confidence interval	P
Age (per year)	1.09	1.06–1.12	<0.0001
Male vs. female	7.87	3.39–20.18	<0.0001
Genotype C vs. B	1.37	0.66–2.89	0.38
ALT ≥ 40 vs. <40 IU/l	0.41	0.20–0.86	0.02
Adiponectin (per $\mu\text{g/ml}$)	1.07	1.03–1.12	0.0003

Table 9 Baseline characteristics of 25 patients with HBeAg sero-conversion during follow-up

Age, years, range (median)	21–52 (25)
Sex, male/female	17/8
HBV genotype, B/C	20/5
HBV DNA levels, copies/ml, range (median)	<100 to 4.0×10^8 (5.6×10^6)
Adiponectin level, $\mu\text{g/ml}$, range (median)	5.7–32.0 (10.0)

Values expressed as number (percentage) or range (median)

To our knowledge, only few studies examined the role of adiponectin in patients with chronic HBV infection [28, 29, 31]. We have examined the change of serum adiponectin levels before and after interferon α therapy in 10 patients with chronic HBV infection and found that the adiponectin levels did not correlate with the response to interferon therapy (responders versus nonresponders: 17.7 ± 4.1 vs. 9.2 ± 1.0 $\mu\text{g/ml}$, $P = 0.10$) [31]. However, a significant improvement in the insulin resistance after interferon therapy was noted in the responders but not in the nonresponders. Our data suggested that interferon α might result in a decrease of serum adiponectin levels but

Table 7 High serum adiponectin levels correlate with the development of HCC and abnormal serum ALT level: age- and sex-adjusted multivariate analysis

Overall	Adiponectin, $\mu\text{g/ml}$				P	Age/sex-adjusted	
	≤ 9.7	%	> 9.7	%		Odds ratio	95% confidence interval
Health controls	61	52.6	55	47.4		1.0	
Patients with CHB	68	56.7	52	43.3		0.85	0.42–1.74
Patients with cirrhosis	12	30	28	70		2.36	0.99–5.64
Patients with HCC	19	15.8	101	84.2		5.56	2.94–10.52*
ALT, IU/L	<40	132	44.4	165	55.6	0.0045	1.0
	≥ 40	28	28.3	71	71.7		1.74
Genotype	B	79	39.5	121	60.5	0.045	1.0
	C	18	26.1	51	73.9		1.56

Values expressed as number (percentage). The cut-off value of serum adiponectin 9.7 $\mu\text{g/ml}$ is selected because it represents the median of all values from cases and controls

CHB chronic hepatitis B, HCC hepatocellular carcinoma

* $P < 0.001$, ** $p < 0.05$

Fig. 1 Dynamic profile of median serum adiponectin level ($\mu\text{g/mL}$) in 25 patients at different time points during the process of HBeAg seroconversion (SC). Time points were defined as 1 year (T1), 6 months (T2), and 3 months (T3) before, at the time of (T4), and 6 months (T5) and 1 year (T6) after HBeAg SC

an improvement of insulin resistance in responders. These results contradict previous concept of the inverse relationship between degree of insulin resistance and adiponectin levels and prompted us to conduct further studies. Kaser et al. [29] evaluated serum adiponectin level in 87 patients with cirrhosis of different etiologies, including HBV-related cirrhosis ($n = 8$) and 21 healthy controls. They found that serum adiponectin level increased in patients with cirrhosis independent of the etiology of liver disease [29]. Hui et al. [28] recently assessed serum adiponectin level in 100 patients with biopsy-proven different fibrosis stages of chronic HBV infection and 38 patients with paired liver biopsies before and after antiviral treatment. They found that serum adiponectin level was increased in HBV-related advanced liver fibrosis and declined with post-treatment reduction in fibrosis [28]. They thus concluded that serum adiponectin might have a role in fibrosis progression in chronic HBV infection.

Taking these lines of evidence together, serum adiponectin level is consistently higher in patients with advanced liver fibrosis than those with no or mild fibrosis, and this protein may play a role in the fibrosis progression of chronic HBV infection. Nevertheless, the case number in previous studies was limited and prospective data were lacking. We therefore aimed to clarify the role of adiponectin in the pathogenesis of chronic HBV infection in a larger cohort of patients. Our data confirmed that serum adiponectin correlated well with the presence of advanced liver diseases, including cirrhosis and HCC in HBV carriers.

Serum adiponectin in patients with advanced liver diseases such as cirrhosis is increased independently of metabolic profiles [20]. This could be explained by the effect of altered metabolism and/or excretion of adiponectin in these patients. Furthermore, elevated serum adiponectin level might be the consequence of hepatocyte injury. Actually, patients with cirrhosis are characterized by a chronic

inflammatory state with elevated plasma levels of several cytokines [34]. In this case, high serum adiponectin might play a protective role in hepatocytes. A recent study from France indeed demonstrated that adiponectin level is higher in chronic HCV-infected patients with severe fibrosis than those with mild fibrosis [18]. To clarify the role of adiponectin in the fibrosis progression of chronic HBV infection, further long-term follow-up study on the same population from the beginning of early-stage disease is needed.

The impact of adiponectin on the natural course of chronic hepatitis B remains unclear. Since the development of HBeAg SC is closely related to underlying host immune response as reflected by serum ALT fluctuation (flare and remission), we therefore hypothesized that the dynamic profile of serum adiponectin level may be associated with the development of HBeAg SC. However, we found that adiponectin did not contribute to the development of HBeAg SC. Since the sequel associated with chronic HBV infection is closely linked to prolonged and repeated hepatic necroinflammation and fibrosis, whether adiponectin plays a pathogenic role in the development of advanced liver diseases awaits further examinations.

The major limitation of our study was the cross-sectional design and hospital-based cohort. Like most other series, this design did not exclude the possibility of referral bias, nor examined other confounding factors. Besides, the liver biopsy specimen was not obtained in patients with chronic hepatitis infection and thus the stage of fibrosis and its correlation with the level of serum adiponectin could not be analyzed in this study. Furthermore, parameters of hepatic metabolism, levels of inflammatory cytokines including $\text{TNF-}\alpha$ and other adipocyte-derived hormones, were not assessed in our study. Future studies should focus on these issues.

In conclusion, serum adiponectin level correlates with the progression of HBV-related liver diseases but not with the development of HBeAg SC.

Acknowledgments The study was supported by grants from the National Taiwan University Hospital; the National Taiwan University; the National Science Council (NSC 95-2314-B-002-094), Department of Health, Executive Yuan, Taiwan; National Health Research Institutes (NHRI-EX93-CD9201 and NHRI-EX94-CD9201), Taiwan; and Liver Disease Prevention and Treatment Research Foundation, Taiwan.

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