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The Histological Assessment of Hepatitis B Viral Activity in Patients with Heavy Alcohol Consumption

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Abstract

Objectives: Taiwan has a high prevalence of hepatitis B viral (HBV) infection with rising alcoholic liver disease. We investigated the histological assessment of viral hepatitis B activity in patients with concomitant HBV infection and alcoholism.

Methods: 229 patients (33 with concomitant heavy alcoholism and HBV infection, 114 with HBV infection alone, and 82 with heavy alcoholism alone) were enrolled between 2009 and 2012 at Cathy General hospital and E-Da hospital.

Results: Patients with concomitant alcoholism and HBV infection are male predominant and younger. 97.4% and 91.4% patients have detectable HBV DNA in patients with HBV infection without or with alcoholism, respectively. Patients with concomitant HBV infection and alcoholism have much piecemeal necrosis, confluent necrosis, focal necrosis, portal inflammation, necroinflammatory grading, and cirrhosis with Ishak stage 5-6 fibrosis. Moreover, patients with concomitant HBV infection and alcoholism also have much pericelluar fibrosis, sclerosing hyaline necrosis, non-alcoholic fatty liver disease (NAFLD) ballooning, NAFLD activity score (NAS) and NAFLD Stage 4 fibrosis ($P<0.001$). However, patients with alcoholism alone have much more steatosis than those with HBV infection with and without alcoholism.

Conclusions: Patients having concomitant alcoholism and HBV infection develop the histological features of both alcoholic liver disease and viral hepatitis B. The assessment of hepatitis B viral activity in alcoholic liver disease depends on detectable viral load and histological features of viral hepatitis B in patients with concomitant HBV infection and alcoholism.

Keywords: Hepatitis B virus infection; Alcoholism; Histology; Viral activity; Steatosis

Abbreviations: HBV: Hepatitis B Virus; CHB: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; NAFLD: Non-alcoholic Fatty Liver Disease

Introduction

Asia-Pacific region is a region with a high prevalence of hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC) [1,2]. Alcoholic liver disease is a major cause of chronic liver disease worldwide and can lead to fibrosis, cirrhosis, HCC, and mortality [3,4]. Economic progress in this region has led to an increase of alcohol consumption and changes in drinking behavior, which have resulted in an increased number of cases of alcoholic liver disease in Taiwan [5-8].

Alcohol abuse is not uncommon among those patients with HBV infection. The synergism and interaction between HBV infection and alcohol consumption have been reported [9-12]. Alcoholic consumption may increase viral replication and exacerbate liver injury, which results in the much more rapid progression of chronic hepatitis to cirrhosis and HCC [9-13]. Our recent study confirmed that the heavy alcohol consumption significantly increased the risk of HCC in HBV-related cirrhotic patients [13]. The clinical diagnosis for the role of concomitant HBV infection in alcoholic patients is difficult and remains uncertain. Furthermore, the histological assessment between chronic hepatitis B (CHB) and alcoholic liver disease has never been discussed in the literature. Thus, we investigated the impact of heavy alcohol consumption and HBV infection on histological findings and clinical diagnosis.

Patients and Methods

Patients

We prospectively collected 229 patients (33 with concomitant heavy alcoholism and HBV infection, 114 with HBV infection alone, and 82 with heavy alcoholism alone) at the Cathay General Hospital/Fu-Jen Catholic University, Taipei, Northern Taiwan, and E-DA Hospital/I-SHOU University, Kaohsiung, Southern Taiwan, between 2009 and 2012. The evaluations commenced after approval of the

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study protocols by the Institutional Review Board of Cathay General hospital and E-DA hospital. The behavior of alcohol consumption was routinely evaluated by interviewing patients and family members for the duration, types, and amount of alcohol consumed per day. Heavy alcoholism was defined as consuming more than 80 g of ethanol each day for at least 5 years.

Hepatitis B marker

All patients had blood chemistry and were tested for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and anti-HBe antibody (Abbott Laboratories, Chicago, IL, USA), α-fetoprotein (AFP), and serum HBV DNA (Cobas Amplicor, Hepatitis B Virus Test; Roche Diagnostics, Branchburg, NJ, USA) with with a minimum detection limit of 300 copies/ml. CHB was defined as the positivity for serum HBsAg for more than 6 months as well as chronic liver disease based on the clinical findings of laboratory tests, sonography, and upper gastrointestinal endoscopy. All patients had blood sampling and liver biopsy collected on the same day. All patients without liver histology due to decompensated liver function, international normalized ratio>1.5 and the occurrence of ascites were excluded. All patients with other hepatitis or liver malignancies were excluded.

Scoring system of alcoholic liver disease according to histology

The clinical classification of alcoholic liver disease was based on the histological changes as steatosis, alcoholic hepatitis, alcoholic fibrosis, alcoholic cirrhosis, and alcoholic hepatitis on cirrhosis [14]. The scoring system for alcoholic liver disease was based on the Kleiner non-alcoholic steatohepatitis scoring system [15,16]; briefly defined as steatosis (0: <5%, 1: 5%-33%, 2: >33%-66%, 3: >66%), lobular inflammation (0: no foci, 1: <2 foci, 2: 2-4 foci, 3: >4 foci per 200X field), hepatocellular ballooning (0: none, 1: few, 2: many/prominent balloon cells), and fibrosis (0: none; 1A: mild, zone 3, perisinusoidal; 1B: moderate, zone 3, perisinusoidal, 1C: portal/periportal; 2: zone 3+perisinusoidal and portal/periportal; 3: bridging fibrosis; 4: cirrhosis). Two key histological features of alcoholic liver disease were also defined [17]; briefly defined as Mallory's hyaline (0: absent, 1: occasional, 2: several) and perisinusoidal fibrosis in zone 3 (0: none, 1: <33%, 2: 33-66%, 3: >66%) [18].

Histology of chronic hepatitis

The histological features of chronic hepatitis were based on Ishak modified Hepatic Activity Index (HAI) for necroinflammatory grading (periportal or periseptal piecemeal necrosis: 0-4; confluent necrosis: 0-6; focal lytic necrosis: 0-4; and portal inflammation: 0-4) and fibrosis staging (0-6) [19,20].

Statistical analysis

Data were expressed either as median (range) or percentage (%). Continuous variables were analyzed using Student's t-test. Categorical variables were analyzed using Pearson's Chi-square test or Fisher's exact test, as appropriate. All analyses were performed using the Statistical Package for Social Sciences (SPSS, version 15.0; Chicago, IL, USA).

Results

Baseline demographic data

The clinical and biochemical features of all patients were shown in Table 1. Patients with alcoholism with and without HBV infection were male predominant. Patients with concomitant alcoholism and HBV infection were younger, less platelet, and less platelet to spleen ratio than patients with alcoholism alone or HBV infection alone. Compared with patients with HBV infection with and without alcoholism, patients with alcoholism alone had significantly lower body mass index, hemoglobin, leukocyte, and albumin but higher mean corpuscular volume, serum bilirubin, alkaline-phosphate, gamma-glutamyl transpeptidase, and AST/ALT ratio (p<0.001). For the patients with HBV infection alone, 111 of 114 (97.4%) patients with HBV infection had detectable HBV DNA. For the patients with concomitant HBV infection and alcoholism, 29 of the 32 (90.6%) patients with HBV infection had detectable HBV DNA. None of the patients with alcoholism alone had detectable viral load (p<0.001).

Histological features of viral hepatitis B

The histological features of viral hepatitis B were shown in Table 2. Compared with those patients with alcoholism alone, patients with HBV infection with and without alcoholism had much more piecemeal necrosis, confluent necrosis, focal necrosis, portal inflammation and necroinflammatory grading (p<0.001) regardless of HBV infection. However, patients with concomitant HBV infection and alcoholism or alcoholism alone had much more cases having cirrhosis with Ishak stage 5-6 fibrosis than those with HBV infection alone (p<0.001).

Histological features of alcoholic liver disease

The histological features of alcoholic liver disease are shown in Table 3. Compared with those with HBV infection alone, patients

Characteristics	HBV+Alcoholism (n=33)	HBV (n=114)	Alcoholism (n=82)
Age (year)	41.29 ± 9.98[a,b]	47.63 ± 9.32[c]	45.78 ± 8.42
Sex (male)	31 (93.2)[a]	66 (58.3)[c]	74 (90.2)
Body mass index (kg/m^2)	25.3 ± 3.7[a]	25.0 ± 3.7[c]	23.6 ± 3.8
Alcohol intake amount (g/day)	179 ± 47[a]	0[c]	165 ± 41
Alcohol intake duration (year)	16.6 ± 4.3[b]	0[c]	18.8 ± 6.7
Presence of Diabetes	5 (15.2)	12 (10.5)	13 (15.9)
Presence of Hyperlipidemia	3 (9.1)	13 (11.4)	15 (18.3)
Hemoglobin (g/dL)	13.5 ± 2.1[b]	14.2 ± 1.7[c]	12.9 ± 2.6
Mean corpuscular volume (fL)	89.7 ± 6.3[b]	89.6 ± 4.9[c]	97.0 ± 11.0
White blood cell (10^3 μL)	5890 ± 1926[b]	5779 ± 1634[c]	2877 ± 1040
Platelet count (x10^3/ml)	152 ± 61[a,b]	172 ± 53[c]	198 ± 87
Platelet/spleen	1599 ± 779[a,b]	1857 ± 749[c]	2125 ± 1118
INR	1.18 ± 0.27	1.10 ± 0.14	1.12 ± 0.24
Total bilirubin (mg/dl)	1.36 ± 1.89[b]	0.85 ± 0.51[c]	2.02 ± 2.46
Albumin (g/dl)	3.65 ± 0.63[a]	4.11 ± 0.42[c]	3.55 ± 0.67
Globulin (g/dl)	3.10 ± 0.56	2.86 ± 0.46	2.94 ± 0.70
AST (IU/L)	130.5 ± 169.5[a,b]	79.1 ± 94.7	87.7 ± 72.0
ALT (IU/L)	193.5 ± 265.3[a,b]	137.6 ± 197.0	68.7 ± 68.6
AST/ALT	0.89 ± 0.60[a,b]	0.69 ± 0.26[c]	1.62 ± 0.83
Alkaline phosphatase (IU/L)	105.2 ± 54.5[a,b]	75.6 ± 46.5[c]	150.1 ± 109.0
γ-glutamyltransferase (IU/L)	162.8 ± 210.1[a,b]	72.1 ± 78.5[c]	484.5 ± 506.7
Ferritin	579 ± 631[b]	n.a.	953 ± 1431
α-fetoprotein (ng/ml)	16.4 ± 20.8[b]	27.8 ± 193.0[c]	10.3 ± 38.1
HBV DNA: positive	29 (90.6)	111 (97.4)	0 (0)

Data shown as mean ± standard deviation (SD) or number (%). AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; INR: International Normalized Ratio; HBV: Hepatitis B virus; N.A: Data not Available.
[a]p value<0.05, HBV and alcoholism vs HBV.
[b]p value<0.05, HBV and alcoholism vs Alcoholism.
[c]p value<0.05, HBV vs Alcoholism.

Table 1: Demographic data of all patients.

Viral hepatitis histology features	HBV+Alcoholism (n=33)	HBV (n=114)	Alcoholism (n=82)
Piecemeal necrosis			
0	1 (3.0)[b]	8 (7.0)[c]	41 (50.0)
1	13 (39.4)[b]	47 (41.2)[c]	33 (40.2)
2-4	19 (57.6)[b]	59 (51.8)[c]	8 (9.8)
Confluent necrosis			
0	18 (54.5)[b]	66 (57.9)[c]	76 (92.7)
1	5 (15.2)[b]	26 (22.8)[c]	5 (6.1)
2-6	10 (30.3)[b]	22 (19.3)[c]	1 (1.2)
Focal necrosis			
0	1 (3.0)[b]	1 (0.9)[c]	6 (7.3)
1	11 (33.3)[b]	40 (35.1)[c]	42 (51.2)
2-4	21 (63.7)[b]	73 (64.0)[c]	34 (41.5)
Portal inflammation			
0	1 (3.0)[b]	4 (3.5)[c]	52 (63.4)
1	11 (33.3)[b]	43 (37.7)[c]	24 (29.3)
2-4	21 (63.7)[b]	67 (58.8)[c]	6 (7.3)
Necroinflammatory Score: Grading			
Mean ± SD	6.39 ± 2.89[b]	5.56 ± 2.55[c]	3.13 ± 2.27
Ishak Fibrosis: Staging			
F1-4	17 (51.5)[a]	89 (78.1)[c]	45 (54.9)
F5-6	16 (48.5)[a]	25 (21.9)[c]	37 (45.1)
Mean ± SD	3.76 ± 1.98[a]	3.08 ± 1.72[c]	3.39 ± 2.18

Data shown as mean ± standard deviation (SD) or number (%).
[a]p value<0.05, HBV and alcoholism vs. HBV.
[b]p value<0.05, HBV and alcoholism vs. alcoholism.
[c]p value<0.05, HBV vs. alcoholism.

Table 2: Histological features of viral hepatitis B in all patients.

with alcoholism with and without HBV infection had much more pericelluar fibrosis, sclerosing hyaline necrosis, NAFLD ballooning, NAFLD activity score (NAS) and NAFLD Stage 4 fibrosis (p<0.001). Patients with alcoholism alone had much more steatosis than those with HBV infection with and without alcoholism (p<0.001).

Discussion

Liver biopsy has been the most sensitive and specific method for evaluating the degree of hepatic injury and fibrosis to help the clinical diagnosis and therapeutic decision [20,21]. In the present results, the patients having concomitant alcoholism and HBV infection developed the histological features of both alcoholic liver disease (steatosis, hepatocyte ballooning, focal necrosis and fibrosis) [17] and viral hepatitis B (piecemeal necrosis, confluent necrosis, focal necrosis, portal inflammation and fibrosis) [19]. Typical histological changes of viral hepatitis B are important in the clinical differentiation from alcoholic liver disease. Furthermore, typical histological changes of alcoholic liver disease were also important in the clinical differentiation from viral hepatitis B in high HBV endemic area, such as Taiwan and Asian Pacific region. To the best of our knowledge, this result has not previously been reported in the literature.

All but three patients had detectable hepatitis B viral load showing their underlying hepatitis activities in patients with concomitant HBV infection and alcoholism. The histology also showed that typical histological changes of viral hepatitis B in patients with concomitant HBV infection and alcoholism. The assessment of viral activity B in alcoholic liver disease depends on detectable viral load and histological features of viral hepatitis B in patients with concomitant HBV infection and alcoholism. Moreover, some studies show that chronic ethanol consumption stimulates hepatitis B virus replication in animal [22,23]. In clinics, our study presents that patients with concomitant HBV infection and alcoholism have high percentages of hepatitis B viral load and high levels of HBV DNA. This could be possibly due to patients with alcoholic liver disease having poor nutrition status and relatively weaker immune status. HBV replication is mediated by immune system and is the key role of immune-mediated liver injury and disease progression [21,24].

HBV infection and heavy alcohol consumption has been recognized as major risk factors for fibrosis, cirrhosis, and HCC [10,24]. Our recent study presented that heavy alcohol consumption significantly increases the risk of HCC in HBV-related cirrhotic patients and elevated baseline serum HBV DNA is a strong risk predictor of HCC [11]. In this study, patients with concomitant HBV infection and alcoholism had much more cirrhosis with Ishak stage 5-6 fibrosis and NAFLD activity score with stage 4 fibrosis than those with HBV infection alone in histological findings. Our study demonstrates that patient with concomitant HBV infection and alcoholism have more advanced fibrosis and cirrhosis.

Alcohol intake increases the prevalence of fatty liver and hepatic steatosis is positively associated with moderate alcohol consumption [25]. Our study presented that patients with alcoholism alone had much more steatosis than those with HBV infection with and without

Alcoholic liver disease histology features	HBV+Alcoholism (n=33)	HBV (n=114)	Alcoholism (n=82)
Pericelluar fibrosis			
0	9 (27.3)[a,b]	112 (98.2)[c]	3 (3.7)
1	13 (39.4)[a]	2 (1.8)[c]	31 (37.8)
2-3	11 (33.3)[a,b]	0 (0.0)[c]	48 (58.5)
Sclerosing hyaline necrosis			
0	18 (54.5)[a,b]	113 (99.1)[c]	5 (6.1)
1	11 (33.3)[a,b]	1 (0.9)[c]	47 (57.3)
2-3	4 (12.1)[a,b]	0 (0.0)[c]	30 (36.6)
Kleiner NAFLD score			
NAFLD steatosis			
0	19 (57.6)[b]	67 (58.8)[c]	28 (34.1)
1	8 (24.2)	29 (25.4)	23 (28.0)
2-3	6 (18.2)[b]	18 (15.8)[c]	31 (37.9)
NAFLD inflammation			
0	0 (0.0)	1 (0.9)	5 (6.1)
1	13 (39.4)	38 (33.3)	44 (53.7)
2-3	20 (60.6)	75 (65.8)	33 (40.2)
NAFLD ballooning			
0	8 (24.2)[a]	34 (30.1)[c]	6 (7.3)
1	10 (30.3)[a,b]	56 (49.1)	39 (47.6)
2-3	15 (45.5)[a]	24 (20.8)[c]	37 (45.1)
NAFLD activity score: Grading			
Mean ± SD	3.79 ± 2.01[a,b]	3.34 ± 1.63[c]	4.27 ± 1.98
NASH fibrosis: Staging			
0-3	18 (53.8)[a]	88 (77.0)[c]	46 (55.6)
4	15 (46.2)[a]	26 (23.0)[c]	36 (44.4)
Mean ± SD	2.91 ± 1.16[a]	2.12 ± 1.38[c]	2.82 ± 1.21

Data shown as mean ± standard deviation (SD) or number (%). NAFLD: Non-alcoholic fatty liver disease.
[a]p value<0.05, HBV and alcoholism vs. HBV.
[b]p value<0.05, HBV and alcoholism vs. alcoholism.
[c]p value<0.05, HBV vs. alcoholism.

Table 3: Histological features of alcoholic liver disease in all patients.

alcoholism. However, patients with concomitant HBV infection and alcoholism had much less steatosis than those with alcoholism alone. In some studies, HBV infection is associated with a lower prevalence of fatty liver, hypertriglyceridemia and metabolic syndrome [26]. Moreover, hepatitis B viral replication may affect lipid metabolism and the secretion of various adipokines [25-27]. Indeed, hepatitis B viral load is negatively associated with hepatic steatosis and may suggest a protective effect on hepatic steatosis in alcohol and non-alcohol induced hepatic steatosis and liver disease.

The current study excludes patients with decompensated liver function, who were unsuitable for liver biopsy. Most alcoholic patients with decompensated liver function developed severe degree of alcoholic hepatitis or cirrhosis clinically. The percentage of patients having alcoholic hepatitis and alcoholic cirrhosis in this study was less than our previous studies and was underestimated.

Conclusion

The patients having concomitant alcoholism and HBV infection had developed the histological features of both alcoholic liver disease and viral hepatitis B. In high HBV endemic area, the histology presents the features of alcoholic liver disease (steatosis, hepatocyte ballooning, and focal necrosis) in patients with HBV infection. These patients should provide full details of their alcohol consumption history and the disease prognosis should be handled with extra care. Furthermore, the assessment of hepatitis B viral activity in alcoholic liver disease depends on detectable viral load and histological features of viral hepatitis B in patients with concomitant HBV infection and alcoholism.

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References

1. Sung JL, Chen DS, Lai MY, Yu JY, Wang TH, et al. (1984) Epidemiological study on hepatitis B virus infection in Taiwan. Gastroenterol J Taiwan 1: 1-9.
2. Chen DS, Kuo GC, Sung JL, Lai MY, Sheu JC, et al. (1990) Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. J Infect Dis 162: 817-822.
3. Gao B, Bataller R (2011) Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology 141: 1572-1585.
4. O'Shea RS, Dasarathy S, McCullough AJ; Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology (2010) Alcoholic liver disease. Hepatology 51: 307-328.
5. Lin CW, Chen YS, Lai CH, Perng DS, Weng HC, et al. (2010) Esophagogastric varices predict mortality in hospitalized patients with alcoholic liver disease in Taiwan. Hepatogastroenterology 57: 305-308.
6. Hu JT, Huang SF, Lin CL, Lin PH, Tseng TL, Yang SS (2011) Current status of alcoholic liver disease in Taiwan. Gastroenterol J Taiwan 28: 234-241.
7. Yang SS (2008) Alcoholic liver disease: clinical and Sonographic features. Journal of Medical Ultrasound 16:140-149.
8. Huang YW, Chen PJ (2010) Overview of alcoholic liver disease in Taiwan. J Clin Hepatol 26:247-248.
9. Gao B (2002) Interaction of alcohol and hepatitis viral proteins: implication in synergistic effect of alcohol drinking and viral hepatitis on liver injury. Alcohol 27:69-72.
10. Balasubramanian S, Kowdley KV (2005) Effect of alcohol on viral hepatitis and other forms of liver dysfunction. Clin Liver Dis 9: 83-101.
11. Morgan TR, Mandayam S, Jamal MM (2004) Alcohol and hepatocellular carcinoma. Gastroenterology 127: S87-S96.
12. Hassan MM, Hwang LY, Hatten CJ, Swaim M, Li D, et al. (2002) Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 36: 1206-1213.
13. Lin CW, Lin CC, Mo LR, Chang CY, Perng DS, et al. (2013) Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol 58: 730-735.
14. Alcoholic liver disease: Morphological manifestations (1981) Review by an international group. Lancet 1: 707-711.
15. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, et al. (2005) Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 41: 1313-1321.
16. Yeh MM, Brunt EM (2014) Pathological features of fatty liver disease. Gastroenterology 147: 754-764.
17. Crawford JM (2012) Histologic findings in alcoholic liver disease. Clin Liver Dis 16: 699-716.
18. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR (1999) Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 94: 2467-2474.
19. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, et al. (1995) Histological grading and staging of chronic hepatitis. J Hepatol 22: 696-699.
20. Bedossa P, Poynard T (1996) An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 24: 289-293.
21. Talley NJ, Roth A, Woods J, Hench V (1988) Diagnostic value of liver biopsy in alcoholic liver disease. J Clin Gastroenterol 10: 647-650.
22. Larkin J, Clayton MM, Liu J, Feitelson MA (2001) Chronic ethanol consumption stimulates hepatitis B virus gene expression and replication in transgenic mice. Hepatology 34: 792-797.
23. Min BY, Kim NY, Jang ES, Shin CM, Lee SH, et al. (2013) Ethanol potentiates hepatitis B virus replication through oxidative stress-dependent and -independent transcriptional activation. Biochem Biophys Res Commun 431:92-97.
24. Liaw YF, Chu CM (2009) Hepatitis B virus infection. Lancet 373: 582-592.
25. Machado MV, Oliveira AG, Cortez-Pinto H (2011) Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol 26: 1361-1367.
26. Wong VW, Wong GL, Chu WC, Chim AM, Ong A, et al. (2012) Hepatitis B virus infection and fatty liver in the general population. J Hepatol 56: 533-540.
27. Wong VW, Wong GL, Yu J, Choi PC, Chan AW, et al. (2010) Interaction of adipokines and hepatitis B virus on histological liver injury in the Chinese. Am J Gastroenterol 105: 132-138.