Original Article

Effect of alcohol on the progress of hepatitis B cirrhosis

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Background: Hepatitis B virus (HBV) and alcohol are primary causes of cirrhosis. Alcohol can result in replication of HBV, an increase in oxidative stress, a compromised immune response to the virus and an increase in liver inflammation, all of which can result in progression of cirrhosis. The aim was to explore the interaction of alcohol with HBV and to show the effect of different levels of alcohol intake on liver fibrosis and cirrhosis.

Methods: We selected 90 patients with hepatitis B cirrhosis and divided them into three groups: non-drinking, moderate drinking and excessive drinking. Indicators of fibrosis (type III procollagen, type IV collagen, laminin, hyaluronic acid), HBV-DNA load, transaminases, quantitative detection of hepatitis B surface antigen (HBsAg), Child-Pugh scoring system rating and the number of complications were tested at three time points: 0, 3 and 6 months after quitting drinking and after medical treatment.

Results: We found that all indicators of fibrosis, HBV-DNA load, alanine (ALT) and aspartate (AST) transaminases in the excessive drinking group were highest among the three groups at any time. There were almost no differences between the moderate drinking and non-drinking groups at 0, 3 and 6 months after quitting drinking and treatment. We also found no difference among the three groups in quantitative detection of HBsAg at any time. It was observed that there are more patients with excessive drinking were in Child-Pugh C class and had more complications compared with the other two groups.

Conclusions: Patients with chronic HBV infection and an excessive drinking habit activate HBV-DNA which increases liver inflammation, thus accelerating the progress of liver cirrhosis. Moderate drinking had no significant effect on the progress of liver cirrhosis. Hepatitis B cirrhosis patients with excessive drinking had more complications and were more likely to be in Child-Pugh C class compared with the other groups.

Keywords: Alcohol intake; chronic hepatitis B; disease progression; liver cirrhosis

Submitted Nov 03, 2020. Accepted for publication Jan 17, 2021.
doi: 10.21037/apm-20-2353
View this article at: http://dx.doi.org/10.21037/apm-20-2353

Introduction

Hepatitis B virus (HBV) is a major global public health problem, and worldwide approximately 250 million people are infected (1). Long-term complications of infection include liver cirrhosis and hepatocellular carcinoma (HCC), which together cause over 500,000 deaths annually (2,3). The proportion of cirrhosis and HCC caused by HBV infection is respectively about 30% and 45% worldwide (4,5), and about 60% and 80% in China (6). Alcohol abuse also has important public health implications. The World Health Organization has reported that 3.3 million deaths, or 5.9% of all global deaths, are attributable to excess alcohol use (7). In particular, heavy alcohol consumption commonly causes progressive liver fibrosis, resulting in cirrhosis and eventually death. For those who have been infected with HBV, whether alcohol

will promote progression of hepatitis B cirrhosis is a subject of interest. The effect of the complex interaction between HBV and alcohol on liver damage is not fully understood. Alcohol will result in oxidative stress and weaken the body's immune response to the virus, which may contribute to the progression of cirrhosis (8). Whether or not there is an increase in the incidence of cirrhosis through synergy of alcohol and HBV remains controversial.

In this study we asked whether there were significant differences in indicators of fibrosis, alanine (ALT) and aspartate (AST) transaminases, HBV-DNA load, quantitative detection of hepatitis B surface antigen (HBsAg), Child-Pugh scoring system rating and the number of complications among three groups (excessive drinking, moderate drinking and non-drinking), and we explored whether and to what extent alcohol affects hepatitis B cirrhosis.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2353).

Methods

Patients

The study group of 90 patients with hepatitis B cirrhosis was selected from January 2016 to March 2019 at the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (No. 2020-479) and informed consent was taken from all the patients. The inclusion criteria were: (I) age between 20 and 80 years; (II) HBsAg detected in the serum for at least 6 months; and (III) clear diagnosis of hepatitis B cirrhosis by medical imaging, B-ultrasound, pathological biopsy and other auxiliary examinations.

The exclusion criteria were: (I) cirrhosis caused by autoimmune factors, non-alcoholic fatty cirrhosis, parasitic infection; and (II) co-infection with other viruses, including hepatotropic viruses (hepatitis A, C, D, E), human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, and others; and (III) presence of malignant tumor.

Grouping criteria

We asked patients about their drinking history and divided them into non-drinking, moderate drinking and excessive drinking groups of 30 people each, according to the 2018 updated Guidelines of Prevention and Treatment for Alcoholic Liver Disease (9).

Moderate drinking refers to a period of drinking ≤5 years and alcohol intake for men ≤40 g/day or ≤20 g/day for women. Excessive drinking refers to a period of drinking >5 years, and alcohol intake in excess of 40 g/day for men and 20 g/day for women. Amount of ethanol was calculated as alcohol consumption (mL) × ethanol content (%) × 0.8.

Patient treatment and monitoring

All patients were administered medical therapy after they were diagnosed with hepatitis B cirrhosis, which included nucleoside analogs against viruses, antifibrotic agents and regular liver protective treatment. In addition, patients in the moderate and excessive drinking groups ceased drinking during the experimental period. We recorded ALT and AST, bilirubin, HBV-DNA load, liver fibrosis serological indexes [type III procollagen (PIIINP), type IV collagen (CIV), laminin (LN), hyaluronic acid (HA)], HBsAg, Child-Pugh scoring system rating and the number of complications for each patient at 0, 3, and 6 months.

Statistical analysis

Statistical analysis was performed using IBM SPSS 20.0 (IBM Corp., NY, USA). Continuous variables are expressed as mean ± standard deviation or median (25–75th percentiles), as appropriate. Qualitative data are presented as number and percentage. The normal distribution of the measurement data is expressed as $\bar{x}\pm s$, and the data analysis was performed by k2 test and analysis of variance. Tukey's HSD (Tukey's honestly significant difference) method with two-by-two comparisons was applied to analyze the statistical differences between indicators of the testing groups. A P value <0.05 (two-tailed) was considered statistically significant.

Results

Clinical characteristics of the subjects

The sex ratio, age, HBV infection history, total bilirubin, albumin, and HBsAg of the three groups did not differ significantly, but ALT, AST, serum HBV-DNA, and the indicators of fibrosis differed significantly among the three

Table 1 Patients' characteristics (N=90)

Indicator	Median (interquartile range)/ composition frequency
Age (years)	51.2 (20.0–80.0)
Sex (female/male)	16/74
Albumin (g/day)	34.0 (16.0–50.0)
TBil* (μmol/L)	33.1 (6.6–389.6)
DBil* (μmol/L)	15.8 (0.3–346.0)
HBsAg* (log10 IU/mL)	1321.4 (0.0–25,000.0)
HA (ng/mL)	433.5 (167.0–1,489.0)
LN (ng/mL)	260.3 (88.0–581.0)
PIIINP (ng/mL)	23.3 (8.0–68.0)
CIV (ng/mL)	254.9 (256.0–638.0)
AST (IU/L)	138.7 (37.0–402.0)
ALT (IU/L)	90.8 (28.0–216.0)
HBV-DNA $<10^3$ copies	11/90
HBV-DNA: 10^3–10^5 copies	45/90
HBV-DNA $>10^5$ copies	34/90

*, data are expressed as median (interquartile range). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CIV, type IV collagen; DBil, direct bilirubin; HA, hyaluronic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LN, laminin; PIIINP, procollagen III peptide; TBil, total bilirubin.

groups (*Table 1*).

Factors influencing HBV-DNA

The excessive drinking group had more patients with higher HBV-DNA loads at any time among the three groups (*Table 2*). We found no difference in the number of patients with different HBV-DNA loads between the non-drinking and moderate drinking groups (*Table 2*).

Factors influencing AST and ALT

The excessive drinking group had the highest AST when compared with the other groups at any time (P<0.01, *Figure 1*, *Table 3*). However, AST decreased dramatically with time in every group. We found no difference between the moderate drinking and non-drinking groups at 6 months (P>0.05, P=0.124, *Figure 1*). Excessive drinkers had the highest ALT at any time compared with the other two groups (P<0.05, *Figure 1*, *Table 3*). ALT also progressively decreased after treatment in all group. Throughout, we found no difference between the moderate drinking and non-drinking groups at the 3rd and 6th months (P>0.05, P=0.526, P=0.134) (the P value in *Table 3* is the result of comparing three groups together).

Factors influencing indicators of fibrosis (HA, LN, PIIINP and CIV)

By univariate analysis, all indicators of fibrosis in the excessive drinking group were the highest among the three groups at any time (*Table 4*, *Figure 2*). We only observed a difference between the non-drinking and moderate drinking groups at 0 month for LN and CIV, and at 6 months for PIINP. No difference was observed between the non-drinking and moderate drinking groups for most of the time periods for the four indicators of fibrosis (*Figure 2*). We found all indicators of fibrosis among the three groups declined significantly after treatment. The period from 0 to 3 months after treatment showed a sharp decline in HA, LN and CIV for the non-drinking group compared with the other two groups (*Figure 2*).

Factors influencing quantitative detection of HBsAg

We found all 90 HBV-infected patients to have HBsAg at the beginning and after every 3 months of treatment. We found no difference between any two groups at any time (P>0.05) (*Figure 3*, *Table 5*).

Factors influencing the number of patients in Child-Pugh scoring system rating in each group

At the 0, 3, and 6 months, the number of patients with excessive drinking in Child-Pugh C class was highest among the three groups (P<0.001) (*Table 6*). Similarly, the number of non-drinking patients in Child-Pugh A class was the highest among the three groups (P<0.001) (*Table 6*). After 3–6 months of treatment, the number of patients in Child-Pugh C was still high (P>0.05) (*Figure 4*).

Factors influencing the number of complications in each group

The number of patients without complications was highest in the non-drinking group among the three groups at 0, 3, and 6 months (P<0.001) (*Table 7*).

Table 2 Comparison of HBV-DNA quantitative distribution among the three drinking groups at 0, 3 and 6 months

Group	No. of copies/mL	A	B	C	χ^2	P value	P (A *vs.* B)	P (A *vs.* C)	P (B *vs.* C)
0 month	$<10^3$	6	3	2	22.368	<0.001	0.242	<0.001	<0.001
	10^3–10^5	20	18	7					
	$>10^5$	4	9	21					
3 months	$<10^3$	15	13	6	16.841	0.002	0.807	<0.001	<0.05
	10^3–10^5	13	13	10					
	$>10^5$	2	4	14					
6 months	$<10^3$	21	19	9	14.279	0.006	0.83	<0.001	<0.05
	10^3–10^5	8	9	13					
	$>10^5$	1	2	8					

A, non-drinking group; B, moderate drinking group; C, excessive drinking group.

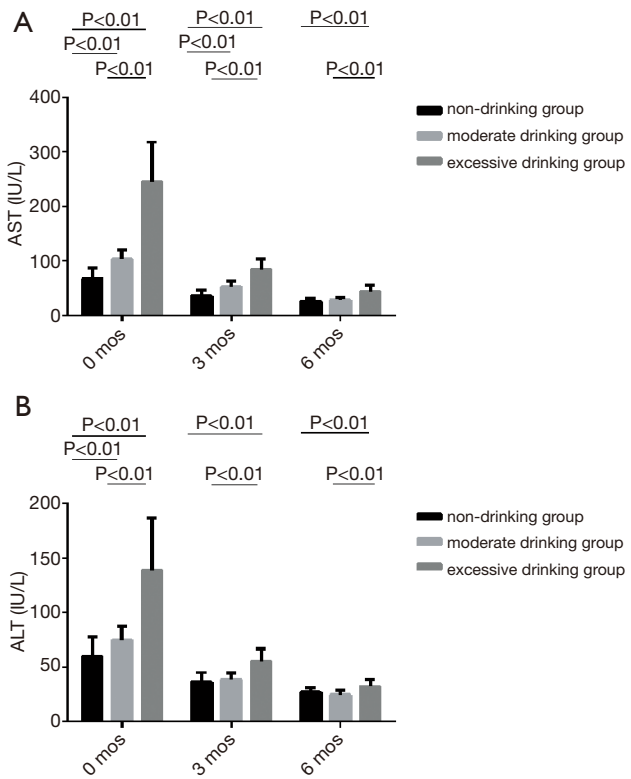

Figure 1 Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values at 0, 3 and 6 months for non-drinking, moderate drinking and excessive drinking groups. (A) AST values at 0, 3 and 6 months for non-drinking, moderate drinking and excessive drinking groups. (B) ALT values at 0, 3 and 6 months for non-drinking, moderate drinking and excessive drinking groups.

Discussion

HBV-DNA plays an important role in the progress of cirrhosis and HCC. Previous studies have shown that an elevated serum HBV-DNA level (≥10,000 copies/mL) is a strong, independent predictor of disease progression to cirrhosis and liver cancer (10,11). High HBV-DNA load activates the host's immune response to target and destroy infected liver cells, resulting in constant inflammation and necrosis of liver tissue. Repeated periods of immunologic activity with associated liver injury leads to liver fibrosis and HCC (12). Discussion of whether alcohol synergizes with HBV to accelerate the progress of liver cirrhosis is limited. In our study, we observed that the HBV-DNA load in the excessive drinking group was much higher than in the moderate drinking group. This result was consistent with previous work on HBV transgenic C.B-17 SCID mice fed a standard Lieber-DeCarli ethanol liquid diet, showing viral DNA in serum increased by up to 7-fold in the experimental mice compared with mice fed the control diet (13). Similarly, Ganne-Carrié *et al.* (14) showed that in the HEP G2 hepatitis B DNA positive cell line the concentration of HBsAg increased after exposure to ethanol, in both the cells and the culture medium, although the increase was only significant with 200 mM ethanol. Pre-S1 and Pre-S2 envelope proteins levels also increased in the culture medium. In addition, CYP2E1-induced oxidative stress potentiates the ethanol-induced transactivation of HBV (15). Conclusions can also be drawn from clinical research results combined with laboratory research results that excessive alcohol may influence the HBV-DNA load, whereas moderate drinking may have less influence. Previous

Table 3 Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values for the non-drinking, moderate and excessive drinking groups at 0, 3 and 6 months

Group	Transaminase	A	B	C	P value
0 month	AST	67.73±20.31	103.43±17.39	245.03±73.74	<0.001
	ALT	59.67±18.37	74.70±12.78	138.10±48.45	<0.001
3 months	AST	37.13±9.01	53.33±10.70	84.53±18.51	<0.001
	ALT	36.63±8.44	38.70±6.10	55.07±11.61	0.001
6 months	AST	26.57±5.17	29.07±4.54	43.90±12.35	<0.001
	ALT	26.93±4.41	24.80±4.05	32.43±6.31	0.021

Data are expressed as the mean ±standard deviation. A, non-drinking group; B, moderate drinking group; C, excessive drinking group.

Table 4 HA, LN, PIIINP and CIV values at 0, 3 and 6 months for the non-drinking, moderate drinking and excessive drinking groups

Group	Indicators of fibrosis	A	B	C	P value
0 month	HA	385.04±77.03	357.98±108.75	557.64±269.69	<0.001
	LN	261.85±63.85	186.63±73.94	332.39±148.04	<0.001
	PIIINP	19.51±5.53	23.50±8.58	26.66±12.18	0.02
	CIV	268.72±53.01	191.44±73.34	304.61±145.65	<0.001
3 months	HA	261.37±71.11	258.71±87.05	479.89±218.51	<0.001
	LN	176.31±46.26	133.72±51.39	273.14±133.65	<0.001
	PIIINP	16.25±3.39	15.12±2.98	22.39±7.82	<0.001
	CIV	188.03±50.45	134.77±46.88	254.12±119.71	<0.001
6 months	HA	161.51±31.58	191.99±70.34	378.88±182.95	<0.001
	LN	108.84±22.23	105.93±37.66	200.27±88.22	<0.001
	PIIINP	11.18±2.48	13.55±2.57	19.48±4.91	<0.001
	CIV	119.07±24.93	112.77±39.91	207.61±99.42	<0.001

A, non-drinking group; B, moderate drinking group; C, excessive drinking group. CIV, type IV collagen; HA, hyaluronic acid; LN laminin; PIIINP, type III procollagen.

studies have shown that an elevated serum HBV-DNA level (≥10,000 copies/mL) is an independent risk predictor of disease progression to cirrhosis and HCC (16,17). When the HBV-DNA load is high, specific cytotoxic T cells are at a low level but HBV can be cleared by non-specific CD8+ cells. Excessive drinking can also elevate the HBV-DNA load by weakening the cellular immune response to viral structural proteins (18). The weakening of the immune response causes the human body to be in an immune-tolerant state, compromising the clearance of HBV by the immune system, resulting in persistent inflammation.

We also observed that the levels of ALT and AST in the serum of the excessive drinkers were highest among all groups at the beginning of treatment and at the 3rd month, but there was no significant difference between the three groups at 6 months. We therefore conclude that excessive alcohol is more likely to cause liver inflammation. Nonetheless, the levels of ALT and AST in the excessive drinkers decreased to a normal level after prolonged treatment including nucleoside analogs against viruses, antifibrotic treatment and regular liver protective treatment etc. Acetaldehyde produced by alcohol during liver oxidation is highly toxic; for example, it can prompt Kupffer cells to release inflammatory substances such as tumor necrosis factor (19). Alcohol itself can cause liver inflammation (19); Ha *et al*. showed that the level of ALT

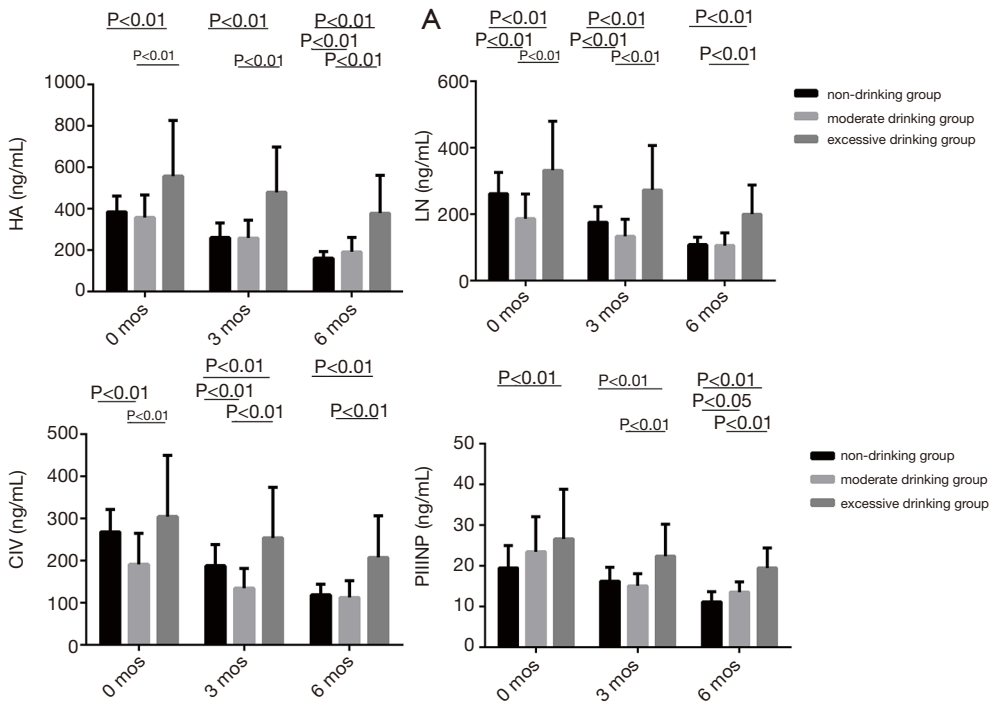

Figure 2 Indicators of fibrosis [type III procollagen (PIIINP), type IV collagen (CIV), laminin (LN), hyaluronic acid (HA)] at 0, 3 and 6 months for non-drinking, moderate drinking and excessive drinking groups.

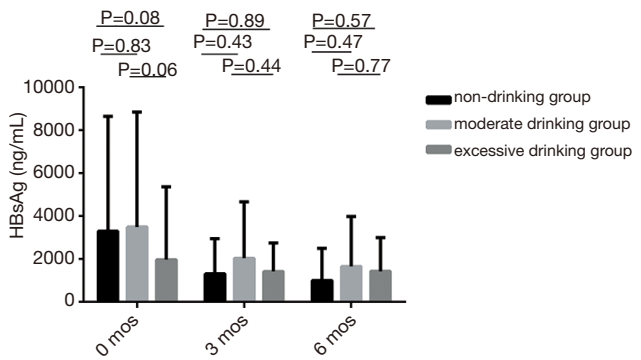

Figure 3 Hepatitis B surface antigen (HBsAg) values at 0, 3 and 6 months for non-drinking, moderate drinking and excessive drinking groups.

was elevated in HBx (hepatitis B virus X gene) transgenic mice fed a 25% ethanol liquid diet for 12 weeks relative to water-fed controls (20), which is consistent with our finding. Compared with the effect of alcohol alone, HBV combined with alcohol can accelerate histological changes in the liver. In histological evaluations, the livers of ethanol-fed HBx transgenic rats showed more evident hepatocyte enlargement and fatty changes compared with those of ethanol-fed control rats, suggesting that antioxidant defenses are compromised by HBx-promoted alcoholic liver injury. We observed that when the HBV-DNA load was the highest in the excessive drinking group at 0 and 3 months, AST and ALT are also at their highest levels. We therefore conclude that HBV-DNA might be associated with AST and ALT in liver inflammation. Recently, the intracellular HBV covalently closed circular DNA level was reported to be positively correlated with serum ALT level and liver histological inflammation grade in some cross-sectional studies (21,22). When HBV DNA is integrated into host DNA, covalently closed circular DNA, which serves as a template for transcription of viral RNA, can persist indefinitely within the long-lived hepatocyte nucleus, and serve as a reservoir of viral replication (23). This indicates that high HBV-DNA load will readily cause high AST and ALT levels.

Finally, we observed that the highest indicators of fibrosis consistently occurred in the excessive drinking group at 0, 3 and 6 months, and that there were no significant differences between moderate drinkers and non-drinkers for HA and PIIINP at 0 and 3 months. These results showed that

Table 5 Hepatitis B surface antigen (HBsAg) values at 0, 3 and 6 months for the non-drinking, moderate drinking and excessive drinking groups

Group	A	B	C	P value
0 month	1,483.2 (568.12–3,462.23)	1,458.6 (109.74–4,381.07)	1,131.7 (504.52–1,675.47)	0.413
3 months	843.71 (312.90–1,513.43)	1,044.3 (109.77–2,928.93)	1,004.8 (654.07–1,766.49)	0.302
6 months	415.68 (157.91–898.75)	839.47 (108.34–2,014.76)	909.99 (542.68–1,539.26)	0.38

Data expressed as the median (interquartile range). A, non-drinking group; B, moderate drinking group; C excessive drinking group.

Table 6 Number of patients in the Child-Pugh scoring system in each group at the three time points

Group	Child A	Child B	Child C	P value
0 month				<0.001
Non-drinking	24	2	4	
Moderate drinking	6	21	3	
Excessive drinking	0	4	26	
3 months				<0.001
Non-drinking	23	4	3	
Moderate drinking	8	20	2	
Excessive drinking	0	4	26	
6 months				<0.001
Non-drinking	23	6	1	
Moderate drinking	11	18	1	
Excessive drinking	0	8	22	

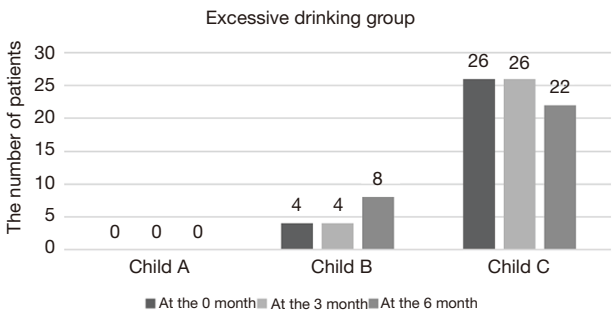

Figure 4 Numbers of patients in Child-Pugh scoring system in the excessive drinking group at 0, 3, and 6 months.

excessive alcohol intake may have some influence on liver fibrosis, which results in cirrhosis. Rapid progression of fibrosis is usually the consequence of several factors, with HBV-DNA load being most important. When HBV-DNA was the highest in excessive drinkers at 0, 3 and 6 months, the indicators of fibrosis were also at their highest. Repetitive or long-lasting inflammation is another factor, driving progressive fibrogenesis (enhanced synthesis of the extracellular matrix) by induction of profibrogenic cytokines/growth factors and other mediators that activate the downstream effectors of fibrosis (24-29). Nuclear factor-κB and activin 1 further induce Kupffer cells to promote stellate cell activation to produce excess extracellular matrix (mainly type I and type III collagen), promote liver fibrosis, cirrhosis, and even progress to HCC (30). Importantly, HBV-DNA levels correlate with necroinflammatory activity, and because liver fibrosis is mainly stimulated by hepatic necroinflammatory activity, the fibrogenic process could be reduced as a result of suppression of HBV (31). In a retrospective cohort study of 966 cirrhotic patients in Taiwan, with a mean follow-up period of 2.9–5.2 years, the annual incidence of cirrhosis and HCC was significantly higher in 632 cirrhotic patients with HBV infection and heavy alcohol consumption (≥80 g/day for ≥5 years) than in 132 patients with HBV infection alone (32). The study in reference 32 is also consistent with the findings of Donato *et al.*, who further quantified the synergistic effect of drinking and HBV infection on cirrhosis and HCC: when alcohol consumption was >60 g/day, the synergy index of ethanol and HBV infection promoting cirrhosis and HCC was 1.8 (33), although the exact mechanism needs further research.

Table 7 Number of complications in each group

Group	No. of complications						P value
	0	1	2	3	4	5	
Non-drinking	12	10	5	2	1	0	<0.001
Moderate drinking	4	11	9	4	2	0	
Excessive drinking	0	5	8	12	4	1	

Different alcohol intake has different effects on liver fibrosis with HBV. Excessive drinking may promote liver

fibrosis and cirrhosis. Ribes *et al*. followed 2,352 HBsAg-positive patients for 20 years in a prospective cohort study, and found that lifetime alcohol consumption (>60 g/day) was associated with a 6-fold increase in the risk of death from cirrhosis and HCC (34). Moderate drinking habits might not directly cause liver fibrosis. A prospective cohort study in Korea that followed 4,495 HBsAg-positive and 433,239 HBsAg-negative men for a median observation period of 10 years suggested that moderate alcohol consumption (≥25 g/day of ethanol) raised the RR (relative risk) of mortality from HCC to 1.13 in HBsAg-positive men but no significant effect was observed (35). Liver biopsy is the gold standard for detecting liver fibrosis (36), but being an invasive test, it was unacceptable for many patients. Also, some patients were not regularly tested for transient elastography, and therefore the data were not sufficient for statistical analysis.

This study showed that the number of patients with excessive drinking who were in Child-Pugh C class was the highest among the three groups. Similarly, the number of non-drinking patients in Child-Pugh A class was the highest among the three groups. This finding indicated that chronic hepatitis B patients with alcohol abuse will show accelerated progress of cirrhosis and even a decompensation period, which is consistent with some evidence suggesting that excessive alcohol intake by HBsAg-positive patients was associated with an increase in liver necroinflammatory changes (37). Moreover, we found that after 3–6 months of treatment, the number of patients with excessive drinking in Child-Pugh C class was still high, which suggested permanent damage to these patients' livers from alcohol abuse. It is also likely that alcohol abuse may impair the response to therapy in chronic hepatitis B patients. We also found that hepatitis B patients with excessive drinking were likely to be in the decompensation stage during which patients usually die, Marcellin *et al*. found an obvious link between alcohol consumption and death in these patients (38).

We also found that after taking some effective measures, the level of cirrhosis in the three groups improved. There is now increasing evidence in animal models as well as in humans that fibrosis and even cirrhosis can regress or even revert to normal architecture if there is no further injury to the liver. In a rodent model of cirrhosis induced by repeated injections of carbon tetrachloride, once cirrhosis was established and injections were discontinued, the architecture of the liver became nearly normal and fibrosis regressed significantly, resulting in a lobular architecture as well as some focal nodular organization (39). Schiff *et al*. (40) evaluated the improvement in liver histology in 10 patients with advanced fibrosis or cirrhosis (Ishak fibrosis score 4–6), who received long-term antiviral treatment (≈6 years, range: 267–297 weeks). All patients had liver biopsies at baseline, week 48, and long term, and histological improvement of at least 1 point on the Ishak fibrosis score was found in all patients after long-term treatment. Those results clearly show that cessation of the source of injury is the major and probably only condition needed for regression of cirrhosis (41). Our research showed that the indicators of fibrosis improved after patients adopted treatment involving quitting drinking, antiviral therapy and anti-inflammatory treatment, indicating that after appropriate treatment, cirrhosis may be reversible to some extent.

Interestingly, we found no differences in HBsAg among the three groups of a limited number of patients. Further research on a larger scale and for a longer period of time is required to reach more concrete and reliable conclusions. Due to the short 6-month period we could not be confident that we had observed the full changes in HBsAg. With regard to patients with chronic HBV infection, excessive drinking, but not moderate drinking, has a significant effect on the process of liver cirrhosis. Our work is therefore of significance to drinkers with chronic HBV infection whose risk of progression of hepatitis B cirrhosis can be prevented by changes to lifestyle and appropriate medical intervention.

Acknowledgments

Funding: This work was supported by the Chongqing Medical University First Affiliated Hospital Infectious Diseases Department.

Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2353

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-20-2353

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2353). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (No. 2020-479) and informed consent was taken from all the patients.

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(English Language Editor: K. Brown)

Cite this article as: Zhou E, Yang C, Gao Y. Effect of alcohol on the progress of hepatitis B cirrhosis. Ann Palliat Med 2021;10(1):415-424. doi: 10.21037/apm-20-2353

