CORRESPONDENCE

HBV Genotypes and Outcome of HBV Infection

To the Editor:

We read with interest the editorial on the correlation between hepatitis B virus (HBV) genotypes and outcome of HBV infection by Fung and Lok.[1] This article made a succinct outline of the epidemiology of HBV genotypes and their association with hepatitis B e antigen seroconversion, activity of liver disease, and response to treatment. We believe that this article will be helpful to hepatologists when facing the explosion of knowledge regarding HBV genotypes in the literature. However, the authors inferred from our previous data[2] that genotype B may be associated with accelerated progression to hepatocellular carcinoma (HCC). This may be somewhat misleading, and we would like to address some comments to clarify this issue.

In Taiwan, our first cross-sectional study indicated that more than 50% of HBV-related HCC patients were infected with genotype B. In addition, genotype C was more prevalent in patients with HCC who were older than 50 years, whereas genotype B was more common in those with HCC who were age 50 years or younger. This predominance of genotype B was more substantial in younger patients with HCC, amounting to 90% in those age 35 years or younger, and most of them did not have cirrhosis. To confirm this preliminary observation from only 80 HCC patients, a further survey of 200 surgical cases showed that the prevalence of genotype C was indeed higher in older HCC patients, while that of genotype B was higher in young HCC patients.[3] This observation also extends to HBV-related childhood HCC. In a recent study, we demonstrated that genotype B was still the major genotype (74%) in 26 children with HCC.[4] Taken together, these lines of evidence strongly suggest that certain genotype B subtypes or strains are associated with the earlier development of HCC in Taiwan.

Thus, the genotype B strains in Taiwan may be different from those in Japan and China where HCC development is less frequent and occurs at an older stage in patients with genotype B.[5–7] We have proposed that genotype B can be divided into three phenotypes based on the rate of liver disease progression.[8] The first is the slowly progressive phenotype that is associated with a tendency for early hepatitis B e antigen seroconversion during a carrier's lifetime or in the course of chronic hepatitis, which subsequently leads to the low death rate from HCC. The second is the intermediately progressive phenotype that runs a typical natural course of chronic HBV infection with the development of HCC, usually in the patient's 50s. The third is the rapidly progressive phenotype that is associated with the development of HCC in young HBV carriers before they reach 40 years of age, even in the absence of cirrhosis.

In summary, HBV genotypes do account for the heterogeneity in clinical manifestations and treatment response among patients with chronic hepatitis B in different parts of the world; however, the paradoxical findings of genotype predominance in HCC patients between Taiwan and other countries deserve further examinations.

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References

1. Fung SK, Lok AS. Hepatitis B virus genotypes: do they play a role in the outcome of HBV infection? Hepatology 2004;40:790–792.
2. Kao JH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology 2000;118:554–559.
3. Kao JH. Hepatitis B viral genotypes: clinical relevance and molecular characteristics. J Gastroenterol Hepatol 2002;17:643–650.
4. Ni YH, Chang MH, Wang KJ, Hsu HY, Chen HL, Kao JH, et al. Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma. Gastroenterology (in press).
5. Sumi H, Yokosuka O, Seki N, Arai M, Imazeki F, Kurihara T, et al. Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease. Hepatology 2003;37:19–26.
6. Orito E, Mizokami M, Sakugawa H, Michitaka K, Ishikawa K, Ichida T, et al. A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Japan HBV Genotype Research Group. Hepatology 2001;33:218–223.
7. Ding X, Mizokami M, Yao G, Xu B, Orito E, Ueda R, et al. Hepatitis B virus genotype distribution among chronic hepatitis B virus carriers in Shanghai, China. Intervirology 2001;44:43–47.
8. Kao JH. Hepatitis B virus genotypes and hepatocellular carcinoma in Taiwan. Intervirology 2003;46:400–407.

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Reply:

We thank Drs. Kao and Chen for their comments on our recent editorial.[1] They provided additional data to support the finding that in Taiwan, HBV genotype B is associated with HCC at a younger age, suggesting that the subtype of HBV genotype B encountered in Taiwan is associated with accelerated progression to HCC. Recent studies showed that there are two major subtypes of HBV genotype B: Ba, which represents recombination between genotype B and C and is found in many parts of Asia; and Bj, which does not have recombination with genotype C and is predominantly found in Japan.[2] It is certainly possible that the discrepant findings between studies from Taiwan and Japan are related to different subtypes of genotype B. However, Ba is also the predominant subtype in China and yet studies from Hong Kong and China found that patients with genotype B had lower risk of HCC than those with genotype C.[3]

We agree that each HBV genotype may be associated with more than one phenotype and that further studies are needed to identify the factors that are associated with each phenotype.

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References

1. Fung SK, Lok AS. Hepatitis B virus genotypes: do they play a role in the outcome of HBV infection? Hepatology 2004;40:790–792.
2. Sugauchi F, Orito E, Ichida T, Kato H, Sakugawa H, Kakumu S, et al. Epidemiologic and virologic characteristics of hepatitis B virus genotype B having the recombination with genotype C. Gastroenterology 2003;124:925–932.
3. Chan HLY, Hui AY, Wong ML, Tse AML, Hung LCT, Wong VWS, et al. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. Gut 2004;53:1494–1498.

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Benefit of TIPS for Patients With Refractory or Recidivant Ascites: Serum Bilirubin May Make the Difference

To the Editor:

The recent Italian trial of transjugular intrahepatic portosystemic stent shunt (TIPS) versus paracentesis for patients with refractory or recidivant ascites[1] provides valuable information and stimulates considerations regarding the real value of TIPS for these patients. The study also adds to the three other large randomized trials recently published.[2–4] These four studies, with a total of 305 patients, provide unanimous evidence that TIPS allows for much better control of ascites compared with repeated paracentesis: a complete response following TIPS has been observed in 51% to 79% compared with 3% to 24% in the paracentesis groups. Furthermore, quality of life is improved in patients with ascites after TIPS, particularly in patients with a complete response,[5] supporting earlier investigations of quality of life after TIPS for various indications.[6,7]

However, the effect of TIPS on patient survival has been controversial. The present study[1] confirms our previous observations[2] and tips the balance toward improved survival. A North American trial[3] found a nonsignificant trend in favor of TIPS, while a Spanish study[4] clearly argued against a survival benefit for TIPS. How can these discrepant results be reconciled? The etiology of cirrhosis (alcoholic in 42% and 79% of the trials showing survival benefit[1,2] vs. 51% and 62%, respectively, in the trials without survival benefit[3,4]) does not seem a likely explanation. Nor is the proportion of patients with Child-Turcotte-Pugh class C (76% and 38% vs. 37% and no detailed information in the Sanyal trial). Rather, we hypothesize that inclusion of patients with a serum bilirubin level above 3 mg/dL may make the difference. In our study,[2] as well as in the Spanish trial,[4] serum bilirubin was found to be an independent predictor of survival in multivariate and univariate analyses, respectively. The present study did not analyze bilirubin because it is a part of the MELD (model for end-stage liver disease) score, which was identified as a survival predictor by the authors.[1] Interestingly, baseline serum bilirubin was also described as a powerful independent predictor of mortality after TIPS for variceal bleeding.[8] Table 1 shows that in the Spanish trial, patients could be included with a serum bilirubin level of up to 10 mg/dL, whereas cutoff values were much lower for the other studies. Although the actual baseline values do not seem to differ much when given as mean and standard error, a closer look reveals that a substantial proportion of the Spanish trial must have been patients with a baseline bilirubin level greater than 3 mg/dL. Unfortunately, the exact percentage is only available in our trial (21%). Serum bilirubin concentrations 3 and 6 months after TIPS were increased in all studies. Interestingly however, the variation is much lower in the trials with survival benefit[1,2] compared with the studies showing no benefit.[3,4] Judging from the mean values and standard error provided, some patients in the Spanish and United States trials had serum bilirubin levels above 12 mg/dL 6 months following TIPS. Not surprisingly, liver failure was reported as the most common cause of death in these studies.

Table 1. Bilirubin Serum Concentrations (mg/dL) in TIPS Trials (Mean ± SEM)

	Italian[1]	German[2]	Spanish[4]	U.S.[3]
Cutoff for study inclusion	6	5	10	5
Baseline	1.6 ± 0.1	1.7 ± 0.2	2.0 ± 0.2	1.9 ± 0.2
Follow-up	2.1 ± 0.2	2.9 ± 0.9	4.6 ± 2	2.2 ± 2.1

Another aspect deserves attention. All studies were analyzed as intent-to-treat and allowed for crossover of treatments. Interestingly, the proportion of patients randomized to paracentesis but ultimately receiving TIPS was higher in the Italian and German trials (11 of 33 and 10 of 31, respectively) than in the other two studies (3 of 35 and 2 of 57). Thus, one may speculate that the actual benefit of TIPS may be even higher than demonstrated. Altogether, the publication by Salerno et al.[1] is in accordance with our contention that TIPS may be particularly useful for patients with massive ascites and serum bilirubin levels below 3 mg/dL.

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References

1. Salerno F, Merli M, Riggio O, Cazzaniga M, Valeriano V, Pozzi M, et al. Randomized conrolled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. HEPATOLOGY 2004;40:629–635.
2. Rössle M, Ochs A, Gülberg V, Siegerstetter V, Holl J, Deibert P, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342:1701–1707.
3. Sanyal AJ, Genning C, Rajender Reddy K, Wong F, Kowdley KV, Benner K, et al. The North American study for the treatment of refractory ascites. Gastroenterology 2003;124:634–641.
4. Ginès P, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Ruiz Del Arbol L, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123:1839–1847.
5. Gülberg V, Liss I, Bilzer M, Waggershauser T, Reiser M, Gerbes AL. Improved quality of life in patients with refractory or recidivant ascites after insertion of transjugular intrahepatic portosystemic shunts. Digestion 2002;66:127–130.
6. Nazarian GK, Ferral H, Bjarnason H, Castaneda-Zuniga WR, Rank JM, Bernadas CA, et al. Effect of transjugular intrahepatic portosystemic shunt on quality of life. AJR Am J Roentgenol 1996;167:963–969.
7. Zhuang ZW, Teng GJ, Jeffery RF, Gemery JM, D'Othee BJ, Bettmann MA. Long-term results and quality of life in patients treated with transjugular intrahepatic portosystemic shunts. AJR Am J Roentgenol 2002;179:1597–1603.
8. Rajan DK, Haskal ZJ, Clark TW. Serum bilirubin and early mortality after transjugular intrahepatic portosystemic shunts: results of a multivariate analysis. J Vasc Interv Radiol 2002;13:155–161.

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Dietary Fiber Decreases Ammonia Levels in Patients With Cirrhosis

To the Editor:

We read with interest the paper by Liu et al. recently published in HEPATOLOGY in which they demonstrated that oral coadministration of fermentable fiber and live bacteria significantly improved gut flora, plasma ammonia levels, neuropsychological tests, endotoxemia, and the Child-Turcotte-Pugh score in patients with liver cirrhosis.[1] They also demonstrated that fermentable fiber alone has similar therapeutic benefit. They assessed the effect of fermentable fiber by quantitative bacteriological and pH analysis of fecal samples.[1] We have also under-

Table 1. Changes in Blood Tests and Nutritional Element in Food Intake Before and After Fermentable Fiber Therapy

Blood Tests	Fiber Group		Control Group	
	At entry	After 30 days	At entry	After 30 days
Albumin (g/dL)	3.4 ± 0.6	3.3 ± 0.6	3.1 ± 0.4	3.1 ± 0.4
Ch-E (ΔpH)	0.48 ± 0.19	0.48 ± 0.2	0.4 ± 0.12	0.4 ± 0.13
Plasma ammonia (μmol/L, normal <40)	49.5 ± 26.8	37.1 ± 19.8*	43.8 ± 24.3	52.9 ± 20.9
Prothrombin time (%)	73.7 ± 14.6	75.5 ± 15.2	70.7 ± 12.9	70.5 ± 14.9
SCFA (μmol/L, normal 60–100)	31.2 ± 9.8	39.7 ± 6.9*	24.3 ± 6	26.6 ± 8
DAO (U/L, normal 10–15)	11.1 ± 4.3	14 ± 5*	10.6 ± 3.2	10.1 ± 3.4

Nutritional Element in Food Intake	Fiber Group		Control Group	
	At entry	After 30 days	At entry	After 30 days
Energy (kcal)	1618 ± 203	1659 ± 235	1857 ± 319	1913 ± 261
Protein (g)	58 ± 12	63 ± 13	58 ± 16	64 ± 15
Fat (g)	40 ± 10	40 ± 7	34 ± 10	39 ± 12
Carbohydrate (g)	256 ± 32	269 ± 51	320 ± 51	318 ± 40
Fiber (g)	12 ± 5	26 ± 6*	11 ± 4	11 ± 4

NOTE. Data are mean ± standard deviation.
Abbreviation: Ch-E, cholinesterase.
*$P < .05$ vs. data at entry.

taken a similar study but evaluated the effect by measuring plasma ammonia, serum short-chain fatty acid (SCFA) levels, and serum diamine oxidase (DAO) activity.[2]

In our study, 24 outpatients with viral cirrhosis were randomly assigned into 2 groups. A fermentable fiber product, Healsh Fiber (Ajinomoto Co., Ltd., Tokyo, Japan), containing 5 g of galactomannans per package was used. It was supplemented to food and given to 12 patients in the fiber group (7 men and 5 women; mean age, 60 ± 6 years; Child-Turcotte-Pugh classification: 6 patients in Group A, 3 in Group B, and 3 in Group C) at 5 g ter in die for 30 days. The blood levels of albumin, cholinesterase, ammonia, prothrombin time, SCFA, and DAO were measured before and 30 days after treatment. To evaluate nutrition status, meals for 3 days were recorded, and the fiber and energy intakes were calculated. To use as controls, blood tests and diet recordings were performed in 12 patients with cirrhosis (6 men and 6 women; mean age, 65 ± 5 years; Child-Turcotte-Pugh classification: 7 patients in Group A, 2 in Group B, and 3 in Group C) without fiber intake. During the observation period, other medications were not changed. Informed consent was obtained from all patients, and the Ethics Committee of Mie University School of Medicine approved the investigation protocol. Serum SCFA levels and DAO activity were measured by high-performance liquid chromatography and high sensitivity colorimetric methods.[3–5] The sum of acetic acids, propionic acid and *n*-butyric acids levels was regarded as the level of SCFA. The background and changes in test results between the 2 groups were compared by using Mann-Whitney *U* test and Wilcoxon rank test, respectively. A *P* value less than .05 was considered as statistically significant.

There was no significant difference in patients' background and dietary intake at entry. High individual variability was observed in fiber intake, ranging from 7 to 21 g/d before the test. In the fiber group, ammonia levels significantly decreased from 49.5 ± 26.8 to 37.1 ± 19.8 μmol/L ($P < .05$), while SCFA levels and DAO activity significantly increased from 31.2 ± 9.8 and 11.1 ± 4.3 to 39.7 ± 6.9 μmol/L and 14.0 ± 5.0 U/L, respectively (both, $P < .05$). The results of other tests were not significantly changed. In the control group, neither blood test results nor nutritional element in food intake significantly changed during the observation period (Table 1).

Fermentable fiber intake appears to change gut flora and increase SCFA, resulting in decreased plasma ammonia levels but increase in DAO activity. A decrease in pH with SCFA production in large intestine also appears to improve plasma ammonia levels.[1] Fermentable fiber intake may be a supplementary treatment for patients with cirrhosis.

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References

1. Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. HEPATOLOGY 2004;39:1441–1449.
2. Rokkas T, Vaja S, Murphy GM, Dowling RH. Postheparin plasma diamine oxidase in health and intestinal disease. Gastroenterology 1990;98: 1493–1501.
3. Nakao M, Ogura Y, Satake S, Ito I, Iguchi A, Takagi K, et al. Usefulness of soluble dietary fiber for the treatment of diarrhea during enteral nutrition in elderly patients. Nutrition 2002;18:35–39.
4. Takagi K, Nakao M, Ogura Y, Nabeshima T, Kunii A. Sensitive colorimetric assay of serum diamine oxidase. Clin Chem Acta 1994;226:67–75.
5. Hoshi S, Sakata T, Mikuni K, Hashimoto H, Kimura S. Galactosylsucrose and xylosylfructoside alter digestive tract size and concentrations of cecal organic acids in rats fed diets containing cholesterol and cholic acid. J Nutr 1994;124:52–60.

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