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ScienceDirect

Journal of the Chinese Medical Association 79 (2016) 179−184

www.jcma-online.com

Original Article

The impact of chronic carrier of hepatitis B virus on liver function in a 7-day ultramarathon race

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Received August 14, 2015; accepted October 22, 2015

Abstract

Background: Several changes in physiological characteristics occur during long-distance and 24-hour ultramarathons, including hyponatremia, skeletal muscle breakdown, plasma volume changes, iron depletion, anemia, and possible hepatic damage. The purpose of this study was to investigate the impact of hepatitis B virus (HBV) carrier status on liver function during multi-day races.
Methods: This prospective study recruited 10 Taiwanese runners who were scheduled to participate in the 7-day 2008 Athens Ultramarathon Festival Race, and three of them were chronic carriers of HBV. Blood samples were collected before, during, and 3 days after the race, including alkaline phosphatase (ALP), albumin (ALB), total protein (TP) levels, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (T-BIL)
Results: Ten Taiwanese runners (40% female; average age 52.3 ± 7.9 years) who all planned to run in the race were recruited. Three runners were chronic carriers of HBV (HBV carrier), and all participants were anti-HCV antibody-negative and anti-hepatitis A virus (HAV) IgG-positive. There were no significant time-by-group effects on ALP, ALB, and TP levels, but the change over time effects were significant ($p < 0.001$, $p = 0.001$ and $p = 0.010$, respectively). ALT, AST, and T-BIL increased significantly to markedly higher levels in the HBV carrier group compared to the non-carrier group (group effect $p = 0.009$, $p = 0.004$, and $p = 0.05$, respectively), and the time-by-group interaction was also significant for these liver function markers ($p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively).
Conclusion: Compared to their counterparts, runners who are HBV carriers had significantly greater increases in levels of ALT, AST, and T-BIL during a 7-day ultramarathon, indicating that the liver function of carriers is more highly impacted in these races.

Keywords: hepatitis B virus (HBV); liver function; 7-day races; ultramarathon

1. Introduction

In recent decades, ultramarathons have become increasingly popular. An ultramarathon is a sporting event where participants run distances longer than the traditional marathon length of 42.195 km (26 miles), according to the official definition of marathon originating from ancient Greece.[1] There are two general types of events: (1) those covering a

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2015.10.006

specified distance; and (2) those covering a specified period of time. In recent years, an increasing number of athletes have been participating in multiday races, such as 6- or 7-day ultramarathons. In such races, athletes can independently allocate their time spent resting and racing during each day. In preparation for the race, most participants schedule and undergo a moderate-intensity ultra-endurance running exercise, which includes hours of scheduled rest every day. As a gauge of their overall race capacity and performance, many participants view recovering physiological stability to be more important than maintaining explosive force.

Numerous reports have been published on changes in physiological characteristics that occur during long-distance and 24-hr ultramarathons,[2–8] including hyponatremia, skeletal muscle breakdown, plasma volume changes, iron depletion, anemia, and possible hepatic damage. It has been established that physical exercise results in elevated liver function tests for enzymes such as lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T-BIL), and alkaline phosphatase (ALP).[9–11] These results indicate that liver cell damage does occur in runners, and additionally that reduced albumin (ALB) levels reflect damage to the proper anabolic functioning of hepatic cells. The liver damage observed in these runners is directly proportional to the workload experienced.[2] However, to the best of our knowledge, there have been no previous studies investigating liver function in runners participating in 7-day ultramarathons.

Hepatitis B virus (HBV) infection is one of the most common infectious diseases in the world. An estimated 240 million people are chronically infected with the disease,[12] as manifested by persistence of the virus and HBV surface antigen (HBsAg) in serum, and production of viral antigens and HBV DNA in the liver. HBV attacks the liver, causing acute and chronic disease; more than one million individuals die annually of HBV-related chronic liver disease.[13] Taiwan is a hyperendemic area for liver disease, where the seroprevalence of HBV and HCV is estimated to be 17.3% and 4.4%, respectively.[14,15]

In Taiwan, the first 100-km ultramarathon was held in 1998, and a 24-hour ultramarathon has taken place annually since 1999. Because increasing numbers of runners participate in such events each year, understanding changes in the athletes' physiological conditions has become increasingly important; however, the impact of being a chronic HBV carrier in such circumstances remains unclear.

The first objective of our study was to determine the changes in runners' liver function as demonstrated by tests on consecutive days of a 7-day ultramarathon, while the secondary objective was to explore the impact under those conditions of being a chronic carrier of HBV.

2. Methods

All Taiwanese entrants into the 7-day 2008 Athens Ultramarathon Festival Race were invited to participate in the study. For those who chose to enroll, all participants completed pre-race (Day 0), in-race (Days 1–7), and post-race (Days 8 and 10) examinations, as follows: (1) pre-race (Day 0): height and weight were recorded, and blood samples were collected in the afternoon for basic measurements by the medical team. Participants signed a consent form and filled out a health questionnaire; (2) in-race (Days 1–7): blood samples were collected in the mornings of all 7 days of the race. Running distances were recorded each day, as was any physical discomfort noted by the athletes. The clinical experience of each athlete guided administration of any necessary medication, and the athletes' regular medications were assessed by the medical team for the possibility of causing liver damage; (3) post-race (Days 8 and 10): blood samples were taken on these 2 days of the 3-day rest period following the competition. Day 10 samples were also used for checking hepatitis markers, including HBsAg, HBV surface antibody (HBsAb), anti-HCV antibody, and IgG antibody to hepatitis A virus (anti-HAV IgG).

Venous blood samples were collected from the athletes by vein puncture. Four vacutainer tubes were centrifuged at 1500*g* for 10 minutes, and then plasma was dispensed into Eppendorf tubes (1.5 mL capacity) and immediately stored at −80ºC for future analysis. The Piccolo Comprehensive Metabolic Panel was used for analysis of ALB, total protein (TP), ALP, AST, ALT, and T-BIL. This study was approved by the Ethics Committee of the Institutional Review Board of Taipei Veterans General Hospital, VAC, and was furthermore conducted according to international ethical standards as described by Harriss and Atkinson.[16]

2.1. Statistical analysis

Means and standard deviations were calculated for blood test results. Due to the small number of cases involved, we used the Mann-Whitney U test for numerical data to evaluate the association between HBV carrier and non-HBV carrier runners. The numerical data of serum enzymes of daily and post-race were compared to the values of pre-race, respectively, using the Wilcoxon Signed-Rank test. Effects were tested using general linear models that take into consideration the fact that repeated measurements were made. Commercially available statistical software (SPSS version 18.0, SPSS Inc, Chicago, IL, USA) was used for statistical analysis. All statistical analyses were 2-sided, and p values < 0.05 were considered statistically significant.

3. Results

Of the 11 Taiwanese runners participating in the race, 10 agreed to join our study. Among them, four (40%) were female, the average age was 52.3 ± 7.9 years, average height was 163.3 ± 5.1 cm, average weight was 54.6 ± 6.2 kg, mean marathon training duration was 11.0 ± 6.2 years, and mean accumulated running distance during the race was 553 ± 101 km. The demographic data of the ultra-runners are shown in Table 1. All participants denied any history of diabetes, hypertension, and renal disease. Three runners were

Table 1
Demographic characteristics of hepatitis B virus (HBV) carrier and non-HBV carrier runners in the 7-day ultramarathon race.

	Mean ± SD (Range)			HBV carrier vs non-HBV carrier p
	Total participants $n = 10$	HBV carrier $n = 3$	Non-HBV carrier $n = 7$	
Parameter				
Age (y)	52.3 ± 7.9 (41–62)	52.0 ± 8.9 (45–62)	52.4 ± 8.3 (41–62)	1.000
Weight (kg)	54.6 ± 6.2 (41.0–62.0)	55.3 ± 4.0 (51.0–59.0)	54.2 ± 7.3 (41.0–62.0)	1.000
Height (m)	1.63 ± 0.05 (1.53–1.70)	1.64 ± 0.06 (1.58–1.69)	1.62 ± 0.05 (1.53–1.70)	0.729
BMI (kg/m^2)	20.5 ± 1.7 (17.5–22.5)	20.6 ± 1.9 (18.7–22.4)	20.5 ± 1.8 (17.5–22.5)	0.909
Years of running marathon	11.0 ± 6.2 (5–21)	10.3 ± 6.8 (5–18)	11.3 ± 6.5 (5–21)	0.538
Training distance (km/wk)				0.192
> 100 km/wk	6 (100%)	1 (17%)	5 (83%)	
60–100 km/wk	3 (100%)	1 (33%)	2 (67%)	
40–60 km/wk	1 (100%)	1 (100%)	0	
Best marathon time (min)	211.7 ± 21.2 (191–248)	202.0 ± 8.7 (192–208)	215.9 ± 21.2 (191–248)	0.425
Best 100 km UM time (min)	651 ± 80 (558–820)	618.7 ± 27.2 (588–640)	664.3 ± 92.8(558–820)	0.425
This UM score (km)	553 ± 101 (410–785)	537 ± 41 (501–582)	561 ± 121 (410–785)	0.833
Baseline liver function				
ALT (U/L)	29.7 ± 11.0	33.3 ± 5.7	28.1 ± 12.7	0.183
AST (U/L)	34.7 ± 8.6	39.7 ± 8.5	32.6 ± 8.3	0.383
ALP (U/L)	8.9 ± 3.8	9.0 ± 4.3	8.9 ± 3.9	1.000
GGT (U/L)	25.7 ± 14.4	34.5 ± 29.0	23.1 ± 10.2	1.000
T-BIL (mg/dL)	0.73 ± 0.16	0.73 ± 1.53	0.73 ± 0.18	0.833
ALB	3.75 ± 0.21	3.73 ± 0.32	3.76 ± 0.18	0.833
TP	7.05 ± 0.46	7.17 ± 0.42	7.00 ± 0.49	0.517
CK (U/L)	96.8 ± 43.2	135.0 ± 9.9	85.9 ± 43.0	0.143

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CK = creatine kinase; GGT = γ-glutamyltransferase; HBV = hepatitis B virus; HBV carrier = hepatitis B virus carrier; SD = standard deviation; T-BIL = total bilirubin; UM = ultramarathon; TP = total protein.

chronic carriers of HBV (positive for HBsAg and negative for HBsAb) and one of them was female. All of the participants were anti-HCV antibody-negative and anti-HAV IgG-positive. All the HBV carriers denied any history of admission for acute hepatitis events within 5 years.

Table 2 shows the primary outcomes after general linear model analysis for ALP, ALT, AST, T-BIL, ALB, and TP levels. There were no significant time-by-group effects for ALP, ALB, and TP, but the change-over-time effects were significant ($p < 0.001$, $p = 0.001$, and $p = 0.010$, respectively). ALT, AST, and T-BIL increased significantly to markedly higher levels in the HBV carrier group compared to the non-HBV carrier group (group effect $p = 0.009$, $p = 0.004$ and $p = 0.05$, respectively), and the time-by-group interaction was also significant for these liver function markers ($p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively).

Fig. 1 shows the ALT results. Levels were higher in the HBV carrier group (group effect $p = 0.009$), increasing from 33.3 ± 5.7 U/L at baseline to 235.3 ± 112.4 U/L on Day 7, and then decreasing to 144.7 ± 72.3 U/L on Day 10; whereas those in the non-HBV carrier group increased from 28.1 ± 12.7 U/L at baseline to 84.9 ± 61.9 U/L on Day 5, and then decreased to 48.6 ± 25.4 U/L on Day 10; the time-by-group interaction was significant ($p < 0.001$).

Fig. 2 shows the AST results. Levels were higher in the HBV carrier group (group effect $p = 0.004$), increasing from 39.7 ± 8.5 U/L at baseline to 263.7 ± 98.9 U/L on Day 3, and then decreasing to 86.3 ± 39.6 U/L on Day 10; while those in the non-HBV carrier group increased from 32.6 ± 8.3 U/L at baseline to 92.1 ± 62.5 U/L on Day 5, and then decreased to 41.4 ± 9.3 U/L on Day 10; the time-by-group interaction was significant ($p < 0.001$).

Fig. 3 shows the T-BIL results. Levels were higher in the HBV carrier group (group effect $p = 0.05$), increasing from 0.7 ± 0.2 mg/dL at baseline to 1.8 ± 0.4 on Day 3, and then decreasing to 0.7 ± 0.2 mg/dL on Day 10; while those in the non-HBV carrier group increased from 0.7 ± 0.2 mg/dL at baseline to 1.1 ± 0.2 mg/dL on Day 2, and then decreased to 0.7 ± 0.1 mg/dL on Day 10; the time-by-group interaction was significant ($p = 0.001$).

4. Discussion

Ultramarathons are becoming increasingly popular globally; there were 256 official races in 2000, rapidly escalating to 604 races per year by 2014.[17] Therefore, determining athletes' physiological changes during these events has become increasingly important. Our study revealed clear changes in liver enzyme levels during the course of a 7-day ultramarathon, for HBV carriers and non-HBV carriers alike.

There were significant differences between HBV carriers and non-HBV carriers regarding AST and ALT changes. Our results indicate that the chronic carrier state leads to more extensive liver cell damage. Progression to hepatic fibrosis is commonly found in patients with chronic HBV infections, and up to 40% will develop cirrhosis and hepatocellular

Table 2
Data of liver function between HBV carrier and non-HBV carrier runners along the 7-day ultra-marathon race.

	HBV	Measured time point										Effects		
		Pre-Race	In-Race						Post-Race					
		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Time	Group	T × G
ALP (U/L)	(−)	8.9 ± 3.9	63.4 ± 15.6	64.1 ± 11.2	65.6 ± 11.8	65.9 ± 13.2	72.4 ± 18.3	72.4 ± 21.4	78.9 ± 21.1	71.6 ± 18.3	69 ± 18.9	< 0.001	0.176	0.090
	(+)	9 ± 4.4	87.3 ± 23.4	76.7 ± 22.6	77.3 ± 18.1	73 ± 13	74.3 ± 6.1	91.7 ± 31.6	103.3 ± 42.1	87.7 ± 24	107.3 ± 45.4			
ALT (U/L)	(−)	28.1 ± 12.7	29.7 ± 8	39.7 ± 13.1	49.7 ± 32.7	56.9 ± 34.6	84.9 ± 61.9	78.3 ± 56.4	70.4 ± 43.1	56.3 ± 32.7	48.6 ± 25.4	< 0.001	0.009	< 0.001
	(+)	33.3 ± 5.7	80.3 ± 40.1	127 ± 61.8	157 ± 78.5	176.7 ± 94.1	193.3 ± 112.4	224.7 ± 126.8	235.3 ± 112.4	213 ± 98.9	144.7 ± 72.3			
AST (U/L)	(−)	32.6 ± 8.3	47 ± 9.5	67.7 ± 42.7	75.3 ± 56	72 ± 42.3	92.1 ± 62.5	77.6 ± 48.9	65.4 ± 26.3	49.4 ± 14.2	41.4 ± 9.3	< 0.001	0.004	< 0.001
	(+)	39.7 ± 8.5	148.3 ± 60.1	261.3 ± 97.2	263.7 ± 98.9	235 ± 98.2	222.7 ± 114.7	231 ± 131.7	236 ± 109.2	186 ± 96.7	86.3 ± 39.6			
T-BIL (mg/dL)	(−)	0.7 ± 0.2	1 ± 0.2	1.1 ± 0.2	1 ± 0.3	1.1 ± 0.3	1 ± 0.4	0.9 ± 0.3	0.8 ± 0.2	0.9 ± 0.2	0.7 ± 0.1	< 0.001	0.050	0.001
	(+)	0.7 ± 0.2	1.4 ± 0.3	1.8 ± 0.4	1.8 ± 0.4	1.6 ± 0.6	1.5 ± 0.3	1.4 ± 0.9	1.5 ± 1	1 ± 0.2	0.7 ± 0.2			
ALB (mg/dL)	(−)	3.8 ± 0.2	4.2 ± 0.5	3.9 ± 0.3	3.9 ± 0.3	4.1 ± 0.4	3.8 ± 0.2	3.8 ± 0.1	3.9 ± 0.3	3.6 ± 0.2	3.8 ± 0.2	0.001	0.326	0.678
	(+)	3.7 ± 0.3	4.1 ± 0.3	4.1 ± 0.4	4 ± 0.3	3.9 ± 0.3	3.7 ± 0.2	3.8 ± 0.2	3.8 ± 0.1	3.4 ± 0.2	3.5 ± 0.1			
TP (mg/dL)	(−)	7 ± 0.5	7.1 ± 0.4	6.9 ± 0.3	6.9 ± 0.4	6.8 ± 0.5	6.7 ± 0.4	6.8 ± 0.3	7.2 ± 0.7	6.9 ± 0.6	7.1 ± 0.5	0.010	0.869	0.127
	(+)	7.2 ± 0.4	7.5 ± 0.6	7.1 ± 0.8	7 ± 0.6	6.8 ± 0.4	6.6 ± 0.3	6.7 ± 0.4	6.8 ± 0.5	6.4 ± 0.8	6.7 ± 0.5			

Data presented with mean ± standard deviation. Data of Day 0 was measured before 7-day ultramarathon race and Day 8 was measured after race.
ALB = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBV = hepatitis B virus; HBV carrier = hepatitis B virus carrier; T-BIL = total bilirubin; TP = total protein.

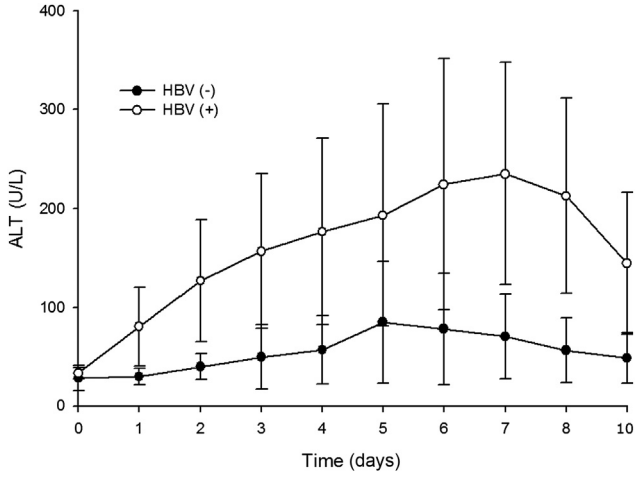

Fig. 1. Differences in alanine aminotransferase (ALT) between hepatitis B virus (HBV) carrier and non-HBV carrier runners in a 7-day ultramarathon race. ALT = alanine aminotransferase; HBV = hepatitis B virus; HBV(+) = HBV carriers; HBV(−) = non-HBV carriers.

carcinoma.[18,19] Perhaps chronic fibrotic changes render the hepatic cells of HBV carriers more fragile and more easily injured during the stress of long-distance running. Fortunately, ALT and AST levels in these patients improved gradually after the race. Because the effect seen in this study appears to be transient, more data is needed to determine whether long-distance running has longer-term consequences for HBV carriers' liver function.

T-BIL increased significantly during the race, a result compatible with previous studies.[8,20] Paz et al showed that increased T-BIL after long-distance running might be explained by both hemolysis and hepatic disturbances.[20] Wu et al[8] hypothesized that the increase could be associated with the hemolysis that follows ultra-long-distance running, because serum T-BIL levels normalized after 2 days of rest as red cell turnover decreased. In our study, there were significant

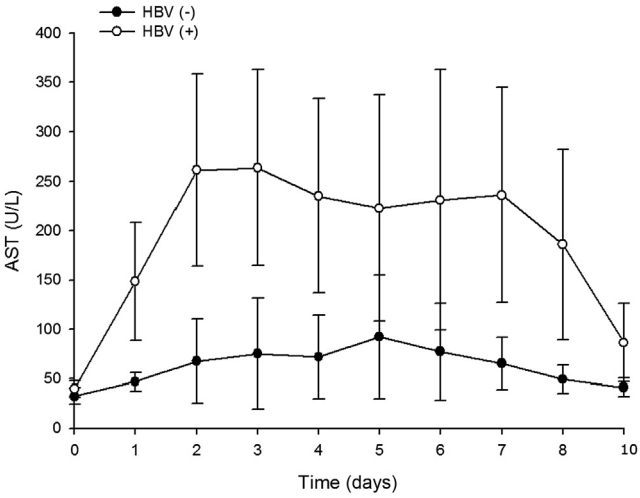

Fig. 2. Differences in AST between HBV carrier and non-HBV carrier runners in a 7-day ultra-marathon race. HBV = hepatitis B virus; HBV(+) = HBV carriers; HBV(−) = non-HBV carriers; AST = aspartate aminotransferase.

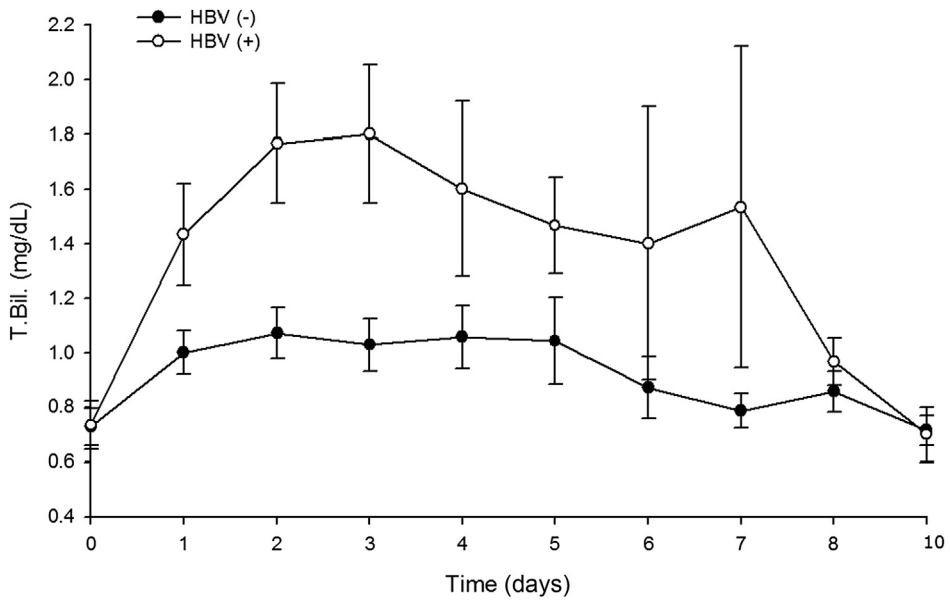

Fig. 3. Differences in total bilirubin between HBV carrier and non-HBV carrier runners in a 7-day ultra-marathon race. HBV = hepatitis B virus; HBV(+) = HBV carriers; HBV(−) = non-HBV carriers; T. Bil = total bilirubin.

differences in changes in T-BIL levels between HBV carriers and non-HBV carriers; and both groups normalized within the 3-day post-race rest period, implying that the changes could be attributed to both hemolysis and hepatic damage. Further studies are needed to evaluate the association of the degree of hepatic fibrosis and the extent of elevated T-BIL in chronic HBV carriers.

ALP increased significantly during the course of the ultramarathon, a result consistent with previous studies. Kaplan et al suggested that this effect is due to liver injury. However, ALP is found in many parts of the body, including liver, bone, and intestines, and its precise function is not yet known.[21] Fallon et al[2] thought that ischemic damage to the gut is a less likely explanation for increased ALP levels, because there is adequate hydration during races. However, significant bone stress does occur in these athletes. Except for the liver, bone was thought to be the most likely source of ALP, indicating high bone turnover. In our study, ALP increased during prolonged running, but there was no significant difference between HBV carrier and non-HBV carrier groups, suggesting that hepatic cell damage was not the only contributing factor. Future studies should be designed to detect levels of the various ALP isoenzymes in order to determine major sources of the increase observed.

Although a recent study by Chiu et al[22] showed no significant differences between HBV carrier and non-HBV carrier in ALT, AST, and T-BIL of 100-km ultra-runners. For more vigorous exercises like this 7-day ultramarathon race, HBV carrier runners may demonstrate more hepatic cell damage than that of non-HBV carrier runners. Among HBV carrier runners, baseline liver function should be evaluated and post-race liver function should be followed closely.

There were some limitations in this study. First, the number of participants was low. Second, we did not check the titer of HBV DNA before and after the race, so we were unclear about the effect of ultramarathons on serum HBV DNA dynamics in chronic HBV carriers and the relationship to the greater increases of AST, ALT, and T-BIL levels than for non-HBV carriers. Third, we did not check the liver sonography or liver fibrosis scan tests for HBV carriers. Globally, the number of runners that participate in ultramarathons is quite low, especially races 7 days in duration, so it is quite important to collect the 7 days' serial change over liver function. Despite the aforementioned limitations, the main strength of this study was that we illustrated the serial change between HBV carriers and non-HBV carriers during a 7-day ultramarathon.

In conclusion, overall, athletes' ALP levels increased and ALB and TP decreased significantly during a 7-day ultramarathon, and then recovered gradually during a 3-day rest period. Among athletes who were chronic HBV carriers, ALT, AST, and T-BIL were elevated to significantly higher levels during the race than in those not infected with the virus. We suggest that chronically-infected individuals participating in a 7-day ultramarathon should be informed of this phenomenon.

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