Branched-chain Amino Acids Prevent Hepatocarcinogenesis and Prolong Survival of Patients With Cirrhosis

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BACKGROUND & AIMS: **Although a low plasma level of branched-chain amino acids (BCAAs) is a marker of cirrhosis, it is not clear whether BCAA supplements affect disease progression. We performed a multicenter study to evaluate the effects of BCAA supplementation on hepatocarcinogenesis and survival in patients with cirrhosis.**

METHODS: **We enrolled 299 patients from 14 medical institutions in Japan in a prospective, multicenter study in 2009; 267 patients were followed through 2011. Patients were given BCAA supplements (5.5–12.0 g/day) for more than 2 years (n = 85) or no BCAAs (controls, n = 182). The primary end points were onset of hepatocellular carcinoma (HCC) and death. Factors associated with these events were analyzed by competing risk analysis.**

RESULTS: **During the study period, 41 of 182 controls and 11 of 85 patients given BCAAs developed HCC. On the basis of the Cox and the Fine and Gray models of regression analyses, level of α-fetoprotein, ratio of BCAA:tyrosine, and BCAA supplementation were associated with development of HCC (relative risk for BCAAs, 0.45; 95% confidence interval, 0.24–0.88; $P = .019$). Sixteen controls and 2 patients given BCAAs died. Factors significantly associated with death were Child–Pugh score, blood level of urea nitrogen, platelet count, male sex, and BCAA supplementation (relative risk of death for BCAAs, 0.009; 95% confidence interval, 0.0002–0.365; $P = .015$) in both regression models.**

Abbreviations used in this paper: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCAA, branched-chain amino acid; BMI, body mass index; BUN, blood urea nitrogen; CT, computed tomography; HbA1c, glycosylated hemoglobin; HCC, hepatocellular carcinoma; HOMA-IR, homeostasis model assessment of insulin resistance; MRI, magnetic resonance imaging; TIBC, total iron binding capacity.

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CONCLUSIONS: **On the basis of a prospective study, amino acid imbalance is a significant risk factor for the onset of HCC in patients with cirrhosis. BCAA supplementation reduces the risk for HCC and prolongs survival of patients with cirrhosis.**

Keywords: Liver Cancer; Hepatoma; Nutrition; Treatment Outcome.

The liver is a central organ in the metabolism of many nutrients. Thus, cirrhosis of the liver frequently results in metabolic disarray.[1,2] Decreased serum levels of branched-chain amino acids (BCAAs) are a hallmark of cirrhosis[1,2] that are contributed to by several factors, including reduced nutritional intake, hypermetabolism, and ammonia detoxification in skeletal muscle.[3] Low serum levels of BCAAs are also important in the pathogenesis of hepatic encephalopathy and hypoalbuminemia and are associated with overall mortality.[1–3]

BCAAs are a source of glutamate, which detoxifies ammonia via glutamine synthesis in skeletal muscle.[4] BCAAs have recently been considered as pharmacologic nutrients in cirrhotic patients.[1] In vitro studies have demonstrated that BCAAs prevent the proliferation of hepatocellular carcinoma (HCC) cells by inducing apoptosis.[5] In addition, BCAA supplementation was shown to stimulate antioxidant DNA repair in a rat model of liver injury[6] and to prevent hepatocarcinogenesis in an animal model.[7] In HCC patients, BCAA supplementation reduces early recurrence of HCC after hepatic resection or radiofrequency thermal ablation.[8,9] To investigate the effects of BCAA supplementation on the development of cirrhosis-related complications, multicenter randomized controlled trials were conducted in Italy and Japan at the end of the 1990s.[10,11] Although these studies showed that BCAA supplementation prevented hospital admissions related to cirrhosis complications and improved the quality of life of cirrhotic patients,[10,11] the effects of BCAA supplementation on hepatocarcinogenesis remain unclear.

BCAAs are also known to enhance hepatic regeneration and immunity.[1,2] BCAAs stimulate the production of hepatocyte growth factor in hepatic stellate cells[12] and increase hepatic parenchymal cell mass.[13] In addition, BCAA supplementation increases lymphocyte counts and improves the phagocytic function of neutrophils in cirrhotic patients.[14] BCAAs also reverse functional impairment and stimulate the maturation of myeloid dendritic cells, leading to the production of interleukin-12, a potent activator of natural killer cells.[15] Recently, bacterial infection has become one of the major causes of death in cirrhotic patients.[16] Taken together, these findings suggest that BCAA supplementation may prevent hepatic failure and bacterial infection, leading to prolonged survival in cirrhotic patients. Hitherto, a survival benefit of BCAA supplementation has not been demonstrated.[17]

In Japan, BCAA supplementation is an approved medication for decompensated liver cirrhosis, and thus, a randomized control trial that uses BCAA supplementation cannot ethically be performed. Moreover, the onset of HCC and death are considered as competing risks. Therefore, the aim of this study was to evaluate the effects of BCAA supplementation on the onset of HCC and survival in cirrhotic patients by competing risk analysis.

Methods

Study Design and Ethics

This study was designed in 2009 by the steering committee as a multicenter investigation for evaluating the effects of BCAA supplementation on hepatocarcinogenesis and prognosis in cirrhotic patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the prior approval given by the institutional review board of each institution. None of the subjects were institutionalized.

Subjects and Observation Period

In 2009, 299 cirrhotic patients without HCC were enrolled from 14 medical institutions in Japan. Diagnosis of liver cirrhosis was based on an aspartate aminotransferase (AST)-to-platelet ratio index >1.5,[18] morphologic changes of the liver such as hypertrophy of the left lateral and caudate lobes and atrophy of the right posterior hepatic lobe as evidenced by ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI), or a pseudo-lobule formation finding on histopathologic examination. The etiologies of liver cirrhosis were hepatitis C virus infection (n = 171), hepatitis B virus infection (n = 31), alcohol intake (n = 24), autoimmune hepatitis (n = 22), nonalcoholic fatty liver disease (n = 12), and others (n = 7).

Enrolled patients were followed up until 2011. The median observation period was 728 days (range, 22–1069 days), and the mean observation period was 677.9 ± 220.0 days. During the course of the study, 32 patients could not be followed up because of a change of residence (n = 12), failure to attend appointments (n = 17), or data unavailability (n = 3). The remaining 267 cirrhotic patients were analyzed (follow-up rate, 89.3%) (Supplementary Figure 1). A total of 16 patients had hepatic encephalopathy at study entry and were treated with BCAA supplementation, and 4 patients developed hepatic encephalopathy during the study period.

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