Nutrition 54 (2018) 83–88

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Skeletal muscle fat deposition is associated with hepatocellular carcinoma development in patients with chronic liver disease

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ARTICLE INFO

Article history:
Received 1 October 2017
Received in revised form
2 February 2018
Accepted 1 March 2018

Keywords:
Chronic liver disease
Hepatocellular carcinoma
Sarcopenia
Skeletal muscle fat deposition
Skeletal muscle attenuation

ABSTRACT

Objectives: The effect of skeletal muscle fat deposition on the prognosis of patients with chronic liver disease remains unclear. Skeletal muscle fat deposition can be estimated by attenuation of skeletal muscle in Hounsfield units (HU) on computed tomography (CT). The aim of this retrospective cohort study was to investigate the association between skeletal muscle fat deposition assessed by skeletal muscle attenuation (SMA), and hepatocellular carcinoma (HCC).

Methods: We enrolled 288 patients with chronic liver disease (139 men, 149 women; mean age 67.5 ± 10.4 y; hepatitis C virus, 239; hepatitis B virus, 17; without viral infection, 32; chronic hepatitis, 227; and cirrhosis, 61) who underwent liver biopsy and CT scanning between January 2013 and February 2017. The patients were divided into two groups based on SMA levels, with the cutoff value of 31 HU. We analyzed the effect of SMA on HCC development.

Results: During the study follow-up period (median, 2.50 y; range, 0.5–4.7 y), HCC was identified in 19 patients (7%). The cumulative incidence of HCC in patients with lower SMA (<31 HU) was significantly higher than in patients with SMA ≥31 HU ($P = 0.007$). Cox proportional hazards regression analysis confirmed cirrhosis (hazard ratio [HR], 6.626; 95% confidence interval [CI], 2.57–17.12; $P < 0.001$) and lower SMA (HR, 3.502; 95% CI, 1.25–9.83; $P = 0.017$) as significant independent factors associated with HCC development in patients with chronic liver disease.

Conclusions: Patients with cirrhosis and skeletal muscle fat deposition assessed by SMA had a higher risk for developing HCC.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Chronic liver disease (CLD) is a major cause of cirrhosis and HCC and is a major global public health issue [1,2]. Previous studies reported that advanced fibrosis and advanced age are important predictors of HCC [3,4]. The emergence of novel antiviral treatments for hepatitis C virus and hepatitis B virus infections has increased the number of patients who achieve a sustained virologic response [5,6]. Patients treated with antiviral therapy are at low risk for developing HCC. However, the development of HCC is sometimes observed even after antiviral therapy. Therefore, continuous surveillance for HCC after antiviral therapy is necessary.

Analysis of body composition by computed tomography (CT) has been used to evaluate the prevalence of skeletal muscle depletion [7,8]. Severe muscular depletion has more recently been recognized as an indicator of cachexia and appears to be a strong negative prognostic factor in aging and several chronic diseases [9] as well as in malignancies, regardless of cancer diagnosis, stage, and treatment [10–14]. Sarcopenia, characterized by the loss of skeletal muscle mass, is one of the most common complications of CLD [15–18]. However, the association between sarcopenia and the development of HCC among patients with chronic hepatitis remains to be elucidated.

Y.T. was responsible for the study concept and design. Y.T., T. Hirai, and Y.K. acquired the data. Y.T. and Y.K. analyzed and interpreted the data. Y.T. drafted the manuscript and provided statistical analysis. Y.I., T. Honda, T.K., K.H., M.I., and H.G. supervised the study. All of the authors gave final approval of the study. The authors have no conflicts of interest to declare.

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https://doi.org/10.1016/j.nut.2018.03.011
0899-9007/

The role of increased intramuscular fat deposition has been the subject of several recent studies. Intramuscular fat deposition increases with age and adiposity [19,20] and is strongly associated with metabolic abnormalities [21]. Skeletal muscle attenuation (SMA), assessed by CT, is expressed as the mean number of Hounsfield units (HU) of a measured cross-sectional muscle area. Based on a study indicating concordance between muscle attenuation on CT and muscle lipid content in 45 volunteers who underwent percutaneous muscle biopsies of the vastus, low muscle attenuation indicates increased muscle lipid content [22]. This has been observed in rectus abdominis biopsies from 19 cancer patients [23]. The negative prognostic effect of reduced SMA has come up in several other cancer populations, including patients with malignancy of the lung and gastrointestinal tract [7], pancreatic cancer, distal cholangiocarcinomas [24], or advanced non-small cell lung cancer [11]. A recent study reported that the SMA is closely related to recurrence of HCC in patients receiving curative HCC treatment [8]. However, the effect of skeletal muscle fat deposition on HCC development in patients with CLD remains unclear.

On the basis of the previous reports, we hypothesized that skeletal muscle fat deposition has a role in increasing disease severity and that SMA closely related to muscle fat deposition is a risk factor for future HCC development in patients with CLD. To examine this hypothesis, we conducted a retrospective cohort study seeking to elucidate the association between SMA levels and the risk for hepatocarcinogenesis in patients with CLD.

Materials and methods

Patients

The present retrospective study examined the records of 550 consecutive patients with CLD who underwent liver biopsy between January 2013 and February 2017 at Komaki City Hospital. Patients were excluded if they had not undergone multiple CTs within 3 mo before the liver biopsy. Of the patients who underwent liver biopsy, 188 were excluded due to absence of multiple CT reports and 74 due to a history of HCC. In all, 288 patients with CLD who underwent liver biopsy and multiple CTs were analyzed in the present study. Demographic information, treatment history, and data regarding the development of HCC were obtained from medical records. The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent for liver biopsy and use of clinical data was obtained from all patients at the time of liver biopsy. The Ethical Committee of Komaki City Hospital approved this study.

Assessment of skeletal muscle mass and SMA

A transverse CT image of each scan at the third lumbar vertebra (L3) in the inferior direction was used to evaluate skeletal muscle tissues [7,8]. The areas of skeletal muscle mass and attenuation of skeletal muscle density were measured using the Volume Analyzer Synapse Vincent (Fujifilm, Tokyo, Japan). Skeletal muscle was identified and quantified by HU thresholds of –29 to +150, according to previous reports. According to the HU scale, the density of water is 0 HU and that of air is –1000 HU. As a measure of skeletal muscle mass, the total cross-sectional skeletal muscle area (cm^2) was normalized for stature by dividing by height squared (m^2) and expressed as skeletal muscle index (SMI; cm^2/m^2). As sarcopenia criteria differ between Japanese and Western individuals, we divided the patients into two subgroups according to the presence of sarcopenia based on median skeletal muscle mass in men and women (42 cm^2/m^2 in men and 38 cm^2/m^2 in women) according to the Japan Society of Hepatology guidelines for sarcopenia in liver disease [21]. SMA was assessed as the mean density (HU) of the entire measured cross-sectional muscle area at L3 in enrolled patients.

Diagnosis of HCC and follow-up

Before liver biopsy, all patients without a history of previous HCC underwent abdomen ultrasound and multiple CT scans to exclude the presence of HCC. After liver biopsy, the patients attended medical consultations at the Komaki City Hospital outpatient clinic every 1 to 6 mo. Biochemical measurements, including α-fetoprotein and tumor marker levels, were assessed from whole blood samples every 1 to 6 mo; ultrasonography, magnetic resonance imaging, and dynamic CT were performed every 6 mo. Typical imaging findings for HCC included a high-density mass in the arterial phase and a low-density mass in the portal phase of dynamic CT or MRI studies. To investigate the incidence of HCC, the start date of follow-up was defined as the date of liver biopsy and the endpoint was the development of HCC or the date of latest medical follow-up visit before August 2017. Factors associated with the development of HCC were retrospectively analyzed.

Histologic evaluation

Liver biopsy was recommended for assessment of diagnoses such as fibrosis stage, inflammation grade, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, and autoimmune hepatitis. However, patients with Child Pugh scoring system class B or C were excluded from this study. This is because liver biopsy of these patients was avoided due to high risk for complications such as hemorrhage. An ultrasound-guided, percutaneous needle liver biopsy was performed in all patients. A pathologist who was blinded to the clinical data, evaluated all liver biopsy samples. Fibrosis staging scores were assigned according to the criteria of METAVIR score [25]. Fibrosis was staged on a scale of 0 to 4: F0 (*no fibrosis*), F1 (*portal fibrosis without septa*), F2 (*few septa*), F3 (*numerous septa without cirrhosis*), or F4 (*cirrhosis*). Necroinflammatory activity was also graded on a 4-point scale (A0, *none*; A1, *mild*; A2, *moderate*; A3, *severe*).

Statistical analysis

Categorical data were presented as numbers (percentages). Continuous data were presented as means ± SD, and medians (ranges). Normally distributed variables were compared using Student's *t* test and non-normally distributed variables were compared using the Mann–Whitney *U* test between the patients groups that did and did not develop HCC. Frequency data were compared using a χ^2 test or Fisher's exact test, as appropriate. The cumulative incidence of HCC was calculated using the Kaplan–Meier method. Differences between patients with and without SMA were assessed using the log-rank test. The time frame for HCC incidence was defined as the time from the date of liver biopsy to the date of HCC diagnosis. The Cox proportional hazard model was used for multivariate analyses of factors associated with the incidence of HCC. The predictive performances of SMA value were assessed using receiver operating characteristic (ROC) analyses and the areas under the ROC curves (AUROC) were calculated. The point at which the Youden index (sensitivity + specificity – 1) became the maximum was used as the cutoff value of each index. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the prediction of HCC development. Associations between clinical factors and SMA were analyzed by univariate and multivariate logistic regression analyses. Statistical analyses were performed using SPSS Statistics 21.0 (IBM SPSS; Chicago, IL, USA). $P < 0.05$ was considered statistically significant when using a two-tailed test.

Results

Baseline characteristics of enrolled patients

The overall study population of 288 patients consisted of 139 men (48.3%) and 149 women (51.7%). The mean age was 67.5 ± 10.4 y (range: 26–88 y). Detailed demographic data are shown in Table 1. The METAVIR fibrosis stage distribution was as follows: stage 0, 24 (8.3%); stage 1, 117 (40.6%); stage 2, 48 (16.7%); stage 3, 37 (12.8%); stage 4, 61 (21.2%). The median SMI was 42.2 (range, 24.5–70.5). The median SMA level was 32.6 HU (range, 8.65–49.9 HU; Table 1).

Development of HCC in patients with chronic hepatitis

During the follow-up period (median, 2.50 y; range, 0.5–4.7 y), HCC was identified in 19 patients (7%). The median time between the date of liver biopsy and the development of HCC was 1 y (range, 0.3–3.5 y). The cumulative incidence of HCC at 1, 2 and 3 y after the date of liver biopsy was 3.2%, 5.3%, and 7.3%, respectively. HCC patients included 8 men and 11 women; 12 patients with cirrhosis and 7 without cirrhosis.