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短　報
Note

Zinc Deficiency in End-Stage Hepatocellular Carcinoma Patients Treated with Chemotherapy

By

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Summary : Malnutrition frequently occurs in end-stage hepatocellular carcinoma patients, and can influence survival in the patients. The objective of the present study was to investigate the relationships between clinical and dietary indices in the patients. The clinical data of 33 patients affected by hepatocellular carcinoma (stage IV) who had been hospitalized to receive chemotherapy were retrospectively analyzed. A multiple regression analysis was performed based on the blood data (albumin, total bilirubin, direct bilirubin, AST, ALT, LDH, ALP, α-fetoprotein, and C-reactive protein) and the mean values of daily dietary indices (intake rate, dietary intake, energy intake, NaCl intake, iron intake, zinc intake, and vitamin K intake) during hospitalization. Both the intake rate and the zinc intake were significantly correlated with the C-reactive protein and α-fetoprotein levels, while the albumin level was significantly correlated with the zinc intake and the ALT level. These results showed that zinc deficiency is correlated with a relatively poor prognosis. Thus, it is necessary to improve the problem in the affected patients.

Key words : diets, hepatocellular carcinoma, humans, nutrition, zinc

Introduction

Hepatocellular carcinoma is the third leading cause of death from cancer in Japan, and conservative palliative care is very important for patients affected by this carcinoma[1,2]. Malnutrition frequently occurs in end-stage hepatocellular carcinoma patients, regardless of the presence of liver cirrhosis, and may represent a risk factor influencing both short-term and long-term survival in these patients[3-6]. For example, hypoalbuminemia has been often found in patients during the end stages of hepatocellular carcinoma. Consequently, the disorder leads to a contraindication for chemotherapy[7]. One of the most important causes of nutritional disorders in these patients is obviously their low dietary intake, which automatically induces an insufficiency of such micronutrients as iron (Fe) and zinc (Zn). Impairments in dietary intake may therefore influence the clinical condition of hepatocellular carcinoma. However, the relationship between the clinical and dietary indices in patients affected by hepatocellular carcinoma has not yet been fully analyzed. The objective of the present study was to investigate the relationship between clinical and dietary indices in the patients with end-stage hepatocellular carcinoma using a multiple regression analysis.

Materials and Methods

1) Patients

The clinical data of 33 patients with the carcinoma (stage IV) who were hospitalized to receive chemotherapy at Kyoundo Hospital were retrospectively analyzed. The patient profiles are shown in Table 1. All the patients had an abnormally high range of α-fetoprotein (AFP), did not receive intravenous hyperalimentation, and were eventually discharged under their own power. Blood data (serum concentrations of albumin [Alb], total bilirubin [T-Bil], direct bilirubin [D-Bil], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase [LDH], alkaline phosphatase [ALP], AFP, and C-reactive protein [CRP]) were used for the

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Table 1 Subjects profiles (n = 33)

Sex: Men/Women	22/11
Age (years)	64.7 ± 9.4
Height (cm)	163.1 ± 6.9
Body weight (kg)	60.3 ± 10.6
Body mass index (kg/m^2)	22.6 ± 3.2
Admission period (days)	10.4 ± 8.0

Data were expressed as the mean ± SD.

Table 2 Blood data (n = 33)

Alb (g/dL)	3.4 ± 0.6
T-Bil (mg/dL)	1.4 ± 1.1
D-Bil (mg/dL)	0.8 ± 0.9
AST (IU/L)	121 ± 180
ALT (IU/L)	60 ± 46
LDH (IU/L)	336 ± 543
ALP (IU/L)	482 ± 297
AFP (ng/mL)	22590 ± 69130
CRP (mg/dL)	2.8 ± 4.4

Data were expressed as the mean ± SD.

Table 3 Daily dietary indices (n = 33)

Intake rate* (%)	73.5 ± 20.8
Dietary intake (g/day)	1443 ± 408
Energy (kcal/day)	1268 ± 371
NaCl** (g/day)	7.5 ± 2.2
Fe (mg/day)	6.2 ± 1.9
Zn (mg/day)	6.0 ± 2.0
Vitamin K (μg/day)	176.6 ± 50.1

*Intake rate indicates the dietary intake/provided meals.
**NaCl was calculated based on the Na intake.
Data were expressed as the mean ± SD.

analysis. The mean values for the dietary indices during hospitalization were calculated based on the daily dietary intakes (g/day), the intake rates (%), and the nutrient values for the provided meals (energy, NaCl, Fe, Zn, vitamin K). The dietary intake (g/day) was calculated by subtracting the leftover amounts (g/day) from the provided meals (g/day). The intake rate (%) was calculated by dividing the dietary intake (g/day) by the provided meals (g/day). The nutrient intake contents were calculated by multiplying the intake rate by the nutrient values for the provided meals (g/day).

2) Statistical analysis

All the data were presented as the mean values ± SD. A simple linear regression analysis was performed to evaluate the association between the two variables, and a multiple linear regression analysis was also performed using SPSS for Windows (Ver. 11.0J, SPSS Japan Inc.). In the case of multicollinearity, some of the variables that demonstrated a lower correlation to the dependent variables were excluded. A value of $P<0.05$ was considered to indicate statistical significance.

Results

The blood data, the dietary data, and the correlation coefficients among variables are shown in Tables 2, 3 and 4, respectively. The intake rate was significantly correlated with age and the CRP, Alb, AFP, D-Bil and T-Bil levels in simple regression analyses. A multiple regression analysis for the intake rate and four explanatory variables (CRP, Alb, AFP, and D-Bil) revealed significant correlations ($r = 0.727$, $P<0.001$) with the CRP ($r = -0.468$, $P<0.01$) and AFP ($r = -0.350$, $P<0.05$) levels. Two explanatory variables (age and T-Bil) were excluded from the multiple regression analysis because of multicollinearity with Alb and D-Bil, respectively.

The CRP level was significantly correlated with the Zn intake, the intake rate, and the LDH, Alb, and AST levels according to simple regression analyses. A multiple regression analysis for the CRP level that included three explanatory variables (Zn, LDH, and Alb) revealed a significant correlation ($r = 0.643$, $P<0.005$) with the Zn intake ($r = -0.529$, $P<0.005$) ; one explanatory variable (ALT) was excluded from the analysis because of multicollinearity with the LDH level.

The AFP level was significantly correlated with the intake rate, Zn intake, and the T-Bil and D-Bil levels according to simple regression analyses. A multiple regression analysis for the AFP level that included three explanatory variables (intake rate, T-Bil level, and Zn intake) failed to show any significant correlation; one explanatory variable (D-Bil) was excluded from the analysis because of multicollinearity with the T-Bil level.

The Zn intake was significantly correlated with age and the CRP, Alb, AFP, and D-Bil levels according to simple regression analyses. A multiple regression analysis

Table 4 Correlation coefficients among variables

	Intake rate	CRP	AFP	Zn	Alb
Age	-0.414*	0.174	0.197	-0.380*	-0.429*
Alb	0.483**	-0.372*	-0.176	0.536**	-
T-Bil	-0.346*	0.240	0.405*	-0.331	-0.546**
D-Bil	-0.364*	0.291	0.361*	-0.351*	-0.532**
AST	-0.316	0.357*	0.115	-0.317	-0.421*
ALT	-0.042	0.137	-0.094	-0.074	-0.351*
LDH	-0.246	0.381*	0.008	-0.250	-0.312
ALP	-0.239	0.165	0.285	-0.244	-0.214
AFP	-0.411*	0.063	-	-0.383*	-0.176
CRP	-0.578**	-	0.063	-0.597**	-0.372*
Intake rate	-	-0.578**	-0.411*	0.965**	0.483**
Dietary intake	0.976**	-0.571**	-0.385*	0.969**	0.458**
Energy	0.980**	-0.575**	-0.387*	0.984**	0.477**
NaCl	0.979**	-0.588**	-0.388*	0.980**	0.478**
Fe	0.978**	-0.587**	-0.387*	0.989**	0.495**
Zn	0.965**	-0.597**	-0.383*	-	0.536**
Vitamin K	0.911**	-0.553**	-0.376*	0.883**	0.336

$*P < 0.05$, $**P < 0.01$

for the Zn intake that included four explanatory variables (CRP, Alb, AFP, and D-Bil) revealed significant correlations ($r = 0.750$, $P < 0.001$) with the CRP ($r = -0.472$, $P < 0.005$) and AFP ($r = -0.324$, $P < 0.05$) levels ; one explanatory variable (age) was excluded because of multicollinearity with the Alb level.

The Alb level was significantly correlated with the Zn intake, intake rate, age, and the T-Bil, D-Bil, AST, CRP, and ALT levels according to simple regression analyses. A multiple regression analysis for the Alb level that included six explanatory variables (T-Bil, Zn, age, AST, CRP, and ALT) failed to reveal any significant correlations ; two explanatory variables (D-Bil and intake rate) were excluded because of multicollinearity with the T-Bil level. Next, a multiple regression analysis for the Alb level that included four explanatory variables (T-Bil, Zn, age, and ALT) and that had a lower probability (*P* value) was re-performed, resulting in a significant correlation ($r = 0.736$, $P < 0.001$) with the Zn intake ($r = 0.319$, $P < 0.05$) and the ALT level ($r = -0.299$, $P < 0.05$).

Discussion

The intake rate is undeniably important for maintaining a good nutritional condition in patients in the end-stage who are not receiving intravenous hyperalimentation. By combining simple and multiple linear regression analyses, we revealed that the CRP and AFP levels influence the intake rate and that the Zn intake, in turn, influences the CRP level. No factors that influenced the AFP level were identified. We then revealed that the CRP and AFP levels influence the Zn intake, while the Zn intake influences the Alb level. The Alb level was also influenced by the intake rate ; however, the effect of the intake rate ($r = 0.483$) on the Alb level was smaller than that of the Zn intake ($r = 0.536$). As a result, Zn intake was found to be closely related to the CRP, AFP, and Alb levels. The CRP and AFP levels indicate the activity of carcinoma, while the Alb level reflects the nutritional status. The amount of Zn (6.0 ± 2.0 mg/day) consumed by the patients investigated herein was below the recommended amount (11 mg/day), even though the patients' energy intake (1268 ± 371 kcal/day) was considered to be within the satisfactory range. Therefore, Zn deficiency may cause a deterioration in the nutritional status and prognosis of patients with hepatocellular carcinoma.

Zn also acts as an antioxidant to protect proteins and DNA[8-10] and is important for host defense against the initiation and progression of cancer[11]. In addition, Zn deficiency decreases one's ability to taste[12]. An impairment in gustatory acuity may thus influence nutrient intake and hence negatively impact the nutritional status, such as causing an increase in Na intake resulting in edema and ascites. Zn deprivation also induces deteriorations in both liver cirrhosis and hepatic encephalopathy[13]. The usefulness of Zn supplement in the treatment of liver disease has already been reported[14]. These results showed that Zn deficiency is correlated with a relatively poor prognosis. Thus, it is necessary to improve the problem in the affected patients.

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化学療法下にある末期肝細胞癌患者の亜鉛欠乏

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要約：末期肝細胞癌患者では栄養状態の悪化が多く見られ，これは予後を左右する重要な因子である。化学療法目的で入院した 33 名の IV 期肝細胞癌患者で，食事摂取状況と臨床検査データとの関連を調べた。血清中の直接ビリルビン，間接ビリルビン，LDH，AST，ALT，ALP，アルブミン，CRP，AFP さらに入院中の平均食事摂取率，食事摂取量，摂取エネルギー量，摂取食塩相当量，鉄摂取量，亜鉛摂取量，ビタミン K 摂取量および年齢を変数として重相関分析を行った。食事摂取率に影響を及ぼしているものは CRP と AFP であり，CRP に影響を及ぼしているものは亜鉛摂取量であった。亜鉛摂取量に影響を及ぼしているものは CRP と AFP であり，亜鉛摂取量はアルブミンにも影響を及ぼしていた。以上の結果から，亜鉛欠乏は本病状と深い関係があることを示しており，これらの患者においてこの問題を改善することが必要と考える。

キーワード：亜鉛，栄養，肝細胞癌，食餌摂取，ヒト

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