D. 考察

従来の診療ガイドラインは利用者として医師を対象としたものが多く、各領域の専門医により作成されていたが、欧米では患者・家族を含めた様々な“stekeholder（利害関係者）”が作成過程に関わることが推奨され、国際的な診療ガイドライン評価ツールであるAGREEチェックリスト（Appraisal of Guidelines for Rsearch & Evaluation Instrument）の評価項目においても「患者の視点や選考の考慮の有無」が明記されている（4）。本邦でも患者向け診療ガイドラインの作成が各領域で徐々に進められてはいるが、本邦の消化器疾患関連のガイドラインにおいては3疾患にとどまり、いずれにおいても作成過程における患者参加の記述はなかった。また、医師向けガイドラインを含め、食事・栄養に関するClinical QuestionやPatient Questionに関する推奨や解説を記載したガイドラインはなかったことから、栄養療法ガイドの作成にあたっては管理栄養士の参加も必要と考えられた。

本邦でも患者向け診療ガイドライン作成の場に患者や支援者が参加した事例はあるが、ガイドライン作成委員会が知りうる範囲の患者団体に参加を依頼するという手法が多くとられているのが現状であることから、患者選定にあたっては公平性と透明性の確保の観点から選定過程や選定理由を公表可能な手続きを経る必要あり、PIGLが有用な指針であると考えられた。

結論

肝硬変の患者向け栄養療法ガイドの作成にあたっては、「患者・支援者」の視点に考慮するとともに、成果の共有や患者委員へのフィードバックが必要である。

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E．健康危険情報

無し

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|---|---|
| １．特許取得 | 無し |
| ２．実用新案登録 | 無し |
| ３．その他 | 無し |

# Ⅲ．研究成果の刊行に関する一覧表

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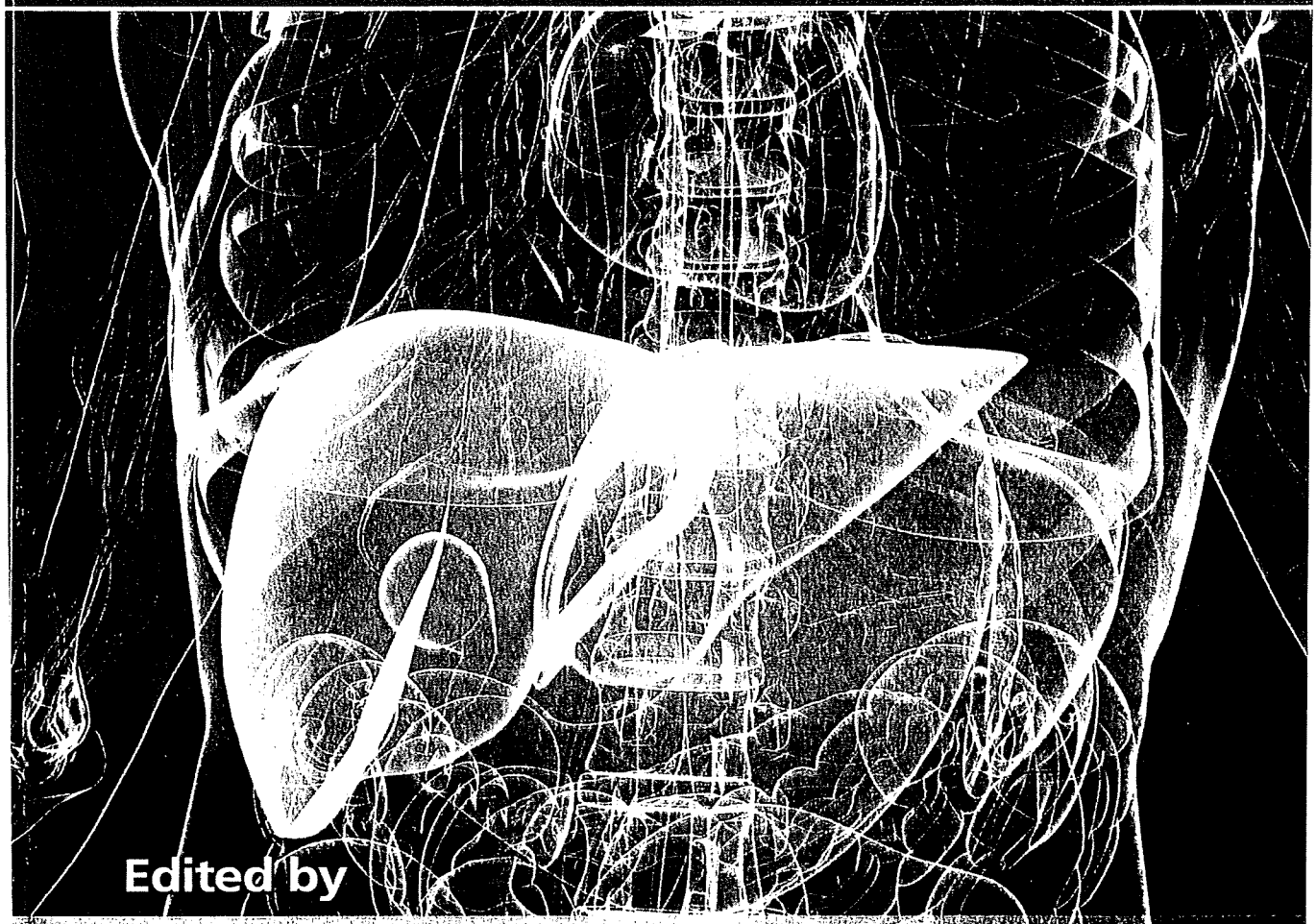
# Ⅳ．研究成果の刊行物

# 書　　籍

# Nutrition, Diet Therapy, and the Liver



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Ronald Ross Watson

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# 13 Biomarkers of Malnutrition in Liver Cirrhosis

*Kazuyuki Suzuki and Yasuhiro Takikawa*

## CONTENTS



## 13.1 INTRODUCTION

The liver plays a central role in the metabolism of carbohydrate, protein, fat, vitamins, and minerals. Therefore, the metabolism of these nutritional elements is gradually disturbed with progressive chronic liver disease, resulting in undernourishment and/or malnutrition. Malnutrition is an established complication among patients with liver cirrhosis (LC) (Caregaro et al., 1996; Roongpisuthipong et al., 2001; Campillo et al., 2003; Riggio et al., 2003; Cabre and Gassull, 2005). It is characterized by protein-energy malnutrition (PEM) in LC, which is closely associated with the prognosis of LC, and many factors directly contribute to the pathogenesis of PEM in LC (Tajika et al., 2002; Guglielmi et al., 2005; Tsiaousi et al., 2008).

A flowchart to assess the nutritional status in patients with LC is shown in Figure 13.1. Indeed, statistical and dynamic nutritional assessments are generally recommended to assess the nutritional status of patients with LC (Table 13.1). Dietary assessment by a skilled dietitian, body composition analysis [height, body weight, body mass index (BMI), and anthropometric parameters], biochemical examinations (red blood cell count, hemoglobin, liver function tests, albumin, rapid turnover proteins, cholesterol, cholinesterase, prothrombin time activity, 3-methylhistidine

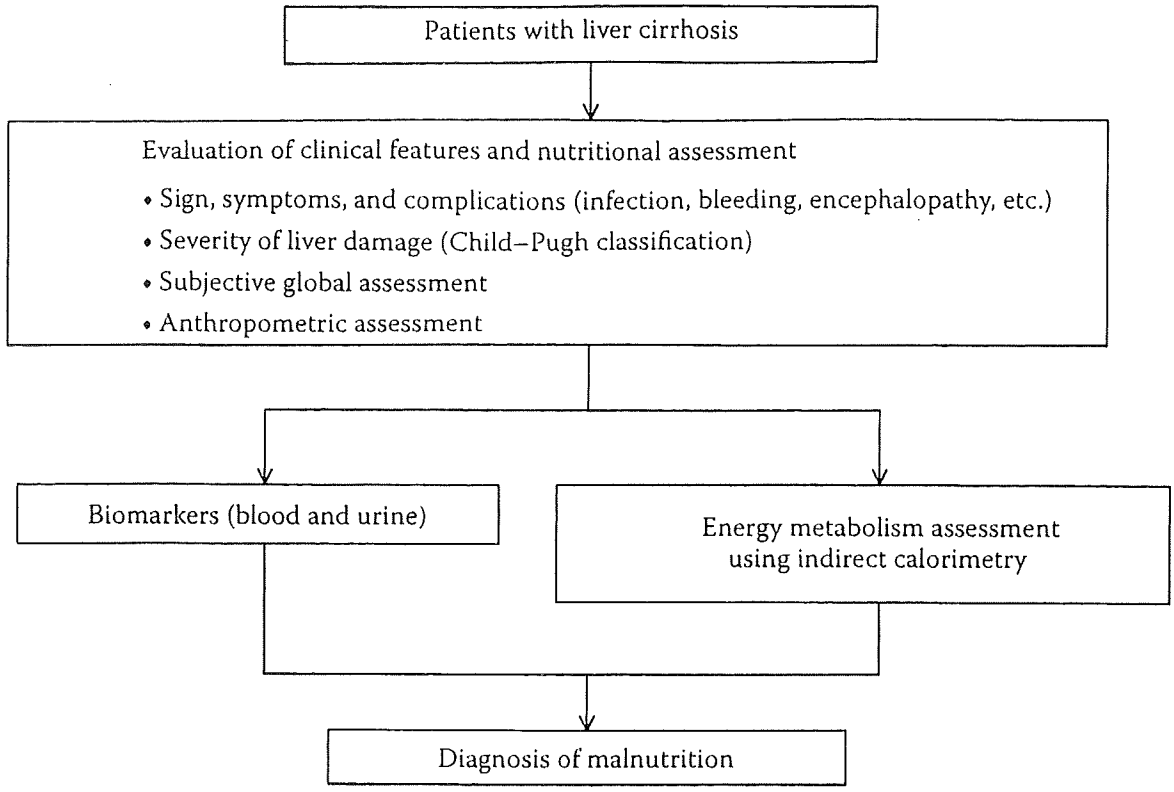


**FIGURE 13.1** Flowchart detailing the process of diagnosing malnutrition in patients with LC. SGA and anthropometric parameters should be evaluated to assess the nutritional status in addition to the observation of clinical signs, symptoms, and complications in patients with LC. Because many biomarkers are synthesized by the liver and influenced by factors such as infections, burns, surgery, gastrointestinal disorders, chronic renal failure, and inadequate food intake, care is required to correctly interpret the biomarkers when evaluating PEM in LC. LC, liver cirrhosis; PEM, protein-energy malnutrition; SGA, subjective global assessment.

in urine, etc.), immune competence (total lymphocyte count, delayed cutaneous hypersensitivity, and reaction against purified protein derivative of tuberculin), and energy metabolism assessment [e.g., resting energy expenditure, nonprotein respiratory quotient (npRQ), and substrate oxidation rate for glucose, protein, and fat] using indirect calorimetry are needed to assess the complete nutritional status of patients with LC (Madden and Morgan, 1999; Peng et al., 2007). Although simple and easily applied methods such as the subjective global assessment and anthropometric parameters are recommended in the assessment of nutritional status (Atalay et al., 2008), an examination of biomarkers is essential for an accurate assessment of nutritional status in patients with LC. However, many biomarkers are synthesized by the liver and influenced by factors such as infections, burns, surgery, gastrointestinal disorders, chronic renal failure, and inadequate food intake (Johnson, 1999; Gabay and Kushner, 1999; Kalender et al., 2002). Care is required to correctly interpret the biomarkers when evaluating PEM in LC.

This chapter describes representative biomarkers with which to assess nutritional status in patients with LC.

**TABLE 13.1**
**Recommended Nutritional Assessment in Patients with Liver Cirrhosis**

1. Static nutritional status
   a. Daily food intake
   b. Body composition analyses
      Height, body weight, body mass index, anthropometric parameters
   c. Biomarkers
      Red blood cell count, hemoglobin, routine liver function tests, cholesterol, cholinesterase, albumin, rapid turnover protein, prothrombin time, etc. (adipocytokines, ghrelin, vitamins, minerals, etc.), creatinine height index in urine
   d. Immune competence
      Total lymphocyte count, delayed cutaneous hypersensitivity, purified protein derivate of tuberculin
2. Dynamic nutritional status
   a. Energy metabolism (indirect calorimetry)
   b. Nitrogen balance
   c. Urinary 3-methylhistidine excretion
   d. Biomarkers
      Plasma free amino acids (Fischer ratio, BTR)

*Note:* List of items in the assessment of nutritional status in patients with liver cirrhosis. Fischer ratio, total branched chain amino acids (BCAA)/aromatic amino acids (phenylalanine + tyrosine) molar ratio; BTR, BCAA/tyrosine ratio.

## 13.2 ALBUMIN, RAPID TURNOVER PROTEINS

Serum albumin is the main secretion protein synthesized by the liver and has multiple functions such as the maintenance of colloid osmotic pressure, ligand binding and transport, and enzymatic and antioxidative activities (Quinlan et al., 2005). The synthesis and degradation rate of serum albumin in patients with LC are decreased as compared with those in healthy individuals whose liver function is normal. The half-life of serum albumin is extended in patients with LC (Moriwaki et al., 2004). Albumin synthesis in the liver is influenced by the severity of liver damage, various hormones, and nutritional and catabolic status such as that conferred by infections and burns (Johnson, 1999; Gabay and Kushner, 1999). However, serum albumin is still frequently applied as a biomarker of malnutrition and/or the severity of liver damage in patients with LC (Child-Pugh classification) (Pugh et al., 1973). When serum albumin is used to assess malnutrition in patients with LC, physicians should confirm whether the daily food intake and pathophysiological conditions are properly and individually estimated.

Serum albumin assumes microheterogeneous, oxidized, and reduced forms (Kawakami et al., 2006). Serum total albumin decreases, whereas the ratio of oxidized albumin increases with LC progression (Watanabe et al., 2004). Furthermore, a recent study has also shown that the oxidation status of serum albumin changes in patients with LC after supplementation with branched-chain amino acids (BCAAs)

(Fukushima et al., 2007). Oxidative stress is an important factor in the progression of chronic liver disease (Moriya et al., 2001). These findings suggest that the oxidative state of serum albumin could be important as a novel marker of not only the severity of liver damage, but also of malnutrition in patients with LC. However, measurements of the oxidative states of serum albumin are time-consuming and rarely performed in the clinical setting.

Prealbumin (transthyretin), retinol-binding protein, and transferrin are markers of short-term nutritional status (Brose, 1990; Calamita et al., 1997; Devakonda et al., 2008) that are synthesized by the liver, and their half-lives are much shorter than that of albumin (Tables 13.2 and 13.3). These proteins are also influenced by baseline conditions such as surgery, infection, and anemia (Johnson, 1999; Gabay and Kushner, 1999).

Retinol-binding protein 4 (RBP-4) has been recently identified as an adipokine, which functions in the pathogenesis of insulin resistance associated with type 2 diabetes and obesity (Yang et al., 2005; Graham et al., 2006). Elevated serum RBP-4 level is an independent predictive marker of early insulin resistance and identifies individuals at risk of developing diabetes (Graham et al., 2006). Because hyperinsulinemia and glucose intolerance are frequently seen in patients with LC and because insulin resistance is an established risk factor for disease progression and survival in patients with chronic liver disease, serum RBP-4 might be a useful biomarker of malnutrition in patients with LC. Indeed, serum RBP-4 levels are decreased and closely correlated with the degree of liver damage according to the Child-Pugh classification (Yagmur et al., 2007). On the other hand, serum RBP-4 levels are impaired because of decreased hepatic production, but they are not associated with insulin resistance (Bahr et al., 2008). The features of serum RBP-4 in patients with LC are

**TABLE 13.2**
**Biomarkers in Assessing the Nutritional State in Patients with Liver Cirrhosis**

1. Biomarkers in the blood
   - Albumin
   - Rapid turnover proteins (prealbumin, retinol-binding protein, transferrin, etc.)
   - Fischer ratio (BTR)
   - Adipocytokines (leptin, adiponectin, resistin, etc.)
   - Ghrelin
   - Vitamins (A, D, E, K, thiamine, riboflavin, niacin, $B_6$, $B_{12}$, C, and folate)
   - Minerals (copper, zinc, iron, manganese, selenium, etc.)
   - Hormones (insulin-like growth factor, insulin-like growth factor–binding protein 3, reverse triiodothyronine, etc.)
2. Biomarkers in the urine
   - Nitrogen (nitrogen balance)
   - Creatinine (creatinine height index)
   - 3-Methylhistidine

*Note:* Biomarkers used in assessing the nutritional state of patients with liver cirrhosis. BTR, total branched chain amino acids/tyrosine ratio.

## TABLE 13.3
## Characteristics of Albumin and Rapid Turnover Proteins

| | Albumin | Prealbumin | RBP | Transferrin |
|---|---|---|---|---|
| Half-life time | 17–21 days | 2 days | 0.4–0.7 day | 7–10 days |
| MW | 67,000 | 55,000 | 21,000 | 76,500 |
| Functions | Maintenance of colloid osmotic pressure, ligand, and transport of substances including hormones, and antioxidant action | Binding protein of thyroxin, vitamin A transport | Vitamin A transport | Carrier protein of iron, synthesis of hemoglobin |
| Baseline level | 3.5–5.5 g/dL | 20–40 mg/dL | 2.2–7.4 mg/dL | 200–400 mg/dL |
| Changes in serum level | | | | |
| Increased | Dehydration, administration of hormones (steroid, insulin, thyroxin) | Chronic renal failure, hyperthyroidism, pregnancy | Chronic renal failure, fatty liver | Iron deficiency anemia, pregnancy, sex hormone administration |
| Decreased | Liver injury, nephrotic syndrome, protein-losing gastrointestinal diseases, acute inflammations, infections, burns | Protein malnutrition, liver injury, nephritic syndrome, gastrointestinal diseases, acute inflammations | Vitamin A deficiency, hyperthyroidism, liver injury, infections, burns | Protein malnutrition, liver injury, nephrotic syndrome, inflammations |

*Note:* Characteristic features of albumin and rapid turnover proteins. RBP, retinol-binding protein; MW, molecular weight.

## TABLE 13.4
## Summary of Serum RBP-4 in Patients with LC

1. Serum RBP-4 levels are decreased in patients with LC and directly related with the severity of liver damage.
2. Serum RBP-4 levels do not correlate with insulin resistance in patients with LC.
3. Lowest RBP-4 levels are seen in cirrhotic patients with histological progression.
4. Hepatic RBP-4 expression is decreased in cirrhotic liver compared with normal liver.

*Note:* Indications of serum RBP-4 in patients with LC. LC, liver cirrhosis; RBP-4, retinol-binding protein 4.

summarized in Table 13.4. Further studies are required to elucidate how the serum RBP-4 contributes to the development of malnutrition in patients with LC.

## 13.3 PLASMA FREE AMINO ACIDS

The profile of plasma free amino acids shows characteristic changes in patients with LC (Fischer et al., 1976; Morgan et al., 1978). Levels of BCAAs (valine, leucine, and isoleucine) metabolized in the skeletal muscle are decreased, whereas those of aromatic amino acids (AAA; phenylalanine and tyrosine) metabolized in the liver are increased, resulting in a decreased BCAA/AAA molar ratio (Fischer ratio). These alterations are affected by the severity of liver damage and are closely associated with the development of hepatic encephalopathy (Fischer et al., 1976; Suzuki et al., 2004). However, analyzing amino acid profiles using high-performance liquid chromatography is expensive and time-consuming. Therefore, a straightforward and inexpensive enzymatic method of determining total BCAA and tyrosine levels in serum has been widely applied in Japan to measure the serum BCAA/tyrosine ratio (BTR) and to determine the amino acid balance and severity of liver damage (Azuma et al., 1989). Serum BTR is positively correlated with the plasma Fischer ratio and the serum albumin level in patients with LC (Figure 13.2A and B). A recent report has shown that BTR can help to predict a decrease in serum albumin levels associated with chronic liver disease (Suzuki et al., 2008). Thus, serum BTR might serve as a reliable biomarker of malnutrition in patients with LC.

## 13.4 ADIPOCYTOKINES

Leptin is a peptide hormone that is produced by adipose tissue affecting both food intake and energy metabolism via sympathetic nerves originating in the hypothalamus, and thus controls the ratio (%) of body fat (Zhang et al., 1994; Weigle et al., 1995). Leptin is involved in the pathogenesis of liver fibrosis (Din et al., 2005). Serum leptin levels are higher in females than males among patients with LC and healthy individuals, and levels positively correlate with BMI, but not with severity of liver damage (McCullough et al., 1998; Campillo et al., 2001). Moreover, serum leptin levels also correlate with arm muscle circumference (AMC) and triceps skinfold thickness (TSF) (Onodera et al., 2001). Because AMC and TSF are commonly decreased in LC patients with malnutrition, the serum leptin level might be useful in assessing malnutrition in such patients, although the gender difference should be considered.

Adiponectin, a peptide hormone produced by adipose tissue, is also an adipocytokine (Schere et al., 1995). Although its physiological role has not been fully elucidated, adiponectin critically influences several components of the metabolic syndrome such as diabetes mellitus and arteriosclerosis (Kadowaki and Yamauchi, 2005; Wang and Scherer, 2007). In particular, plasma adiponectin levels are invariably correlated negatively with BMI and body fat mass, fasting glucose and insulin levels, degree of insulin resistance, blood pressure, and serum total cholesterol and triglyceride levels (Hara et al., 2006). Several reports have described the relationship

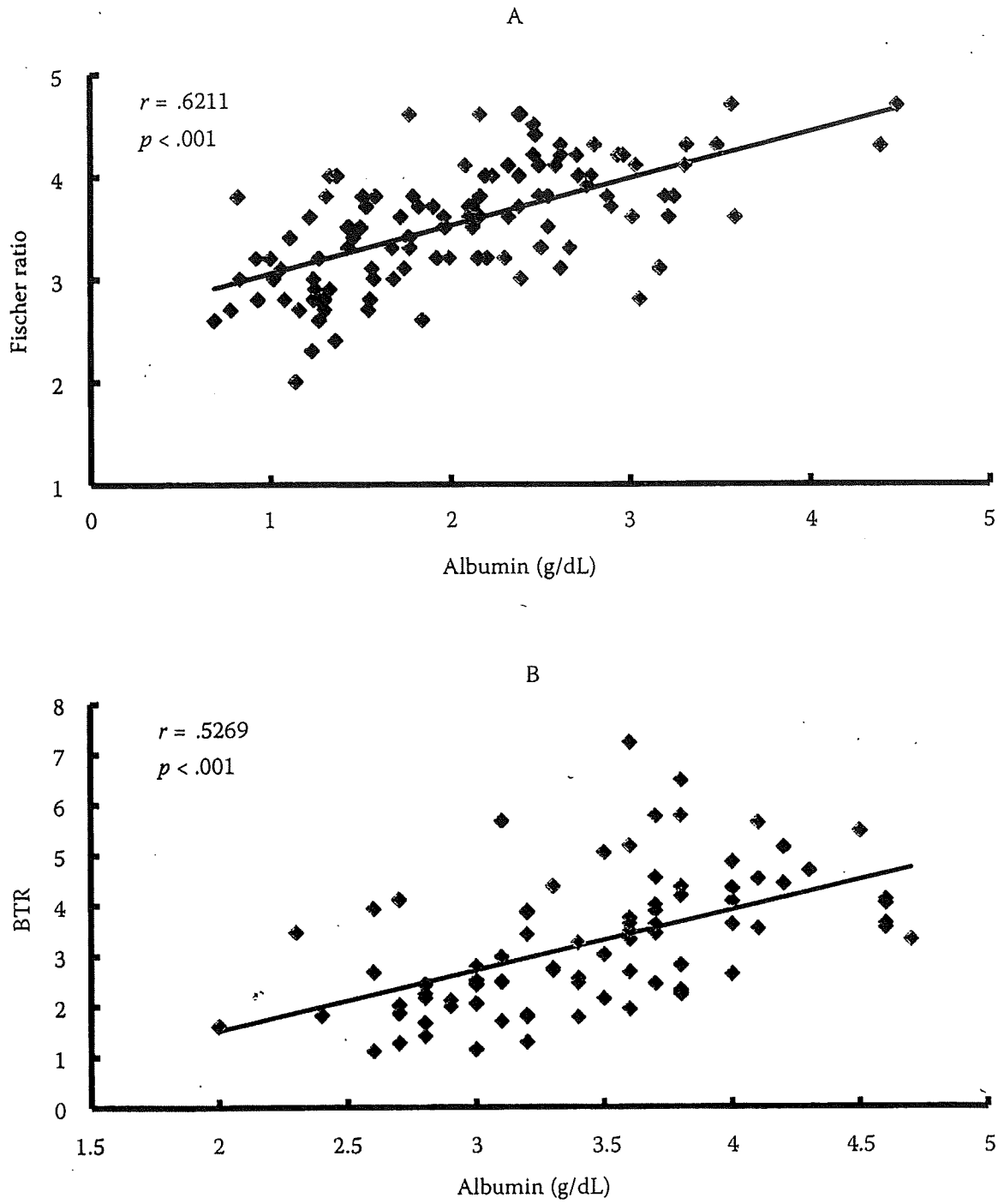


**FIGURE 13.2** Correlation between levels of serum albumin and plasma amino acids in patients with LC. Eighty-five cirrhotic patients with or without hepatocellular carcinoma who were admitted at the Iwate Medical University Hospital were investigated. (A) Correlation between serum albumin levels and plasma Fischer ratio. (B) Correlation between serum albumin levels and serum BTR. Fischer ratio, valine + leucine + isoleucine/phenylalanine + tyrosine. BTR, valine + leucine + isoleucine/tyrosine.

between plasma adiponectin levels and steatosis in liver diseases including nonalcoholic steatohepatitis and hepatitis C virus–related chronic hepatitis (Jonsson et al., 2005; Petit et al., 2005). Tietge et al. (2004) and Sohara et al. (2004) have shown that circulating adiponectin levels are significantly increased in LC patients compared

with healthy individuals and that they correlate with the severity of liver damage according to the Child-Pugh classification.

Serum adiponectin assumes three forms—low molecular weight, middle molecular weight, and high molecular weight (HMW)—and the latter is deeply involved in the pathogenesis of diabetes mellitus and metabolic syndrome (Kadowaki and Yamauchi, 2005; Hara et al., 2006). Figure 13.3 shows the relationship between plasma HMW adiponectin levels and malnutrition in LC patients. Plasma HMW adiponectin levels are elevated according to the severity of liver damage. Although the clinical significance of the HMW adiponectin remains somewhat obscure, it might be a promising biomarker of nutritional status in LC.

Resistin is a recently identified adipocytokine that might function in obesity and insulin resistance, although its role in humans is controversial (Bahr et al., 2006). However, circulating resistin levels correlate with the severity of liver damage in patients with LC (Kakizaki et al., 2008).

## 13.5 GHRELIN

Ghrelin was originally discovered as an orexigenic hormone that stimulates growth hormone release (Kojima et al., 1999). This hormone is mainly found in the gastric wall, and it plays a role in the hypothalamic centers to regulate feeding and caloric status (Nakazato et al., 2001). Recent reports have shown that ghrelin controls feeding

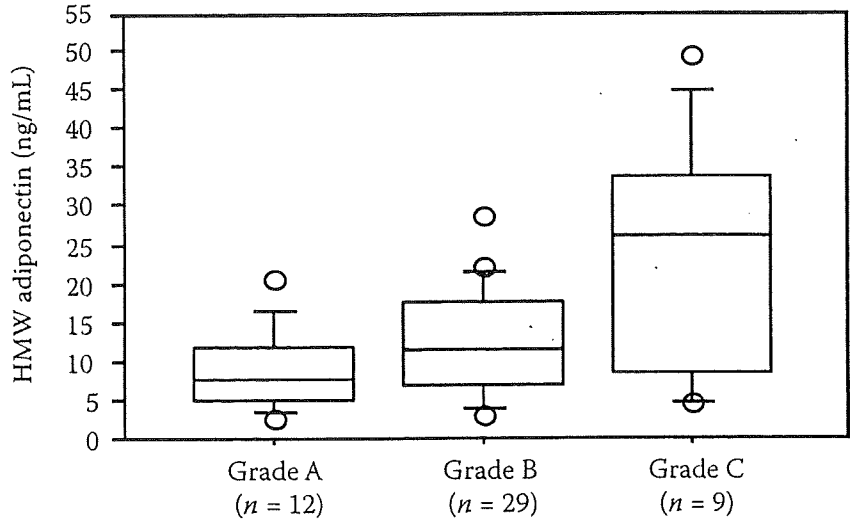


**FIGURE 13.3** Relationship between plasma HMW adiponectin levels and severity of liver damage. Forty-seven cirrhotic patients (male 29, female 18) with or without hepatocellular carcinoma who were admitted at Iwate Medical University Hospital were investigated. Etiologies of these patients were HBV ($n$ = 3), HCV ($n$ = 23), HCV + alcohol ($n$ = 11), alcohol ($n$ = 3), primary biliary cirrhosis ($n$ = 3), nonalcoholic steatohepatitis ($n$ = 1), and unknown ($n$ = 3). The severity of liver damage was classified into grade A, B, or C based on the Child-Pugh classification. Peripheral plasma samples were collected from all patients after overnight fasting and HMW adiponectin levels were measured using enzyme-linked immunosorbent assay (ELISA) (Fujirebio Co., Tokyo, Japan). LC, liver cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HMW, high molecular weight.

behavior and the long-term regulation of body weight in association with leptin in the hypothalamic centers (Nakazato et al., 2001; Cummings et al., 2003). Circulating plasma ghrelin level has been considered a marker of pathological conditions such as obesity, insulin resistance, type 2 diabetes mellitus, hypertension, and *Helicobacter pylori* (HP) infection (Nwokolo et al., 2003; Kalaitzakis et al., 2007). Evaluation of plasma ghrelin levels in patients with LC has generated conflicting data (Tacke et al., 2003; Marchesini et al., 2004). However, we have recently shown that plasma ghrelin (desacyl form) levels in patients with LC are not higher than those in healthy controls, and that they do not correlate with the severity of liver damage; rather, the ghrelin level is closely associated with renal failure and inflammatory status (Takahashi et al., 2006). Figures 13.4 and 13.5 (reproduced with permission) show that the plasma ghrelin level significantly correlates with anthrometric parameters such as BMI, AMC, and TSF, and energy metabolic parameters such as npRQ, substrate oxidation rates for glucose (%CHO), and fat (%FAT) in patients with LC. Furthermore, plasma ghrelin level is negatively correlated with the level of serum leptin. Infection with HP did not influence the plasma ghrelin level in our study. Therefore, fasting plasma ghrelin level might be an interesting marker of malnutrition in patients with stable LC who do not have severe complications such as renal failure and infection.

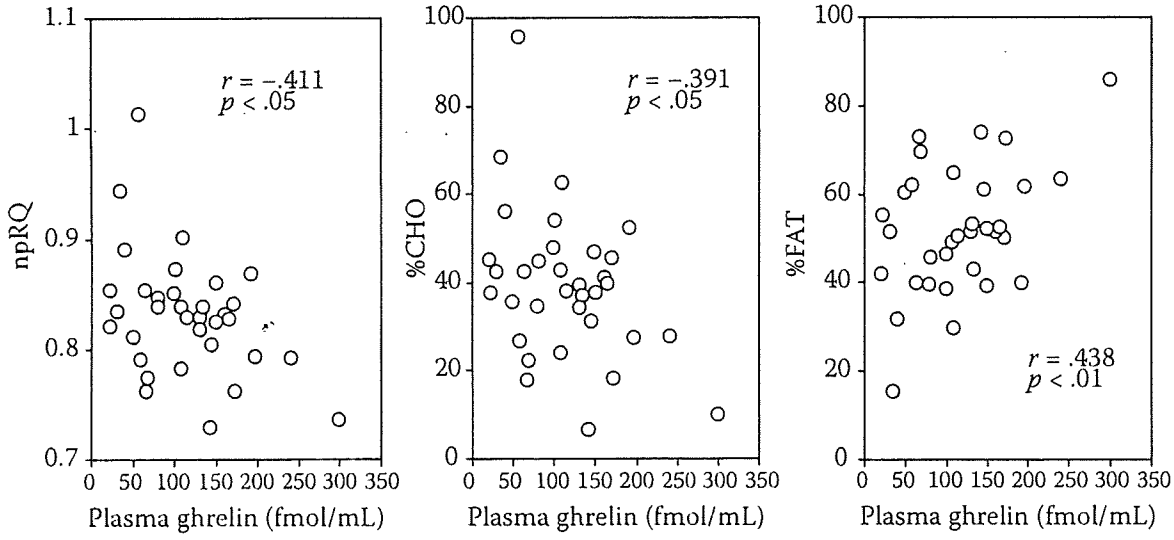


**FIGURE 13.4** Relationship between plasma ghrelin levels and energy metabolism determined using indirect calorimetry. Thirty-four cirrhotic patients (male 20, female 14) with or without hepatocellular carcinoma who were admitted at Iwate Medical University Hospital were investigated. Etiologies of patients were HBV ($n$ = 1), HCV ($n$ = 18), HCV + alcohol ($n$ = 3), alcohol ($n$ = 8), primary biliary cirrhosis ($n$ = 1), and unknown ($n$ = 3). The severity of liver damage was classified into grade A, B, or C based on the Child-Pugh classification. Peripheral plasma samples were collected from all patients during the morning after overnight fasting and ghrelin levels were measured using ELISA (Mitsubishi Kagaku Iatoron Inc., Tokyo, Japan). Energy metabolism was measured using direct calorimeter (Deltatrac-II Metabolic Monitor, Datax Division Inst. Corp., Helsinki, Finland). npRQ, nonprotein respiratory quotients; %CHO, oxidation rate of glucose; %FAT, oxidation rate of fat; LC, liver cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus. (From Takahashi, T., Kato, A., Onodera, K., and Suzuki, K., *Hepatol Res*, 24, 117–123, 2006. With permission.)

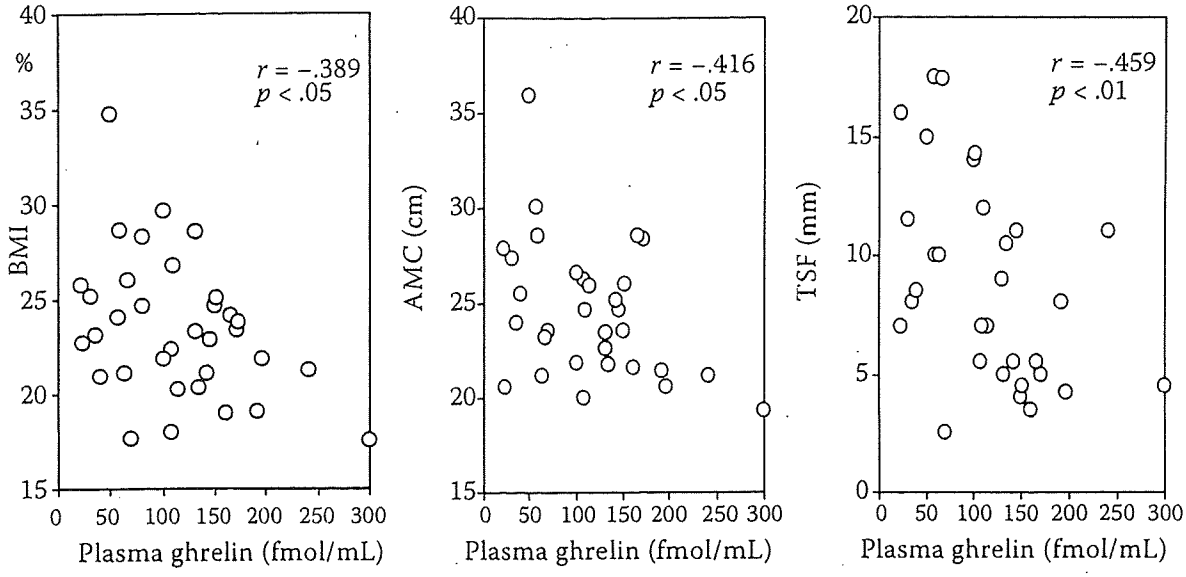


**FIGURE 13.5** Relationship between plasma ghrelin levels and anthrometric parameters. AMC and TSF were measured using a commercial anthropometer. BMI, body mass index; AMC, arm muscle circumference; TSF, triceps skin-fold thickness. (From Takahashi, T., Kato, A., Onodera, K., and Suzuki, K., *Hepatol Res*, 24, 117–123, 2006. With permission.)

## 13.6 OTHER MARKERS

The nutritional status of patients with chronic liver diseases is often assessed using levels of vitamins (fat-soluble; A, D, E, K, and water-soluble; thiamine, riboflavin, niacin, $B_6$, $B_{12}$, C, and folate), minerals (mainly copper, zinc, iron, manganese, and selenium), and hormones (insulin-like growth factor 1, insulin-like growth factor–binding protein 3, reverse triiodothyronine, etc.) (Assy et al., 1998; Cabre and Gassull, 2005; Morgan and Heaton, 2008). However, because these biomarkers are also influenced by the severity of liver damage and baseline conditions such as food intake, alcohol abuse, cholestasis, and infection, the data must be carefully interpreted.

## 13.7 SUMMARY POINTS

- Subjective global assessment and measurement of anthrometric parameters are essential to accurately evaluate nutritional status in patients with LC.
- Malnutrition, in particular PEM type, is closely associated with the prognosis of patients with LC.
- Biomarkers, such as albumin, rapid turnover protein, amino acids, adipocytokines, ghrelin, vitamins, and minerals, are useful in assessing malnutrition.
- Data of biomarkers must be carefully interpreted, because they are often influenced by the severity of liver damage and other factors including diminished nutrient intake, alcohol, impaired digestion, absorption of nutrients, hypermetabolic, or catabolic state.