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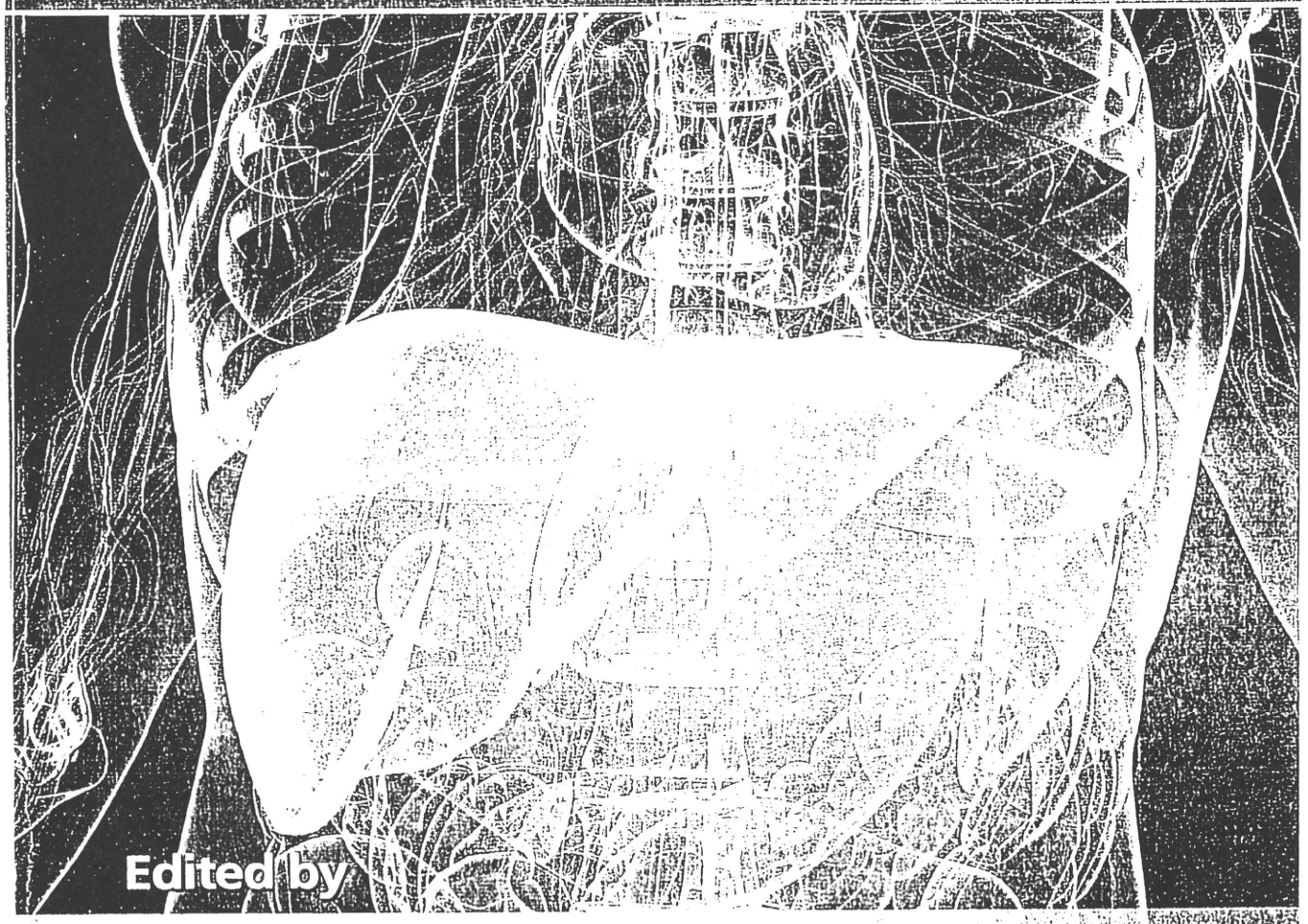

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13 Biomarkers of Malnutrition in Liver Cirrhosis

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

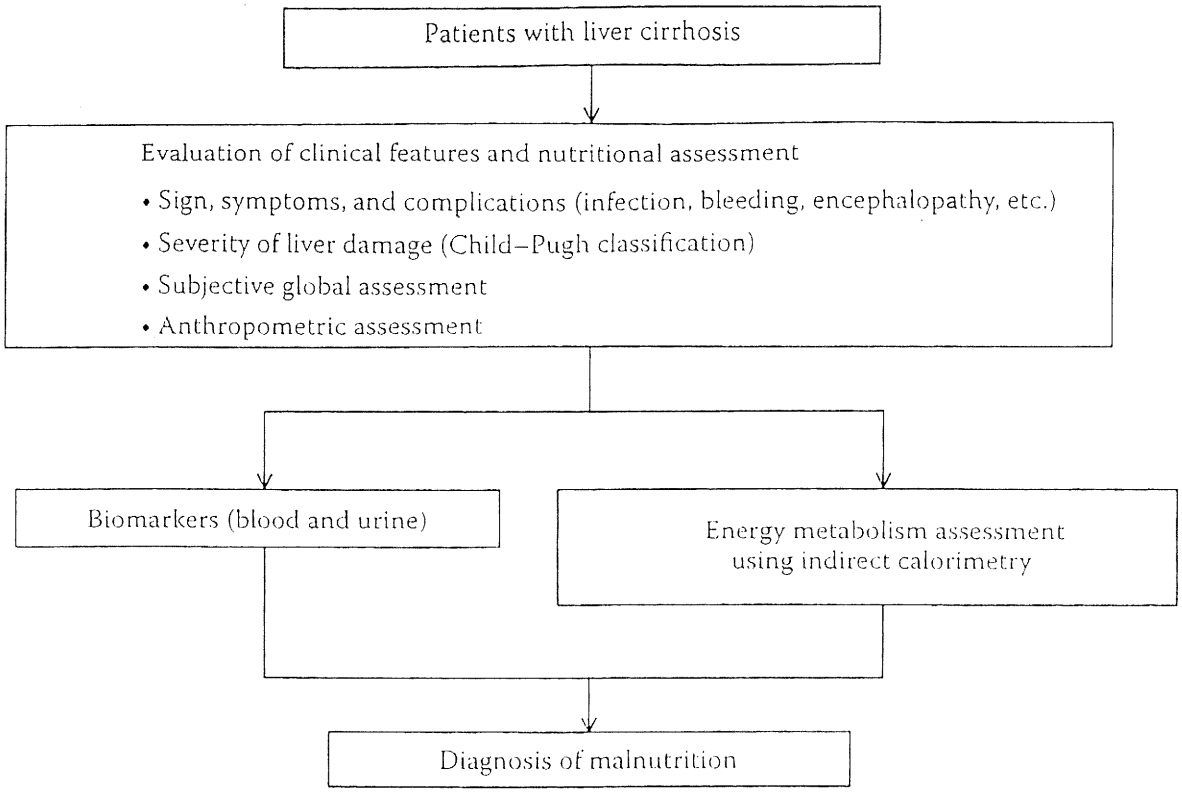

FIGURE 13.1 Flowchart detailing the process of diagnosing malnutrition in patients with LC. SGA and anthropometric parameters should be evaluated to assess the nutritional status in addition to the observation of clinical signs, symptoms, and complications in patients with LC. Because many biomarkers 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

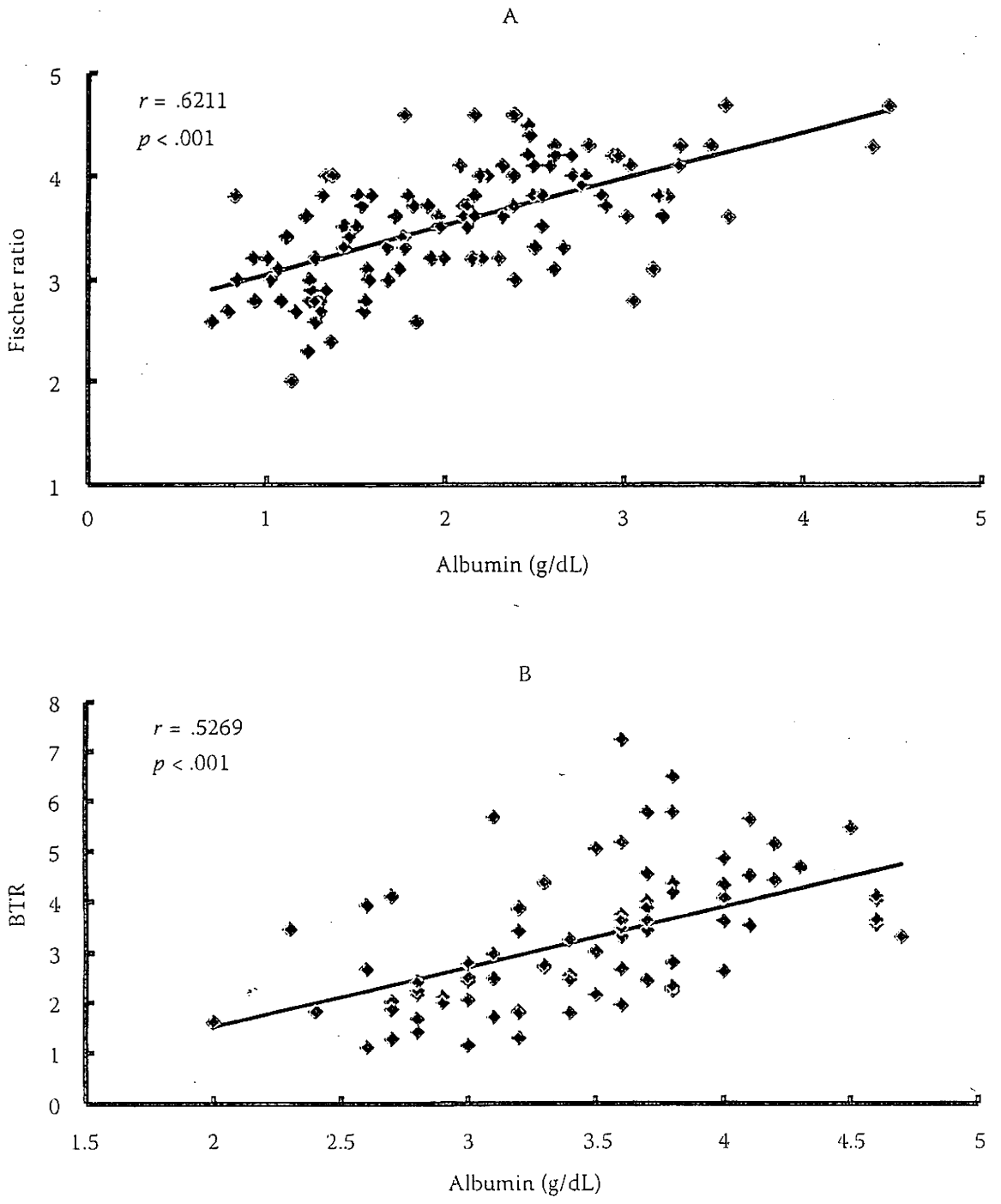

FIGURE 13.2 Correlation between levels of serum albumin and plasma amino acids in patients with LC. Eighty-five cirrhotic patients with or without hepatocellular carcinoma who were admitted at the Iwate Medical University Hospital were investigated. (A) Correlation between serum albumin levels and plasma 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

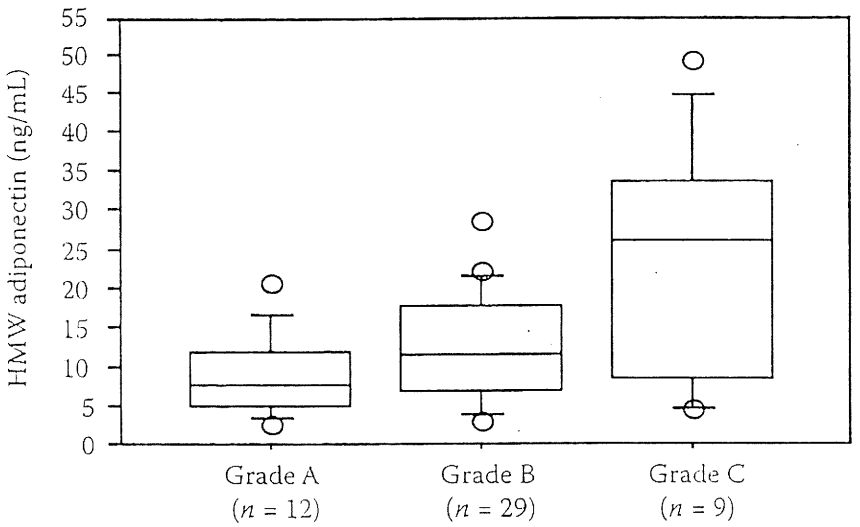

FIGURE 13.3 Relationship between plasma HMW adiponectin levels and severity of liver damage. Forty-seven cirrhotic patients (male 29, female 18) with or without hepatocellular carcinoma who were admitted at Iwate Medical University Hospital were investigated. Etiologies of these patients were HBV (n = 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.

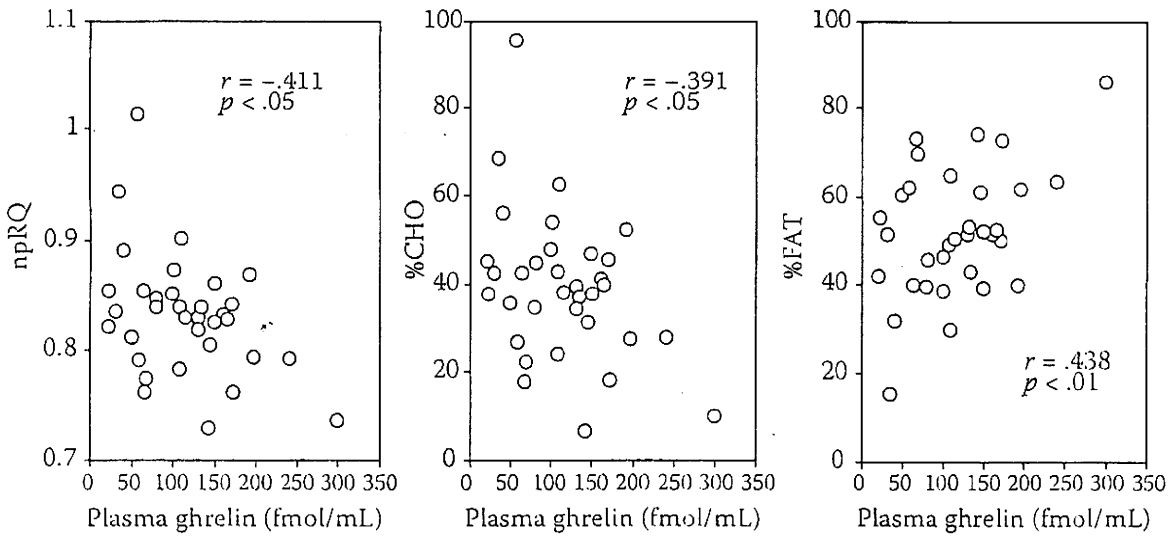

FIGURE 13.4 Relationship between plasma ghrelin levels and energy metabolism determined using indirect calorimetry. Thirty-four cirrhotic patients (male 20, female 14) with or without hepatocellular carcinoma who were admitted at Iwate Medical University Hospital were investigated. Etiologies of patients 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.)

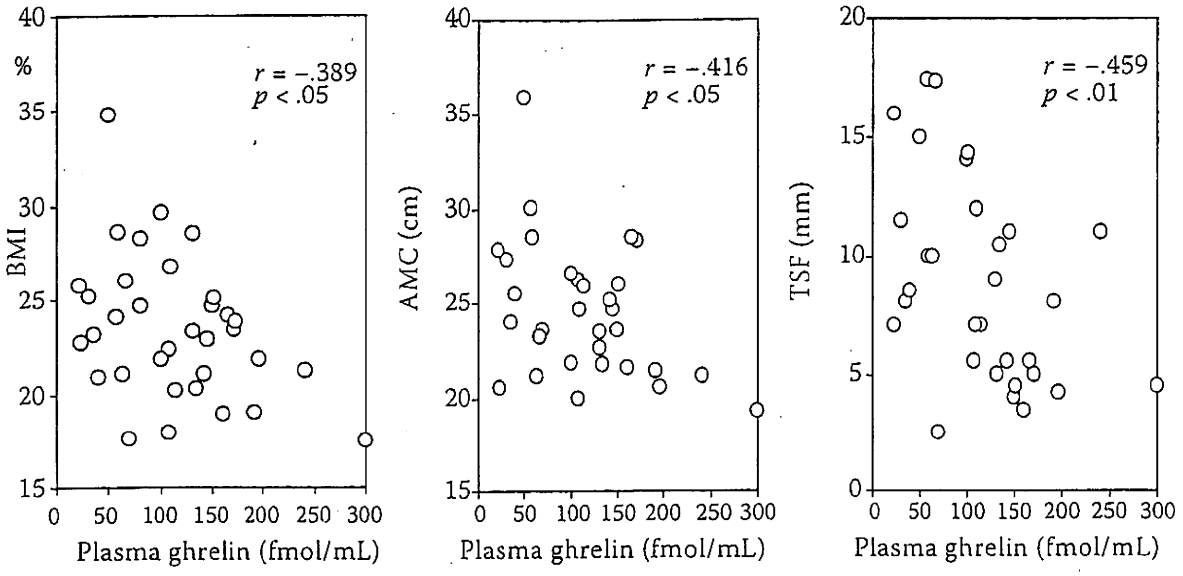

FIGURE 13.5 Relationship between plasma ghrelin levels and anthrometric parameters. AMC and TSF were measured using a commercial anthropometer. BMI, body mass index; AMC, arm muscle circumference; TSF, triceps skin-fold thickness. (From Takahashi, T., Kato, A., Onodera, K., and Suzuki, K., *Hepatol Res*,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

REFERENCES

Assy, N., Z. Hochberg, R. Enat, et al. 1998. Prognostic value of generation of growth hormone-stimulated insulin-like growth factor–1 (IGF-1) and its binding protein-3 in patients with compensated and decompensated liver cirrhosis. *Dig Dis Sci* 43:1317–1321.

Atalay, B. G., C. Yagmur, T. Z. Nursal, et al. 2008. Use of subjective global assessment and clinical outcomes in critically ill geriatric patients receiving nutrition support. *JPEN J Parenter Enteral Nutr* 32:454–459.

Azuma, Y., M. Maekawa, Y. Kuwabara, et al. 1989. Determination of branched-chain amino acid and tyrosine in serum of patients with various hepatic diseases and its clinical usefulness. *Clin Chem* 35:1399–1403.

Bahr, M. J., K. H. Boeker, M. P. Manns, et al. 2008. Decreased hepatic RBP4 secretion is correlated with reduced hepatic glucose production but not associated with insulin resistance in patients with liver cirrhosis. *Clin Endocrinol (Oxf)* 68:1–22. http://www.blackwell-synergy.com/loi/cen.pdf.

Bahr, M. J., J. Ockenga, K. H. W. Böker, et al. 2006. Elevated resistin levels in cirrhosis are associated but not with insulin resistance. *Am J Physiol Endocrinol Metab* 29:E199–E206.

Brose, L. 1990. Prealbumin as a marker of nutritional status. *J Burn Care Rehab* 11:372–375.

Cabre, E., and M. A. Gassull. 2005. Nutrition in liver cirrhosis. *Curr Opin Clin Nutr Metab Care* 8:545–551.

Calamita, A., I. Dichi, S. J. Papini-Berto, et al. 1997. Plasma levels of transthyretin and retinol-binding protein in Child-A cirrhotic patients in relation to protein-calorie status and plasma amino acids, zinc, vitamin A and plasma thyroid hormones. *Arq Gastroenterol* 34:139–147.

Campillo, B., J. P. Richardet, E. Scherman, et al. 2003. Evaluation of nutritional practice in hospitalized cirrhotic patients: Results of a prospective study. *Nutrition* 19:515–521.

Campillo, B., E. Sherman, J. P. Richardet, et al. 2001. Serum leptin levels in alcoholic liver cirrhosis: Relationship with gender, nutritional status, liver function and energy metabolism. *Eur J Clin Nutr* 55:980–988.

Caregaro, L., F. Alberino, P. Amodio, et al. 1996. Malnutrition in alcoholic and virus-related cirrhosis. *Am J Clin Nutr* 63:602–609.

Cummings, D. E., D. S. Weigle, S. Frayo, et al. 2003. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *New Engl J Med* 346:1623–1630.

Devakonda, A., L. George, S. Raoof, et al. 2008. Transthyretin as a marker to predict outcome in critically ill patients. *Clin Biochem* 41:1126–1130.

Din, X., N. K. Saxena, S. Lin, et al. 2005. The role of leptin and adiponectin: A novel paradigm in adipocytokine regulation of liver fibrosis and stellate cell biology. *Am J Pathol* 166:1655–1699.

Fischer, J. E., H. M. Rosen, A. M. Ebeid, et al. 1976. The effect of normalization of plasma amino acids on hepatic encephalopathy. *Surgery* 80:77–91.

Fukushima, H., Y. Miwa, M. Shiraki, et al. 2007. Oral branched-chain amino acid supplementation improves the oxidized/reduced albumin ratio in patients with liver cirrhosis. *Hepatol Res* 37:765–70.

Gabay, C., and I. Kushner. 1999. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 340:448–454.

Graham, T. E., Q. Yang, M. Bluher, et al. 2006. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. *N Engl J Med* 354:2552–2563.

Guglielmi, F. W., C. P. Panella, A. Buda, et al. 2005. Nutritional state and energy balance in cirrhotic patients with or without hypermetabolism. Multicenter prospective study by the 'Nutritional Problems in Gastroenterology' Section of the Italian Society of Gastroenterology (SIGE). *Dig Liver Dis* 37:681–688.

Hara, K., M. Horikoshi, T. Yamauchi, et al. 2006. Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. *Diabetes Care* 29:1357–1362.

Johnson, A. M. 1999. Low levels of plasma proteins malnutrition or inflammation? *Clin Chem Lab Med* 37:91–96.

Jonsson, J. R., A. R. Moschen, I. J. Hickman, et al. 2005. Adiponectin and its receptors in patients with chronic hepatitis C. *J Hepatol* 43:929–936.

Kadowaki, T., and T. Yamauchi. 2005. Adiponectin and adiponectin receptors. *Endocr Rev* 26:439–451.

Kakizaki, S., N. Sohara, Y. Yamazaki, et al. 2008. Elevated plasma resistin concentrations in patients with liver cirrhosis. *J Gastroenterol Hepatol* 23:73–77.

Kalaitzakis, E., I. Bosaeus, L. Ohman, et al. 2007. Altered postprandial glucose, insulin, leptin, and ghrelin in liver cirrhosis: Correlations with energy intake and resting energy expenditure. *Am J Clin Nutr* 85:808–815.

Kalender, B., B. Mutlu, M. Ersöz, et al. 2002. The effects of acute phase proteins on serum albumin, transferrin and haemoglobin in haemodyalysis patients. *Int J Clin Pract* 56:505–508.

Kawakami, A., K. Kubota, N. Yamada, et al. 2006. Identification and characterization of oxidized human serum albumin. A slight structural change impairs its ligand-binding and anti-oxidant functions. *FEBS J* 273:3346–3357.

Kojima, M., H. Hosoda, Y. Date, et al. 1999. Ghrelin is a growth-hormone–releasing acylated peptide from stomach. *Nature* 402:656–660.

Liu, C. J., P. J. Chen, Y. M. Jeng, et al. 2005. Serum adiponectin correlates with viral characteristics but not histological features in patients with chronic hepatitis C. *J Hepatol* 43:235–242.

Madden, A. M., and M. Y. Morgan. 1999. Resting energy expenditure should be measured in patients with cirrhosis, not predict. *Hepatology* 30:655–664.

Marchesini, G., N. Villanova, G. Bianchi, et al. 2004. Plasma ghrelin concentrations, food intake, and anorexia in liver disease. *J Clin Endocrinol Metab* 89:2136–2141.

McCullough, A. J., E. Bugianesi, G. Marchesini, et al. 1998. Gender-dependent alterations in serum leptin in alcoholic cirrhosis. *Gastroenterology* 115:947–953.

Morgan, M. Y., and K. W. Heaton. 2008. Nutrition, the liver, and gallstones. 2000. In *Human Nutrition and Dietetics*, ed. J. S. Garrow, W. P. T. Janes, and A. Ralph. London: Churchill Livingstone, pp. 575–603.

Morgan, M. Y., J. P. Milsom, and S. Sherlock. 1978. Plasma ratio of valine, leucine and isoleucine to phenylalanine and tyrosine in liver disease. *Gut* 19:1068–1073.

Moriwaki, H., Y. Miwa, M. Tajika, et al. 2004. Branched-chain amino acids as a protein- and energy-source in liver cirrhosis. *Biochem Biophys Res Commun* 313:405–409.

Moriya, K., K. Nakagawa, T. Santa, et al. 2001. Oxidative stress in the absence of inflammation in a mouse model for hepatitis C virus–associated hepatocarcinogenesis. *Cancer Res* 61:4365–4370.

Nakazato, M., N. Murakami, Y. Date, et al. 2001. A role of ghrelin in the central regulation of feeding. *Nature* 409:194–198.

Nwokolo, C. U., D. A. Freshwater, P. O'Hare, et al. 2003. Plasma ghrelin following cure of *Helicobacter pylori*. *Gut* 52:637–640.

Onodera, K., A. Kato, and K. Suzuki. 2001. Serum leptin concentrations in liver cirrhosis: Relationship to the severity of liver dysfunction and their characteristic diurnal profiles. *Hepatol Res* 21:205–212.

Peng, S., L. D. Plank, J. L. McCall, et al. 2007. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: A comprehensive study. *Am J Clin Nutr* 85:1257–1266.

Petit, J. M., A. Minello, V. Jooste, et al. 2005. Decreased plasma adiponectin concentrations are closely related to steatosis in hepatitis C virus–infected patients. *J Clin Endocrinol Metab* 90:2240–2243.

Pugh, R. N. H., I. M. Murray-Lyon, J. L. Dawson, et al. 1973. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 60:646–649.

Quinlan, G. J., G. S. Martin, and T. W. Evans. 2005. Albumin: Biochemical properties and therapeutic potential. *Hepatology* 41:1211–1219.

Riggio, O., S. Angeloni, L. Ciuffa, et al. 2003. Malnutrition is not related to alterations in energy balance in patients with stable liver cirrhosis. *Clin Nutr* 22:553–559.

Roongpisuthipong, C., A. Sobhonslidsuk, K. Nantiruj, et al. 2001. Nutritional assessment in various stages of liver cirrhosis. *Nutrition* 17:761–765.

Schere, P. E., S. Williams, M. Fogliano, et al. 1995. Novel serum protein similar to Clq produced exclusively in adipocytes. *J Biol Chem* 270:26746–26749.

Sohara, N., H. Takagi, S. Kakizaki, et al. 2004. Elevated plasma adiponectin concentrations in patients with liver cirrhosis correlate with plasma insulin levels. *Liver Int* 25:28–32.

Suzuki, K., A. Kato, and M. Iwai. 2004. Branched-chain amino acid treatment in patients with liver cirrhosis. *Hepatol Res* 30S:S25–S29.

Suzuki, T., K. Suzuki, K. Koizumi, et al. 2008. Measurement of serum branched-chain amino acid to tyrosine ratio level is useful in a prediction of a change of serum albumin level in chronic liver disease. *Hepatol Res* 38:267–272.

Tacke, F., G. Brabant, E. Kruck, et al. 2003. Ghrelin in chronic liver disease. *J Hepatol* 38:447–454.

Tajika, M., M. Kato, H. Mohri, et al. 2002. Prognostic value of energy metabolism in patients with viral liver cirrhosis. *Nutrition* 18:229–234.

Takahashi, T., A. Kato, K. Onodera, et al. 2006. Fasting plasma ghrelin levels reflect malnutrition state in patients with liver cirrhosis. *Hepatol Res* 24:117–123.

Tietge, U. J., K. H. Boker, M. P. Manns, et al. 2004. Elevated circulating adiponectin levels in liver cirrhosis are associated with reduced liver function and altered hepatic hemodynamics. *Am J Physiol Endocrinol Metab* 287:E82–E89.

Tsiaousi, I. E., A. I. Hatzitolios, S. K. Trygonis, et al. 2008. Malnutrition in end stage liver disease: Recommendations and nutritional support. *J Gastroenterol Hepatol* 23:527–533.

Wang, Z. V., and P. E. Scherer. 2007. Adiponectin, cardiovascular function, and hypertension. *Hypertension* 51:8–14.

Watanabe, A., S. Mastuzaki, H. Moriwaki, et al. 2004. Problem in serum albumin measurement and clinical significance of albumin microheterogeneity in cirrhosis. *Nutrition* 20:351–357.

Weigle, D. S., T. R. Bukowski, D. C. Foster, et al. 1995. Recombinant ob protein reduces feeding and body weight in the *ob/ob* mouse. *J Clin Invest* 96:2065–2070.

Yagmur, E., R. Weiskirchen, A. M. Gressner, et al. 2007. Insulin resistance in liver cirrhosis is not associated with circulating retinol-binding protein 4. *Diabetes Care* 30:1168–1172.

Yang, Q., T. E. Graham, N. Mody, et al. 2005. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* 436:356–362.

Zhang, Y., R. Procnca, M. Maffei, et al. 1994. Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425–432.

□ II. 肝臓

7. 肝硬変の治療

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動 向

肝硬変の成因には肝炎ウイルス（HBV, HCV），アルコール，自己免疫などがあげられるが，最近，非アルコール性脂肪性肝炎 non-alcoholic steatohepatitis（NASH）によるものが注目されており，NASHからの発癌例も報告されてきている[1]．治療ではウイルス性肝硬変に対する抗ウイルス療法が積極的に試みられてきており，肝炎の鎮静化と線維化の改善とともに発癌抑制にも期待されている．肝硬変では経過中に多彩な合併症が出現し，これらの病態が肝硬変の予後に密接に関係している．これらの合併症に対する治療法が確実に進歩し，肝硬変の予後の改善に寄与してきている．一方，肝不全への進行例あるいは肝癌合併例に対しては肝移植（生体）による治療例が増加してきている．

A. 食道・胃静脈瘤，門脈圧亢進症

食道・胃静脈瘤に対する予防的あるいは出血時の緊急的治療法として内視鏡的硬化療法（EIS），結紮術（EVL）が行われているが，EISとEVLの両者の使い分けあるいは優劣性については必ずしも明確にされていない．最近，Villanuevaら[2]は急性の出血例に対してソマトスタチンを併用して両者の比較試験（5日間）を行っているが，副作用，安全性の面でEVLが優れていることを報告している．薬物療法では門脈圧の降下を期待したバゾプレシン，β-ブロッカー，ソマトスタチンなどが使用されているが，肝線維化抑制作用をもつアンジオテンシンII受容体拮抗薬，アンジオテンシン変換酵素阻害薬も門脈圧亢進症の改善に期待されている．

胃静脈瘤，薬物療法にてコントロールが困難な肝性脳症例に対してはB-RTO（ballon occulded retrograde transvenous obliration）が適応となる．B-RTOは門脈血行動態（血流量，門脈圧），肝予備能（Child-Pugh分類）により術後成績や予後が異なるが，TIPS（transjugular intrahepatic portosystemic shunt）よりも安全に施行できる．しかし，B-RTO後に発生した巨大胃潰瘍例の報告[3]もみられる．最近，Tanoueら[4]は新たなバルーンカテーテルを開発し，胃・腎シャント例への応用を行い，簡便で安全な方法であることを報告している．TIPSは難治性の腹水，内視鏡治療抵抗性の静脈瘤が対象となるが，Chil-Pugh分類のgrade Cで治療成績が不良である．さらに，TIPSでは治療後の潜在性あるいは顕性

肝性脳症の出現とそのコントロールが問題となる．しかしながら，B-RTOおよびTIPSなどのIVR (interventional radiology) による精神神経症状の出現や改善に関する詳細な検討は少ない．最近，コンピュータを用いた定量的精神神経機能検査をIVR前後で行い，EISに比べてB-RTOで改善がみられるとの報告[5]があるが，今後，門脈血行動態，肝病態との関連を含めて多数例での検討が期待される．

部分的脾動脈塞栓術partial splenic embolization (PSE) は脾機能亢進症の改善のみならず，門脈圧の高い胃静脈瘤の治療，血清アルブミン値の改善に有効とされている．最近，C型肝硬変に対する抗ウイルス療法の導入のため血小板数の増加を期待したPSEが摘脾とともに試みられてきている．PSE治療後の血小板数の増加に関しては脾臓の塞栓範囲によって左右される．吉松ら[6]は門脈血流が求肝性であった肝硬変例に対してPSEによる門脈血行動態と血清アルブミン値との関係について検討し，PSEによる（門脈－脾静脈）血流量変化率が血清アルブミン値の上昇率と正の相関を示すことを報告している．

B. 腹 水

肝硬変による腹水の治療は塩分制限食と利尿薬投与（抗アルドステロン薬，ループ系利尿薬）が基本であり，低アルブミン血症（2.5g/dl以下）を伴う場合にはアルブミン製剤の併用を行う．また最近は，蛋白・アミノ酸代謝異常の是正を目的とした分枝鎖アミノ酸製剤を用いた栄養療法（後述）が積極的に試みられてきており，軽度の浮腫・腹水例ではコントロールが容易となってきている．しかしながら，これらの治療に抵抗性の難治性腹水が約10%存在する．難治性腹水に対しては腹水濾過濃縮静注法，TIPS，腹腔－静脈シャント術などが試みられている．これらの治療法は患者のQOLを改善しうるが，最終的な予後は肝予備能に左右される．難治性腹水の病態にはTNFαなどの炎症性サイトカインの関与が重視されているが，山崎ら[7]は腹水中のVEGF family (VEGF-A，VEGF-C，VEGF-D) を測定し，VEGF-Aは腹水の難治性と，VEGF-Cは尿中ナトリウム排泄量と有意の正相関を示すことを報告している．また，Esteva-Fontら[8]は，肝硬変患者の尿中のアクアポリン1，2をウエスタンブロット法で測定し，肝硬変では健常者に比較してアクアポリン2の排泄量が低下していること，この低下は腹水を伴う肝硬変例や肝腎症候群合併例で低下していること，血漿バゾプレシン濃度とは相関しないことなどを報告している．このような新たな指標を用いた検討によりSBPを含めた難治性腹水の発生機序の解明，治療法の開発につながることが期待される．

C. 肝不全（肝性脳症）

肝性脳症の研究では，MRI (magnetic resonance imaging)，functional MRI (fMRI)，H_1MRS (proton magnetic resonance spectroscopy)，DWI (diffusion-weighted imaging)，CBF (cerebral blood flow) などによる病態解析が進められてきている[9]．これらの画像検査は肝性脳症患者における脳の物質代謝動態や血行動態を直接検討することが可能であり，病態研究のみならず各種治療法の評価法としても今後さらに発展が期待される．

潜在性肝性脳症の診断法および診断基準についてはいまだ確立していない．定量的精神神経機能検査とともに脳波，大脳誘発電位，事象関連電位，臨界フリッカー試験などの電気生理学的検査が行われているが，わが国ではコンピュータを用いた定量的精神神経機能検査が開発され臨床的に用いられてきている[5]．最近の報告ではP 300（事象

関連電位）潜時が他の神経機能検査より有用との報告[10]がみられる．

肝性脳症の発生機序にはアンモニアが重要である．アストロサイトにおけるアンモニア解毒はグルタミン酸—グルタミン回路を介して行われるが，グルタミン自体が毒性物質として働くことが指摘されている．Norenbergら[11]は培養アストロサイトを用いてミトコンドリアへのグルタミンのトランスポートを阻害するL-ヒスチジンを添加するとアストロサイトにおけるフリーラジカルの産生，細胞膨化，ミトコンドリアの膜透過性亢進，ATPの消費の低下などが観察されることよりグルタミンの重要性を証明した．

血液アンモニア濃度の上昇には*H. pylori*感染の関与も以前より指摘されている．Abdel-Hadyら[12]は肝性脳症を伴う肝硬変患者と非肝硬変患者の血中（動脈血）アンモニア濃度，血中エンドトキシン濃度と*H. pylori*感染の有無との関連を検討し，脳症を伴う患者と非脳症患者では年齢，腹水の有無，血中アンモニアおよびエンドトキシン濃度，*H. pylori*感染率に有意差があり，除菌療法により血中アンモニア濃度の低下と昏睡度の改善をみている．わが国の中・高齢者の*H. pylori*の感染率は高いため同様の結果が得られるかどうかは今後の検討が必要であろう．

高度の甲状腺機能低下症を伴い合成二糖類および抗生物質による肝性脳症治療薬でも改善がみられなかった高アンモニア血症を伴う慢性肝疾患の1例において抗甲状腺薬の投与により高アンモニア血症の改善を認め，甲状腺機能とアンモニア代謝との関連について論じている[13]．

D. 肝移植

末期肝不全例，肝癌合併例は肝移植の適応となる．わが国では生体肝移植にたよらざるを得ないのが現状であるが，移植適応の判定はそれぞれMELDスコア，ミラノ基準に準じて行うのが一般的である．MELDスコアに関しては，血清クレアチニンの測定法の違いにより，特に高度の黄疸例ではMELDスコアに影響する[14]．

ウイルス性肝硬変・肝癌に対する移植では，移植後のウイルス対策がきわめて重要である．HBVについてはHBIG，ラミブジン（エンテカビル），HBVワクチンなどの使用により再発防止が図られその成績もよい．HCVについては抗ウイルス療法として最近はPEG-IFNとリバビリン併用療法が行われているが，投与時期，投与方法などについてはいまだコンセンサスは得られていない[15]．

E. 抗ウイルス療法

ウイルス性肝硬変に対しては原因療法である抗ウイルス療法が試みられてきている．HBVによる肝硬変ではこれまでラミブジンの投与が行われてきたが，2007年よりエンテカビルの使用が可能となっている．前者については長期投与によりYMDD変異が高頻度で出現し肝炎の再燃をきたす可能性が高いことが明らかとなっているが，本剤の使用によりB型慢性肝疾患患者の肝不全への移行を阻止し，肝発癌のリスクを低下させる[16]．また，肝硬変患者においてはラミブジン治療前後の血清アルブミンの増加量が治療前のHBV-DNA量あるいはHBV-DNA変化量と相関することが報告されている[17]．

C型肝硬変ではIFN製剤単独あるいはPEG-IFNとリバビリンの併用療法が行われている．抗ウイルス療法においては白血球数や血小板数の低下（脾機能亢進症）が治療の適応を決めるうえで問題となるが，最近は先に述べたPESや脾摘などによりその問題点をクリアし安全に抗ウイルス療法を完遂することが可能となってきている．ウイルス消失率については慢性肝炎例と異なり高く