PROCEEDING

Nutritional treatment of a patient with hepatic cirrhosis with the novel low glycemic index liquid food (Inslow)

Dai Matsumoto[1], Hisami Yamanaka-Okumura[1], Hidekazu Arai[1], Masae Sakuma[1], Hironori Yamamoto[1], Yutaka Taketani[1], Yoshiko Tani[3], Yuji Morine[2], Mitsuo Shimada[2], and Eiji Takeda[1]

[1]*Department of Clinical Nutrition, and Department of Digestive and Pediatric Surgery*[2]*, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima ; and* [3]*Department of Nutritional Management, Tokushima University Hospital, Tokushima, Japan*

Abstract : A sixty-six year-old patient with liver cirrhosis and diabetes was nutritionally treated by administration of the low glycemic index liquid food (Inslow) as a late evening sack (LES) for 6 weeks. The mean energy intake increased from 825±48 kcal/d to 1567±66 kcal/d after the 6-week treatment period. The fasting glucose level did not change, remaining at about 100 mg/dl throughout this period. Interestingly, the amount of insulin administered was reduced from 38 units before treatment to 28 units in the fifth week of treatment without a change in the fasting glucose level. This indicates a marked improvement in insulin sensitivity due to Inslow administration in this patient. In conclusion, the long-term administration of Inslow as an LES may be an effective treatment for cirrhotic patients. J. Med. Invest. 54 : 375-380, August, 2007

INTRODUCTION

The nutritional state of patients with liver cirrhosis is frequently poor, and about 70% of patients show some signs of malnutrition (1). Patients with liver cirrhosis exhibit abnormal metabolism, including increased fat oxidation and decreased glucose oxidation (2-4). Increased fat oxidation manifests as starvation after an overnight fast because of a lack of glycogen stores in patients (5). Furthermore, liver cirrhosis frequently impairs postprandial glucose tolerance, with 20 to 40% of patients developing diabetes mellitus. Therefore, supplementation of a late evening snack (LES) with a low glycemic index (GI) may be advisable in such patients to prevent early-onset starvation and energy deficiency and to maintain a good nutritional status.

The GI was introduced by Jenkins, *et al.* as a quantitative assessment of foods based on the postprandial blood glucose response (6, 7), and is expressed as a percentage of the response to an equivalent carbohydrate portion of a reference food, such as white bread or glucose (8). The novel enteral liquid formula designated Inslow was prepared by replacing dextrin in the standard balanced formula (SBF) with palatinose at 55.7% of the carbohydrate content (Table 1). Palatinose was completely cleaved and absorbed, and the hydrolysis of palatinose by a homogenate of human intestinal mucosa was one-fourth that of sucrose (9, 10). A previous study in our laboratory demonstrated that the increase in plasma glucose and insulin after Inslow ingestion was significantly smaller than that after SBF ingestion (11, 12). In this study, because lack of energy intake was assessed in a patient with liver cirrhosis and diabetes controlled with insulin, 250 kcal of Inslow was administered.

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Address correspondence and reprint requests to Eiji Takeda, Department of Clinical Nutrition, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-7094.

Table 1 Composition of Inslow and standard balanced formula (SBF)

	Inslow		Standard balanced formula (SBF)
○Energy	1kcal/ml		1kcal/ml
○Protein	20.0 %		16.0 %
○Fat	29.7 %		25.0 %
SFA	9.5 %		9.0 %
MUFA	68.5 %		45.0 %
PUFA	16.8 %		40.0 %
○Carbohydrate	50.3 %		59.0 %
Maltodextrin	22.8 %	Sucrose	2.8 %
Xylitol	8.9 %	Dextrin	97.2 %
Paratinose	68.3 %		

Abbreviations : SFA, saturated fatty acid ; MUFA, monounsaturated fatty acid ; PUFA, polyunsaturated fatty acid.

CASE REPORT

The patient was a 66-year old man who was diagnosed with hepatocellular carcinoma, liver cirrhosis, hepatitis B and C virus infection and diabetes, and had received a hepatectomy in 1997. Insulin treatment was started four months later, resulting in an increase in body weight. The patient was treated repeatedly with percutaneous ethanol injection therapy, radio frequency ablation, transcatheter arterial embolization, and chemotherapy in 2004-2006.

In July 2006, his body weight, height and body mass index were 71.3 kg, 160 cm and 27.9 kg/m^2, respectively, although his ideal body weight was 56.3 kg. Fasting blood glucose levels were controlled to about 90 to 105 mg/dl by injection of 38 units of insulin (Novorapid : 22 units before breakfast, 4 units before lunch and 12 units before dinner). ESPEN guidelines (13) recommend a non-protein energy of 25-35 kcal/kg for cirrhotic patients without malnutrition. His required energy intake was estimated as 1,500-1,700 kcal/d by using either indirect calorimetric analysis or the Harris-Benedict equation. Because his actual energy intake was 825±48 kcal/d, an in increase in energy intake without an elevation in blood glucose level was absolutely required for this patient. As the first step of nutritional care for this patient, an intake of 250 kcal of Inslow, a liquid balanced formula with a low glycemic index manufactured by the Meiji Dairy Company, as an LES was recommended by the nutritional support team in Tokushima University Hospital.

As shown in Fig. 1, the patient's energy intake gradually increased to 1049±77 kcal/d after 1 week of treatment, 1195±48 kcal/d after 2 weeks, 1340±42 kcal/d after 3 weeks, 1219±77 kcal/d after 4 weeks, 1517±60 kcal/d after 5 weeks and reached 1567±66 kcal/d after 6 weeks. His fasting glucose level did not change, remaining at about 100 mg/dl throughout this period. Interestingly, the amount of insulin administered decreased to 32 units (Novorapid : 20 units before breakfast, 4 units before lunch and 8 units before dinner) in the third week of treatment and to 28 units (Novorapid : 16 nits before breakfast,

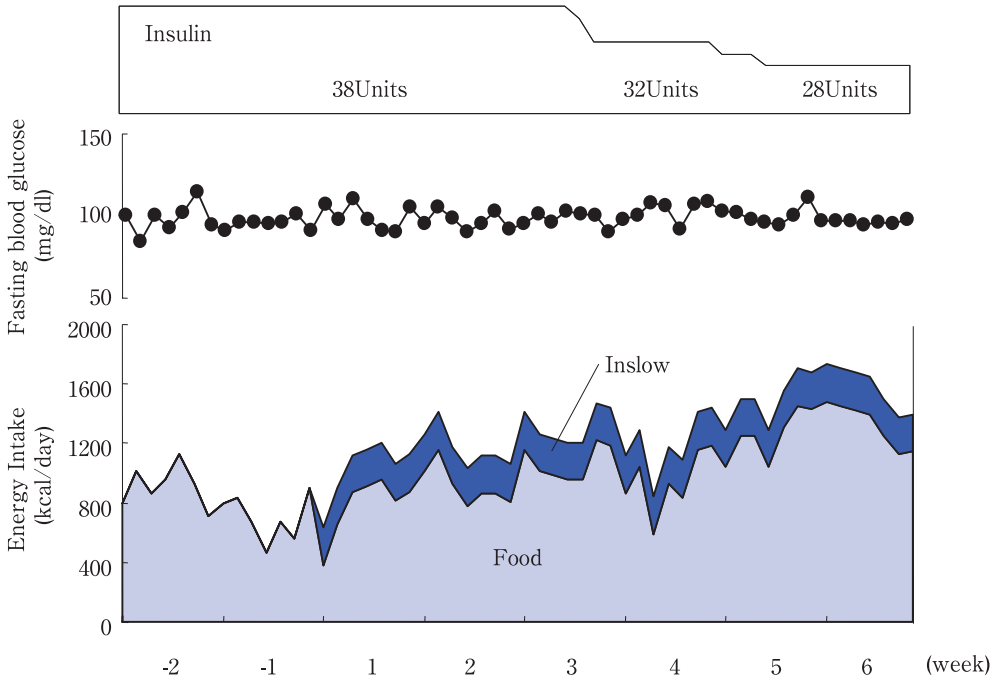

Fig. 1 Energy intake, fasting blood glucose level and amount of insulin injected during the course of nutritional treatment

4 units before lunch and 8 units before dinner) in the fifth week of treatment. Thus, 10 units of insulin was saved by nutritional therapy, even though the daily energy intake increased by about 700 kcal.

The daily pattern of blood glucose fluctuated highly in the initial period of nutritional treatment, but interestingly blood glucose levels became constant in the fifth week of treatment (Fig. 2). The cumulative area under the curve (AUC) for daily blood glucose in the fifth and sixth weeks of nutritional treatment was significantly lower than that in the first and second weeks (Fig. 3). Laboratory data, including serum levels of albumin, α-fetoprotein and protein induced by vitamin K absence of antagonist-II (PIVKA-II), lactate dehydrogenase activity and other biomarkers of hepatic function and nutritional status, did not show any significant changes after this nutritional treatment (Table 2).

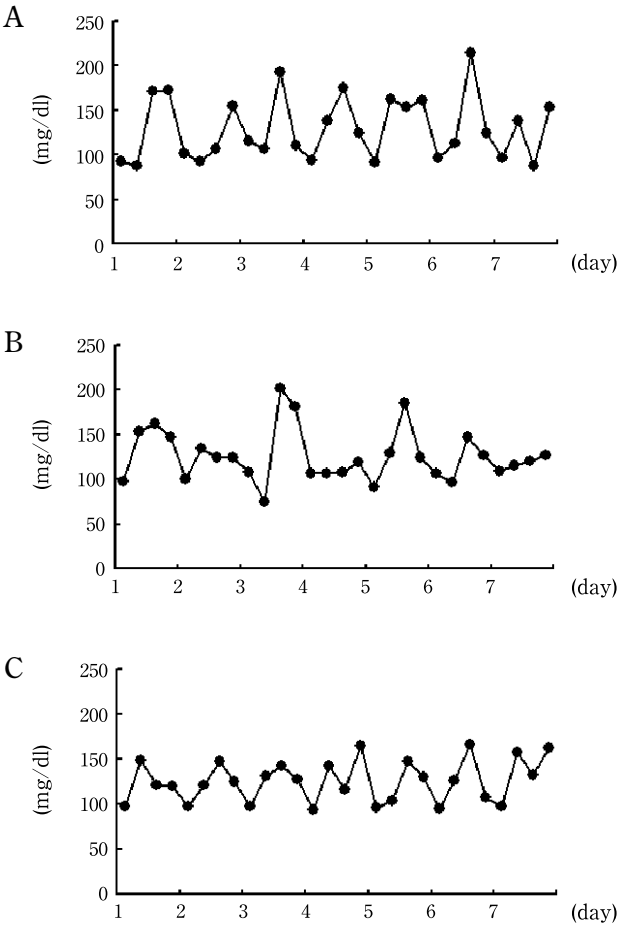

Fig. 2 Daily pattern of blood glucose levels before and during the fourth and sixth weeks of nutritional treatment.
A : Before, B : 4th week, C : 6th week

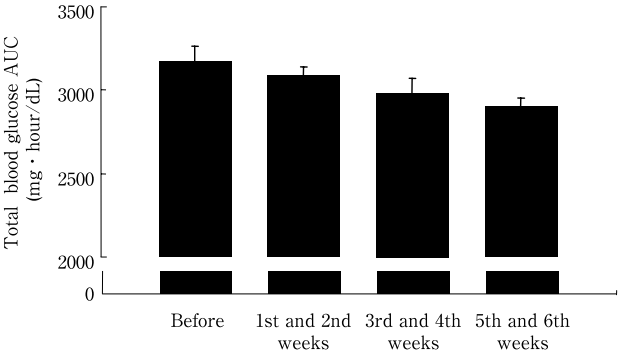

Fig. 3 Cumulative area under the curve for daily blood glucose during the course of nutritional treatment.
Values are means ± SE (n=14). * : $p<0.05$ (vs. before treatment, by student t test)

Table 2 Laboratory data during the course of nutritional treatment

		Before	Week of treatment					
			1st	2nd	3rd	4th	5th	6th
WBC	($\times 10^3/\mu l$)	3.3	0.9	4	3.4	3.3	3.3	3.6
RBC	($\times 10^6/l$)	3.06	2.7	2.57	2.61	2.68	2.68	2.9
HGB	(g/dl)	10.3	9.3	8.8	9.7	10.1	10.1	10.6
HCT	(%)	29.2	25.5	25	27.7	29	29	32
PLT	($\times 10^3/\mu l$)	93	34	62	105	115	115	85
AST	(IU/l)	23	32	26	26	34	34	31
ALT	(IU/l)	15	19	15	13	13	13	17
LDH	(IU/l)	133	177	190	181	240	240	170
T-BIL	(mg/dl)	0.6	0.9	0.5	0.7	0.9	0.9	0.8
D-BIL	(mg/dl)	0.1						
ALP	(IU/l)	302	301	346	347	324	324	291
γ-GPT	(IU/l)	52	49	45	58	73	73	90
TP	(g/dl)	6.2	6	5.8	6.5	6.6	6.6	6.4
ALB	(g/dl)	2.7		2.3	2.5	2.6	2.6	2.6
BUN	(mg/dl)	17	18	14	13	13	13	14
Crea	(mg/dl)	0.65	0.55	0.55	0.6	0.52	0.52	0.58
Na	(mEq/l)	139	139	143	140	140	140	138
K	(mEq/l)	4.6	4.4	4.6	4.7	4.6	4.6	4.5
Cl	(mEq/l)	104	104	107	108	105	105	104
ChE	(IU/l)	98						
AMY	(IU/l)	49	22					
A/G		0.77		0.66	0.66	0.65	0.65	0.68
CRP	(mg/dl)	1.33	4.5	1.27	0.89	0.78	0.78	0.21
AFP	(ng/ml)	4960			6010			
PIVKA-II	(mAU/ml)	1310			376			
ICG	(%)	30						

Abbreviations : WBC : white blood cell, RBC : red blood cell, HGB : hemoglobin, HCT : hematocrit, PLT : platelet, ALT : alanine aminotransferase, AST : aspartate aminotransferase, LDH : lactate dehydrogenase, T-BIL : total bilirubin, D-BIL : direct bilirubin, ALP : alkaline phosphatase, γ-GTP : γ-glutamyl transpeptidase, TP : total protein, ALB : albumin, BUN : blood urea nitrogen, Crea : creatinine, Na : sodium, K : potassium, Cl : chloride, ChE : choline esterase, AMY : amylase, A/G : albumin to globulin ratio, CRP : C-reactive protein, AFP : α-fetoprotein, PIVKA-II : protein induced by vitamin K absence of antagonist-II, ICG : indocyanin green test

DISCUSSION

Characteristic hormonal and metabolic alterations, including depleted hepatic glycogen storage and impaired hepatic glycogenolysis, have been shown in cirrhotic subjects (14-18). An LES has been shown to improve fuel utilization (19, 20) and nitrogen economy (21, 22). An LES comprising a liquid nutrient (Ensure Liquid) has also been shown to increase RQ and carbohydrate oxidation rates (23). For these reasons, LES administration was recommended to minimize early starvation for overnight fasting in this patient because of an insufficient energy intake.

Cirrhotic patients usually exhibit postprandial hyperglycemia and hyperinsulinemia. Depending on the etiology, degree of liver damage and diagnostic criteria, the reported incidence of impaired glucose tolerance in liver cirrhosis varies between 60 and 80% and that of diabetes varies between 20 and 63% (24). Studies using the 'euglycemic hyperinsulinemic glucose clamp technique' show that nearly all patients with cirrhosis have peripheral insulin resistance at 30-60% of the control level (25, 26). Peripheral insulin resistance in cirrhosis is characterized by decreased glucose transport and reduced glycogen synthesis in skeletal muscle, whereas the insulin-induced increases in glucose phosphorylation, glycolysis and glucose oxidation are normal in cirrhosis (27-30). Similarly, the increased amounts of insulin cannot normalize the capacity of glycogen synthesis, but disproportionally increase lactate production in cirrhosis (29).

The energy intake of this patient increased from 825 kcal to 1567 kcal through nutritional therapy with the low GI food Inslow as an LES for 6 weeks. In contrast, the amount of insulin injected decreased from 38 units to 28 units, indicating a marked improvement in insulin sensitivity due to Inslow administration. These findings may explained by our previous data showing that Inslow suppressed postprandial hyperglycemia and reduced hepatic and visceral fat accumulation better than another commercially available SBF, despite the fact that the daily food intake remained the same in both groups over the long term (11). Furthermore, expression of the PPAR-γ and adiponectine genes in the adipose tissue was higher in the Inslow group than in the SBF group (31). The PPAR-γ is a major regulator of adipocyte differentiation and controls the expression of various kinds of adipocyte-specific genes (32). Pharmacological activators of PPAR-γ, such as thiazolidinedione (TZD), significantly improve insulin sensitivity in type 2 diabetes (33). Furthermore, Inslow enhanced expression of the β-oxidation enzyme gene in adipose tissue. Therefore, it was suggested that Inslow promotes an insulin-sparing effect, raises the number of small adipocytes, and increases the expression of PPAR-γ mRNA to stimulate fatty acid utilization.

Inslow supplementation as an LES for 6 weeks did not improve the laboratory data of hepatic function and nutritional status. However, we conclude that the long-term administration of Inslow as an LES may be a useful and novel treatment for increasing energy intake and improving insulin resistance in cirrhotic patients, although further studies are required.

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