Table 3 Changes in laboratory parameters of patients undergoing α-glucosidase inhibitor administration combined with a late evening snack

	Baseline	3 months
BTR	3.30 ± 1.04	3.35 ± 0.89
Total protein (g/dL)	7.14 ± 0.87	7.08 ± 0.39
Albumin (g/dL)	2.89 ± 0.30	3.04 ± 0.41*
RBC count ($\times 10^4/\mu L$)	369 ± 45	370 ± 36
Total bilirubin (mg/dL)	1.51 ± 0.52	1.39 ± 0.49
AST (IU/L)	55.9 ± 30.3	51.1 ± 20.9
ALT (IU/L)	39.4 ± 28.2	34.7 ± 16.6
Ammonia (μmol/L)	56.5 ± 22.0	59.3 ± 39.6
PT (%)	65.9 ± 7.5	66.1 ± 8.9
BUN (mg/dL)	14.6 ± 5.0	15.7 ± 5.7
Creatinine (mg/dL)	0.83 ± 0.25	0.83 ± 0.23
T.CHO (mg/dL)	131.4 ± 29.6	134.5 ± 28.5
TG (mg/dL)	70.9 ± 30.4	73.5 ± 29.6
FPG (mg/dL)	115.3 ± 20.7	108.2 ± 14.5
HbA_{1c} (%)	5.84 ± 1.18	5.74 ± 0.91

Data expressed as mean ± SD. *$P < 0.05$ compared with baseline. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTR, molar ratio of branched-chain amino acids to tyrosine; BUN, serum urea nitrogen; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; PT, prothrombin time; RBC, red blood cell; T.CHO, total cholesterol; TG, triglyceride.

(Table 2). However, there were no significant differences in fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) after 3 months of concomitant voglibose and LES use (Table 3).

There were no significant differences in AUC insulin values at 1 week and 3 months after concomitant voglibose use compared with baseline (Table 2). However, the AUC insulin showed the tendency that the insulin secretion was decreased at 3 months after the concomitant use compared to prior to its use (Table 2).

Energy metabolism

Table 4 shows the resting energy expenditure (REE), non-protein respiratory quotient (npRQ), and oxidation ratio of substrates. There were no significant changes in REE levels at 1 week and 3 months after concomitant voglibose use compared to baseline. There was no significant change in the oxidation ratio of substrates 1 week after concomitant voglibose use. However, carbohydrate oxidation was significantly increased and fat oxidation was significantly decreased 3 months after voglibose use, and these values approached the normal levels. npRQ was significantly increased 3 months after concomitant voglibose use, and the catabolic state improved.

The correlation between npRQ and glucose intolerance and nutritional parameters

We examined the correlation between the changes in npRQ after concomitant voglibose use and improvements in glucose tolerance. (The change in npRQ is ⊿npRQ = [npRQ after 3 months of combination therapy] minus [npRQ prior to combination therapy], and the change in glucose tolerance is ⊿AUC glucose = [AUC glucose after 3 months of combination therapy] minus [AUC glucose prior to combination therapy].) In this study, there was no significant correlation between ΔnpRQ and ΔAUC glucose (Fig. 2). However, there was a significant correlation between ΔnpRQ and creatinine height index (CHI) at baseline ($P < 0.05$) (Fig. 3). There was no significant correlation between ΔnpRQ and body mass index, albumin, total bilirubin, or ammonia (data not shown).

Blood biochemistry

Table 3 shows the changes in laboratory parameters. The serum albumin level was significantly increased at 3 months after concomitant voglibose use compared to baseline. However, there were no significant differences in nutritional parameters such as BCAA-to-tyrosine ratio (BTR), total protein, and red blood cell (RBC) count.

Table 4 Effects of α-glucosidase inhibitor administration combined with a late evening snack on metabolic parameters in cirrhosis

	Baseline	1 week	3 months
REE (kcal)	1270 ± 262	1254 ± 270	1176 ± 193
npRQ	0.807 ± 0.460	0.838 ± 0.460	0.879 ± 0.055*
%CHO	31.1 ± 14.5	38.4 ± 11.8	50.5 ± 16.2*
%FAT	55.3 ± 12.6	45.3 ± 13.5	33.3 ± 15.1*
%PRO	13.6 ± 4.5	16.3 ± 6.4	16.2 ± 4.1

Data expressed as mean ± SD. *$P < 0.005$ compared with baseline. npRQ, non protein respiratory quotient; REE, resting energy expenditure; %CHO, substrate oxidation ratio for glucose; %FAT, substrate oxidation ratio for fat; %PRO, substrate oxidation ratio for protein.

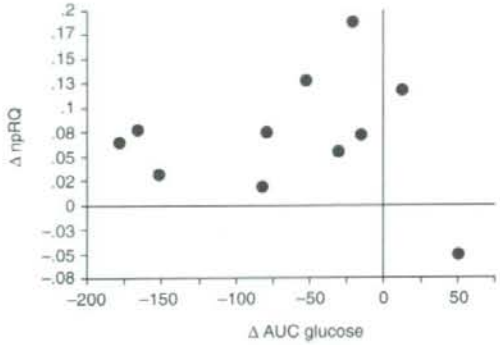

Figure 2 The correlation between the changes in non protein respiratory quotient (npRQ) after concomitant voglibose use and improvements in glucose tolerance. AUC glucose, area under the concentration curve for glucose.

There were no significant differences in the levels of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT), and ammonia after concomitant voglibose use compared to baseline. The serum lipid levels, total cholesterol (T-CHO) and triglyceride (TG), were also unchanged.

Compliance with oral voglibose

Only one of eleven subjects had mild abdominal distention and increased flatulence. These symptoms improved with time and they did not affect the taking of oral medication. Hypoglycemic attack was not seen in any subject, and voglibose use was not stopped in any subject.

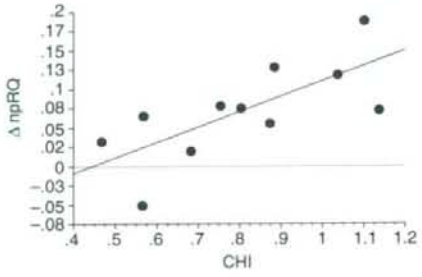

Figure 3 The correlation between the changes in non protein respiratory quotient (npRQ) after concomitant voglibose use and creatinine height index (CHI) at baseline. $r = 0.718$, $P < 0.05$, $n = 11$.

Clinical course

Figure 4 shows a specific case. The patient was a 72-year-old female (case 4). On 17 May 2003, percutaneous radiofrequency ablation (RFA) was performed for hepatocellular carcinoma with type-C liver cirrhosis. After RFA, her overall condition stabilized. The BTR value was low at 1.96 on 22 May 2003, and LES administration was started. Prior to starting LES, npRQ was 0.841. It increased to 0.873 one week after LES was started, and her catabolic state was improved. Since the patient continued LES consumption without changing her normal food intake, she gained 5 kg body weight 2.5 years after LES therapy started. Her FPG level and HbA1c level were 152 mg/dL and 8.6%, respectively, indicating aggravation of glucose intolerance. On 30 November 2005, the patient was started on voglibose (1 tab, 0.2 mg/day) which was taken in combination with LES. Her FPG level and hemoglobin A1c (HbA1c) level were decreased due to the combination therapy with voglibose (Fig. 4). In a 75-g OGTT, the glucose level after glucose load was markedly decreased 1 week after concomitant voglibose use. Postprandial hyperglycemia was also improved 3 months and 1 year after concomitant voglibose use compared to before its use (Fig. 5). For energy metabolism, npRQ did not change with 1 week of concomitant voglibose use, but it was markedly improved to 0.859 after 3 months of its use. It was 0.818 after one year of concomitant voglibose use. npRQ was maintained at a high level compared to that before its use (Fig. 4). Follow-ups have been performed from the start of combination therapy until the present time (period of 2.5 years), and there has not been any serious side effects of concomitant voglibose use.

DISCUSSION

ALES IS being recommended as a measure against the catabolic state in cirrhotic patients. It has been made evident that an intake of the following types of foods increases RQ values and improves energy metabolism: high-carbohydrate foods[4] and enteral nutrition (liquid nutrient)[5] before bedtime, and a BCAA-enriched nutrient mixture (BCAA mixture).[6] For the protein metabolism, a LES of a BCAA mixture lowered urinary 3-methylhistidine[7] and improved nitrogen balance.[8] For fat metabolism, the serum non-esterified fatty acid[9] and free fatty acid[7,10] concentrations decreased during

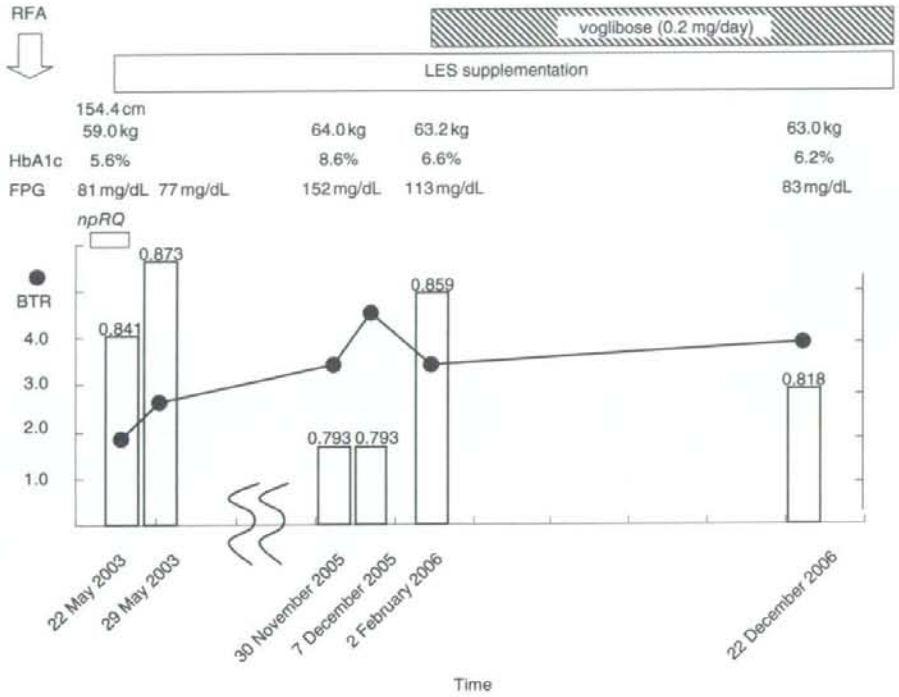

Figure 4 The clinical course of a 72-year-old female patient (case 4, Child–Pugh B) undergoing α-glucosidase inhibitor administration combined with a late evening snack. RFA, radiofrequency ablation; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; npRQ, non-protein respiratory quotient; BTR, molar ratio of branched-chain amino acids to tryrosine.

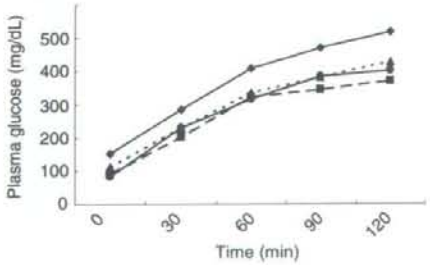

Figure 5 Plasma glucose level in a 75-g oral glucose tolerance test of a 72-year-old female patient (case 4, Child–Pugh B) undergoing α-glucosidase inhibitor administration combined with a late evening snack. ◆, baseline; ▲, 3 months; ●, 1 year; ■, 1 week.

early-morning fasting since the LES. It was also indicated that the reduction in plasma ketone bodies led to a decreased drive for fat as an energy substrate.[10,21] In a long-term LES administration of 3 months, subjective symptoms related to the QOL were reported to improve. These symptoms included weakness and easy fatigability, in particular, with a LES of a BCAA mixture.[8] A LES with a BCAA mixture increases protein synthesis and improves protein catabolism, resulting in decreased muscle cramp.[21] Therefore, LES has the possibility of improving QOL.

As shown above, a treatment with LES is a superior nutritional therapy, and we reported previously that a LES had also improved postprandial hyperglycemia.[22–24] Inpatients with liver cirrhosis were given a LES of a BCAA mixture for 1 week, and the circadian variation in glucose levels was significantly less after LES intake than before.[22–24] Although postprandial glucose oxidation in

the peripheral tissues was slow in liver cirrhosis patients, it eventually accelerated to a rate comparable to that in healthy individuals.[17] A LES improved postprandial hyperglycemia because the glucose load per meal was decreased by fractionated meals including a LES, and glucose was properly oxidized in the tissues. Another reason might be the effect of leucine and isoleucine that is in BCAA of LES. Leucine and isoleucine promote the glucose uptake in skeletal muscle.[25] Leucine also increases the activity of p70S6 kinase via the mammalian target of rapamycin pathway, and the ability to synthesize glycogen is improved.[25] Recently, it was reported that isoleucine depresses gluconeogenesis in the liver, in addition to stimulating both glucose uptake in the muscle and whole body glucose oxidation, thereby leading to the hypoglycemic effect.[26] In previous study,[14] we sought to confirm the reproducibility of postprandial hyperglycemia improvement by LES use in long-term follow-ups. We continuously examined LES therapy for 3 months in out-patients. After LES therapy began, glucose tolerance was worse compared to before the therapy in a group which was indicated to be diabetic by a 75-g OGTT[14]. The major cause of the aggravation by long-term LES use was considered to be the excess calories from LES because dietary management was not performed strictly on the individuals. It indicated the importance of nutritional guidance for continuous long-term LES used on an out-patient basis. It is essential to have a dietician provide dietary guidance before LES therapy is begun. Considerations must also be given during the treatment concerning excess calorie intake. For instance, a modification is important such as subtracting the calorie of LES from the calorie allowance of dinner.

There has not been sufficient data on the efficiency of long-term LES use. It cannot be denied that long-term LES therapy can worsen glucose tolerance in some liver cirrhosis patients with markedly impaired glucose tolerance. Diabetes could affect the survival rate of patients with cirrhosis,[27] and therefore, it is necessary to find a clinical measure to prevent the aggravation of glucose intolerance.

In this present study, AUC glucose was significantly decreased at 1 week and 3 months of concomitant voglibose use compared to the level before its use. FPG and HbA1c were not significantly decreased. These results can be explained by the fact that the majority of the patients had FPG and HbA1c within normal limits at baseline. We cannot deny the possibility that the improvement of glucose tolerance on 75g-OGTT might not be only due to the effect of the concomitant use of voglibose but to an appropriate diet after hospitalization and professional nutritional guidance. To clarify the exact effect of the concomitant use of voglibose with LES, it is essential to have a control study between the control groups: a group with a combination therapy of α-glucosidase inhibitor and LES and a group with LES monotherapy. Our study should be regarded as preliminary, suggesting that the concomitant use of α-glucosidase inhibitor with LES might improve the glucose tolerance.

Recently, it was reported that postprandial hyperinsulinemia could be involved in the acceleration of the hepatocellular carcinoma growth.[28] Since hyperinsulinemia also increases the uptake of BCAAs in the skeletal muscles,[29] hyperinsulinemia accompanying liver cirrhosis is undesirable. Therefore, it is interesting to examine whether or not there were changes in the insulin secretion from concomitant voglibose use. In our study, even if AUC glucose was significantly decreased due to concomitant voglibose use with LES therapy, AUC insulin was not changed significantly. In studies examining the effect of voglibose on insulin secretion, the administration schedule of voglibose was 0.6 mg per day (3 tabs, 0.2 mg) for 4 weeks in NIDDM patients[30] and for 12 weeks in IGT and normal glucose tolerance patients with hyperinsulinemia.[31] In both reports, insulin sensitivity was significantly improved by voglibose, and postprandial insulin levels were also decreased. Long-term hyperglycemia has been known to decrease insulin secretion due to glucose toxicity. By correcting the postprandial hyperglycemia with an α-glucosidase inhibitor, secondary insulin resistance is speculated to improve. In our study, although the results differed from previous studies of insulin secretion, the concomitant voglibose use showed tendency of reduced hyperinsulinemia without significance. This result could have occurred because the dose of voglibose was smaller compared with that for diabetic patients, and further study with many subjects is necessary.

In the aspect of the energy metabolism, we hypothesized that the concomitant use of α-glucosidase inhibitor might improve metabolic efficiency with prolonging nocturnal load of glucose as a source of energy. Zillikens *et al.*[32] reported that acarbose, a typical α-glucosidase inhibitor, given with LES reduced β-hydroxybutyrate levels the next morning in alcoholic cirrhotic patients. They suggested that the concomitant use of α-glucosidase inhibitor might reduce the need for lypolysis and ketogenesis.

In our study, there were no significant changes in the ratio of energy substrates from 1 week of concomitant

voglibose use. However, the carbohydrate oxidation rate was significantly increased 3 months after concomitant voglibose use, the fat oxidation rate was significantly decreased, and energy metabolism was improved. npRQ was significantly increased after 3 months of concomitant voglibose use, and the catabolic state during early morning fasting was improved. In a relatively short treatment time of 1 week, npRQ was not significantly increased. Even if glucose tolerance improved, the improvement in energy metabolism could have taken a longer period of approximately 3 months to become apparent. From the above findings, concomitant use of α-glucosidase inhibitor with LES improved not only glucose tolerance but also energy metabolism.

In our study, a direct correlation was not found between the change in npRQ (ΔnpRQ) after concomitant voglibose use and improvement in glucose tolerance (ΔAUC glucose). Trelan G (liquid glucose) was used in a 75-g OGTT for the evaluation of glucose tolerance. Trelan G has relatively a high glucose content (34% glucose, 36% maltose, 16.5% polysaccharide, and 13.5% oligosaccharide). Consequently, it should reflect the secondary effect of the α-glucosidase inhibitor on glucose utilization. Aminoleban EN for LES food, which greatly affects npRQ during early-morning fasting, contains not only BCAA and a glucose mixture, but also proteins, fats, and other nutrients. Therefore, a direct correlation might not have been found between npRQ and the results of an OGTT using liquid glucose. Nakaya *et al.*[8] examined the effect of LES for 3 months. In a group using a BCAA mixture, RQ and nitrogen balance were improved. In contrast, they did not improve in a group using ordinary food composed mainly of carbohydrates. These findings indicated that the improvement of glucose metabolism alone does not result in the improvement of RQ. Well and smoothly balanced glucose, protein, and fat metabolisms can be said to be essential in improving energy metabolism. There was a significant correlation between ΔnpRQ and CHI. CHI is a useful marker which reflects skeletal muscle volume.[33] Similar to liver, skeletal muscles are important organs for the metabolism of glucose, amino acids, and ammonia.[34] The correlation between ΔnpRQ and CHI supports our aforementioned thinking that the improvement of glucose metabolism alone does not result in the improvement of npRQ, although we showed that an improvement of glucose metabolism using an α-glucosidase inhibitor is useful in increasing npRQ. These nutritional therapies need to not only maintain glucose metabolism but also muscle mass. Namely, an increase in protein synthesis and consistent performance of an appropriate amount of exercises might be necessary.

In one study, the same BCAA mixture as in our study was used as a LES. After 3 months of LES therapy, serum BTR, albumin, and RBC count were improved.[8] In our study, the concomitant use of voglibose did not improve these nutritional parameters. The fact that our subjects were already receiving LES prior to voglibose use could have resulted in no improvement in these parameters. Total bilirubin, AST, and ALT values were not significantly changed, and there was no liver dysfunction caused by the concomitant use of voglibose. There was no change in urea nitrogen and creatinine, and no renal dysfuction was observed. None of the subjects experienced hypoglycemic attack. In a study of voglibose administration in IGT patients, triglyceride levels were markedly decreased and high density lipoprotein (HDL)-cholesterol levels were significantly increased.[33] In our study, T-CHO and TG levels were not significantly changed possibly due to the low dose of voglibose, and there was no effect on serum lipid levels. From the above findings, voglibose administration was indicated to be safe in patients with liver cirrhosis. Yoshitsugu *et al.*[35] administered 0.6 mg/day of voglibose to diabetic patients with liver cirrhosis. Postprandial hyperglycemia was improved without adverse effects on the liver function. They also reported that fasting blood ammonia levels were significantly decreased with voglibose administration.[35] It was speculated to be caused by the α-glucosidase inhibitor promoting a decrease in fecal pH. The decrease in pH is caused by the production of short chain fatty acids and hydrogen via carbohydrate utilization by colonic bacteria.[36] In our study, we did not observe a significant decrease in the ammonia levels as seen in the study of Yoshitsugu *et al.*[35] This lack of significant ammonia decrease was due to the difference in the dose of voglibose used between that study and our study.

In conclusion, the concomitant use of an α-glucosidase inhibitor with LES therapy has the possibility of improving glucose tolerance and energy metabolism. In cirrhotic patients with impaired glucose tolerance, the concomitant use of an α-glucosidase inhibitor with LES therapy is shown to be a useful adjuvant therapy from the aspect of nutritional management. As the results of this study are still preliminary, the future study, using control groups with the examination of the patient's QOL, is necessary.

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