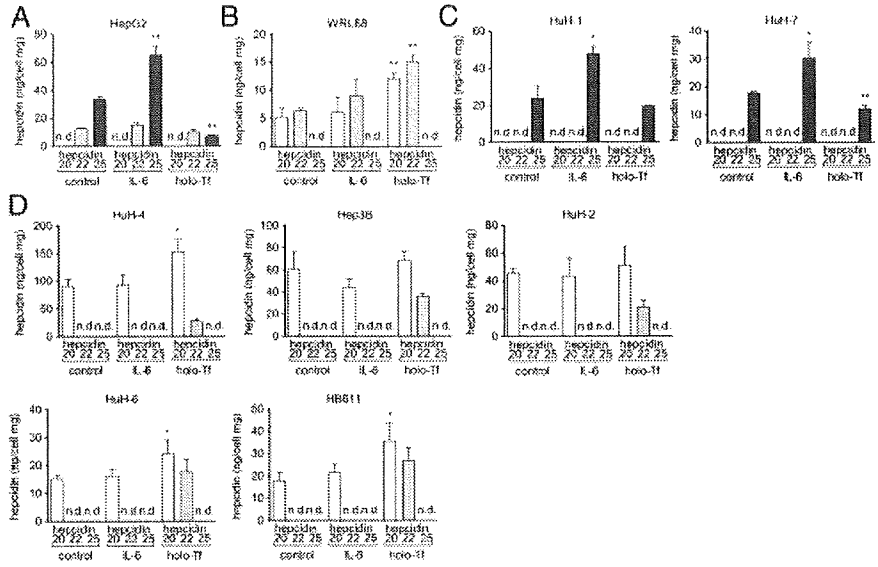

Figure 4. Quantification of hepcidin isoforms in the culture media of hepatoma-derived cell lines. The patterns of the expression of hepcidin isoforms were different among cell lines, and divided into four groups. (A) HepG2 cells, (B) WRL68 cells, (C) HuH-1 and HuH-7 cells, and (D) HB611, Hep3B, HuH-2, HuH-4, and HuH-6 cells. $^{*}p<0.05$, $^{**}p<0.01$, n.d.: not detected.

hepcidin secreted in culture media by hepatoma-derived cell lines. Our present assay, using MS with trichloroacetic acid precipitation, succeeds in this. Moreover, the new method can simultaneously detect and distinguish hepcidin-20, -22, and -25. The linear relationship between the peak area and hepcidin concentration provides simultaneous quantification of hepcidin-20, -22, and -25 isoforms. To our knowledge, this is the first report for simultaneous and quantitative measurement of hepcidin isoforms, applicable to evaluating hepcidin levels and their response to various stimulations for research using cultured cells. We believe that this method can be applied to clinical as well as research studies, thereby providing new information about hepcidin isoforms levels in serum. Determination of hepcidin isoforms may also be a biomarker for differential diagnosis and evaluation of disease activity in clinical studies, although further investigation is needed.

One advantage of our method is that it does not depend upon an antibody against hepcidin. Specificity of antibodies used for quantification of hepcidin requires validation to exclude the possibility that they recognize two or three isoforms of hepcidin simultaneously. Our method can also measure many samples in a relatively short time, so that it is useful for clinical samples and samples from *in vitro* research. However, it does require internal standards of hepcidin isoforms and mass spectrometers but still may be of interest in diverse laboratories.

We found differences in expression of *HAMP* mRNA among cell lines derived from hepatocytes. This finding indicates that such differences must be considered in using these cell lines for research in hepcidin expression.

HLE, HLF, and SK-HEP-1 cells exhibited low *HAMP* mRNA expression in qRT-PCR and did not secrete detectable hepcidin. They may have lost some physiological functions common to hepatocytes.

There were unexpected differences of secretion and response to various stimulations of hepcidin isoforms among cell lines. The cell lines that secreted detectable hepcidin in our study can be divided into at least four groups, suggesting that hepatocytes in the liver *in vivo* might possess different characteristics from each other. We believe this is the first report of the variety of hepcidin isoforms' expression patterns in hepatoma-derived cell lines. Possibly, one subset of hepatocytes is involved in only iron metabolism, while another line is involved in both iron metabolism and the antimicrobial system.

Care should be taken in evaluating hepcidin expression from transcriptional levels because we did not find any obvious correlation between *HAMP* mRNA expression and hepcidin secretion (Figs. 3 and 4). Moreover, different cell lines exhibit different patterns of hepcidin isoforms' secretion. Our data indicate that HuH-7 cells and Hep3B cells each express an mRNA of the *HAMP* gene as determined by RT-PCR. However, HuH-7 cells secrete only hepcidin-25 into the culture medium, and Hep3B cells secrete hepcidin-20 but no detectable hepcidin-25. These observations indicate a risk of misinterpretation if only transcriptional studies are performed for investigation of hepcidin expression, especially for *in vitro* research.

In this study, we subjected HepG2 cells to various stimulations, and observed changes of hepcidin-22 and -25 levels in culture media. The changes of hepcidin-22 and -25 were not parallel; therefore, again the determination of only *HAMP* mRNA might lead to misinterpretation, so simultaneous determination of hepcidin isoforms is strongly recommended. We observed changes of hepcidin-25 that are

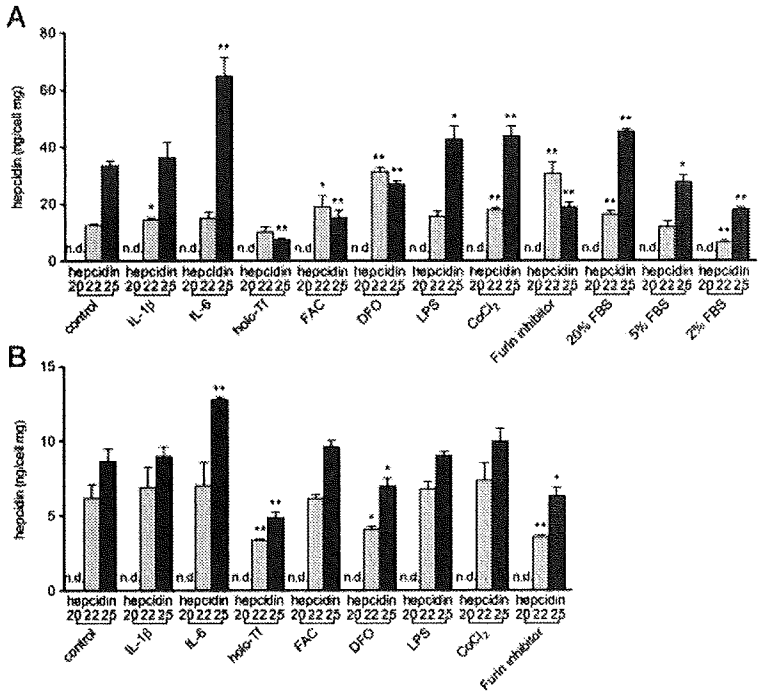

Figure 5. (A) Changes of hepcidin isoforms' expressions induced by various stimulations in the HepG2 cells. IL-6 (20 ng/mL), IL-1β pg/mL, holo-Tf (30 μM), FAC (100 μM), DFO (100 μM), $CoCl_2$ (50 μM), LPS (1 μg/mL), and furin inhibitor (50 μM) were added to the culture media of HepG2 cells as indicated. In addition, the effect of the concentrations of FBS on the expressions of hepcidin isoforms was determined. (B) HepG2 cells were incubated with serum-free medium UltraCulture. Hepcidin expression levels were all lower than those observed in FBS-containing medium. IL-6, IL-1β, holo-Tf, FAC, DFO, $CoCl_2$, LPS and furin inhibitor were also added to observe their effects on hepcidin isoforms' expressions. $^{*}p<0.05$, $^{**}p<0.01$, n.d.: not detected.

consistent with data previously reported elsewhere so that our method for quantification of hepcidin isoforms would be useful for investigating responses of hepatocytes to various stimulations. Observed changes that remain unexplained indicate a need for further investigation of the responses of hepatocytes to various stimulations in their expression of hepcidin isoforms.

We realize that varying concentrations of FBS might lead to different results even in the presence of identical stimulations. For example, the furin inhibitor decreased hepcidin-25 while hepcidin-22 was increased (Fig. 5A) in the presence of FBS. This suggests that the pathway for producing hepcidin-22 was activated when the pathway for producing hepcidin-25 was inhibited by furin inhibitor, thereby maintaining the total concentration of hepcidin although skewing the balance between isoforms. However, the precise mechanism of the effect is not known. Both hepcidin-22 and -25 were suppressed when cells were treated with furin inhibitor in FBS-free conditions (Fig. 5B), and this is contrary to the result observed in the presence of FBS. We speculated that the absence of FBS may stress the cells, increasing the sensitivity to furin inhibitor. We recognize that furin is a proprotein convertase acting on hepcidin expression at the posttranslational level [13], so that its inhibition should not be selectively affected by FBS. It is also possible, however, that unknown factors in FBS might upregulate hepcidin-22, since its concentration in FBS-free conditions could not be increased in our study. It may be advisable, therefore, to provide precisely controlled concentrations of FBS in further studies of expression of hepcidin isoforms *in vitro*, since FBS may already contain stimulants of hepcidin expression.

In conclusion, we have devised a method for simultaneous quantification of hepcidin-20, -22, and -25 in culture media by hepatoma-derived cell lines. Using this method, we determined the expression patterns of hepcidin isoforms and their responses to various stimulations in cultured cells, and we found that there are substantial differences among cell lines. We also found no obvious correlation between *HAMP* mRNA expressions and hepcidin isoforms' secretion. Levels of prohepcidin in the culture medium were too low to be detected by ELISA, indicating the necessity of directly measuring hepcidin instead of estimating it from prohepcidin measured by ELISA, especially *in vitro* studies. We believe that our method can contribute to *in vitro* research on the regulation of hepcidin expression, needed because the regulation of hepcidin expression is complex and difficult to investigate precisely *in vivo*.

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The authors have declared no conflict of interest.

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特集・消化器疾患におけるNST（Nutrition support team）

病態別にみたNSTの実際

肝疾患に対するNST

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Summary

肝疾患，特に肝硬変に対する栄養治療は薬物治療以上に重要である。肝疾患にかぎらず栄養治療を行うに際して肝疾患の栄養評価として適切な栄養指標を用いて栄養評価を行い，栄養障害患者と栄養障害のリスクのある患者を抽出する。栄養治療としては食事療法を中心に行い，食事療法で十分な効果が得られない場合にはリーバクト®顆粒を併用する。また，食事摂取量が十分でない場合や肝性脳症によりたんぱく制限が必要な場合には肝不全用栄養剤を併用するが，指示エネルギー量とたんぱく量は併用薬剤を含めてとする。

Key Words　肝疾患／NST／チーム医療／分岐鎖アミノ酸

はじめに

最近，栄養治療の必要性が認識されるようになり，各医療施設においてNutrition support team（NST）が活動するようになってきた。また肝疾患，特に肝硬変に対する栄養治療の必要性も認識されるようになった。「肝硬変を含めたウイルス性肝疾患の治療の標準化に関するガイドライン2009」においても栄養治療の重要性が指摘され，抗ウイルス療法が行えない場合には分岐鎖アミノ酸（BCAA）製剤の投与を含めた栄養療法を行うべきであるとされている。そこで本項では，肝疾患に対してNSTを実践するために必要な基礎的事項と当院での肝疾患NSTについて述べる。

栄養アセスメント

栄養評価は栄養治療を行う上で最も重要である。それは栄養治療を行う上で適切な栄養評価がまず行われ，栄養障害患者を抽出し栄養障害患者に対して栄養治療が行われる。欧州静脈経腸栄養学会（The European Society for Clinical Nutrition and Metabolism：ESPEN）のガイドライン[1]では自覚的包括的栄養評価（Subjective global assessment：SGA）や身体計測などの簡単な栄養指標で栄養アセスメントを推奨している。我々の施設では，表1に示すような栄養評価項目を中心として用いて栄養評価を行っている。

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表1　肝疾患の栄養アセスメント

1）身長，体重
2）%上腕筋囲（% AMC）
3）%握力（% Grip strength）
4）血清アルブミン値
5）血清 BCAA/Tyr 比（BTR）
6）血清コリンエステラーゼ値
7）末梢血総リンパ球数

表2　肝疾患における栄養補給基準

	非窒素エネルギー (kcal/kg/日)	蛋白質・アミノ酸 (g/kg/日)
代償性肝硬変	25～35	1.0～1.2
合併症		
栄養障害あり	35～40	1.5
経口摂取不十分		
肝性脳症（Ⅰ～Ⅱ）	25～35	一時的に0.5，その後1.0～1.5 蛋白不耐症があれば，植物性蛋白や分岐鎖アミノ酸補給
肝性脳症（Ⅲ～Ⅳ）	25～35	0.5～1.2 分岐鎖アミノ酸輸液

標準体重で算出する。

肝硬変に対する食事療法

肝硬変では蛋白質とエネルギーの両方または一方が約9割の患者で欠乏しており[2]，この代謝異常を改善することにより生活の質の向上や予後が改善される。したがって肝硬変に合併したタンパク・エネルギー代謝異常に対しては日本病態栄養学会のガイドライン（2003年）や1997年のESPEN[3]のガイドライン（表2）に準じた栄養療法を基本に行う。肝硬変では間接カロリーメーターを用いた検討で早朝空腹時に呼吸商は低下し，飢餓状態にあるため就寝前夜食（Late evening snack：LES）の有用性が報告[4]されており，American Society for Parenteral and Enteral Nutrition（ASPEN）のガイドライン[5]にもLESが推奨されている。したがって肝硬変に対して，まずLESを含めた食事療法を行い，食事療法単独で十分な効果が得られない場合や肝性脳症合併例に対してBCAAを用いた栄養療法を行う。

分岐鎖アミノ酸を用いた栄養療法

わが国における分岐鎖アミノ酸製剤を表3に示すが，これらの薬剤は医薬品として用いられるものであり，その他食品としての分岐鎖アミノ酸製剤としてはアミノフィール®（テルモ），ヘパス®やヘパス®Ⅱ（クリニコ）などがある。

1．肝性脳症の合併の有無による分岐鎖アミノ酸製剤と肝不全用栄養剤の選択

明らかな肝性脳症がなく，食事摂取状況も

表3　経口用分岐鎖アミノ酸製剤

		成分栄養剤	半消化態栄養剤
	リーバクト®	ヘパン®ED	アミノレバン®EN
1日投与量（g）	3包（12.45 g）	2包（160 g）	3包（150 g）
糖質（g）	—	123.4	93.2
脂質（g）	—	5.6	10.5
総エネルギー（kcal）	48	620	630
アミノ酸（g）	12	22.4	40.5
BCAA（g）	12	10.9	18.3
AAA（g）	—	0.23	0.63

満足できる場合でも，低アルブミン血症がみられる場合やアミノ酸インバランスがみられる場合には積極的にリーバクト®顆粒を投与する。アミノ酸インバランスの存在下では低アルブミン血症が進行する[6]ことから，経口摂取されるBCAA量を増加させ，アミノ酸インバランスを改善し，タンパク栄養障害を改善するように努める。

肝性脳症時にはまず腸管レベルにおけるアンモニアの産生を抑制するためにたんぱく制限が必要である。たんぱく制限を行うことにより低アルブミン血症が進行する（蛋白不耐症）。したがって**表2**に示すようにたんぱく制限時には分岐鎖アミノ酸製剤，特に肝不全用栄養剤を用いる。ESPENのガイドライン(2006)[7]においても，通常の食事で肝性脳症を発症した場合にはBCAAを多く含んだ製剤（肝不全用栄養剤）を用いることが推奨されている。しかし臨床の現場では適切な食事療法が行われていなかったり，肝不全用栄養剤の選択の誤りのために高血糖を呈したり，逆に高アンモニア血症が悪化し，肝不全用栄養剤を中止したりする場合が少なくない。筆者らの施設においては肝不全栄養剤にかぎらず，経腸栄養剤を使用する場合には**図1**に示すように肝不全用栄養剤を含めてエネルギー量を標準体重1 kg当たり約30 kcal/日，たんぱく量を1.0 g/日となるようにしている。したがって肝性脳症の程度により食事たんぱく質の摂取量を決定し，たんぱく制限による不足たんぱく量を補えるアミノ酸量を含有した肝不全用栄養剤を選択し投与している。したがって当院では肝不全用栄養剤の常用量（アミノレバン®ENでは1日3包，ヘパン®EDでは1日2包）にこだわらず，たんぱく制限による不足たんぱく量と不足エネルギー量を補えるエネルギー量とアミノ酸量を含んだ肝不全用栄養剤を選択し投与している。

2．食事摂取状況による分岐鎖アミノ酸製剤の選択

栄養士による栄養指導を行っても十分なエネルギー摂取状況とたんぱく摂取状況とならない場合には，肝不全用栄養剤を選択し投与する。その場合も**図1**に示すように，食事から得られるエネルギー量とたんぱく量に肝不全用栄養剤から得られるエネルギー量とアミノ酸量が適切な量（エネルギー量：約30 kcal/kg/日，たんぱく（アミノ酸）量：約1.0 g/kg/日）となるようにする。

必要摂取エネルギー量（30～35 kcal/kg・IBW/日）

食事エネルギー量　＋　肝不全用栄養剤のエネルギー量

必要摂取たんぱく量（1.0～1.2 g/kg・IBW/日）

食事たんぱく摂取量（たんぱく制限）　＋　肝不全用栄養剤のアミノ酸量

図1　肝不全用栄養剤の簡単な使用法

	役割	関わる医療スタッフ
入院患者	栄養アセスメント	看護師・医師
↓	栄養状態	看護師・医師
↓	←家庭環境・食事摂取状況（家庭）	
↓	栄養に対する認識調査	
NST依頼	栄養治療の再検討	医師・看護師・栄養士・
↓	外来栄養治療の必要性の検討	薬剤師
退院	外来栄養指導予約	看護師・栄養士
↓		
外来栄養治療	外来栄養治療継続	栄養士←→医師

図2　当院における肝疾患NST

当院における肝疾患に対するNSTの実際

当院では先に述べたような肝疾患に対する栄養治療法をすべての医療スタッフが理解し，チーム医療として肝疾患患者に関わっている。2005年11月～2006年11月の1年間の肝硬変入院患者は141名であり，その33.3%（47名）は浮腫や腹水の治療，11.3%（16名）は肝性脳症の治療が目的であった。外来で栄養士による栄養指導を受けることによりそれらの入院を減少させることが可能と考え，NSTのシステムを構築した（**図2**）。当院における肝疾患NSTは退院後の外来での継続した栄養指導を行うことにより患者自身に栄養治療の必要性を認識させ，浮腫・腹水や脳症での再入院を防止するだけでなく，最終的には肝硬変患者の生活の質の向上，予後改善を目的としている。

入院患者に対して看護師が中心となり栄養アセスメントを行うが，分岐鎖アミノ酸製剤を投与されている患者は家庭での食生活を考慮して問題があると判断された場合にもNSTの介入を依頼する。また入院中に家庭環境や栄養に対する意識調査を看護師が行い，問題があると判断された場合にもNSTを依頼することとしている。NSTは栄養治療に詳しい医師と日本静脈経腸栄養学会のNST専門療法士の資格を持った薬剤師，管理栄養士が中心となって栄養療法を再検討し，治療の変更をリンクナースや病棟薬剤師に指示し

ている。外来での継続した栄養治療が必要な場合には退院時に外来栄養指導を予約し，外来で栄養治療を継続するようにしている。これは主治医に外来栄養指導を依頼しても必ずしも行われない場合があるためである。その結果，当院の肝疾患の外来栄養指導件数は病院全体の個別栄養指導の約60％を占めている。

おわりに

肝疾患に対して栄養治療は不可欠であるが，適切な栄養治療を肝疾患患者に提供するためには肝疾患栄養治療を十分に理解し，実践できる薬剤師，栄養士，看護師をまず育成し，病院の特性に合ったNSTをつくることが必要である。

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＜速　報＞

検査前食のエネルギー代謝に及ぼす影響—血清遊離脂肪酸による検討—

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緒言：肝硬変（LC）患者は早朝空腹時に飢餓状態にあるため検査前の絶食時間の延長によりエネルギー代謝状態が悪化することが報告[1)]されている．そのため飢餓状態の改善に検査前食が用いられている[2)]．遊離脂肪酸（NEFA）はLCで早朝飢餓状態で高値を呈することが知られている[3)]．そこで今回ウイルス性慢性肝疾患を対象にNEFAを空腹時に測定し，さらに腹部超音波検査（US）前後にも測定した．

対象と方法：検討対象は慢性肝炎（CH）123例（HBV 26例，HCV 97例，男性62例，女性61例，平均63歳）とLC 54例（HBV 3例，HCV 51例，男性19例，女性35例，平均68歳）である．食事群（16例：Child-Pugh Grade A 6例，B 10例）はUS終了まで絶食とし，US終了後とUS後の食事（600 kcal，蛋白20 g）摂取3時間後にNEFAを測定した．検査前食群（5例：Child-Pugh Grade B5例）はUS前にNEFAを測定し，カロリーメイトゼリー（大塚製薬株式会社）摂取3時間後にUSを施行し，NEFAも測定した．NEFAの測定は酵素法にて測定した．

結果：CHのNEFAは571±240 μEq/Lでありは780±240 μEq/LとLCで有意に高値（$p<0.0001$）であった．食事摂取およびカロリーメイト摂取後にNEFAは有意に低下した（Table 1）．

考察：検査前食群においても食事群と同様に検査前食によりNEFAは有意に低下した．飢餓状態により上昇したNEFAは食事摂取によりグルコースとNEFAから中性脂肪を再合成する．したがって食事群と同様にカロリーメイトゼリーでもNEFAが低下したことは200 kcalのカロリーメイトゼリーでもエネルギー代謝状態を改善でき，US検査前食として有用である．

索引用語：遊離脂肪酸，肝硬変，補食

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英文要旨

Effect of a nutritional supplement before abdominal ultrasonography on energy metabolism

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The serum free fatty acid levels were 571±240 μEq/L in patients with chronic hepatitis and 780±240 μEq/L; the serum free fatty acid levels were significantly higher in chronic hepatitis than in chronic hepatitis than in cirrhosis. The elevation of serum free fatty acid in cirrhosis is caused by starvation.

The serum free fatty acid levels were significantly decreased after the meal. 200 kcal of a nutritional supplement (Calorie Mate JERRY; Otsuka Pharmaceutical, Japan) was given to the patients before abdominal ultrasonography.

The free fatty acids levels were significantly decreased after a nutritional supplement.

Calorie Mate JERRY as a nutritional supplement improve metabolic disorder caused by fasting before abdominal ultrasonograhy.

Key words: non-esterified fatty acid, liver cirrhosis, free fatty acid, supplement

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Table 1 Change of serum NEFA level

meal	At fasting NEFA (μEq/L)	3rd hr after meal NEFA (μEq/L)	p
Diet	555.9 ± 328.3	73.3 ± 58.2	< 0.0001
Calorie Mate JERRY	997.8 ± 454.6	353.8 ± 321.0	0.0054

US: Ultrasonography
NEFA: non esterified fatty acid
NEFA (normal range: 140 ～ 850 μEq/L)

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Original Article

Effects of a late evening snack combined with α-glucosidase inhibitor on liver cirrhosis

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Aim: A late evening snack (LES) is recommended for protein-energy malnutrition in patients with liver cirrhosis. However, many cases of liver cirrhosis have accompanying impaired glucose tolerance and there are concerns that LESs might aggravate glucose intolerance. In this study, we concomitantly used an α-glucosidase inhibitor with a LES and examined the effects on glucose tolerance. In addition, we examined whether or not there was an improvement in energy metabolism by slowing glucose absorption with the concomitant use of the α-glucosidase inhibitor.

Methods: The subjects were 11 patients with liver cirrhosis. From before the study, all the patients had been taking a LES supplementation with a branched-chain amino acid (BCAA)-enriched nutrient mixture. The patients were started on the concomitant use of α-glucosidase inhibitor (0.2 mg) taken just prior to the LES. The change of glucose tolerance and energy metabolism were examined using a 75-g oral glucose tolerance test and indirect calorimetry.

Results: One week and three months after the start of the concomitant use of the α-glucosidase inhibitor, the area under the concentration curve for plasma glucose was significantly decreased. Three months after the concomitant use, the non-protein respiratory quotient was significantly improved. There were no serious side effects during the follow-ups.

Conclusion: The concomitant use of the α-glucosidase inhibitor use with LES showed the possibility of improving glucose tolerance and energy metabolism. In patients with impaired glucose tolerance, the concomitant use of an α-glucosidase inhibitor with LES might be a useful measure for nutritional management.

Key words: α-glucosidase inhibitor, branched-chain amino acid, late evening snack, liver cirrhosis, nutritional therapy

INTRODUCTION

THE LIVER PLAYS a central role in the synthesis, metabolism and storage of nutrients. Liver cirrhosis is a condition in which there are impairments in these functions and leads to a variety of nutritional and metabolic disorders.

There is a high incidence of protein-energy malnutrition (PEM) in patients with liver cirrhosis.[1,2] When energy metabolism of liver cirrhosis patients is measured using an indirect calorimetry, their resting energy expenditure (REE) is increased, indicating a hypermetabolic state.[3] Meanwhile, the following also occur: a decrease in glycogen storage due to liver atrophy, insulin resistance (hyperinsulinemia), hyperglucagonemia and increases in serum concentrations of insulin antagonistic hormones such as catecholamines and cortisol. As a result, there is a marked decrease in use efficiency of carbohydrate as a physiological energy substrate. Body protein catabolism can accelerate and a liver cirrhosis patient can become hypercatabolic.[4] As shown by the decrease in the respiratory quotient (RQ) calculated by an indirect calorimetry, the efficiency of energy metabolism is markedly decreased in whole body.[5] In addition, the substrate oxidation rate of endogenous fat is increased more than that of carbohydrate.[6] The metabolic patterns of such patients after an overnight fast are similar to healthy individuals in a state of 2–3 days starvation.[7] This tendency becomes more marked as the severity of liver cirrhosis increases.[8] PEM is a factor that is significant in establishing the vital prognosis of liver cirrhosis

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patients,[12] and thus, appropriate nutritional intervention is necessary.

A late evening snack (LES) is a superior nutritional therapy which improves the catabolic state during starvation in early morning fasting.[4,13] A late evening snack is recommended in the present guidelines of the American Society for Parenteral and Enteral Nutrition[11] and the European Society for Clinical Nutrition and Metabolism.[12]

Approximately 70% of the liver cirrhosis cases have concurrent glucose intolerance, and 40% have concurrent diabetes.[14] We previously reported the effect of the long-term use of LES (3 months) on glucose tolerance.[14] When patients had 2-hr glucose levels of < 200 mg/dl. in a 75-g oral glucose tolerance test (OGTT) before they were started on LES, a nutritional improvement was observed without a significant effect of LES on glucose tolerance. In patients who had 2-hr OGTT glucose levels of ≥ 200 mg/dl., their diabetic pathology became aggravated. There has been only a small number of reports on efficiency of long-term LES, but a new approach might be necessary, including the control of glucose tolerance for continuous long-term efficiency of LES.[15]

An α-glucosidase inhibitor suppresses the final stage of glucose absorption, the hydrolysis of disaccharides to monosaccharides. Thus, it slows glucose absorption into the blood and ameliorates postprandial hyperglycemia.[16] The characteristic feature of diabetes which accompanies liver cirrhosis is postprandial hyperglycemia, and α-glucosidase inhibitor treatment is a sound pharmacotherapy for hepatic diabetes. The objective of our present study was to examine whether or not a combination of LES and α-glucosidase inhibitor could be a new adjuvant therapy. The examination was conducted by investigation of the effect of this nutritional therapy on glucose tolerance.

Liver cirrhosis patients in a state of starvation at fasting were reported to have accelerated postprandial glucose oxidation in the peripheral tissues.[4] Therefore, liver cirrhosis patients can properly oxidize the glucose load accompanying each meal intake, if the glucose load per meal is decreased by fractionating meals (frequent meals and LES). It is speculated that this process will improve not only postprandial hyperglycemia but also energy metabolism. Catabolism was reported to have improved by frequent meals in liver cirrhosis patients.[18] Therefore, our second objective was to examine whether or not energy metabolism efficiency would be improved by a combination of LES and α-glucosidase inhibitor.

MATERIALS AND METHODS

Patients

OUR STUDY WAS conducted on 11 subjects with liver cirrhosis. All patients were receiving LES therapy involving the intake of 1 pack/day of a branched-chain amino acid (BCAA)-enriched nutrient mixture (Aminoleban EN; Otsuka, Japan). The period from the start of LES therapy to the concomitant use of voglibose, a α-glucosidase inhibitor, ranged from 4 weeks to 156 weeks.

Table 1 shows the subject profiles. There were 4 males and 7 females and their ages ranged from 44 to 78 years. The causes or types of liver cirrhosis were hepatitis C virus (HCV) in 7 patients, alcoholic cirrhosis in 1 patient, primary biliary cirrhosis (PBC) in 1 patient, and non-alcoholic steatohepatitis (NASH) in 2 patients. The severity of liver damage was grade A in 3 patients, grade B in 7 patients, and grade C in 1 patient according to the Child-Pugh classification. One patient (case 6) also had hepatocellular carcinoma (HCC). This patient had two lesions which were both < 3 cm. Two other patients had a history of HCC treatment, but they were confirmed to be relapse free in the 2-year period after therapy. From the results of the 75-g OGTT performed immediately before the start of concomitant voglibose use, 9 of 11 patients were determined to have diabetes mellitus (DM) and 2 patients were determined to have impaired glucose tolerance (IGT) according to the World Health Organization criteria.[19] Among the 9 patients who showed a diabetic pattern in the 75-g OGTT, 5 patients had fasting glucose levels of < 110 mg/dl. and 6 patients had HbA1c levels of < 5.8%, indicating levels within normal limits. Only 1 patient (case 6) of 9 patients with a diabetic type OGTT result was receiving insulin administration as a treatment for diabetes. However, the dosage of insulin was not changed during this study. Other patients were not receiving any drugs for diabetes until the start of concomitant voglibose use.

Study protocol

Figure 1 shows the protocol used in our study. The subjects received nutritional guidance from dieticians prior to the start of the study. The daily nutritional intake for each subject was calculated to be 25–30 kcal with 1.2–1.3 g of protein per kilogram of ideal body weight per day.[5] The patients were instructed that the actual daily nutritional intake from meals was found by subtracting the calories of LES (210 kcal) and protein (13.5 g) from the aforementioned calculated nutritional intake. One pack of the BCAA-enriched mixture used as LES food has

Table 1 Characteristics of patients before voglibose administration

Case #	Age	Sex	Etiology of cirrhosis	Body mass index (kg/m^2)	Child–Pugh classification (score)	Period from the start of LES to concomitant use of voglibose (weeks)	75-g OGTT	FPG (mg/dl)	HbA1c (%)
1	73	Female	HCV	23.3	B (7)	30	DM	129	5.6
2	44	Male	alcohol	22.1	A (6)	24	IGT	94	5.3
3	72	Female	HCV	23.0	A (6)	5	DM	96	5.2
4	64	Female	HCV	26.8	B (8)	135	DM	152	8.6
5	72	Male	NASH	28.7	A (6)	5	DM	129	6.4
6	64	Male	HCV	23.4	C (10)	44	DM	143	5.7
7	64	Male	HCV	30.5	B (9)	12	DM	114	5.1
8	69	Female	HCV	26.1	B (8)	4	DM	109	7.4
9	68	Female	PBC	19.0	B (8)	4	IGT	87	4.8
10	78	Female	HCV	24.0	B (7)	156	DM	109	4.9
11	62	Female	NASH	33.0	B (7)	84	DM	106	4.9

DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HCV, hepatitis C virus; IGT, impaired glucose tolerance; LES, late evening snack; NASH, non alcoholic steatohepatitis; OGTT, oral glucose tolerance test; PBC, primary biliary cirrhosis.

210 kcal of energy, 31.05 g of carbohydrate, 13.5 g of protein, 3.5 g of fat, and trace amounts of minerals and vitamins.[7] During our study, the patients received nutritional guidance once a month from nutritional consultants, and considerations were given to prevent excessive intake of calories.

We examined the effectiveness of a combination of LES and α-glucosidase inhibitor. One 0.2-mg tablet of α-glucosidase inhibitor voglibose (Takeda, Japan) was orally administered immediately before LES supplementation. This voglibose dose was less than that used for non-insulin-dependent diabetes mellitus (NIDDM) (3 × 0.2 mg tabs/day, 0.6 mg). A 75-g oral glucose tolerance test (OGTT) was performed before the start of a combination treatment with voglibose, 1 week after the start, and 3 months after the start. A standard 75-g OGTT (TrelanG; Shimizu, Japan) was performed after LES intake the night before but after at least 10 hours of resting fasting state. The plasma glucose levels and insulin levels were measured before glucose load and 30, 60, 90, 120 min after glucose load. The area under the concentration curve for glucose (AUC glucose) and the area under the concentration curve for insulin (AUC insulin) were calculated, and these values were compared before and after the concomitant voglibose use.

Energy metabolism was analyzed with indirect calorimetry (Deltatrac II; Detex Ohmeda, Finland). Indirect calorimetry was performed on the same day and before 75-g OGTT. Indirect calorimetry was performed for 30 min on patients who were in a state of overnight bed rest and fasting after LES intake. We also measured oxygen consumption per minute (VO_2) and carbon dioxide production per minute (VCO_2) during early-morning fasting. The total urine nitrogen (TUN) levels were measured previously. These values were used to calculate the non-protein respiratory quotient (npRQ): (i) oxidation ratio of nutrients; (ii) substrate oxidation of carbohydrate (% CHO); (iii) fat (% FAT); (iv) protein (% PRO); and (v) resting energy expenditure (REE).

A physician provided a medical examination once a month to each patient. In the examination, the physician assessed physical and physiological findings and subjective symptoms and confirmed patient compliance. A multi frequency-bioelectrical impedance analysis method (InBody 3.2; Biospace, Japan) was used for the anthropometric measurements. The creatinine height index (CHI) was calculated by the following formula: CHI = (urinary creatinine excretion per day (mg))/(ideal body weight × A), where A is 23 for males

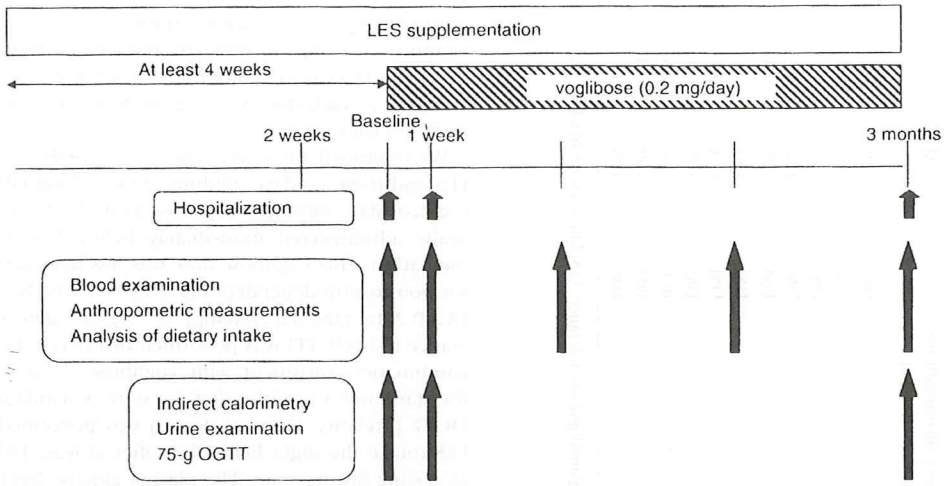

Figure 1 Study protocol to determine effects of a late evening snack combined with α glucosidase inhibitor on liver cirrhosis. All patients, who had been taking late evening snack (LES) supplementation of a branched-chain amino acid-enriched nutrient mixture, were started on a concomitant dose of α-glucosidase inhibitor (voglibose, 1 tab, 0.2 mg) at baseline. OGTT, oral glucose tolerance test.

and 18 for females. Blood biochemical tests were performed following standard methods. The content of the study was approved by the Clinical Trial Review Committee, School of Medicine, Yamaguchi University, Japan, prior to the start of the study. The subjects participated in this study after being thoroughly informed on the content of the study and voluntarily providing consent.

Statistical analysis

Data were expressed as the mean ± SD. Comparisons between data were evaluated by two-tailed paired Student's *t*-test. The Pearson's coefficient of correlation was used. *P*-values of less than 0.05 were considered significant.

RESULTS

Anthropometry

ANALYSIS OF THE results of the 11 subjects indicated no significant changes in weight from the baseline immediately before voglibose was added to LES therapy and 3 months after this combination therapy started (61.9 ± 13.6 kg vs 62.1 ± 13.1 kg). There were also no significant differences before and after the start of the combination therapy in skeletal muscle mass, body fat mass, and percent body fat (data not shown).

Glucose tolerance

The AUC glucose values were significantly decreased in 75-g OGTT 1 week and 3 months after concomitant voglibose use compared with the values before its use

Table 2 Effects of α-glucosidase inhibitor administration combined with a late evening snack on the area under the concentration curve for 2-hour glucose (AUC glucose) and insulin (AUC insulin) during the 75-g oral glucose tolerance test in cirrhosis

	Baseline	1 week	3 months
AUC glucose (mg/dL × h)	622.70 ± 166.65	536.86 ± 140.42*	557.32 ± 141.53*
AUC insulin (mg/dL × h)	206.30 ± 105.72	213.20 ± 69.56	188.73 ± 83.14

Data expressed as mean ± SD. *$P < 0.05$ compared with baseline.

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.

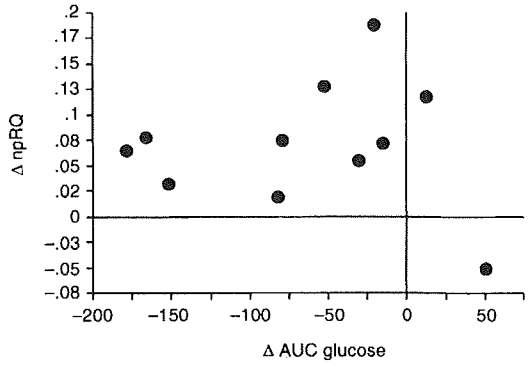

Figure 2 The correlation between the changes in non protein respiratory quotient (npRQ) after concomitant voglibose use and improvements in glucose tolerance. AUC glucose, area under the concentration curve for glucose.

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.

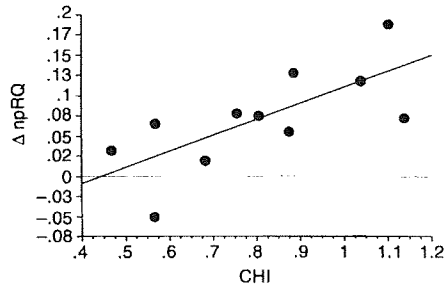

Figure 3 The correlation between the changes in non protein respiratory quotient (npRQ) after concomitant voglibose use and creatinine height index (CHI) at baseline. $r = 0.718$, $P < 0.05$, $n = 11$.

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

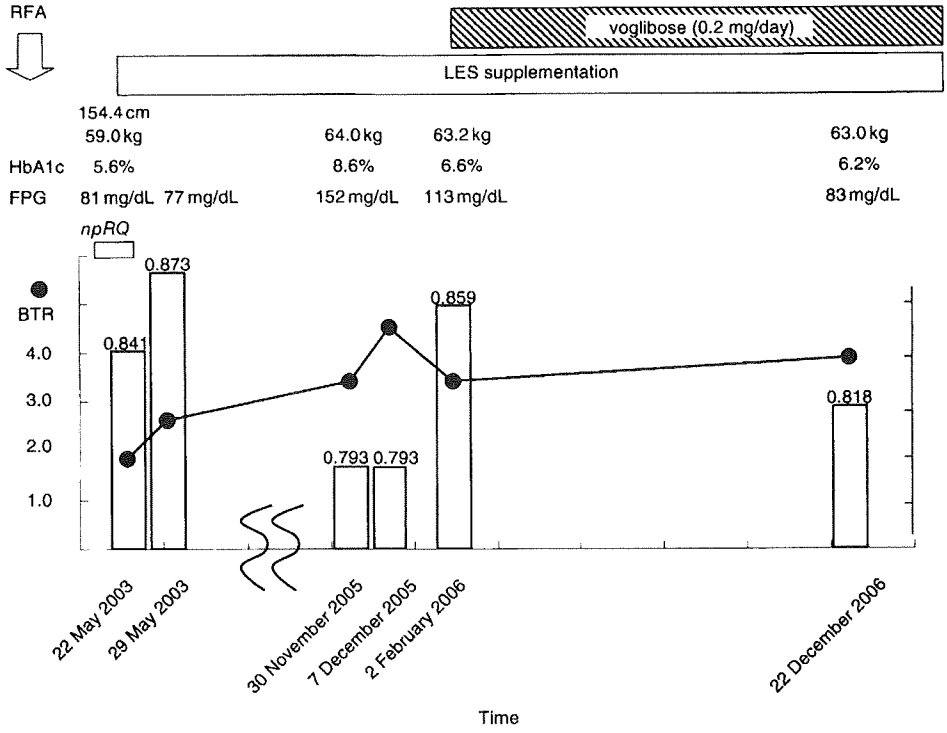

Figure 4 The clinical course of a 72-year-old female patient (case 4, Child–Pugh B) undergoing α-glucosidase inhibitor administration combined with a late evening snack. RFA, radiofrequency ablation; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; npRQ, non-protein respiratory quotient; BTR, molar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

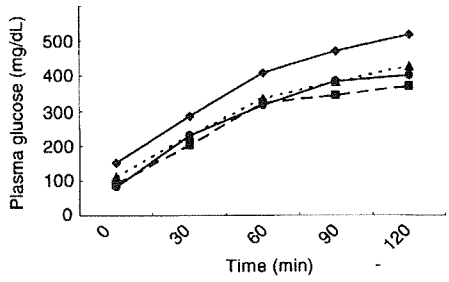

Figure 5 Plasma glucose level in a 75-g oral glucose tolerance test of a 72-year-old female patient (case 4, Child–Pugh B) undergoing α-glucosidase inhibitor administration combined with a late evening snack. ◆, baseline; ▲, 3 months; ●, 1 year; ■, 1 week.

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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