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## Effect of Telmisartan on Blood Pressure and Renal Function of Psoriasis Patients on Cyclosporine MEPC

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Cyclosporine A (CyA) is widely used for psoriasis, but it has adverse effect of hypertension, renal damage, and gingival overgrowth. We have tried telmisartan, an angiotensin Ⅱ receptor blocker, to treat hypertension complicating CyA treated psoriasis. Ten patients were entered and 3 had no history of hypertension medication, and 7 had had preceding treatment with nifedipine and switched to telmisartan. Telmisartan was prescribed 20 to 40mg per day. In two out of 7 switched patients, blood pressure were upregulated after 4 weeks requiring addition of nifedipine, but controlled after 8 weeks. Average of serum creatinine levels were elevated after 4 weeks, but returned to the original level after 8 weeks. Nine patients had shown gingival overgrowth, and switching to telmisartan brought improvement in two patients. Improvement of gingival overgrowth was also obtained by dental treatment. Telmisartan is an effective antihypertension depressant and may help improving the gingival overgrowth caused by combination of CyA and nifedipine.

## 乾癬のシクロスポリン 1.2 mg/kg 内服療法

国家公務員共済組合連合会浜の町病院皮膚科(主任：利谷昭人部長)

今 福 信 一・中 山 樹 一 郎

福岡・沖縄地区 CyA-MEPC 乾癬研究会

近年、乾癬の治療で QOL 向上を目的とした低用量のシクロスポリン(ネオーラル<sup>®</sup>)を用いるケースが少なくない。今回、ステロイド外用剤あるいはビタミン D<sub>3</sub> 外用剤では効果不十分な尋常性乾癬患者 25 人を対象に、シクロスポリン 2.0~2.5 mg/kg/day 外用療法併用群(2.0 mg/kg 群)とシクロスポリン 1.0~1.5 mg/kg/day 外用療法併用群(1.2 mg/kg 群)における有効性と安全性を比較した。その結果、寛解導入での PASI は最終的に 2.0 mg/kg 群で 32.7±10.8 から 15.1±10.2(低下率 54%)、1.2 mg/kg 群で 14.2±12.1 から 6.8±7.9(低下率 52%)と有意な改善が両群ともにみられた。痒痒スコアは 2.0 mg/kg 群で 2.1±0.8 から 1.1±0.8(低下率 50%)、1.2 mg/kg 群でも 1.5±0.8 から 0.5±0.7(低下率 64%)に改善がみられた。血圧、総コレステロール、血清クレアチニン値の平均にはいずれの群もいずれの時点でも有意な変化はみられなかった。投与前と投与 12 週後に行った患者アンケートの結果では、シクロスポリン併用により両群ともに落屑の量、ふけの量、かゆみ、治療の煩わしさは減少し、治療に対する満足度は上昇した。費用負担については両群共に約半数がそれほど気にならないと回答した。シクロスポリン併用療法は 1.2 mg/kg の低用量でも皮疹、痒みを改善し、患者の治療に対する満足度を上昇させる可能性がある治療と考えられた。

### はじめに

現在、本邦ではシクロスポリン A(CyA)は中等症以上の乾癬における治療の中心として位置づけられているが、軽症から中等症においては、ステロイド外用剤や活性型ビタミン D<sub>3</sub> の外用療法が主体となっている。CyA は一般に中等症以上の乾癬に投与するにあたり 3~5 mg/kg/day と投与量が設定されているが、この投与量で長期連用した際の副作用等まだ克服されていない問題点も多い<sup>1)</sup>。最近のガイドライン<sup>2)</sup>では外用治療のみで効果が不十分な中等症以下の乾癬患者に対して従来より低用量の 2.5 mg/kg の CyA でも可としている。さらに最近では CyA のより低用量(2.0 mg/kg 以下)での治療でどの程度の患者満足度が得られるのかが課題となっている。

今回、CyA-MEPC を用いてステロイド外用剤あるいはビタミン D<sub>3</sub> 外用剤では効果不十分な尋常性乾癬患者を対象に CyA-MEPC 2.0~2.5 mg/kg/day 外用療法併用群(2.5 mg/kg 群)と CyA-MEPC 1.0~1.5 mg/kg/day 外用療法併用群(1.2 mg/kg 群)における安全性と有効性を比較検討したので報告する。

### 対象と方法

本試験に参加した施設を一覧に示す(表 1)。

#### 1)対象症例と方法、効果

尋常性乾癬患者でステロイド外用療法、ビタミン D<sub>3</sub> 外用療法にて効果不十分な患者を対象とした。重症型乾癬(剝脱性紅皮症型、膿疱形成を伴う紅皮症型、高度の関節痛を伴う関節症性乾癬、全身紅斑型、膿疱性乾癬)は除く。試験はオープン試験で、連続登録方式とした。A 群(1.2 mg/kg 群)：CyA-MEPC 1.0~1.5 mg/kg/day または B

群(2.0 mg/kg 群)：CyA-MEPC 2.0~2.5 mg/kg/day に振り分けた。服用は 1 日 2 回(朝、夕食後)に分けて内服とした従来の外用治療は変更せず継続した。患者の振り分けは、原則として A 群、B 群の順番にて選択し、投与期間は 12 週とした。主要評価項目を PASI スコアの改善度、副次的評価項目としてその他の症状(痒痒)の改善度を設定した。痒痒は下記のスコア(表 2)で他覚的に評価した。

#### 2)除外規定

原則として以下の患者は除外症例とした。

ネオーラル<sup>®</sup>の成分に対して過敏症の既往歴のある患者、タクロリムス投与中の患者、ピタバスタチン(リパロ<sup>®</sup>)投与中の患者、妊婦、妊娠している可能性のある婦人または授乳婦、腎障害または腎機能低下がある患者、急性または慢性の肝機能障害がある患者、脾機能障害がある患者、高血圧がある患者(降圧剤にて血圧コントロールが可能な患者は慎重に投与可能とする)。急性または慢性の活動性感染症があり、それが本剤で悪化する恐れがある患

表 1 参加施設一覧

琉球大学	主任：上里 博教授
美里皮膚科	院長：廖 明清
高宮城皮膚科	院長：高宮城 敦
石垣皮膚科	院長：山口 宣久
としたに皮膚科	院長：利谷 昭人
Dr. リン皮膚科	院長：林 士弘
清水皮膚科	院長：清水 昭彦
はたもと皮膚科	院長：橋本 明利
つつい皮膚科	院長：筒井 賢一
桐生皮膚科	院長：桐生 美鷹
柳原皮膚科	院長：柳原 憲一
ながせ皮膚科	院長：永瀬 浩一
福岡大学	主任：中山樹一郎教授

表2 痒痒スコア

日中の症状	夜間の症状	スコア(点数)
いてもたってもいられないかゆみ	かゆくてほとんど眠れない	4点
かなりかゆくて、人前でもかく	かゆくて目がさめる	3点
時には手がゆき、軽くかく	かけば眠れる	2点
時にむずむずするが、かく程ではない	かかなくても眠れる	1点
ほとんどかゆみを感じない	ほとんどかゆみを感じない	0点

者、悪性腫瘍またはその既往がある患者、CyA内服中に腎毒性を有する薬剤\*<sup>1</sup>または血清カリウム値を上昇させる薬剤\*<sup>2</sup>の併用が避けられない患者。光線療法を施行中の患者、BおよびC型肝炎の患者、その他、担当医が本試験への組み入れを不適当と判断した患者。

\*<sup>1</sup>:アミノグリコシド系抗生物質(ゲンタマイシン, トブラマイシン等), アムホテリシンB, シプロフロキサシ, バンコマイシン, スルファメトキゾール・トリメトプリル, 非ステロイド系抗炎症薬(ジクロフェナク, ナプロキセン, スリンダク, インドメタシン), 抗ウイルス薬(ガンシクロビル, ホスカルネットナトリウム)

\*<sup>2</sup>:カリウム保持性利尿薬(スピロラクトン等)

### 3) 観察, 調査, および評価判定項目

試験開始時およびCyA-MEPC投与開始2週後, 4週後以降4週毎に12週までPASIスコアと痒痒スコアを測定した。

### 4) 投与期間中の有害事象

試験期間中に有害事象が発現した場合は主治医の判断で治療薬を減量または中止するなど, 症状に応じて適切な処置を行うこととした。投与期間中は原則として乾癬治療を目的とした他の内服療法は行わない。また, 合併症等に対する薬物療法については, 原則として本併用療法の評価に影響を与える可能性のある薬剤は避ける。

### 5) インフォームドコンセント

担当医は被験予定者本人に試験の実施に際し, 説明文書を用いて, 口頭で説明する。

被験予定者本人が試験参加に同意した場合は, その旨カルテに記載する。

### 6) 患者アンケート

終了時(効果判定時)にこの治療法について患者にアンケートを実施した。一部の設問は治療開始前にもアンケートを行い, 前後での変化を統計学的に検討した。検定にはWilcoxon符号付検定を用いて解析を行い, 両側5%を有意とした。アンケートの設問を図1に記載する。

## 結 果

### 1) 患者背景(表3)

2004年3月1日より2005年2月28日までに両群合わせて25例を登録した。2mg/kg群が15例, 男:女=9:6, 年齢25~79歳(平均55.0歳, 中央値55歳), 1.2mg/kg群が10例, 男:女=9:1, 年齢24~76歳(平均50.6歳, 中央値54歳)であった。

### 2) 平均投与量(図2)

A群の平均投与量は2.0mg/kg, B群の平均投与量は1.2mg/kgであった。これらの平均投与量は調査期間中

問1:現在の治療に対する満足度

- 満足している
- 多少満足している
- どちらともいえない
- 多少不満である
- 不満である

問2:ネオール内服併用療法の費用負担について

- 全く気にならない
- たまにあるが殆ど気にならない
- どちらでもない
- 時々気になる事がある
- とても気になる

問3:現在のあなたの症状はいかがですか?  
(A, B, C各々ついて○は1つ)

A:かゆみ

- なし
- 少しかゆい
- ややかゆい
- かなりかゆい
- がまんできないぐらいかゆい

B:フケの量

- なし
- 少しでる
- ややでる
- たくさんでる
- きりが無いぐらいでる

C:はがれ落ちる皮膚の量

- なし
- 少しでる
- ややでる
- たくさんでる
- きりが無いぐらいでる

問4:治療の煩わしさについて

- とてもよくなった
- すこしよくなった
- かわらない
- それほど変わらない
- まったく変わらない

図1 患者アンケート

ほぼ変化がなかった。

### 3) PASIスコアの推移(図3)

PASIスコアはエントリーの時点で2mg/kg群と1.2mg/kg群で有意に差がある結果となった。群内の変化で見ると2.0mg/kg群, 1.2mg/kg群ともに2カ月目以降に有意に低下し(対応のあるt検定), 3カ月目以降もそれが維持される結果となった。最終的には2.0mg/kg群で $32.7 \pm 10.8$ から $15.1 \pm 10.2$ (低下率54%), 1.2mg/kg群で $14.2 \pm 12.1$ から $6.8 \pm 7.9$ (低下率52%)であった。

### 4) 痒痒スコア(図4)

痒痒スコアも最初のエントリーの時点で2mg/kg群と1.2mg/kg群で群間に有意に差がある結果となった。群内の変化で見ると2.0mg/kg群では1カ月以降, 1.2mg/kg群では2カ月目以降に統計上有意に低下し(対応のあるt検定), 3カ月目以降もそれが維持される結果となった。最終的には痒痒スコアは2.0mg/kg群で $2.1 \pm 0.8$ から $1.1 \pm 0.8$ (低下率50%), 1.2mg/kg群でも $1.5 \pm 0.8$ から $0.5 \pm 0.7$ (低下率64%)であった。

表3 患者背景

1.2 mg/kg 群			
性別	年齢	診断名	合併症
女	42	尋常性乾癬	なし
男	33	尋常性乾癬	高脂血症
男	77	尋常性乾癬	高血圧・気管支喘息
女	75	尋常性乾癬	なし
男	55	尋常性乾癬	なし
女	34	尋常性乾癬	なし
女	25	尋常性乾癬	なし
男	57	尋常性乾癬	なし
男	54	尋常性乾癬	なし
男	70	尋常性乾癬	なし
男	66	尋常性乾癬	なし
男	31	尋常性乾癬	なし
女	74	尋常性乾癬	高血圧
女	79	尋常性乾癬	耐糖能異常
男	53	尋常性乾癬	なし
2.0 mg/kg 群			
性別	年齢	診断名	合併症
男	59	尋常性乾癬	なし
男	24	尋常性乾癬	なし
男	31	尋常性乾癬	なし
男	76	尋常性乾癬	なし
男	56	尋常性乾癬	脳梗塞・高脂血症・高血圧
男	30	尋常性乾癬	なし
男	39	関節症性乾癬	なし
男	69	尋常性乾癬	高血圧
女	70	尋常性乾癬	DM 境界域・高脂血症
男	52	尋常性乾癬	DM

### 5) 血圧, 血清総コレステロール, 血清クレアチニン値の推移

副作用としてモニターした血圧(図5), 血清総コレステロール(図6), 血清クレアチニン値(図7)は両群間, また群内のいずれの時点でも有意な変化はみられなかった。

### 6) アンケート結果

#### 患者満足度(図8)

治療開始前後で行った患者満足度は1.2 mg/kg 群, 2.0 mg/kg 群共に満足度は向上した。1.2 mg/kg 群では有意に満足度が上昇した。

#### 痒み(図9)

痒みに対するアンケートでは, 両群共に痒みの軽減がみられた。1.2 mg/kg 群では統計学的に有意に減少がみられた。

#### フケの量(図10)

フケの量は両群共に減少している結果となった。両群共に統計上有意な減少となった。

#### はがれ落ちる皮膚の量(図11)

はがれ落ちる皮膚の量は両群で共に有意に減少した。

#### 費用負担(図12)

CyA を導入した費用負担感については, 1.2 mg/kg 群,

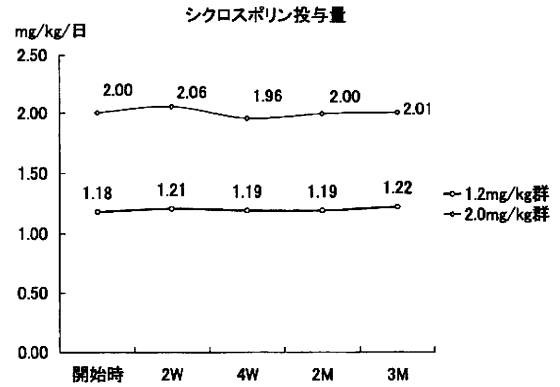


図2 投与量の平均値の推移

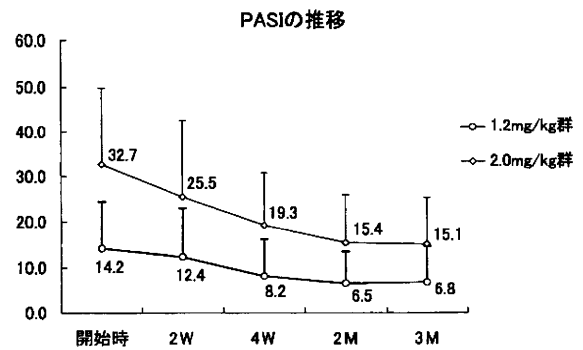


図3 PASIスコアの推移

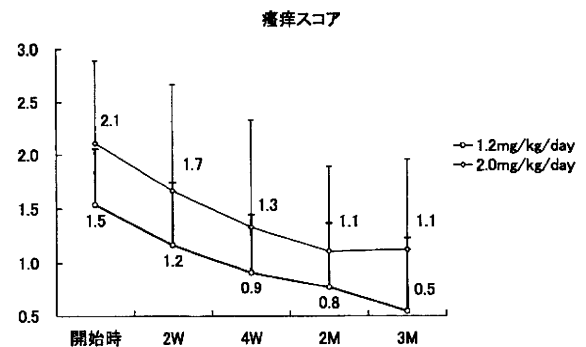


図4 痒痒スコアの推移

2.0 mg/kg 群でそれぞれ50%, 57%が「たまにあるが気にならない」という結果であった。両群間で費用についての感想に差は見られなかった(Fisher's exact test)。

#### 治療の煩わしさについて(図13)

治療の煩わしさについては治療終了時にアンケートを採った。いずれの群でも7割以上がとてもよくなった, または少しよくなった, と回答した。

## か がん が え

CyA は中等症以上の乾癬治療に欠かせない治療であることは論を待たない<sup>2)</sup>。しかし, 安元らのアンケート調査の結果では副作用や費用の点からあまり使用されていないのが現状である<sup>3)</sup>。中等症以下の乾癬患者は大多数が第一



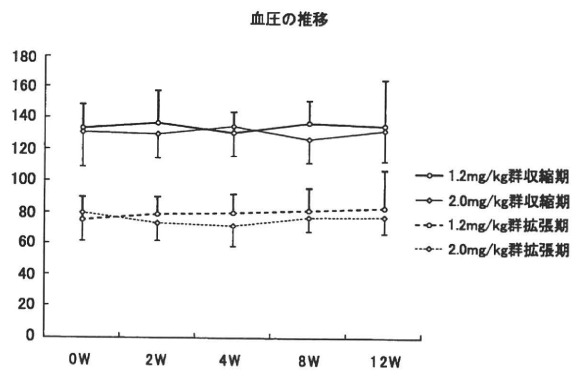


図5 血圧の推移

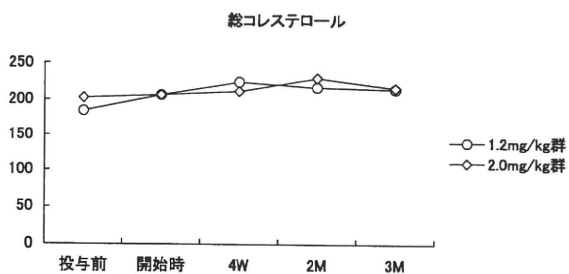


図6 血清総コレステロール値の推移

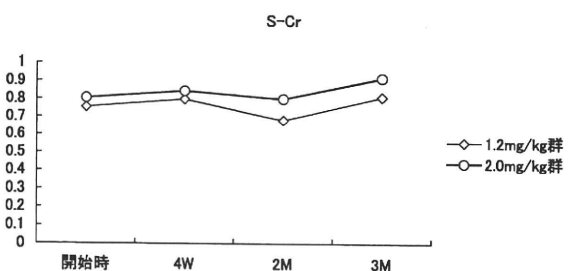


図7 血清クレアチニン値の推移

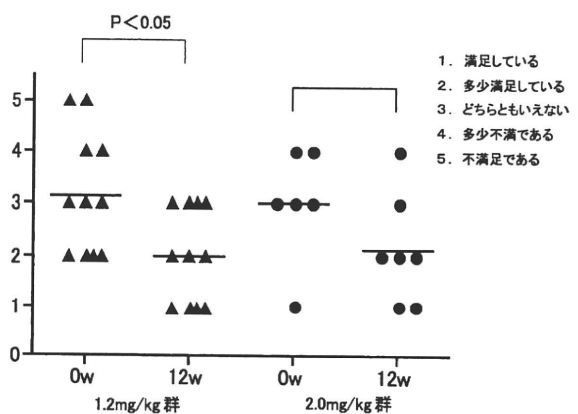


図8 これまでの治療に対する満足度

線の診療所の皮膚科で治療されていると思われるが、一般の診療所においても外用療法のみでは難治性の場合により

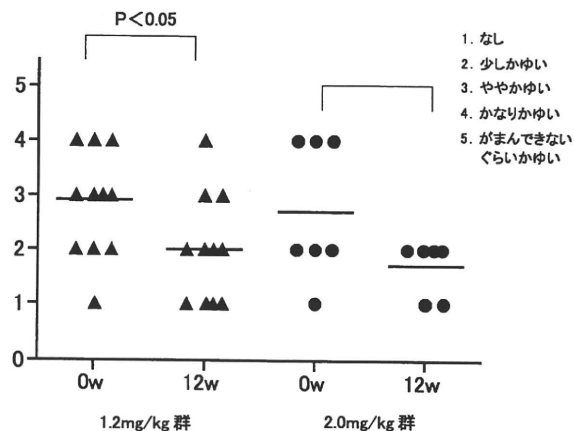


図9 痒み

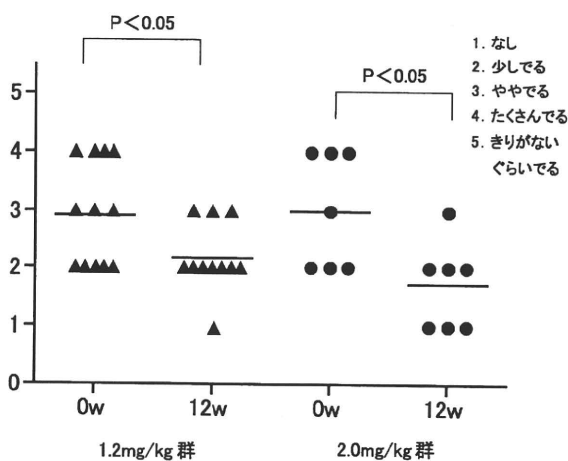


図10 フケの量

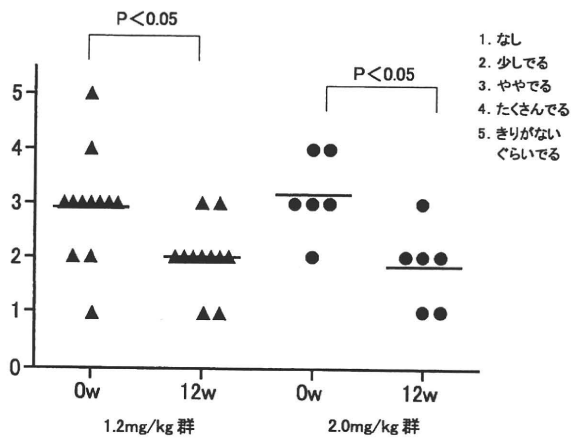


図11 はがれ落ちる皮膚の量

安全で低コストのCyA療法が望まれる。

このような点から中等症以下を対象にした2.0~2.5 mg/kg/day程度の低用量<sup>4)~7)</sup>、あるいは間歇投与<sup>8)9)</sup>での様々なアプローチがなされてきた。近年では機能障害のみならず、生活の質(QOL)の観点から疾病の治療計画を立

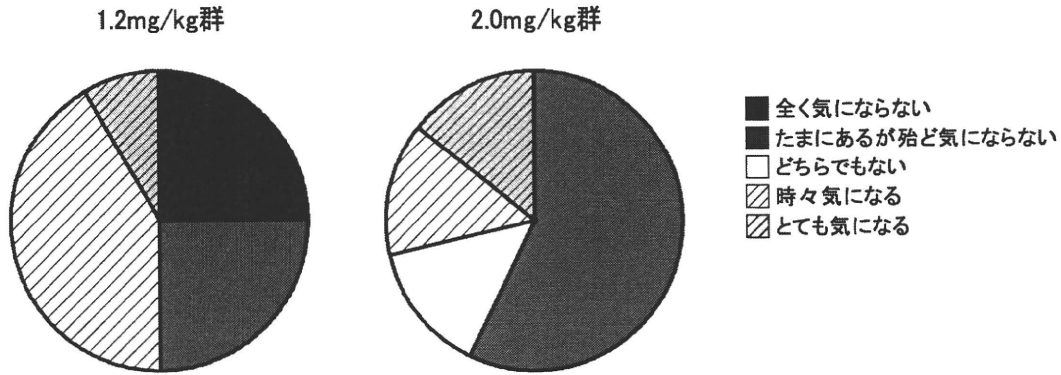


図12 CyA内服併用療法の費用負担について

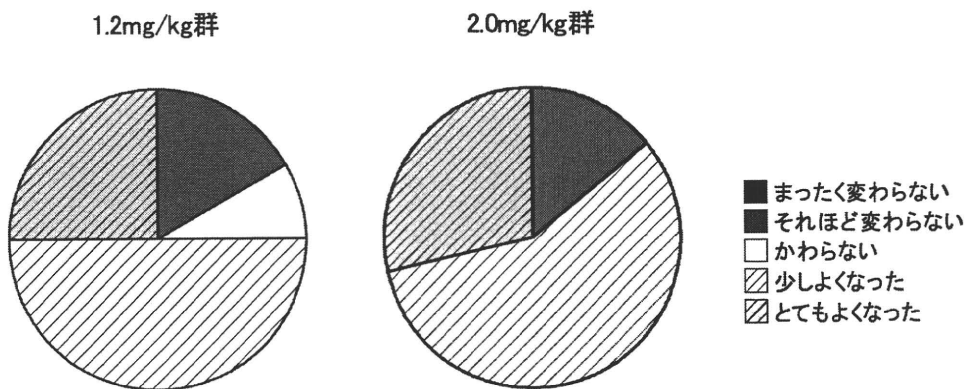


図13 治療の煩わしさについて

てることの重要性が認識され、乾癬に於いてもPDIやself-PASIなどの患者自身が評価するアセスメントツールが普及してきている<sup>10)</sup>。

今回、我々は通常の低用量よりさらに少ない投与量が中等症以下の乾癬においてどのような効果を発現するのかを検討した。結果は統計上1.2mg/kgという低用量でもPASIスコア、癢痒スコア共に有意な改善が見られた。ただし、PASIスコア、癢痒スコアともにエントリーの時点で2mg/kg群と1.2mg/kg群で有意に差がある結果となり、群間の比較は困難であった。この差は、原則的にA、B各群の交互のエントリーがプロトコル上規定されていたが、主治医の判断でエントリーにバイアスがかかった可能性が考えられた。

これらの結果は、通常の外用療法である程度改善はみられるものの十分な満足が得られない患者に対して、身体的・経済的な負担を最小限にしてさらなる改善が得られる可能性を示唆するものと言える。医師による他覚的な評価も改善がみられているが、アンケートにおけるフケ・鱗屑の量、痒みなどの自覚症状の改善がはっきりとみられたことが満足度の上昇に寄与していると考えられた。

近年CyAの治療効果と薬物動態の関係の研究が進み、乾癬においては血中濃度時間曲線下面積(area under the blood concentration time curve, AUC)がトラフレベルよ

りも治療効果と相関すると考えられている<sup>11)</sup>。1.2mg/kg投与は、2.0mg/kgと比較してAUCは小さいと考えられるが、この研究では両者とも十分な臨床効果が得られ、明らかな差がみられなかった。これは、上乘せ効果においては比較的少量でも効果が得られやすいこと、初期のバイアスにより効果が得られやすい軽症例が1.2mg/kg群に入ったことなどが考えられた。

CyAは副作用の面から欧米ではその連続使用期間を2年と推奨している<sup>12)</sup>。しかし、光線治療施設が少なく、生物学的製剤も未だ導入されていない我が国では中等症以上の難治性乾癬患者の外来での管理において、現実的にはCyAの副作用を最小化して安全に長期間投与する方法を工夫する必要がある。今回の研究から1.2mg/kg内服療法は安全で低コストで患者満足度を改善する一つの治療法と考えられた。

本研究の要旨は第22回日本乾癬学会学術大会(2007年9月7、8日、志摩市)において発表した。

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## Very Low Dose (1.2 mg/kg) Cyclosporine A Therapy for Psoriasis

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Cyclosporine A (CyA) was administered at two different low doses (1.2 mg/kg group and 2.0 mg/kg group) orally to psoriasis patients who had not had satisfactory results with topical therapy. Mean PASI scores decreased from  $32.7 \pm 10.8$  to  $15.1 \pm 10.2$  in the 2.0 mg/kg group and from  $14.2 \pm 12.1$  to  $6.8 \pm 7.9$  in the 1.2 mg/kg group. Mean itch scores decreased from  $2.1 \pm 0.8$  to  $1.1 \pm 0.8$  in the 2.0 mg/kg group and from  $1.5 \pm 0.8$  to  $0.5 \pm 0.7$  in the 1.2 mg/kg group. Results of a questionnaire taken before and after the treatment revealed less scale, dandruff and itching in both groups. Approximately half of the patients in both groups answered that the increased cost was of little concern. Very low dose (1.2 mg/kg) CyA therapy improved satisfaction with treatment and may be a new affordable option for patients with mild psoriasis who desire a better quality of life.

## Body cell mass is a useful parameter for assessing malnutrition and severity of disease in non-ascitic cirrhotic patients with hepatocellular carcinoma or esophageal varices

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**Abstract.** Body cell mass (BCM) is a nutritional parameter, however, changes in BCM in patients with non-ascitic liver cirrhosis (LC) in comparison to patients with other malnutritional diseases remains unclear. We investigated the difference in BCM between patients with LC and malnourished gastrointestinal disease controls (M.CON), and examined the relationship between BCM and the severity of LC. Results demonstrated that serum nutritional parameters were not significantly different between the LC (n=56) and M.CON groups (n=25), whereas BCM%BW was significantly lower in the LC group than in the M.CON group (50.9±4.6 vs. 54.4±7.1%, P=0.018). Furthermore, BCM%BW negatively correlated with the model for end-stage liver disease (MELD) score (P=0.04). In conclusion, BCM showed a significant decrease and a negative correlation with the MELD score in the LC group. BCM may be a useful parameter for assessing malnutrition and severity of LC.

### Introduction

The liver is one of the central organs involved in the metabolism of various nutrients. In patients with liver cirrhosis, malnutrition is a common feature and is associated with mortality and reduced quality of life (1). Therefore, routine nutritional assessment is recommended in patients with liver cirrhosis (2,3). Subjective global assessment (SGA) and anthropometric measurements are useful techniques for nutritional assessment in various diseases. However, these assessments are not suitable for precise assessment of malnutrition and do not predict a poor clinical outcome in patients with liver cirrhosis (4). Thus, malnutrition is often under-diagnosed in patients with liver cirrhosis.

Significant changes in body composition are known to occur before physiological changes (5). Therefore, measurement of body composition is an integral part of nutritional assessment. Among all body compartments, body cell mass (BCM) has been regarded as the most meaningful for the assessment of malnutrition. BCM comprises the metabolically active and protein-rich compartments in the body and is known to be depleted in case of protein-energy malnutrition (6). Precise estimation of BCM can be obtained by isotope dilution or via the total-body potassium count (7); however, these methods are not generally available for clinical use. Despite certain limitations in patients with ascites, bioelectrical impedance analyzer (BIA) is a useful tool for the estimation of BCM in cirrhotic patients (8,9). An eight-polar BIA has been developed (10) and is currently a non-invasive bedside tool for estimating BCM.

Depletion of BCM is associated with post-liver transplantation mortality, and the measurement of BCM provides clinically relevant information in patients with end-stage liver cirrhosis (11). However, in patients with liver cirrhosis without ascites and/or edema, the utility of BCM as a nutritional parameter remains unclear. In addition, comparisons have been made between cirrhotic patients and healthy

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*Abbreviations:* BCM, body cell mass; LC, liver cirrhosis; M.CON, malnourished gastrointestinal disease controls; BIA, bioelectrical impedance analyzer; MELD, model for end-stage liver disease; SGA, subjective global assessment; AC, arm circumference; AMC, mid-arm circumference; TSF, tricep skinfold thickness; CV, coefficient of variation; ICF, intracellular fluid; TBW, total body water; ECF, extracellular fluid; FFM, fat free mass

*Key words:* body composition, eight-polar bioelectrical impedance analyzer, nutritional assessment, liver disease, model for end-stage liver disease score

control subjects, but not malnourished disease controls, in previous studies. In order to verify the specificity for depletion of BCM, cirrhotic patients should be compared to malnourished disease controls. Moreover, the correlation between BCM and severity of disease remains unknown. The aim of this study was to examine changes in BCM in cirrhotic patients in comparison with other malnourished patients and the association between BCM and severity of disease in cirrhotic patients.

### Materials and methods

**Subjects.** We conducted a cross-sectional study. Via consecutive entry, a total of 56 men with liver cirrhosis (LC) (hepatitis C virus-related, n=36; hepatitis B virus-related, n=13; alcoholic, n=5; cryptogenic, n=2) and 25 age-matched men with chronic gastrointestinal diseases (inflammatory bowel diseases, n=12; pancreatic cancer, n=3; biliary cancer, n=4; colitis, n=3; colon cancer, n=2; chronic pancreatitis, n=1) who served as controls for nutritional status (malnourished disease controls; M.CON) were enrolled in this study during the period from August 2004 to March 2006 at Kurume University Hospital. In the LC group, 28 patients had co-occurring hepatocellular carcinoma. Among them, 20 patients had a single (<3-cm) nodule which had been treated with radiofrequency ablation. Eight patients had advanced tumors which had been treated with chemoembolization. The rest of the 28 patients had co-occurring esophageal varices. Although none of them had episodes of bleeding, they were treated with preventive endoscopic variceal ligation for the esophageal variceal bleeding. The specificity of changes in body composition in cirrhotic patients can be examined by a comparison with malnourished patients. All of the diagnoses were based on clinical, serological, histological, and/or imaging evidence. All patients were hospitalized. For both the LC and M.CON groups, inclusion criteria were: i) Asian men; ii) 20-70 years of age; iii) no edema nor ascites determined by physical examination and ultrasonography; and 4) serum albumin concentration <4.0 g/dl. Patients with chronic renal failure or those who had been taking corticosteroids were excluded. The regular hepatic diet (total energy 30-40 kcal/kg body weight (BW)/day, protein 1.2-1.5 g/kg BW/day) was fed to patients in the LC group. The proper diet (total energy 30-35 kcal/kg BW/day, protein 1.2-1.5 g/kg BW/day) was fed to patients in the M.CON group. In the analysis for an association between BCM and severity of liver disease, subjects were stratified by age (40-60 years) because of the age-related differences in body water compartments (12). None of the subjects were institutionalized. Informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institutional review board.

**Laboratory determinations.** Venous blood samples were collected in the morning after a 12-h overnight fast. Hemoglobin concentration, total lymphocyte count, international normalized ratio (INR) of prothrombin time, serum albumin, creatinine and total cholesterol concentration were measured using standard clinical methods (Department of Clinical Laboratory, Kurume University Hospital). A

Table I. Precision of eight-polar BIA in patients with liver cirrhosis.

	Right arm	Left arm	Trunk	Right leg	Left leg
R <sub>5</sub>	2.3	2.3	2.9	2.6	2.7
R <sub>50</sub>	2.0	2.4	2.5	2.3	2.5
R <sub>250</sub>	2.1	2.0	2.2	2.3	2.3
R <sub>500</sub>	2.2	2.1	2.4	2.4	2.3

Coefficients of variation were calculated from 2 measurements on 7 of the study subjects (n=14). BIA, direct segmental multifrequency-bioelectrical impedance analyzer; R<sub>x</sub>, resistance at x kHz.

prognostic nutritional index was calculated by using the following formula as previously described (13): Prognostic nutritional index = 10 x Serum albumin concentration (g/dl) + 0.005 x Total lymphocyte count (mm<sup>3</sup>). Poor prognosis is predicted when the prognostic nutritional index is <40 and total lymphocytes count remains <1000/mm<sup>3</sup>.

**Estimations of anthropometry and body composition.** Anthropometry and body composition were estimated by an eight-polar BIA at frequencies of 5, 50, 250 and 500 kHz (InBody 3.2, Biospace, Tokyo, Japan). Two electrodes were placed in contact with the palm and thumb of each hand and two electrodes with the anterior and posterior regions of the sole of each foot. Body mass index (BMI) was calculated as BW in kilograms divided by the square of height in meters (kg/m<sup>2</sup>). Arm circumference (AC), mid-arm circumference (AMC), tricep skinfold thickness (TSF), waist circumference, hip circumference, and waist-hip ratio were estimated using the software supplied with the eight-polar BIA (Lookin'body 2.0, Biospace) based on a hydration model (14). The accuracy of the eight-polar BIA analyzer has been previously reported (10). In our preliminary study, anthropometric data estimated by the eight-polar BIA analyzer also showed a significant positive correlation with anthropometric data derived by direct measurement in the LC group (AMC, n=43, Spearman rank r=0.69, P<0.0001; TSF, n=43, Spearman rank r=0.44, P<0.0046). AC, AMC and TSF were expressed as a percentage of the expected value for age and gender with reference to Japanese Anthropometric Reference Data (JARD, 2001) (15). The validation of BIA as a measure of change in BCM as estimated by comparing whole-body counting of potassium was reported (16); and therefore, BCM was evaluated by an eight-polar BIA in this study. Because absolute values of body composition vary widely, normalization of body compositions including BCM is required. Height is an index for normalization; however, a balance of each body composition is also important, and normalization of BCM by BW is used in the definition of HIV-associated malnutrition (17). Therefore, we normalized BCM by BW and the resulting BCM was expressed as BCM%BW as previously described (11). The precision of InBody 3.2 was determined by measuring resistance two times a day in 7 of the study subjects. The coefficient of variation (CV) [(SD/mean) x 100], calculated from these measurements (n=14) is shown in

Table II. Nutritional status of the patients.

	M.CON	LC	P
No. of patients	25	56	
Age (years)	51.9±13.4	55.6±9.1	N.S.
Height (cm)	165.2±7.9	168.1±6.5	N.S.
Total protein (g/dl)	6.71±0.93	7.01±1.42	N.S.
Albumin (g/dl)	3.36±0.43	3.24±0.39	N.S.
Total cholesterol (mg/dl)	157±90	126±79	N.S.
Total lymphocyte count (/mm <sup>3</sup> )	1330±796	1280±704	N.S.
Hemoglobin (g/dl)	11.6±1.9	11.9±1.9	N.S.
Creatinine (mg/dl)	0.74±0.26	0.77±0.17	N.S.
Prognostic nutritional index	40.2±5.6	38.8±5.0	N.S.
Accompanying malignancy	9/25	28/56	N.S.

Data are expressed as the mean ± SD. Prognostic nutritional index was calculated by using the following formula as previously described (13): Prognostic nutritional index = 10 x Serum albumin concentration (g/dl) + 0.005 x Total lymphocyte count (mm<sup>3</sup>). M.CON, malnourished disease controls; LC, liver cirrhosis.

Table III. Anthropometric assessment.

	M.CON	LC	P
BMI	20.8±3.7	23.1±3.0	0.009
%AC	103.9±17.9	109.6±8.9	N.S.
%AMC	100.3±12.8	107.0±8.4	0.009
%TSF	128.8±80.9	127.4±37.9	N.S.
Waist circumference (cm)	76.7±10.2	83.7±6.6	0.003
Hip circumference (cm)	88.0±6.4	92.9±4.5	0.001
Waist-hip ratio	0.87±0.06	0.90±0.03	0.031

Data are expressed as the mean ± SD. AC, TSF and AMC are expressed as a percentage of the expected value for age and gender according to the Japanese Anthropometric Reference Data (JARD 2001) (15). M.CON, malnourished disease controls; LC, liver cirrhosis; BMI, body mass index; AC, arm circumference; AMC, arm muscle circumference; TSF, triceps skin-fold thickness.

Table I. Similar to a previous report (10), the CV value was <3.0 and comparable to that of a four-polar total-body BIA performed at 50 kHz (CV = 3.0%) (18,19).

**Severity of liver disease.** The severity of cirrhosis was assessed by the model for end-stage liver disease (MELD) score (20). The MELD score was computed using an on-line worksheet (<http://www.mayoclinic.org/gi-rst/mayomodel5.html>). To avoid negative scores, laboratory values such as serum creatinine concentrations that were <1 mg/dl were rounded off to 1 as previously described (21).

**Statistical analysis.** All data are expressed as the mean ± SD. Differences between the two groups were analyzed using the Mann-Whitney U test or the Chi-square test. The Spearman's correlation coefficient was calculated for testing the relationship between different quantities in a bivariate regression model using StatView (version 5.1; SAS Institute, Cary, NC). P-values <0.05 were indicative of significant differences.

## Results

**Patient characteristics.** We enrolled 56 patients with liver cirrhosis and 25 patients with chronic gastrointestinal diseases as malnourished disease controls. Clinical and laboratory data for these subjects are summarized in Table II. Age and height were not significantly different between the LC and M.CON groups. Serum concentrations of total protein, albumin, and total cholesterol, total lymphocyte count, hemoglobin concentration, prognostic nutritional index, and the rate accompanying malignancy were also not significantly different between the two groups.

**Comparison of anthropometry between the LC and M.CON groups.** In the LC group, BMI and %AMC were significantly higher than in the M.CON group, although %TSF was not significantly different when comparing the two groups (Table III). Waist and hip circumferences and waist-hip ratio were significantly higher in the LC group than in the M.CON group.



Table IV. Assessment of body composition.

	M.CON	LC	P
Fat%BW	17.1±8.4	20.8±5.1	N.S.
TBW%BW	61.1±6.4	58.4±3.8	N.S.
ECF%BW	23.2±2.8	22.8±1.6	N.S.
ICF%BW	37.9±4.8	35.5±2.3	0.017
ECF/TBW	0.334±0.028	0.344±0.007	N.S.
Protein%BW	16.4±2.1	15.4±1.0	0.018
Mineral%BW	5.4±1.0	5.5±0.4	N.S.
BCM%BW	54.3±6.9	50.9±4.5	0.018

Data are expressed as the mean ± SD. M.CON, malnourished disease controls; LC, liver cirrhosis; BW, body weight; TBW, total body water; ICF, intracellular fluid; ECF, extracellular fluid; BCM, body cell mass.

*Comparison of body composition between the LC and M.CON groups.* There was a significant decrease in both intracellular fluid (ICF)%BW and protein%BW in the LC group compared to those in the M.CON group, although fat%BW, total body water (TBW)%BW, extracellular fluid (ECF)%BW, ICF%TBW, protein%BW and mineral%BW did not differ significantly when comparing the two groups (Table IV). Fig. 1A shows the compositions for BW, fat free mass (FFM), soft lean mass (SLM) and BCM. FFM%BW did not differ between the two groups (Fig. 1B), however, SLM%BW was significantly decreased in the LC group compared to that in the M.CON group (Fig. 1C). The difference was even more significant when comparing BCM%BW between the two groups (Fig. 1D).

*Comparison of nutritional parameters between cirrhotic patients with HCC and cirrhotic patients without HCC.* There were no significant differences in nutritional status including biochemical tests between cirrhotic patients with HCC and cirrhotic patients without HCC. No significant differences were also found in anthropometric assessment and body composition between cirrhotic patients with HCC and cirrhotic patients without HCC (data not shown).

*An association between BCM and severity of disease in the LC group.* Although there was no significant correlation between BCM and the MELD score when considering all subjects, an association was evident by stratification of the patients in the LC group according to their age. There was a significant negative correlation between BCM and the MELD score in cirrhotic patients aged 40-60 years ( $n=29$ ,  $R^2=0.148$ ,  $P=0.04$ ) (Fig. 2).

## Discussion

In this study, we demonstrated a significant decrease in BCM in patients with liver cirrhosis compared to that in malnourished patients with chronic gastrointestinal diseases, although serum or hematological nutritional parameters were not significantly different between the two groups. Moreover,

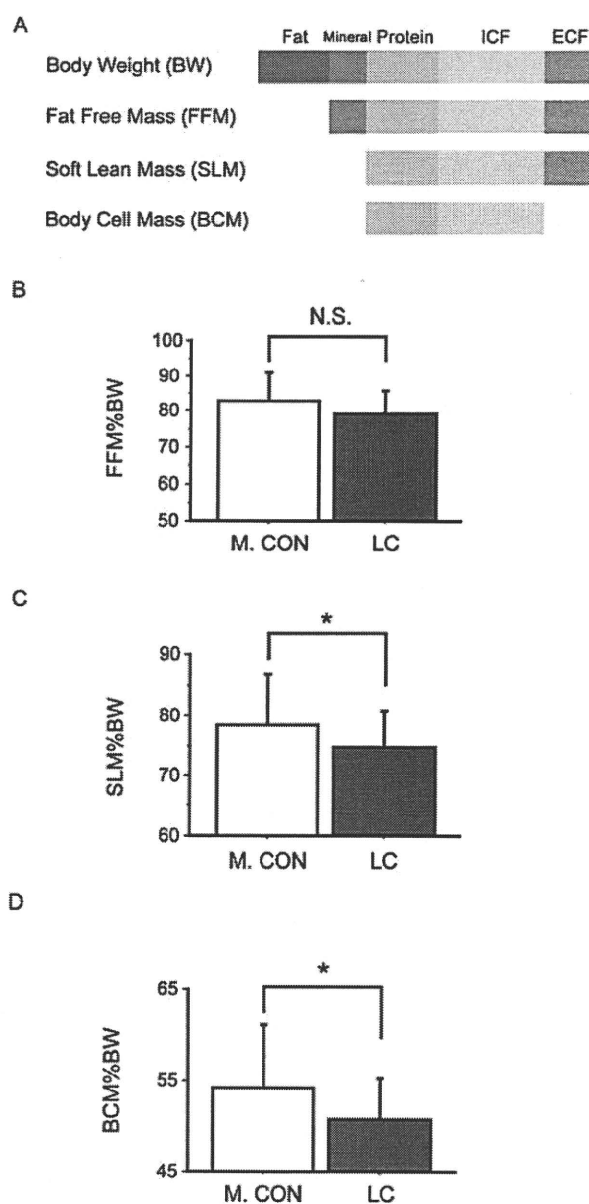


Figure 1. Scheme of body composition (A). Comparison of FFM (B), SLM (C) and BCM (D) between the LC and M.CON groups. Values are expressed as the mean ± SD. Differences between the two groups were analyzed using the Mann-Whitney U test. N.S., not significant. \* $P<0.05$ . BW, body weight; ICF, intracellular fluid; ECF, extracellular fluid; M.CON, malnourished disease controls; LC, liver cirrhosis.

we showed a significant negative correlation between BCM and the MELD score in patients with liver cirrhosis.

Significant changes in body composition are known to occur before physiological changes (5). Similar to previous reports (22,23), an increase in TBW and ECW was also noted in this study when these body compositions were normalized with height (data not shown). In addition, by normalization with BW, we found that ICF%BW and protein%BW were significantly decreased in the LC group compared to those in the M.CON group. In agreement with our data, Figueiredo *et al* recently reported that reduction in ICF, but not fat, occurred

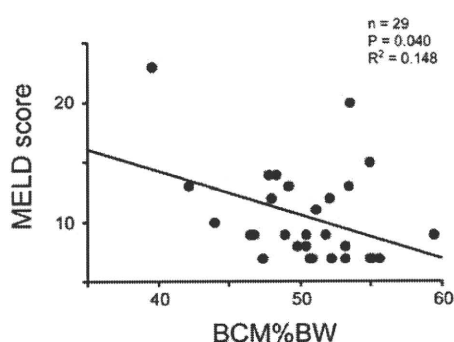


Figure 2. An association between BCM and severity of disease in patients with liver cirrhosis. Subjects was stratified by age because of the age difference in body water compartments (12) (See Materials and methods). An association between BCM and MELD score was analyzed by using the Spearman's correlation coefficient in a bivariate regression model.  $P < 0.05$ , significant difference. MELD, the model for end-stage liver disease; BCM, body cell mass; BW, body weight.

even before fluid retention was noted clinically (22). We did not investigate the mechanisms for decreases in ICF and protein. However, one would think that loss of body protein leads to a decrease in intracellular osmotic pressure and subsequent decrease in ICF, since the rate of endogenous protein degradation is increased in patients with liver cirrhosis (24).

In this study, both groups manifested a characteristic of protein-energy malnutrition. Although we do not have a normal value for BCM for healthy males in Japan, it is believed to be approximately 60% of BW according to the average value for body compartments (20% of ICF%BW plus 40% of protein%BW). In the M.CON group, BCM%BW was <60% of BW which is considered to be lower than that of normal subjects. In the LC group, BCM%BW was also <60% of BW. In addition, BCM was significantly decreased in the LC group compared to the M.CON group, although serum and hematologic nutritional parameters were not significantly different. These findings may indicate that change in body composition is more evident in the LC group than in the M.CON group.

There were no significant differences in nutritional parameters between cirrhotic patients with HCC and cirrhotic patients without HCC. Occurrence of HCC seems to affect the metabolic course of chronic liver disease; however, our data did not show any difference. One would think that HCC does not affect nutritional parameters, because >70% of cirrhotic patients with HCC showed a single (<3-cm) nodule treated with curative therapy. Alternatively, cirrhotic patients without HCC were admitted for preventive therapy of esophageal varices. Thus, cirrhotic patients without HCC also had the complication of LC and therefore, no significant differences in nutritional parameters could be found.

We also showed the significance of BCM in cirrhotic patients. A significant negative correlation between BCM and the MELD score was observed in cirrhotic patients without ascites and/or edema. On the other hand, Muller *et al* reported that there was no significant difference in BCM among patients according to the Child-Pugh classification (25).

Although the reason for this discrepancy is unclear, the explanation may be that BCM was evaluated as the absolute value in the previous study. BW increases with increasing severity in liver disease. Therefore, normalization of BCM by BW could be one of the reasons for this discrepancy. In accordance with our data, Figueiredo *et al* reported that normalized BCM is correlated with the Child-Pugh classification (22). Thus, the estimation of BCM is not only non-invasive but also meaningful. However, we have to be cautious in interpreting BCM values when patients exhibit hyperbilirubinemia. In our analysis for an association between BCM and the MELD score, some patient data did not correspond with the regression line, and hyperbilirubinemia (>6 mg/dl of serum bilirubin levels) was a common characteristic in these patients. The relationship between hyperbilirubinemia and impedance is unclear. However, bilirubin is known to modulate cell-cell contact and results in changes in transepithelial electrical resistance (26). Thus, BCM estimated by eight-polar BIA may not predict prognosis in patients with hyperbilirubinemia.

The limitations of this study included the small sample size, the ratio of cases to controls, and the heterogeneity of the malnourished controls. In order to confirm the significance of BCM in patients with LC, a large-scale multicenter clinical study including healthy individuals is required. In addition, the use of the MELD score may not have been suitable for this study. Since the significance of the correlation between BCM and MELD was poor, the real prognostic relevance of BCM should be evaluated in future studies. Moreover, the number of hospitals that are able to measure BCM is still limited. Changes in BCM are known to correlate with energy and protein intake (27). Thus, food consumption should be assessed cautiously in order to prevent underestimations that may occur by using traditional nutritional assessment measures.

In conclusion, we demonstrated a significant decrease in BCM in patients with liver cirrhosis compared to that in malnourished patients with chronic gastrointestinal diseases. We also showed a significant negative correlation between BCM and MELD score in cirrhotic patients without ascites and/or edema. Thus, BCM may be a useful parameter for assessing malnutrition and severity of disease in patients with liver cirrhosis.

#### Acknowledgements

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## Original Article

# Supplement improves nutrition and stresses caused by examination-associated fasting in patients with liver cirrhosis

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**Aim:** Cirrhotic patients tend to develop malnutrition by fasting, yet the importance of nutritional care during examination-associated fasting has not been investigated. This study aimed to examine the effects of a nutritional supplement on nutrition and stresses caused by examination-associated fasting in cirrhotic patients.

**Methods:** Twenty-nine cirrhotic patients were enrolled in this study. No energy was supplied to patients in the fasting group ( $n = 11$ ) prior to computed tomography or magnetic resonance imaging examination. A supplement of 200 kcal was given to the patients in the supplement group ( $n = 18$ ) prior to computed tomography or magnetic resonance imaging examination. The effect of the supplement on stresses was evaluated by self-rating questionnaire. Changes in biochemical parameters were also investigated before and after computed tomography or magnetic resonance imaging examinations.

**Results:** There were no significant differences in age, sex, body mass index, or liver function tests between the two

groups at the start of the study. In the supplement group, stress scores for physical symptoms (thirst and light-headedness) and mental symptoms (hunger, hypodynamia and fatigue) were significantly lower compared to those in the fasting group. Also in the supplement group, peripheral 3-hydroxybutyric acid and free fatty acids levels were significantly decreased compared to those in the fasting group, to within normal ranges. In addition, a decrease in prothrombin time was significantly inhibited by intake of the supplement.

**Conclusion:** We demonstrated that a nutritional supplement improved nutrition and reduced both the physical and mental stresses associated with examination-associated fasting in cirrhotic patients.

**Key words:** mental stress, physical stress, quality of life, starvation, supplementation

## INTRODUCTION

MALNUTRITION IS FREQUENTLY seen in patients with liver cirrhosis. Malnutrition is associated with clinical complications of cirrhosis and increases mortality.<sup>1,2</sup> Supplemental enteral nutrition improves

nutritional status, liver function, survival, and quality of life (QOL) in cirrhosis patients.<sup>3–11</sup> Thus, nutritional care is an essential element in the management of patients with liver cirrhosis.

The liver has a central role in regulating energy metabolisms. In a fasting state, the liver contributes to about one-half of the body's total caloric requirements by releasing glucose into the blood.<sup>12</sup> In patients with liver cirrhosis, after an overnight fast, hepatic glycogen content is decreased and metabolic profiles are similar to those seen in normal subjects after two to three days fasting.<sup>13</sup> Thus, patients with liver cirrhosis develop a catabolic state of starvation more rapidly than do

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normal subjects and should therefore ensure adequate energy intake and avoid long-term fasting.<sup>1,2,14</sup>

Hepatocellular carcinoma or esophageal varices are major complications in patients with liver cirrhosis.<sup>15–17</sup> For examination and treatment of these complications, abdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), angiography or esophagogastroduodenoscopy (EGD) are commonly used. Nausea and vomiting often occur after the use of ionic high-osmolality contrast media and, thus, patients are fasted before contrast-enhanced examinations. Nonionic low-osmolality contrast media, the current media of choice, are safer than ionic high-osmolality media.<sup>18</sup> Despite this, examination-associated fasting is still used at some institutions and is often required for patients with liver cirrhosis. In addition, frequent examinations are required due to the shortening of hospital stays. However, no study addresses the standard of nutritional care, nor the nutritional status and stresses that exist, for examination-associated fasting in patients with liver cirrhosis. The aim of this study is to examine the effects of supplement on nutrition and stresses caused by examination-associated fasting in patients with liver cirrhosis.

**METHODS**

**Patients**

A TOTAL OF 29 patients with hepatitis C virus (HCV)-related liver cirrhosis (*n* = 25), hepatitis B virus (HBV)-related liver cirrhosis (*n* = 3), or alcoholic liver cirrhosis (*n* = 1) were enrolled in this study during the period from April 2005 to July 2006 at Kurume

University Hospital, Japan. The diagnosis of liver cirrhosis was based on clinical, serological, imaging, and/or histological evidence. All of the patients were hospitalized for the treatment of hepatocellular carcinoma or esophageal varices. Patients with ascites or renal failure were excluded because the effects of nutritional supplements on body composition cannot be precisely evaluated under conditions of abnormal body water distribution. Informed consent for participation in the study was obtained from each patient. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki (1975) and was approved by the Ethics Committee of the Kurume University School of Medicine, Japan.

**Study design**

We conducted a randomized controlled trial on 29 patients with liver cirrhosis. Enrolled patients were randomly assigned to the fasting group or the supplement group. The time schedule of examination and supplement administration are summarized in Figure 1. In both groups, contrast-enhanced CT or contrast-enhanced MRI was conducted between 10.00–11.30 hours. Blood tests, measurement of body weight and body composition analysis were performed a day before examination and after CT or MRI examination. Urine was collected between 06:00–10:00 hours for both groups. There was no energy supply between supper and lunch in the fasting group (*n* = 11), while 200 kcal of a nutritional supplement (Calorie Mate JELLY; Otsuka Pharmaceutical, Japan) was given to the patients in the supplement group (*n* = 18), between 06:00–06:10 hours. The composition of the supplement is shown in Table 1. The effects of the supplement on the CT or MRI

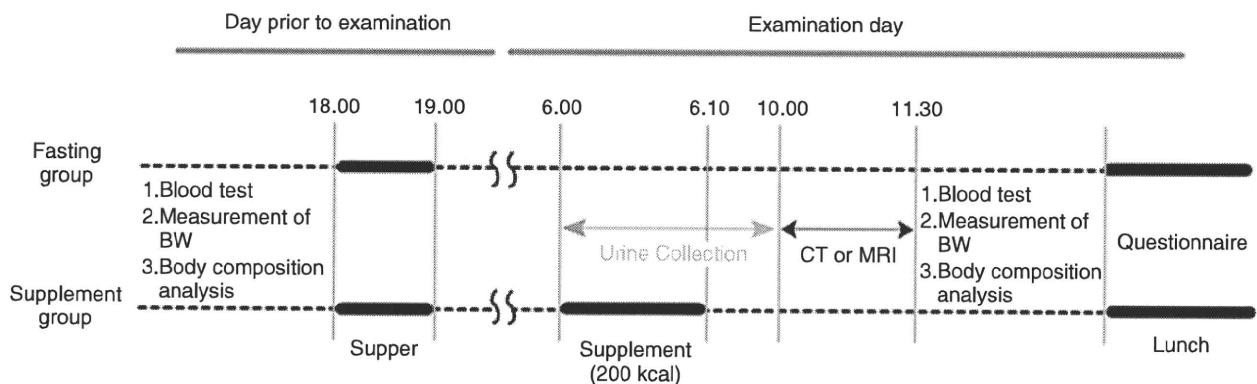


Figure 1 Scheme of time schedule for supplement administration and examination of patients. BW, body weight; CT, computed tomography; MRI, magnetic resonance imaging. (—) Fasting duration; (—) feeding duration.

**Table 1** The composition of supplement (Calorie Mate JELLY; Otsuka Pharmaceutical, Japan)

Component	Content
Serving size (g)	215
Energy (kcal)	200
Protein (g)	7.6
BCAAs	1.7
Fat (g)	4.4
Carbohydrate (g)	32.5
Dietary fiber (g)	2
Sodium (mg)	30
Potassium (mg)	60
Calcium (mg)	200
Magnesium (mg)	50
Phosphorus (mg)	218
Vitamin A ( $\mu\text{g}$ )	225
Vitamin B1 (mg)	0.5
Vitamin B2 (mg)	0.6
Vitamin B6 (mg)	0.5
Vitamin B12 ( $\mu\text{g}$ )	1
Niacin (mg)	5.5
Pantothenic acid (mg)	2.8
Folate ( $\mu\text{g}$ )	100
Vitamin D ( $\mu\text{g}$ )	2.5
Vitamin E (mg)	4

BCAAs, branched-chain amino acids.

imaging diagnoses were evaluated by radiologists blinded to which group the patients belonged.

### Contrast medium for CT or MRI examination

All patients underwent contrast-enhanced CT or MRI examinations using Iopamidol (Bayer Yakuhin, Japan), Iohexol (Bayer Yakuhin), or Iotrolan (Daiichi Sankyo, Japan).

### Effects of supplement on mental and physical stresses

Physical symptoms (thirst, light-headedness, nausea, headache, palpitations, cold sweat) and mental symptoms (hunger, hypodynamia, fatigue, poor thinking, poor concentration, irritability) were evaluated by self-rating questionnaire according to the following scale: 1 = none; 2 = mild; 3 = moderate; and 4 = severe.

### Effects of supplement on biochemical parameters, body weight and composition

Platelet count, prothrombin time, serum albumin, total bilirubin, total cholesterol, creatinine level, osmolality, blood glucose level, blood urea nitrogen concentration

and urine specific gravity were measured using standard clinical methods (Department of Clinical Laboratory, Kurume University Hospital, Japan). Body weight and composition were measured using an eight-polar direct segmental multifrequency-bioelectrical impedance analyzer (DSM-BIA; InBody 3.2, Biospace, Japan). The changes in body composition were assessed by the differences between values obtained a day before and a day after CT or MRI examination and are expressed as  $\Delta$ body composition.

### Statistical analysis

All data are expressed as mean  $\pm$  SE. Differences between the two groups were analyzed using the Mann-Whitney *U*-test. *P* values < 0.05 were considered significant.

## RESULTS

### Patient characteristics

THE CHARACTERISTICS OF all patients are summarized in Table 2. There were no significant differences in etiology of cirrhosis, age, sex, body mass index and liver function tests between patients in the fasting group and those in the supplement group (Table 2). Fasting duration was significantly shortened, by about 4 h, with the administration of supplement (Table 2).

### Interference of supplement on CT or MRI imaging

There was no evidence of retention of the supplement in the gut or the contraction of gallbladder in CT or MRI imaging (Fig. 2A,B). In addition, the intake of the supplement did not induce vomiting and there was no interference with the diagnostic CT or MRI imaging by intake of the supplement (Table 2).

### Effects of supplement on mental or physical symptoms

Among physical symptoms, stress scores for thirst and light-headedness were significantly lower in the supplement group compared to those in the fasting group (Table 3). Among mental symptoms, stress scores for hunger, hypodynamia and fatigue were significantly lower in the supplement group compared to those in the fasting group (Table 3).

### Effects of supplement on biochemical parameters and body weight and compositions

Changes in body weight and body compositions were expressed by the difference between values obtained a

Table 2 Characteristics of all patients

	Normal range	Fasting group (n = 11)	Supplement group (n = 28)	P value
HCV:HBV:Alcohol	–	9:2:0	16:1:1	0.43
Age (years)	–	59.9 ± 3.4	66.6 ± 2.5	0.13
Sex (M:F)	–	6:5	12:6	0.51
BMI	–	22.7 ± 0.8	21.2 ± 0.4	0.13
Albumin (g/dL)	4.0–5.0	3.34 ± 0.15	3.42 ± 0.12	0.71
Total bilirubin (mg/dL)	0.61–1.04	1.85 ± 0.35	1.41 ± 0.26	0.11
Prothrombin time (%)	4.0–5.0	70.5 ± 4.9	79.2 ± 2.7	0.08
Total cholesterol (mg/dL)	150–219	136 ± 36	145 ± 29	0.56
Platelet count (/μL)	70–139	8.6 ± 0.9	11.3 ± 1.7	0.33
Fasting duration (h)	–	13.8 ± 0.3	4.7 ± 0.1	<0.0001
Number of patients that vomited	–	0	0	>0.99
Interference of supplement on imaging	–	NA	0	–

Data expressed as mean ± SE. Differences between the two groups were analyzed using the Mann–Whitney *U*-test. BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not applicable.

day before and after examination. There was no significant difference noted in body weight changes between the fasting group and the supplement group (Table 4). Similarly, changes in body composition showed no significant differences between the fasting group and the supplement group (Table 4). Intake of the supplement did not affect levels of blood glucose, plasma osmolality, blood urea nitrogen, and serum creatinine (Table 4). No significant changes occurred in urine volume and urine specific gravity when comparing the two groups (Table 4).

### Effects of supplement on serum 3-hydroxybutyric acid, plasma free fatty acids levels and prothrombin time

Intake of the supplement resulted in significant decreases in serum 3-hydroxybutyric acid and plasma free fatty acids levels. Further, these levels reached to within in normal ranges (Fig. 3A,B). Decreases in prothrombin time were significantly inhibited by the intake of the supplement compared to that in the fasting group after examination (Fig. 3C).

## DISCUSSION

**I**N THIS STUDY, we first demonstrated that the nutritional supplement improved malnutrition and both physical symptoms and mental stresses caused by fasting before examinations in patients with liver cirrhosis.

Nausea and vomiting occur frequently after the use of ionic high-osmolality contrast media and, therefore, patients are fasted before contrast-enhanced examina-

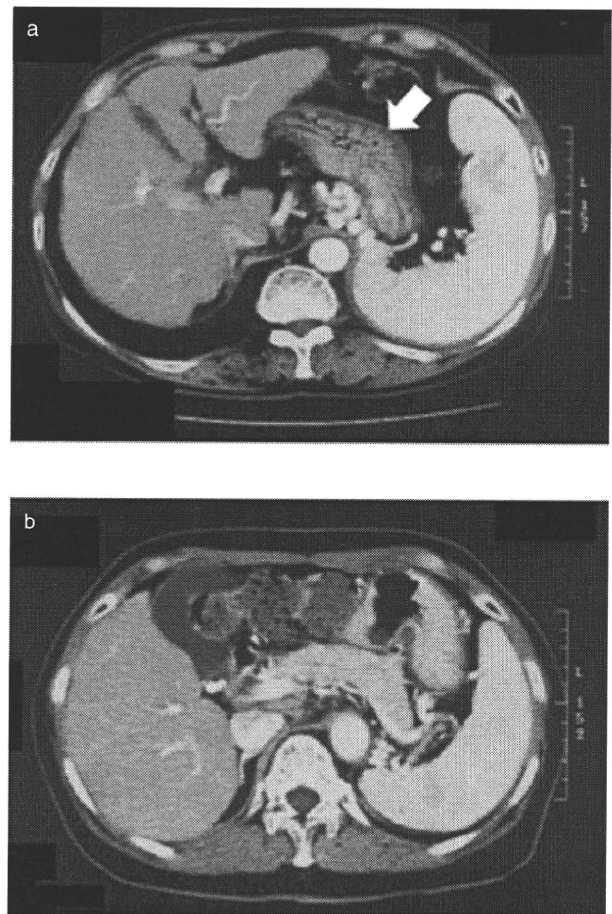


Figure 2 Representative CT images from the supplement group. No retention of the supplement in the (a) gut was detected, or contraction of the (b) gallbladder in CT imaging. Arrows indicate stomach.

**Table 3** Effects of the supplement on physical and mental symptoms as evaluated by a self-rating questionnaire (1 = none; 2 = mild, 3 = moderate, 4 = severe)

	Fasting group	Supplement group	P value
Physical symptoms			
Thirst	2.8 ± 0.4	1.6 ± 0.2	0.01
Light-headedness	2.0 ± 0.4	1.2 ± 0.1	0.04
Nausea	1.5 ± 0.3	1.0 ± 0.0	0.07
Headache	1.3 ± 0.1	1.1 ± 0.1	0.11
Palpitation	1.1 ± 0.1	1.1 ± 0.1	0.72
Cold sweat	1.0 ± 0.0	1.1 ± 0.1	0.43
Mental symptoms			
Hunger	2.6 ± 0.4	1.3 ± 0.1	0.003
Hypodynamia	2.1 ± 0.3	1.2 ± 0.1	0.01
Fatigue	2.2 ± 0.4	1.2 ± 0.1	0.01
Poor thinking	1.7 ± 0.3	1.2 ± 0.1	0.25
Poor concentration	1.7 ± 0.3	1.3 ± 0.1	0.29
Irritability	1.5 ± 0.2	1.2 ± 0.1	0.45

Data expressed as mean ± SE. Differences between the two groups were analyzed using the Mann–Whitney *U*-test.

tions. However, nonionic low-osmolality contrast media is safer than ionic high-osmolality media and is the media of choice today.<sup>18</sup> Although the supplement was given approximately 4 h before examination, none of the patients experienced nausea or vomiting. Further, there was no interference with diagnostic imaging. Thus, the intake of the supplement had no adverse effects on the examination and diagnostic imaging in this study.

Although nutritional supplements vary in form and shape, we chose a jelly-type supplement for this study. Sensory-specific satiety has an important influence on QOL.<sup>19,20</sup> In particular, texture-specific satiety has a sig-

nificant effect.<sup>21</sup> The decision to use a jelly-type supplement was based on the fact that the texture of jelly is more like solid food. In addition, high viscosity formula-diet accelerates gastric emptying, resulting in prevention of gastro-oesophageal reflux and aspiration pneumonia.<sup>22</sup> We also selected a branched-chain amino acids (BCAAs)-rich supplement because serum BCAAs levels are decreased in patients with liver cirrhosis and treatment with BCAAs is known to improve nutritional status and QOL.<sup>9,23</sup>

With intake of the supplement, physical symptoms such as thirst and light-headedness improved signifi-

**Table 4** Effects of supplement on biochemical parameters, body weight and composition

	Fasting group	Supplement group	P value
Biochemical parameters			
Blood glucose (mg/dL)	106.5 ± 6.4	105.1 ± 9.4	0.33
Plasma osmolality (mOsm/L)	285.5 ± 1.7	286.0 ± 1.0	0.77
Blood urea nitrogen (mg/dL)	16.9 ± 2.1	17.9 ± 2.3	0.72
Creatinine (mg/dL)	0.74 ± 0.05	0.90 ± 0.08	0.30
Urine volume (mL)	190 ± 41	200 ± 33	0.93
Urine specific gravity	1.023 ± 0.06	1.016 ± 0.02	0.50
ΔBody weight (kg)	-0.95 ± 0.34	-0.80 ± 0.37	0.70
Body composition			
ΔIntracellular fluid (kg)	-0.26 ± 0.28	-0.57 ± 0.07	0.59
ΔExtracellular fluid (kg)	-0.68 ± 0.14	-0.43 ± 0.07	0.14
ΔProtein (kg)	-0.11 ± 0.12	-0.24 ± 0.03	0.59
ΔMineral (kg)	-0.26 ± 0.13	-0.09 ± 0.14	0.07
ΔFat (kg)	-0.34 ± 0.37	-0.54 ± 0.17	0.44

Data are expressed as mean ± SE. Differences between the two groups were analyzed using the Mann–Whitney *U*-test.



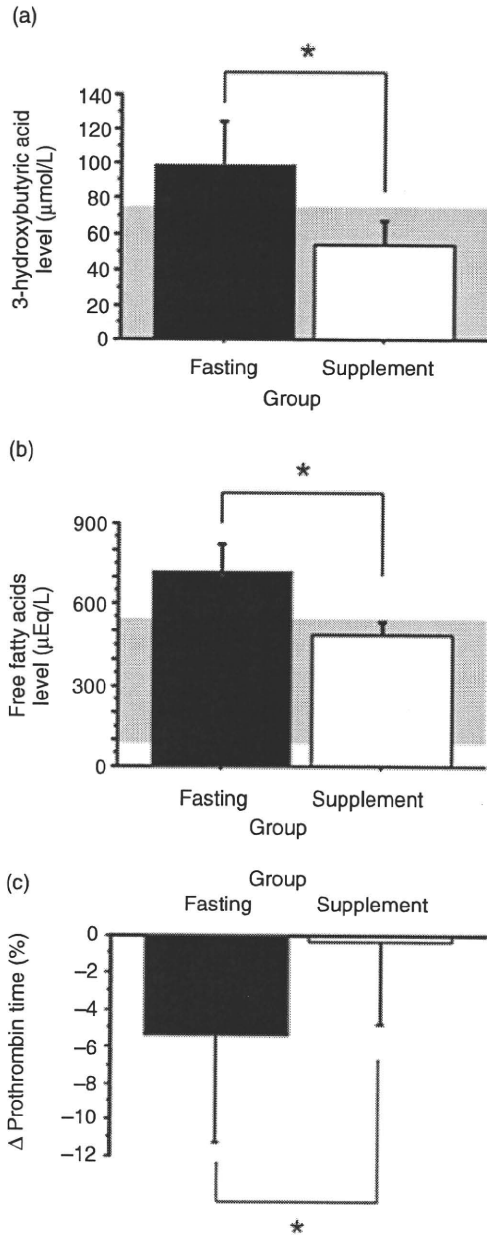


Figure 3 Effects of the supplement on serum (a) 3-hydroxybutyric acid level, (b) plasma free fatty acids level, and changes in (c) prothrombin time. Shaded regions in (a-b) indicate the normal ranges for serum 3-hydroxybutyric acid and plasma free fatty acids, respectively. Values are expressed as mean ± SE. Differences between the two groups were analyzed using the Mann-Whitney *U*-test. \**P* < 0.05.

cantly. Biochemical examination showed that blood glucose concentration, plasma osmolality and urine specific gravity were all within normal ranges, even in the fasting group. In addition, there were no significant

changes in these parameters in the supplement group. Similarly, bioelectrical impedance analysis showed no changes in body weight or composition. Thus, changes in glucose levels or body water distribution do not seem to be the main causative factors for the improvement of thirst and light-headedness. Long-term fasting itself causes stress due to a dissatisfied demand for food and reduction of such stress is known to improve physical symptoms.<sup>24,25</sup> Thus, relief from long-term examination-associated fasting might be responsible for the stress reduction and subsequent improvement of physical symptoms.

Patients with liver cirrhosis develop a catabolic state of starvation more rapidly than do normal subjects. Approximately 80% of the daily non-protein caloric requirement is supplied from fat even after overnight fasting.<sup>13</sup> Peripheral 3-hydroxybutyric acid and free fatty acids are metabolites derived from fat and are used as indicators of starvation. In this study, levels of peripheral 3-hydroxybutyric acid and free fatty acids were significantly higher in the fasting group. Peripheral 3-hydroxybutyric acid stimulates appetite and elevated plasma free fatty acids levels cause hypodynamia and fatigue through increased serotonin release in the brain.<sup>26,27</sup> In the present study, serum 3-hydroxybutyric acid and plasma free fatty acids levels were significantly increased in patients with examination-associated fasting compare to those in age-, BMI-, and liver function tests-matched patients with only overnight fasting ( $51.6 \pm 10.5$  vs  $99.4 \pm 25.0$  μmol/L, *P* < 0.04;  $436 \pm 48$  vs  $686 \pm 93$  μEq/L, *P* < 0.03), indicating the importance of supplementation for the examination-associated fasting. With the intake of the supplement, both 3-hydroxybutyric acid and plasma free fatty acids levels were reduced to within normal range, and hunger, hypodynamia and fatigue were significantly improved. Although it is not clear why the supplement improves mental symptoms, it is possible that glucose supplementation changes the fuel source from fat to glucose and results in a decrease of 3-hydroxybutyric acid and plasma free fatty acids levels, leading to improvement in mental symptoms. Alternatively, hunger is also regulated by gut hormones and food intake stimulates the satiety center through regulation of gut hormones such as ghrelin, polypeptide YY, and glucagon-like peptide-1.<sup>28,29</sup> Thus, intake of the supplement might improve mental symptoms through regulation of gut hormones.

A decrease in prothrombin time was significantly inhibited by intake of the supplement. The half-life of prothrombin is several hours and prothrombin is a rapid turnover protein, used as not only as a prognostic

parameter<sup>30,31</sup> but also as a nutritional parameter.<sup>32</sup> Protein turnover is increased in patients with liver cirrhosis and treatment with glucose is reported to reduce the protein turnover rate and improve the nitrogen balance.<sup>33</sup> The supplement used in this study contains 33.0 g of glucose. Thus, glucose supplementation might be responsible for improved nitrogen balance, leading to a subsequent increase in prothrombin time. In addition, it has been shown that treatment with BCAAs improves nutritional status in patients with liver cirrhosis.<sup>9,23</sup> The supplement used in this study contains 1.7 g of BCAAs, BCAAs might up-regulate the mammalian target of rapamycin, which is a key molecule in protein synthesis.<sup>34</sup>

There are several limitations in this study. First, nutritional validity of this supplement for outcome, survival rate, and long-term QOL is unclear in patients with liver cirrhosis. Second, the supplement was administered for only CT or MRI examination. In order to improve long-term nutritional status, outcome and QOL in liver cirrhosis a supplement verified by scientific research and supplementation should be given in other examinations such as blood test, US, EGD, angiography. Third, even in the supplement group there was an approximately 1 kg decrease in body weight within a day, mainly attributable to the loss of extracellular fluid. Intake of the supplement did not prevent significant changes in body weight or composition. Hypermetabolism is a characteristic of patients with liver cirrhosis,<sup>35</sup> and these patients should ensure energy intake is adequate.<sup>1,2</sup> The principal etiology for liver disease among the patients in this study was HCV infection. A decrease in hepatic glycogen storage and malnutrition are more severe in HCV-related chronic liver disease than in other hepato-biliary disorders.<sup>36,37</sup> A nutritional supplement of 200 kcal may not be a sufficient energy source to prevent loss of body weight in patients with HCV-related liver cirrhosis.

We demonstrate that a nutritional supplement improves nutrition and both physical and mental stresses caused by fasting before contrast-enhanced CT or MRI examination, without inducing any adverse effects in patients with liver cirrhosis.

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