

Original Article

Effect of β -hydroxy- β -methylbutyrate on protein metabolism in bed-ridden elderly receiving tube feeding

Lan-Chi Hsieh MS¹, Chau-Jen Chow PhD², Wen-Chou Chang MS³, Tsung-Han Liu MS⁴, Chen-Kang Chang PhD⁵

¹Department of Dietetics, Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan, ROC

²Department of Seafood Science, National Kaohsiung Marine University, Kaohsiung, Taiwan, ROC

³Medical Laboratory, Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan, ROC

⁴Doctoral Program in Physical Education, Taipei Physical Education College, Taipei, Taiwan, ROC

⁵Sport Science Research Center, National Taiwan College of Physical Education, Taichung, Taiwan, ROC

Malnutrition and muscle loss are common in bed-ridden elderly nursing home residents. Supplementation of β -hydroxy- β -methylbutyrate (HMB) has been shown to prevent muscle loss in several catabolic conditions. The aim of this study was to investigate the effect of HMB supplementation on body composition and protein metabolism in bed-ridden elderly nursing home residents receiving tube feeding. The subjects were randomly assigned to HMB (n=39, 2 g/d) or control group (n=40). Anthropometry measurements, blood sampling, and 24-hr urine collection were performed on the day before and 14 days after the start of the study. A subgroup of subjects (HMB: n=19, control: n=20) continued the study for another 14 days. Changes in body weight and BMI were not significantly different between the groups after 14 or 28 days after controlling for baseline BMI. Blood urea nitrogen significantly decreased in the HMB group, while it remained unchanged in the control group after 14 days. Urinary urea nitrogen excretion significantly decreased in the HMB group, while it showed a trend of increase in the control group after 14 and 28 days, respectively. Changes in blood urea nitrogen and urinary urea nitrogen excretion were significantly different between the groups after controlling for baseline BMI. This study suggested that HMB supplementation for 2-4 weeks could reduce muscle breakdown in bed-ridden elderly nursing home residents receiving tube feeding.

Key Words: muscle wasting, proteolysis, nursing home, malnutrition, urinary urea nitrogen excretion

INTRODUCTION

With the growing elderly population in many countries around the world, the need for long-term care in nursing homes has increased substantially in recent years. However, nutritional problems such as weight loss and concomitant protein energy undernutrition in frail nursing home residents are common.¹ It has been estimated that 25-60% of geriatric patients in long-term care hospitals and nursing homes have shown evidence of malnutrition in western countries.²⁻⁴ A study in Taiwan also revealed that more than 40% elderly nursing home residents had at least 2 indicators of malnutrition.⁵ Insufficient consumption of energy and protein usually results from complex interactions of multiple disease states and medication side effects.^{6,7} The loss in muscle mass and strength may increase the risks of falling, morbidity, and mortality.⁸ The Geriatric Anorexia Nutrition (GAIN) registry showed that weight loss during a 6-month period was associated with nearly a two-fold increase in the likelihood of dying in nursing home residents.⁹ The similar risk of 1-year mortality in nursing home residents with weight loss has also been reported in a retrospective cohort study.¹⁰

Many long-term bed-ridden patients require tube feeding to supplement their oral intake because of swallowing and chewing disorders, anorexia, dementia, or other

medical situations. However, long-term tube feeding did not improve nutritional status in nursing home residents and may produce additional strain on these frail subjects.¹¹ The bed-ridden elderly subjects in nursing homes showed a higher incidence of malnutrition after long-term tube feeding compared to their orally-fed counterparts, even though energy and protein consumption was presumably adequate.¹² Therefore, the 1-year mortality rate was higher in tube-fed elderly nursing home residents compared to their orally-fed counterparts.¹³

Supplementation of β -hydroxy- β -methylbutyrate (HMB) along with resistance training has been shown to be effective in augmenting the gain in lean body mass in young and older subjects.¹⁴⁻¹⁶ HMB has also been suggested to prevent muscle loss in patients with several catabolic conditions. We have shown that 7 days of HMB supplementation had anti-catabolic effects and improved

Corresponding Author: Dr Chen-Kang Chang, Sport Science Research Center, National Taiwan College of Physical Education, 16, Sec 1, Shuan-Shih RD, Taichung, 404, Taiwan, ROC. Tel: +886 (4) 22213108 ext 2210; Fax: +886 (4) 22256937 Email: wspahn@seed.net.tw

Manuscript received 24 September 2009. Initial review completed 11 January 2010. Revision accepted 22 February 2010.

pulmonary function in chronic obstructive pulmonary disease patients in an intensive care unit setting.¹⁷ HMB supplementation also improved nitrogen balance in critically injured subjects.¹⁸ In addition, HMB in combination with arginine and glutamine can also reduce muscle loss in patients with auto immunodeficiency syndrome or cancer cachexia.¹⁹⁻²¹ Recently, it has been reported that long-term supplementation of HMB, arginine, and lysine could increase lean body mass by increasing protein synthesis and reducing protein turnover in elderly subjects living in senior citizen centers and nursing homes.^{22,23} The elderly subjects in these 2 studies were moderately functional, and capable of completing the "Get-up-and Go" test.^{22,23} In addition, the role of HMB is not clear in these studies as the amino acids used may also provide the anti-catabolic effect. As a result, the effect of supplementation of HMB alone on protein metabolism in frail elderly subjects is still unclear. The physical inactivity in bed-ridden elderly subjects, in combination with aging and various disease states, would increase muscle loss.^{24,25} The requirement of long-term tube feeding further complicated the protein balance in these subjects. Therefore, the aims of this study were to investigate the effect of HMB supplementation for 14-28 days on body composition and protein metabolism in bed-ridden elderly nursing home residents receiving tube feeding.

MATERIALS AND METHODS

Subjects

A total of 84 bed-ridden elderly subjects with nasogastric feeding tubes were recruited from 3 nursing homes in Kaohsiung, Taiwan. All subjects had been bed-ridden and had received tube feeding exclusively for at least 6 months. The subjects had been living in the same facility for at least 15 days, and were randomly assigned to either the HMB or the control group. Five subjects (3 in HMB group, 2 in control group) dropped out because of transfer to other facility or development of scabs. The HMB group (n=39, M/F: 18/21) received HMB (calcium salt, Musashi, Victoria, Australia) 2 g/d, in 2 equal doses daily through a nasogastric feeding tube after lunch and dinner by nurses. The control group (n=40, M/F: 25/15) maintained their regular dietary patterns. This study was approved by the review board of Kaohsiung Municipal United Hospital. All subjects or their legal guardians gave informed consents after the procedure and risks of this study was clearly explained.

Experimental procedure

On the day before and 14 days after the start of the study; anthropometry measurements, blood sampling and 24-hr urine collection were performed in all 79 subjects. Blood samples were collected in the early morning after an overnight fast. A subgroup of subjects (HMB group: n=19, M/F: 7/12; control group: n=20, M/F: 13/7) continued the study for another 14 days. The same measurements were performed again on day 29.

Energy requirement

The basal energy requirement for each subject was estimated using the Harris-Benedict equation.²⁶ The daily energy expenditure was calculated by basal energy ex-

penditure times a stress factor of 1.2 and an activity factor of 1.0.²⁷ All subjects were fed mixed commercial formulas in combination with self-prepared full liquid food. The daily diet contained approximately 60% energy from carbohydrate, 15% from protein, and 25% from fat. The daily intake was recorded by nurses.

Anthropometric measurements and biochemical analyses

Body weight was measured with a bed scale. Body height was estimated from knee height with the following equations developed based on a Taiwanese population.²⁸

$$\text{Body height for men (cm)} = 85.1 + 1.73 \times \text{knee height (cm)} - 0.11 \times \text{age (year)}$$

$$\text{Body height for women (cm)} = 91.45 + 1.53 \times \text{knee height (cm)} - 0.16 \times \text{age (year)}$$

Circumferences in thorax, waist, hip, calf and mid-arm and tricep skinfolds were measured by the same experienced dietitian. Mid-arm muscle circumference was calculated from the mid-arm circumference and tricep skinfold.²⁹

Serum was used for the analyses of lipid and biochemical parameters. Blood and urine samples were analyzed immediately after collection in the clinical laboratory, Kaohsiung Municipal United Hospital with standard procedures.

Statistical analysis

All data was expressed as mean±SD. The change percentage of the variables in each individual was calculated as (after-baseline)×100%/baseline. The magnitude of change of the variables was then calculated from the change percentage of each individual. To avoid the potential effect of baseline nutritional status on the measured parameters, the magnitudes of change of the 2 groups were analyzed by regression analysis, controlling for baseline BMI. Variables before and after treatment within each group were compared by paired t-tests. All analysis was performed using SPSS 11.0 for Windows (Chicago, IL, USA). A *p*-value <0.05 was considered significant.

RESULTS

The basic characteristics of the subjects in the control and HMB groups are shown in Table 1. The control group in the 14-day and 28-day study had significantly higher estimated energy requirement and energy intake than the HMB group, mostly due to higher body weight (Table 2). However, the ratio of energy intake/estimated energy requirement was similar between the 2 groups in the 2 studies.

Unexpectedly, the baseline body weight and BMI were significantly lower in HMB group (Table 2). Therefore, the magnitudes of change in anthropometric, hematological and biochemical parameters between the 2 groups were compared after controlling for baseline BMI. Changes in body weight and BMI were not significant after 14 days in the 2 groups. Waist circumference showed an increasing trend in the HMB group, while it significantly decreased in control group. The magnitude of change in waist circumference was significantly higher in the HMB group (*p*=0.026). Table 3 presents the hematological and biochemical parameters before and after the 14-day study. The HMB group showed a decreasing trend in red blood

Table 1. Subject characteristics in the HMB and control groups in the 14-day and 28-day study (mean \pm SD)

	14 Days		28 Days	
	HMB (M/F: 18/21)	Control (M/F: 25/15)	HMB (M/F: 7/12)	Control (M/F: 13/7)
Age (yr)	72.5 \pm 11.8	70.8 \pm 9.8	71.9 \pm 10.6	71.8 \pm 9.3
Height (cm)	153.9 \pm 7.7	155.8 \pm 8.1	152.5 \pm 5.8	155.5 \pm 7.7
Knee length (cm)	46.3 \pm 3.1	46.5 \pm 3.3	45.5 \pm 2.2	46.4 \pm 3.0
Energy requirement (kcal/d)	1484 \pm 138	1483 \pm 184	1462 \pm 61*	1548 \pm 137
Energy intake (kcal/d)	1484 \pm 254*	1597 \pm 231	1282 \pm 113*	1424 \pm 172
Intake/requirement (%)	100 \pm 18.8	110 \pm 25.6	88 \pm 8.2	93 \pm 13.1

HMB, β -hydroxy- β -methylbutyrate* $p < 0.05$, significantly different between the HMB and control groups in the same study.**Table 2.** Body composition in the HMB and control groups before and after the 14-day study (mean \pm SD)

	HMB (M/F: 18/21)			Control (M/F: 25/15)		
	Before	After	Change (%)	Before	After	Change (%)
Weight (kg)	45.8 \pm 11.8 [‡]	46.4 \pm 11.5	1.41 \pm 3.17	52.9 \pm 10.5	52.7 \pm 9.8	-0.08 \pm 3.22
Body mass index (kg/m ²)	19.2 \pm 4.0 [‡]	19.4 \pm 4.0	1.20 \pm 3.76	21.6 \pm 3.1	21.6 \pm 2.9	0.08 \pm 2.72
Thorax (cm)	82.3 \pm 8.2 [‡]	82.9 \pm 7.8	0.74 \pm 3.50	86.8 \pm 6.3	86.3 \pm 6.1	-0.53 \pm 3.28
Waist (cm)	73.8 \pm 10.1 [‡]	74.4 \pm 9.6	0.97 \pm 4.46*	81.2 \pm 8.3	79.5 \pm 7.5 [†]	-1.89 \pm 4.45
Hip (cm)	80.4 \pm 8.0 [‡]	81.2 \pm 8.2	1.06 \pm 3.88	84.3 \pm 7.3	83.5 \pm 6.8	-0.80 \pm 5.29
Waist/Hip	0.92 \pm 0.06 [‡]	0.92 \pm 0.06	-0.24 \pm 5.40	0.99 \pm 0.19	0.95 \pm 0.04	-2.11 \pm 9.99
Triceps skinfold (cm)	0.43 \pm 0.13	0.45 \pm 0.13	8 \pm 26	0.50 \pm 0.25	0.51 \pm 0.28	27 \pm 129
Mid-arm circumference (cm)	22.3 \pm 3.0 [‡]	22.3 \pm 3.2	0.19 \pm 5.24	24.3 \pm 2.6	23.6 \pm 2.4	-2.79 \pm 5.77
Mid-arm muscle circumference (cm)	20.9 \pm 2.8 [‡]	20.9 \pm 3.0	0.05 \pm 5.55	22.8 \pm 2.5	22.0 \pm 2.3	-3.20 \pm 7.46
Calf circumference (cm)	23.3 \pm 3.8 [‡]	23.7 \pm 3.8	1.85 \pm 4.81	26.8 \pm 3.9	26.5 \pm 3.4	-0.52 \pm 4.12

HMB, β -hydroxy- β -methylbutyrate* $p < 0.05$, significantly different between the HMB and control groups after controlling for BMI at the baseline.† $p < 0.05$, significantly different before and after the study within the same group.‡ $p < 0.05$, significantly different between the HMB and control groups before the study.

cell count and hemoglobin, while the control group showed an increasing trend. The magnitudes of change in red blood cell count and hemoglobin concentrations were significantly different between the 2 groups ($p=0.022$ and 0.027 , respectively). Blood urea nitrogen (BUN) significantly decreased in the HMB group while it remained unchanged in the control group. The change in BUN was significantly different between the 2 groups ($p = 0.005$). The change in 24-hr urinary urea nitrogen (UUN) excretion was also significantly different between the 2 groups ($p=0.002$). UUN excretion significantly decreased by an average of 12.46% in the HMB group, while it showed an increasing trend by an average of 29.72% in the control group (Figure 1).

The results after HMB supplementation for 28 days were similar to those of the 14-day study. Body weight and BMI showed small but significant increases after 28 days in the HMB group but were unchanged in the control group. However, the magnitudes of change in body weight and BMI were not significantly different between

the 2 groups (Table 4). Waist, hip and calf circumference significantly increased after 28 days in the HMB group. Nevertheless, only the changes in waist and calf circumference were significantly different between the 2 groups ($p=0.043$ and 0.037 , respectively). Table 5 presents the hematological and biochemical parameters before and after the 28-day study. The increase in plasma uric acid concentration was significantly lower in the HMB group ($p=0.019$). The change in 24-hr UUN excretion was also significantly different between the 2 groups ($p < 0.001$, Figure 2). UUN excretion significantly decreased by an average of 30.69% in the HMB group, while it showed an increasing trend by an average of 15.70% in the control group after 28 days.

DISCUSSION

The significant decrease in BUN and UUN excretion in the HMB group suggested that supplementation of HMB for 2-4 weeks may decrease protein breakdown in elderly nursing home residents receiving tube feeding. However,

Table 3. Hematological and biochemical parameters in the HMB and control groups before and after the 14-day study (mean \pm SD)

	HMB (M/F: 18/21)			Control (M/F: 25/15)		
	Before	After	Change (%)	Before	After	Change (%)
Hematology						
White blood cell ($10^3/\mu\text{L}$)	8.01 \pm 2.32	7.79 \pm 2.96	-0.5 \pm 27.7	7.44 \pm 2.64	8.06 \pm 3.24	11.5 \pm 28.9
Red blood cell ($10^6/\mu\text{L}$)	3.86 \pm 0.51	3.83 \pm 0.59	-0.86 \pm 8.55*	4.18 \pm 0.63	4.30 \pm 0.62 [†]	3.37 \pm 8.55
Hemoglobin (g/L)	118 \pm 19	117 \pm 21	-0.85 \pm 8.73*	129 \pm 22	133 \pm 21	3.51 \pm 9.68
Serum lipids						
Triglyceride (mM)	1.27 \pm 0.59	1.32 \pm 0.86	6.8 \pm 43.5	1.46 \pm 0.70	1.52 \pm 0.74	7.2 \pm 28.7
Total cholesterol (mM)	3.94 \pm 1.04	4.27 \pm 1.19	10.5 \pm 27.0	4.21 \pm 1.09	4.67 \pm 1.01	29.8 \pm 130.9
HDL-cholesterol (mM)	1.25 \pm 0.33	1.24 \pm 0.40	0.3 \pm 25.6	1.11 \pm 0.41	1.06 \pm 0.40	-2.9 \pm 22.3
LDL-cholesterol (mM)	2.20 \pm 0.89	2.46 \pm 0.99	16.3 \pm 37.8	2.55 \pm 0.73	2.92 \pm 0.83	16.7 \pm 24.2
Serum biochemistry						
Total protein (g/L)	69.5 \pm 5.9	68.4 \pm 7.0	-1.39 \pm 7.27	70.3 \pm 7.7	70.2 \pm 7.1	0.30 \pm 9.20
Albumin (g/L)	34.2 \pm 4.1	34.4 \pm 4.9	0.7 \pm 10.3	36.8 \pm 5.2	38.0 \pm 5.2	4.1 \pm 14.1
Blood urea nitrogen (mM)	5.60 \pm 1.98	5.26 \pm 2.06 [†]	-6.0 \pm 17.7*	5.25 \pm 2.02	5.72 \pm 2.82	7.3 \pm 24.6
Creatinine (μM)	69.0 \pm 23.0	71.6 \pm 26.5	3.7 \pm 21.3	80.4 \pm 29.2	79.6 \pm 26.5	0.2 \pm 11.8
Uric acid (μM)	231 \pm 88	249 \pm 92	10.2 \pm 27.7	287 \pm 110	305 \pm 116	13.8 \pm 66.9
Glucose (mM)	5.81 \pm 1.22	6.55 \pm 2.27	12.9 \pm 27.2	6.14 \pm 2.26	6.15 \pm 2.01	6.1 \pm 33.1
GOT (U/L)	28.2 \pm 9.6	25.9 \pm 9.7	-3.2 \pm 36.6	30.2 \pm 17.6	31.3 \pm 16.7	11.1 \pm 48.1
GPT (U/L)	33.3 \pm 16.5	27.9 \pm 11.6	-8.6 \pm 30.5	32.1 \pm 17.1	29.5 \pm 14.3	-4.4 \pm 29.3

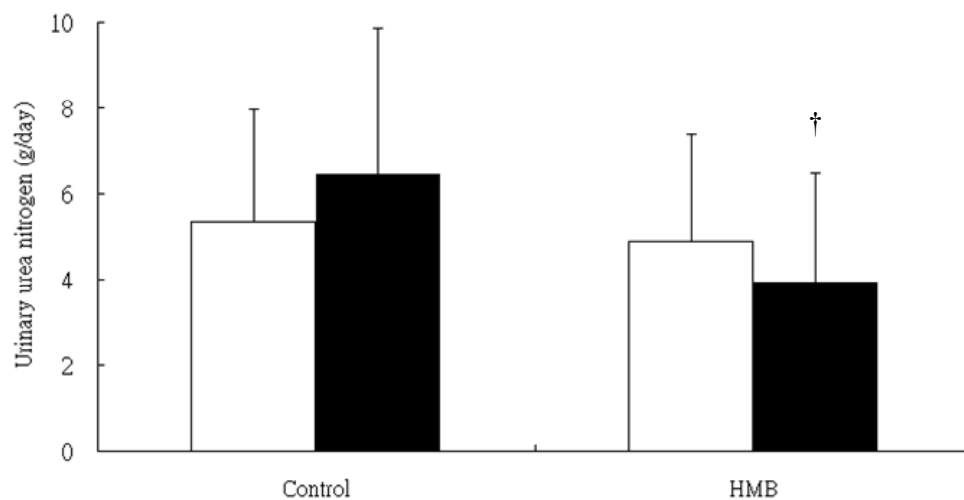
HMB, β -hydroxy- β -methylbutyrate* $p < 0.05$, significantly different between the HMB and control groups after controlling for BMI at the baseline.[†] $p < 0.05$, significantly different before and after the study within the same group.**Figure 1.** 24-hr urinary urea nitrogen excretion in the HMB and control groups before (□) and after (■) the 14-day study (mean \pm SD), [†] $p < 0.05$, significantly different before and after the study within the same group. HMB, β -hydroxy- β -methylbutyrate

Table 4. Body composition in the HMB and control groups before and after the 28-day study (mean \pm SD)

	HMB (M/F: 7/12)			Control (M/F: 13/7)		
	Before	After	Change (%)	Before	After	Change (%)
Weight (kg)	40.0 \pm 5.1 [‡]	40.7 \pm 5.3 [†]	3.42 \pm 3.02	53.4 \pm 8.0	53.7 \pm 7.3	-0.21 \pm 2.47
Body mass index (kg/m ²)	17.2 \pm 2.0 [‡]	17.5 \pm 2.3 [†]	3.66 \pm 3.56	22.1 \pm 2.5	22.2 \pm 2.4	-0.25 \pm 2.44
Thorax (cm)	80.3 \pm 7.2 [‡]	80.6 \pm 6.3	1.09 \pm 4.36	87.1 \pm 4.7	86.7 \pm 4.9	-1.02 \pm 2.24
Waist (cm)	70.0 \pm 6.0 [‡]	71.0 \pm 6.4 [†]	2.34 \pm 4.64*	82.5 \pm 7.7	79.7 \pm 6.2 [†]	-3.42 \pm 4.45
Hip (cm)	76.3 \pm 5.0 [‡]	77.7 \pm 5.6 [†]	1.75 \pm 3.39	83.8 \pm 7.1	84.1 \pm 5.7	-0.88 \pm 4.79
Waist/Hip	0.92 \pm 0.04	0.91 \pm 0.05	0.24 \pm 6.82	1.04 \pm 0.26	0.95 \pm 0.04	-4.43 \pm 12.97
Triceps skinfold (cm)	0.43 \pm 0.12	0.47 \pm 0.16	-3.5 \pm 31.4	0.55 \pm 0.30	0.58 \pm 0.35	10.2 \pm 38.4
Mid-arm circumference (cm)	21.4 \pm 2.6 [‡]	21.6 \pm 2.7	1.21 \pm 5.18	24.4 \pm 1.9	23.7 \pm 1.9 [†]	-3.03 \pm 6.11
Mid-arm muscle circumference (cm)	20.0 \pm 2.4 [‡]	20.1 \pm 2.4	1.9 \pm 6.3	22.7 \pm 1.5	21.8 \pm 1.9	-8.2 \pm 19.9
Calf circumference (cm)	22.3 \pm 2.5 [‡]	22.7 \pm 2.3 [†]	2.57 \pm 5.02*	28.5 \pm 3.0	27.8 \pm 2.7 [†]	-3.63 \pm 4.24

HMB, β -hydroxy- β -methylbutyrate* $p < 0.05$, significantly different between the HMB and control groups after controlling for BMI at the baseline.† $p < 0.05$, significantly different before and after the study within the same group.‡ $p < 0.05$, significantly different between the HMB and control groups before the study.**Table 5.** Hematological and biochemical parameters in the HMB and control groups before and after the 28-day study (mean \pm SD)

	HMB (M/F: 7/12)			Control (M/F: 13/7)		
	Before	After	Change (%)	Before	After	Change (%)
Hematology						
White blood cell (10 ³ / μ L)	7.02 \pm 2.01	6.89 \pm 1.70	-6.8 \pm 21.2	7.07 \pm 1.97	7.12 \pm 1.55	7.2 \pm 30.2
Red blood cell (10 ⁶ / μ L)	3.94 \pm 0.48	3.92 \pm 0.60	-3.6 \pm 8.2	4.41 \pm 0.59	4.44 \pm 0.63	1.1 \pm 16.5
Hemoglobin (g/L)	122 \pm 17	117 \pm 17	-4.0 \pm 8.5	137 \pm 19	133 \pm 22	-2.4 \pm 14.4
Serum lipids						
Triglyceride (mM)	1.26 \pm 0.65	1.17 \pm 0.58	5.5 \pm 61.2	1.44 \pm 0.58	1.34 \pm 0.65	-7.1 \pm 23.3
Total cholesterol (mM)	3.84 \pm 1.03	4.35 \pm 1.19	18.2 \pm 37.4	4.20 \pm 0.74	4.48 \pm 1.02	7.3 \pm 17.9
HDL-cholesterol (mM)	1.25 \pm 0.33	1.25 \pm 0.49	-0.3 \pm 25.9	1.11 \pm 0.28	1.06 \pm 0.23	-2.2 \pm 17.5
LDL-cholesterol (mM)	2.23 \pm 0.96	2.58 \pm 0.90	25.5 \pm 42.9	2.43 \pm 0.64	2.82 \pm 0.86	18.0 \pm 25.1
Serum biochemistry						
Total protein (g/L)	70.0 \pm 6.4	68.0 \pm 7.0	-2.55 \pm 8.91	73.9 \pm 7.6	70.8 \pm 7.2	-3.82 \pm 8.80
Albumin (g/L)	33.5 \pm 3.8	32.3 \pm 4.4	-2.9 \pm 14.4	38.5 \pm 5.5	36.3 \pm 4.6	-4.9 \pm 11.0
Blood urea nitrogen (mM)	4.78 \pm 1.27	4.48 \pm 1.95	-7.5 \pm 26.3	4.84 \pm 1.29	4.93 \pm 2.36	-0.9 \pm 23.1
Creatinine (μ M)	68.1 \pm 19.5	71.6 \pm 18.6	6.9 \pm 19.7	73.4 \pm 20.3	70.7 \pm 19.5	-2.3 \pm 15.7
Uric acid (μ M)	245 \pm 82	253 \pm 94	4 \pm 27*	273 \pm 85	295 \pm 97	26 \pm 119
Glucose (mM)	5.49 \pm 1.13	5.11 \pm 0.95	-4.3 \pm 22.6	5.60 \pm 1.83	5.53 \pm 2.00	1.2 \pm 38.0
GOT (U/L)	26.2 \pm 11.1	23.5 \pm 8.8	-9.6 \pm 28.9	25.9 \pm 9.5	28.1 \pm 10.3	-0.7 \pm 24.7
GPT (U/L)	31.0 \pm 19.8	27.7 \pm 13.5	-8.6 \pm 31.5	28.8 \pm 11.4	26.3 \pm 13.9	-4.7 \pm 34.8

HMB, β -hydroxy- β -methylbutyrate* $p < 0.05$, significantly different between the HMB and control groups after controlling for BMI at the baseline.† $p < 0.05$, significantly different before and after the study within the same group.

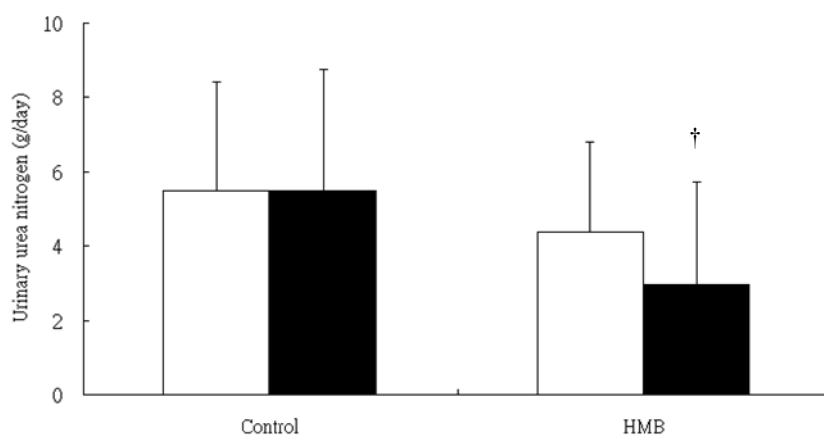


Figure 2. 24-hr urinary urea nitrogen excretion in the HMB and control groups before (□) and after (■) the 28-day study (mean \pm SD), † $p < 0.05$, significantly different before and after the study within the same group.

the changes in body weight and body composition were similar between control and HMB groups. It has been reported that a 12-week supplementation of HMB, arginine, and lysine significantly reduced urine nitrogen excretion in elderly women living in senior citizen centers and nursing homes.²³ It has been observed that whole-body protein synthesis and proteolysis both increased. However, the magnitude of increase in protein synthesis was larger than that in proteolysis, resulting in increases in lean body mass and muscular strength. The same supplementation for one year has also been shown to increase protein turnover and lean body mass in elderly men and women living in senior citizen centers and nursing homes. Nonetheless, protein synthesis and breakdown both increased in the supplementation group, resulting in no change in both the protein balance and nitrogen balance.³⁰ The current study suggested that HMB supplementation can still reduce muscle breakdown in very fragile elderly subjects.

Previous studies generally suggested that several weeks to months of HMB supplementation are required, in combination with resistance training, to increase muscle mass and strength in young healthy subjects.^{16,30} It may require 12 weeks to 1 year to increase body mass in relatively healthy elderly subjects without resistance training.^{23,31} On the other hand, in certain catabolic states, HMB supplementation may reduce proteolysis in as short as 7 days.^{17,18} However, it takes 4–8 weeks to show significant improvements in body weight and muscle mass.^{20,32} In agreement, the current study also showed that HMB supplementation decreased proteolysis after 2 weeks in bedridden elderly receiving tube feeding. This effect was maintained after supplementation for 2 additional weeks. However, body weight and body composition was unchanged after 4 weeks.

HMB has been shown to prevent proteolysis by inhibiting the ubiquitin-proteasome proteolytic pathway,^{31,32} which plays an important role in age-related loss in skeletal muscles.^{33,34} In tumor-bearing mice, HMB supplementation prevented the reduction in protein degradation in gastrocnemius muscle by inhibiting the expression of proteasome subunits and proteasome functional activity.³⁵ HMB also increased protein synthesis in this animal model, leading to an increased protein synthesis/ degrada-

tion ratio and reduced loss in body weight.³⁵ Furthermore, HMB supplementation resulted in lower levels of protein synthesis inhibition and reduced loss in body weight in cachectic mice by reducing phosphorylation of double-strand RNA-dependent protein kinase (PKR) and eukaryotic initiation factor (eIF) 2.³⁶

In mouse myoblast C₂C₁₂, HMB has been shown to prevent protein degradation induced by tumor necrosis factor- α and angiotensin II via attenuation of caspase-3 and -8 activation.³⁷ HMB can also prevent the depression in protein synthesis induced by lipopolysaccharide and tumor necrosis factor- α through increasing phosphorylation of mammalian target of rapamycin (mTOR).³⁸ HMB may also improve muscle cell differentiation and fusion via the PI3K/Akt pathway, resembling the role of insulin-like growth factor-I.³⁹

Another potential mechanism for HMB function is through the conversion to β -hydroxy- β -methylglutaryl-CoA (HMG-CoA), a precursor for cholesterol synthesis, in cytosol.⁴⁰ In muscle cells where the major supply of cholesterol comes from de novo pathways, increased cholesterol synthesis that resulted from dietary supplementation of HMB may help the growth, production, or repair of tissues in stressful or overload conditions.⁴¹ This hypothesis is supported by the fact that several cholesterol synthesis inhibitors can cause severe myopathy.⁴¹

The dose of 2 g per day was selected for this study because it has been shown that 38 mg/kg body weight provided similar effect as higher doses.⁴² The same dose was also used in previous studies on elderly subjects.^{22,23} The dose showed no adverse effect⁴³ and was well-tolerated even in very weak patients with weight loss.^{19,44}

Unexpectedly, red blood cells concentrations significantly increased after 14 days in the control group while it remained unchanged in the HMB group. The changes in red blood cells and hemoglobin in the HMB group were significantly lower than those of the control group. The reason for the difference was unclear. To our knowledge, the side effect of reducing red blood cell or hemoglobin in human subjects has not been reported in any of the HMB studies. These differences in red blood cells and hemoglobin disappeared after 28 days. Even though the increases in the control group might indicate that this

group received better care and/or recovered better during the study period, which is unlikely, these would only further strengthen our findings about HMB's ability to reduce muscle breakdown.

All of our subjects have a long history of cardiovascular diseases and/or diabetes. They were taking the prescribed medications for these chronic diseases during the study period. Since they have been taking these medications for many years before entering the study, it is unlikely that the medications would affect the study results.

In conclusion, this study suggested that supplementation of HMB alone for 2-4 weeks could reduce muscle breakdown in frail elderly nursing home residents receiving tube feeding. HMB supplementation may improve the quality of life and reduce medical cost that result from complications in these subjects.

AUTHOR DISCLOSURES

There is no conflict of interest from financial support.

REFERENCES

- Morley JE, Silver AJ. Nutritional issues in nursing home care. *Ann Intern Med.* 1995;123:850-9.
- Seiler WO. Clinical pictures of malnutrition in ill elderly subjects. *Nutrition.* 2001;17:496-8.
- Nelson KJ, Coulston AM, Sucher KP, Tseng RY. Prevalence of malnutrition in the elderly admitted to long-term-care facilities. *J Am Diet Assoc.* 1993;93:459-61.
- Compan B, di Castri A, Plaze JM, Arnaud-Battandier F. Epidemiological study of malnutrition in elderly patients in acute, sub-acute and long-term care using the MNA. *J Nutr Health Aging.* 1999;3:146-51.
- Chiu YW, Lin WY, Hsieh PC, Li CI, Chiou CH. A survey to identify effective nutritional assessment indicators in long-term care facilities (Chinese). *J Evid Based Nurs.* 2005;1:112-22.
- Aoyama L, Weintraub N, Reuben DB. Is weight loss in the nursing home a reversible problem? *J Am Med Dir Assoc.* 2005;6:250-6.
- Blaum CS, Fries BE, Fiatarone MA. Factors associated with low body mass index and weight loss in nursing home residents. *J Gerontol A Biol Sci Med Sci.* 1995;50:M162-8.
- Cowan DT, Roberts JD, Fitzpatrick JM, While AE, Baldwin J. Nutritional status of older people in long term care settings: current status and future directions. *Int J Nurs Stud.* 2004;41:225-37.
- Sullivan DH, Morley JE, Johnson LE, Barber A, Olson JS, Stevens MR, Yamashita BD, Reinhart SP, Trotter JP, Olave XE. The GAIN (Geriatric Anorexia Nutrition) registry: the impact of appetite and weight on mortality in a long-term care population. *J Nutr Health Aging.* 2002;6:275-81.
- Kiely DK, Flacker JM. Resident characteristics associated with mortality in long-term care nursing homes: is there a gender difference? *J Am Med Dir Assoc.* 2000;1:8-13.
- Kaw M, Sekas G. Long-term follow-up of consequences of percutaneous endoscopic gastrostomy (PEG) tubes in nursing home patients. *Dig Dis Sci.* 1994;39:738-43.
- Okada K, Yamagami H, Sawada S, Nakanishi M, Tamaki M, Ohnaka M, Sakamoto S, Niwa Y, Nakaya Y. The nutritional status of elderly bed-ridden patients receiving tube feeding. *J Nutr Sci Vitaminol (Tokyo).* 2001;47:236-41.
- Mitchell SL, Kiely DK, Lipsitz LA. Does artificial enteral nutrition prolong the survival of institutionalized elders with chewing and swallowing problems? *J Gerontol A Biol Sci Med Sci.* 1998;53:M207-13.
- Nissen SL, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J Appl Physiol.* 2003;94:651-9.
- Vukovich MD, Stubbs NB, Bohlken RM. Body composition in 70-year-old adults responds to dietary beta-hydroxy-beta-methylbutyrate similarly to that of young adults. *J Nutr.* 2001;131:2049-52.
- Rowlands DS, Thomson JS. Effects of beta-hydroxy-beta-methylbutyrate supplementation during resistance training on strength, body composition, and muscle damage in trained and untrained young men: a meta-analysis. *J Strength Cond Res.* 2009;23:836-46.
- Hsieh LC, Chien SL, Huang MS, Tseng HF, Chang CK. Anti-inflammatory and anticatabolic effects of short-term beta-hydroxy-beta-methylbutyrate supplementation on chronic obstructive pulmonary disease patients in intensive care unit. *Asia Pac J Clin Nutr.* 2006;15:544-50.
- Kuhls DA, Rathmacher JA, Musngi MD, Frisch DA, Nielson J, Barber A, MacIntyre AD, Coates JE, Fildes JJ. Beta-hydroxy-beta-methylbutyrate supplementation in critically ill trauma patients. *J Trauma.* 2007;62:125-31.
- Clark RH, Feleke G, Din M, Yasmin T, Singh G, Khan FA, Rathmacher JA. Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy beta-methylbutyrate, glutamine, and arginine: a randomized, double-blind, placebo-controlled study. *J Parent Enter Nutr.* 2000;24:133-9.
- May PE, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. *Am J Surg.* 2002;183:471-9.
- Berk L, James J, Schwartz A, Hug E, Mahadevan A, Samuels M, Kachnic L. A randomized, double-blind, placebo-controlled trial of a beta-hydroxyl beta-methyl butyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). *Support Care Cancer.* 2008;16:1179-88.
- Baier S, Johannsen D, Abumrad N, Rathmacher JA, Nissen S, Flakoll P. Year-long changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of beta-hydroxy-beta-methylbutyrate (HMB), L-arginine, and L-lysine. *J Parent Enter Nutr.* 2009;33:71-82.
- Flakoll P, Sharp R, Baier S, Levenhagen D, Carr C, Nissen S. Effect of beta-hydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. *Nutrition.* 2004;20:445-51.
- Paddon-Jones D. Interplay of stress and physical inactivity on muscle loss: Nutritional countermeasures. *J Nutr.* 2006;136:2123-6.
- Ferrando AA, Paddon-Jones D, Wolfe RR. Bed rest and myopathies. *Curr Opin Clin Nutr Metab Care.* 2006;9:410-5.
- Hwang TL, Huang SL, Chen MF. The use of indirect calorimetry in critically ill patients--the relationship of measured energy expenditure to Injury Severity Score, Septic Severity Score, and APACHE II Score. *J Trauma.* 1993;34:247-51.
- Ferrannini E. The theoretical bases of indirect calorimetry: a review. *Metabolism.* 1988;37:287-301.
- Cheng HS, See LC, Shieh YH. Estimating stature from knee height for adults in Taiwan. *Chang Gung Med J.* 2001;24:547-56.
- Mahan LK, Escott-Stump S. Food, nutrition, and diet therapy. Philadelphia: Saunders Company;1996.
- Thomson JS, Watson PE, Rowlands DS. Effects of nine weeks of beta-hydroxy-beta-methylbutyrate supplementa-

- tion on strength and body composition in resistance trained men. *J Strength Cond Res.* 2009;23:827-35.
31. Wilson GJ, Wilson JM, Manninen AH. Effects of beta-hydroxy-beta-methylbutyrate (HMB) on exercise performance and body composition across varying levels of age, sex, and training experience: A review. *Nutr Metab.* 2008;5:1-17.
 32. Holecek M, Muthny T, Kovarik M, Sispera L. Effect of beta-hydroxy-beta-methylbutyrate (HMB) on protein metabolism in whole body and in selected tissues. *Food Chem Toxicol.* 2009;47:255-9.
 33. Combaret L, Dardevet D, Bechet D, Taillandier D, Mosoni L, Attaix D. Skeletal muscle proteolysis in aging. *Curr Opin Clin Nutr Metab Care.* 2009;12:37-41.
 34. Martinez-Vicente M, Sovak G, Cuervo AM. Protein degradation and aging. *Exp Gerontol.* 2005;40:622-33.
 35. Smith HJ, Mukerji P, Tisdale MJ. Attenuation of proteasome-induced proteolysis in skeletal muscle by beta-hydroxy-beta-methylbutyrate in cancer-induced muscle loss. *Cancer Res.* 2005;65:277-83.
 36. Eley HL, Russell ST, Baxter JH, Mukerji P, Tisdale MJ. Signaling pathways initiated by beta-hydroxy-beta-methylbutyrate to attenuate the depression of protein synthesis in skeletal muscle in response to cachectic stimuli. *Am J Physiol Endocrinol Metab.* 2007;293:E923-31.
 37. Eley HL, Russell ST, Tisdale MJ. Mechanism of attenuation of muscle protein degradation induced by tumor necrosis factor-alpha and angiotensin II by beta-hydroxy-beta-methylbutyrate. *Am J Physiol Endocrinol Metab.* 2008;295:E1417-26.
 38. Eley HL, Russell ST, Tisdale MJ. Attenuation of depression of muscle protein synthesis induced by lipopolysaccharide, tumor necrosis factor, and angiotensin II by beta-hydroxy-beta-methylbutyrate. *Am J Physiol Endocrinol Metab.* 2008;295:E1409-16.
 39. Kornasio R, Riederer I, Butler-Browne G, Mouly V, Uni Z, Halevy O. Beta-hydroxy-beta-methylbutyrate (HMB) stimulates myogenic cell proliferation, differentiation and survival via the MAPK/ERK and PI3K/Akt pathways. *Biochim Biophys Acta.* 2009;1793:755-63.
 40. Nissen S, Sharp R, Ray M, Rathmacher JA, Rice D, Fuller JC, Connelly AS, Abumrad N. Effect of leucine metabolite beta-hydroxy-beta-methylbutyrate on muscle metabolism during resistance-exercise training. *J Appl Physiol.* 1996;81:2095-104.
 41. London SF, Gross KF, Ringel SP. Cholesterol-lowering agent myopathy (CLAM). *Neurology.* 1991;41:1159-60.
 42. Gallagher PM, Carrithers JA, Godard MP, Schulze KE, Trappe SW. Beta-hydroxy-beta-methylbutyrate ingestion, Part I: effects on strength and fat free mass. *Med Sci Sports Exerc.* 2000;32:2109-15.
 43. Baxter JH, Carlos JL, Thurmond J, Rehani RN, Bultman J, Frost D. Dietary toxicity of calcium beta-hydroxy-beta-methyl butyrate (CaHMB). *Food Chem Toxicol.* 2005;43:1731-41.
 44. Rathmacher JA, Nissen S, Panton L, Clark RH, Eubanks May P, Barber AE, D'Olimpio J, Abumrad NN. Supplementation with a combination of beta-hydroxy-beta-methylbutyrate (HMB), arginine, and glutamine is safe and could improve hematological parameters. *J Parent Enter Nutr.* 2004;28:65-75.

Original Article

Effect of β -hydroxy- β -methylbutyrate on protein metabolism in bed-ridden elderly receiving tube feeding

Lan-Chi Hsieh MS¹, Chau-Jen Chow PhD², Wen-Chou Chang MS³, Tsung-Han Liu MS⁴, Chen-Kang Chang PhD⁵

¹Department of Dietetics, Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan, ROC

²Department of Seafood Science, National Kaohsiung Marine University, Kaohsiung, Taiwan, ROC

³Medical Laboratory, Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan, ROC

⁴Doctoral Program in Physical Education, Taipei Physical Education College, Taipei, Taiwan, ROC

⁵Sport Science Research Center, National Taiwan College of Physical Education, Taichung, Taiwan, ROC

補充羥基甲基丁酸鹽影響管灌臥床老人之蛋白質代謝

營養不良與肌肉流失是護理之家老年臥床住民常見的情況。過去研究顯示，補充 β -羥基- β -甲基丁酸鹽(HMB)可以避免數種代謝分解狀態下的肌肉流失。本研究目的為探討補充 HMB 對接受管灌飲食的護理之家老年臥床住民，身體組成與蛋白質代謝的影響。受試者隨機分為 HMB 組(39 位，每天補充 2 g)或控制組(40 位)，於補充 14 天前後進行人體測量，並收集血液與 24 小時尿液樣本；其中部分受試者(HMB 組 19 位，控制組 20 位)繼續補充 14 天。控制身體質量指數(BMI)基準值後，14 天或 28 天後體重與 BMI 改變量，在兩組間並無顯著差異；HMB 組血液尿素氮 14 天後顯著降低，在控制組則無顯著改變；HMB 組尿液尿素氮在 14 與 28 天後顯著降低，控制組則呈現增加的趨勢。控制 BMI 基準值後，血液尿素氮與尿液尿素氮的變化量在兩組間有顯著差異。本研究顯示，補充 HMB 2 至 4 週，可以減緩接受管灌飲食的護理之家老年臥床住民的肌肉損耗。

關鍵字：肌肉流失、蛋白質分解、護理之家、營養不良、尿液尿素氮排泄