ORIGINAL

Low resting energy expenditure in middle-aged and elderly hemodialysis patients with poor nutritional status

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Abstract : Due to high resting energy expenditure (REE) in maintenance hemodialysis patients, an increase in energy intake is usually recommended to improve their nutritional status. However, some patients appear to have poor appetite and low energy intake. In such patients low energy metabolism is expected. We hypothesized that in maintenance hemodialysis patients there are two types of the energy metabolism, high and low. This study was aimed at finding the energy metabolism in maintenance hemodialysis patients, especially in those with poor nutritional status.

Subjects were hemodialysis out-patients (34 males and 20 females, mean age 59.1±10.7y). REE was measured by an indirect calorimeter. Protein intake was obtained from normalized protein catabolic rate (nPCR), and physical activity level (PAL) was obtained by time study. Nutritional status assessed by serum albumin concentration was poor (3.7±0.2g/dL) in spite of the adequate protein intake (1.1±0.3g/kg per day). Only11% of the subjects had appropriate serum albumin concentration. Mean REE was 24.6 kcal/kg per day which was lower than that of healthy Japanese (26.5kcal/kg per day). REE and PAL positively correlated with serum albumin concentration (p<0.01). The results suggest that maintenance hemodialysis patients with poor nutritional status may have low REE. J. Med. Invest. 53 : 34-41, February, 2006

Keywords **:** *hemodialysis patient, resting energy expenditure, physical activity level, serum albumin, poor nutritional status*

INTRODUCTION

Advances in dialysis technology have contributed to an increased survival rate in chronic hemodialysis patients. Appropriate nutritional managements greatly contribute to extension of life expectancy by preventing complications and are becoming more important than ever(1-4). Energy management is one of the most important among them. Energy deficiency leads to hypercatabolism of protein, and requires an increase of dialysis volume. Excess energy intake, on the other hand, leads to hypertriglyceridemia and accumulation of fat, which then cause cardiovascular complications. In addition, water molecules in the excess food and production of water during metabolism may result in increased water retention. In spite of such importance of energy intake, the study on energy metabolism of maintenance hemodialysis patients has not been extensively studied so far, may be because of the high cost of gas monitor.

Ikizler, *et al.*(5) recommended the importance of high-energy intake in maintenance hemodialysis patients. They observed that resting energy expenditure (REE) of hemodialysis patients was higher than that of healthy individuals. They also showed that

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REE of the patients during hemodialysis treatment was higher than that during non-dialysis period. However, from our experience, some patients seem to have poor appetite, low energy intake and poor nutritional status. In such patients low energy metabolism is expected and hence an increase of energy intake is not appropriate until their REE improves. In fact the subjects in the study of Ikizler, *et al.* (5) were young (mean age 38.3±13.0y), had high body mass index (BMI:26.3±5.9)and relatively proper serum albumin level(4.08±0.32g/dL), indicating their nutritional status was not poor. These suggest that energy metabolism of the hemodialysis patients is not the same and may rather be different depending upon their nutritional status. This study was aimed at determining the energy metabolism in maintenance hemodialysis patients with poor nutritional status, so that proper quantity of energy can be recommended for the patients.

SUBJECTS AND METHOD

1. Subjects

The subjects consisted of 81 hemodialysis patients (52 males and 29 females of age range 40-79 y) who were being treated at satellite dialysis clinics, in Osaka, Japan. Seventy eight percent of the subjects were non-diabetic hemodialysis patients. Of all patients, the primary causes of admission included chronic glomerular nephritis (68%), diabetic nephropathy (22%), nephrosis (3%), renal sclerosis (3%) and pregnancy toxemia (4%). The patients underwent three4-h sessions of hemodialysis per wk using bicarbonate-buffered dialysate containing 100 mg glucose/dL and 30 mEq bicarbonate/L. Blood was collected for routine analysis before a hemodialysis session. Laboratory parameters were measured by Nichiyaku Medical Laboratories using an autoanalyzer. The Kt/V as a formula of hemodialysis volume(K:the urea clearance, t: hemodialysis time, V:the urea distribution volume)was calculated by the methods of Daugirdas (single-pool model)(6). Normalized protein catabolic rate (nPCR) was calculated by the methods of Shinzato, *et al*. (7).

The Ethical Committee of The University of Tokushima approved this study. The subjects were provided with full explanation about the purpose and procedures of the study and informed consent was obtained form each patient.

2. Measurement of REE

REE was measured 2h after the last meal (8) before a mid-wk hemodialysis. The subjects refrained from smoking and were trained how to breath through the mask. After resting for at least 15 min at room temperature (24 to 25℃) (9), REE was measured with Metavine (Vine, Tokyo, Japan) over 6min while the subject was in the sitting or supine position (8, 10, 11). The stable value for 3 min was defined as the REE. As described above, the study on energy metabolism has not been extensively explored so far, due to the high cost of the gas monitor. We used Metavine which measures only O_2 concentration. Energy expenditure is calculated by using the fixed respiratory quotient (0.82) (8). It is much cheaper than those which measure both O_2 and CO_2. Another advantage of this procedure is the small size. Therefore if the monitor is good enough to neglect the inaccuracy and the limitation due to the measurement of only O_2, it will be a strong support for treatment of the patients. Results of this device indicated that large errors occur at low flow rates. Under normal conditions the error is less than 5% (10). Even if the estimate was greater, the coefficient of variation was reported to be 10% or less (8).

From the total of 81 subjects (52 males and 29 females) who were enrolled, REE data was generated for 54 hemodialysis patient (34 males and 20 females). Subjects with diabetic nephropathy or unstable REE were excluded.

3. PAL and dietary survey

Average physical activity level (PAL) of a day was estimated by the following equation. PAL=Σ ($Af \times T$/1440). Where Af refers to activity factor for the individual activities (this expresses the ratio to basal metabolic rate), and T refers to time required for the individual activities (min). PAL of each activity was based on the activity factor for Japanese (12, 13). We defined basal metabolic rate (BMR)as 80% of REE(12).

The nutrition survey was conducted by employing the 24h recalling method in 26 hemodialysis patients (19 males, 7 females) who agreed to participate. The information was collected from the patients themselves or a family member who prepared meals for the patient over 3 consecutive days excluding holidays.

4. Statistical analysis

Statistical analysis was performed using SPSS software (version 12.0 J, SPSS Inc., Chicago, IL, USA) for Windows and data were expressed as the mean±SD. All variables were tested for normality of distribution, and logarithmic conversion was performed if the distribution was not normal. Relationships between variables were analyzed by calculating Pearson's correlation coefficients. Principal component analysis was performed using parameters that displayed a significant correlation with REE so that factors could be extracted, and the components were scored. The promax method was used for rotation. In addition, using REE as the dependent variable and the scores for each component as independent variables, multiple regression analysis was performed by both forced entry and stepwise method. In all analyses, $p<0.05$ was considered significant.

RESULTS

1. Profile of the patients

Table 1 shows the mean values of age, duration of dialysis, height, body weight, body mass index (BMI), physical activity level (PAL) and clinical parameters of the 81 patients. The durations of maintenance hemodialysis for male and female were 7.1±6.9y and 10.4±6.7y(range:0.1-22.7y), respectively. Forty three point six percent and 34.6% of the patients had maintenance hemodialysis for less than 5y and more than10y respectively. PAL lower than 1.3 was observed in 59.2% of males and 70.4% of females. As shown in Table 1, mean Kt/V was more than 1.3 and mean normalized protein catabolic rate (nPCR) was more than 1.2 g/kg per day in both male and female patients. These values (1.3 Kt/V and 1.2 nPCR) indicate low levels of mortality. Serum albumin level was 3.7±0.2 g/dL in males and 3.6±0.3g/dL in females. Subjects with appropriate serum albumin level (more than 4.0 g/dL) were only 9 (11.1%). The mean energy intake was 32.3 kcal/kg per day. The protein intake (1.14g/kg per day) was similar to the mean nPCR (1.2 g/kg per day) .

Table 2 shows the profile of the patients from whom REE were measured. REE was 1365±303 kcal per day (24.3±5.5kcal/kg per day) in the male patients and 1141±196kcal per day (25.0±4.7kcal/kg per day) in the females. PAL was 1.3±0.1 in both males and females. In addition, serum C-reactive protein (CRP), an energy metabolism related factor, was a little high in the patients. In 29.6% of the patients the level of CRP was more than 0.3mg/dL. The inflammation and infections-related factors, mean white blood cells (WBC), mean neutrophil and eosinophil counts as % of WBC were higher than standard value. Neutrophil

Table 1. Characteristics of the patients

Variable	Total(n=81)	Male(n=52)	Female(n=29)
Age, y	59.6±11.1	58.0±11.1	62.4±10.8
Duration of dialysis, y	8.3±7.0	7.1±6.9	10.4±6.7
Height, cm	159.8±8.4	163.9±5.8	152.3±7.1
Body weight (DW), kg	52.7±11.0	57.4±10.7	45.0±6.1
BMI	20.6±3.2	21.3±3.3	19.3±2.3
PAL	1.3±0.1	1.3±0.1	1.3±0.1
Kt/V	1.43±0.31	1.30±0.24	1.65±0.29
nPCR, g/kg per day	1.2±0.3	1.2±0.3	1.2±0.3
Serum albumin, g/dL	3.7±0.3	3.7±0.2	3.6±0.3
Serum total protein, g/dL	6.5±0.4	6.6±0.4	6.4±0.4
Serum creatinine, mg/dL	12.8±3.3	13.6±3.4	11.5±2.5
Hemoglobin, g/dL	10.5±1.0	10.5±1.1	10.4±0.9
Serum CRP, mg/dL	0.38±0.66	0.30±0.37	0.52±0.99
WBC, cells/mm^3	6128±1587	6127±1512	6129±1742
Neutrophil (segmented cell), %	66.9±7.7	66.5±7.3	67.6±8.6
Eosinophil, %	4.0±3.6	4.3±3.6	3.5±3.7
Energy intake, kcal/d [a]	1680±437	1720±479	1571±297
Energy intake/DW, kcal/kg per day	32.3±6.9	31.0±7.4	35.6±5.0
Protein intake, g/d [a]	59.2±14.8	59.4±13.2	58.6±19.8
Protein intake/DW, g/kg per day	1.14±0.29	1.07±0.24	1.32±0.36

Data are expressed as the mean±SD. BMI, body mass index, dry weight, the weight measured immediately after patients underwent hemodialysis. PAL, physical activity level : Kt/V, standardized dialysis volume: nPCR, normalized protein catabolic rate, WBC : white blood cell, CRP : C-reactive protein.
Marked a ; data of 26 subjects (19 males and 7 females).

Table 2. Profile of the patients measured resting energy expenditure (REE)

Variable	Total(n=54)	Male(n=34)	Female(n=20)
Age, y	59.1±10.7	57.8±11.2	61.3±9.5
Duration of dialysis, y	10.1±7.3	8.9±7.6	12.2±6.6
Height, cm	159.6±8.4	163.4±5.9	152.9±8.0
Body wt, kg (Dry wt)	53.0±10.3	57.1±10.1	46.1±6.0
BMI	20.7±3.0	21.3±3.3	19.6±2.2
REE, kcal/d	1282±288	1365±303	1141±196
REE/DW, kcal/kg per day	24.6±5.1	24.3±5.5	25.0±4.7
PAL	1.3±0.1	1.3±0.1	1.3±0.1
Kt/V	1.40±0.27	1.30±0.26	1.58±0.20
nPCR, g/kg per day	1.1±0.3	1.2±0.3	1.1±0.2
Serum albumin, g/dL	3.7±0.2	3.7±0.2	3.6±0.3
Serum total protein, g/dL	6.5±0.4	6.6±0.4	6.4±0.4
Serum creatinine, mg/dL	13.1±3.2	13.7±3.6	12.2±2.2
Serum CRP, mg/dL	0.46±0.78	0.34±0.43	0.66±1.15
WBC, cells/mm^3	5990±1576	6035±1584	5913±1600
Neutrophil (segmented cell) %	65.7±7.7	65.6±7.3	65.8±8.7
Eosinophil, %	4.5±4.0	4.8±4.0	4.1±4.2

Data are expressed as the mean±SD. BMI, body mass index ; dry weight, the weight measured immediately after patients underwent hemodialysis. PAL, physical activity level : Kt/V, standardized dialysis volume : nPCR, normalized protein catabolic rate : WBC : white blood cell, CRP : C-reactive protein.

count was more than70% of WBC in 31.5% of the patients.

2. Comparison of basal metabolic rate (BMR) between normal Japanese and patients.

The BMR of the patients was estimated by the following calculation.

BMR=0.8×REE

The percentages of BMR of patients against the BMR in healthy Japanese (12) were 76.4% for males and 81.4% for females (Table 3).

3. Factors related to REE

Forty three variables (age, duration of dialysis, height, body weight, dry weight, BMI, 35 laboratory test results, nPCR, and PAL) were used for analysis of simple correlations with REE. As shown in Table 4, 14 factors displayed a significant correlation with REE. This analysis revealed a positive correlation with factors such as the serum phosphorus level, body weight, height, serum total protein level, and serum albumin level. On the other hand, there was a negative correlation for factors such as age, the Kt/V, and AST level. Principal component analysis was then performed for factors except for age and for the values that were calculated by formula (Kt/V, BMI with dry weight, and BMI) , and this detected 3 components (Table 5) . The first component expressed "obesity," while the second component was "protein nutrition," and the third component was "liver function." Using the scores of these 3 components as independent variables, multiple regression analysis (forced entry method) was performed for more comprehensive examination of the factors influencing REE (Fig. 1) . This analysis revealed that the standardized coefficient (β_1) was the biggest for the second component,"protein nutrition". The multiple regression coefficient was 0.606 (R_1^2 = 0.367, p<0.001) and the contribution rate was 32.8%. On the other hand, the first component, "obesity" (β_2 = 0.342) , and the second component, "protein nutrition"(β_2 = 0.342), were selected by stepwise analysis. In this analysis, the contribution rate was 30.2% (R_2^2 = 0.329, p<0.001) .

Fig 2 shows the relationship between serum albumin and REE of the patients. Serum albumin concentration and REE correlated significantly (p<0.01). From regression analysis, REE with serum albumin concentration of the reference standard (4.0g/dL) was 27kcal/kg per day. Fig 3 shows the relationship between serum albumin and PAL of all the patients. Serum albumin concentration and PAL correlated significantly (p<0.01) . From regression analysis, PAL with serum albumin concentration of the reference standard (4.0g/dL) was 1.33.

DISCUSSION

The purpose of this study was to confirm our hypothesis that there are patients with low REE, yet high-energy intake is recommended to the hemodialysis patients most of whom had poor nutritional status (5,14) . In such patients an increase in energy intake, without increase of REE, is difficult.

Nutritional status of our study subjects was poor. Their mean BMI (20.6±3.2) was which was lower than that of Japanese average (23.4) reported in the Annual National Health and Nutrition Survey (15). Protein nutritional status assessed by serum albumin concentration was poor(3.7±0.3g/dL) in spite of the adequate protein intake (1.14g/kg per day) and mean nPCR (1.2g/kg per day). Only 11% of the subjects had normal serum albumin concentration (4.0g/dL or more). The survey of the Japanese Society of Nephrology showed low survival rate for hemodialysis

Table 3. Comparison of basal metabolism standard in Japanese and resting energy expenditure (REE) in patients aged 50-69 years

	Patient(32)		Basal metabolism standard in Japanese	
variable	Male (n=18)	Female (n=14)	Male	Female
Age, y	59.8±6.4	59.9±6.3	50-69	50-69
Height, cm	162.3±4.6	152.4±7.2	163.9	151.4
Body weight, kg (Dry weight)	56.7±12.0	46.1±5.9	62.5	53.8
BMI	21.4±4.1	19.9±2.5	23.3	23.5
BMR, kcal/d	1032±250[a]	903±132[a]	1350	1110
REE, kcal/d	1291±312	1129±165	1688[b]	1388[b]
REE/DW, kcal/kg per day	23.3±5.7	24.7±4.3	27.0	25.8

Data are expressed as the mean or mean±SD.
BMR, basal metabolic rate.
Letter of the right shoulder, a ; REE×0.8,b ; BMR/0.8.

Table 4. Relationship between resting energy expenditure (REE) and clinical parameters in the patients

Variables	R	*p*-value
Dry weight	0.479	<0.001
Weight	0.473	<0.001
Height	0.471	<0.001
Age	-0.421	0.002
Kt/V	-0.392	0.003
Total protein	0.387	0.004
Albumin	0.377	0.005
Phosphorus	0.333	0.014
AST	-0.305	0.025
TG (log)	0.299	0.028
LDH	-0.290	0.033
BMI (DW)	0.289	0.036
BMI	0.285	0.039
WBC	0.276	0.044

BMI was calculated from the body weight measured immediately before patients underwent hemodialysis and BMI (DW) was calculated from dry weight ; P, serum phosphorus level ; AST, serum Aspartate aminotransferase ; LDH, serum lactate dehydrogenase ; WBC, white blood cell ; TG (lg), serum triglyceride level after logarithmic conversion.

Table 5. Principal component analysis of items correlated with resting energy expenditure (REE)

	1 st	2 nd	3 rd
TG (log)	0.892	-0.225	-0.193
Dry weight	0.802	0.063	0.224
Weight	0.797	0.066	0.230
Albumin	-0.177	0.881	0.057
Total protein	-0.048	0.854	-0.304
Height	0.425	0.645	-0.054
Phosphorus	-0.174	0.542	0.500
AST	0.119	0.198	-0.961
WBC	0.154	-0.095	0.474
LDH	-0.137	-0.079	-0.425

The Promax method incorporating Kaiser's normalization was used for rotation and it was found that rotations converged after 5 repetitions. The hatched areas indicate the first to fourth components.

patients with serum albumin level lower than 4.0g/dL (16). The mean REE (24.6kcal/kg per day) was lower than that of the normal Japanese (26.5kcal/kg per day). The patients of the present study were very different from the subjects of Ikizler *et al* (5) who had high REE. Nutritional status of them was much better than that of our subjects. They had higher BMI (26.3±5.9) and higher serum albumin level (4.08±0.32g/dL) than our subjects. This big contrast of nutritional status may support our findings. Another important difference was the age of the patients. Our subjects were much older (mean age 59.1±10.7y)than those of Ikizler, *et al.*(mean age 38.3±13.0 y) (5) . By aging energy metabolism declines and this should be considered when energy intake is discussed.

It is well known that there is a strong positive relationship between the energy intake and protein utilization (17-19) . If the energy intake is poor, protein will be burned as the source of energy and finally leading to protein malnutrition. In this study we could observe similar results. The value of nPCR (1.2g/kg per day) in this study was not low compared with the protein intake recommended by the Nutritional guidelines of National Kidney Foundation Dialysis-Outcomes-Quality-Initiative (NKF-DOQI) (at least 1.2g/kg per day) (20) and the Japanese Society of Nephrology (1.0-1.2g/kg per day) (16) . These recommendations are higher than those for healthy populations, being 0.8g/kg per day in United States (21) and 0.9g/kg per day in Japan (22) . Serum albumin has been reported to have a strong correlation with the morbidity and mortality of hemodialysis patients (3, 23-27). Our study indicated the correlation between REE and serum albumin. High energy may be required for the patients, however it may be possible only when their REE is improved.

This suggests that, the treatments of inflammation and infections may have to be done first. It is possible that due to the treatment, the appetite and energy intake will recover leading to recovery of protein nutrition. This is because mean of CRP, WBC, neutrophil and eosinophil counts were higher. Especially mean values of CRP and neutrophil (segmented cell) were higher in the patients than the standard value. These results indicate that many of our patients were in condition of chronic inflammation, although it is not an intense inflammation. For the treatment of inflammation and infections, the patients may need to take temporary supplement of high energy.

A decrease in fat-free mass may be considered as the other factor contributing for low REE in these patients. Ravussin, *et al.*(28) have reported that most of the differences in REE related to difference in body size, gender, and age can be corrected by calculating the fat-free mass. In addition, Cunningham (29) reported that 65-90% of the variation in REE among adults can be explained by the fat-free mass. Therefore, the correlation between REE and body size among hemodialysis patients in our study may represent the relationship between REE and fat-free mass. There are reports that indicate the relationship between age-related decrease of lean

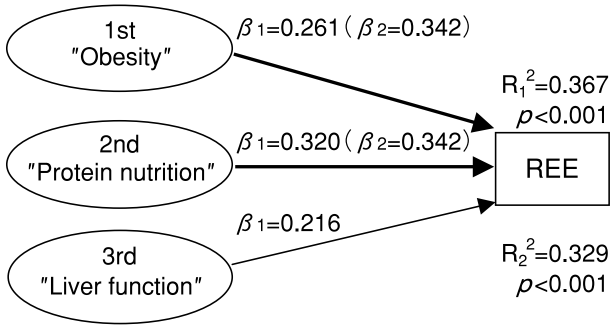

Figure 1. Multiple regression analysis.
Multiple regression analysis (forced entry method) with resting energy expenditure (REE) as the dependent variable and the scores for 3 components detected by principal component analysis as independent variables. β_1, standardized coefficient by forced entry ; multiple regression coefficients : 0.606. β_2, standardized coefficient by stepwise analysis ; multiple regression coefficients : 0.573.

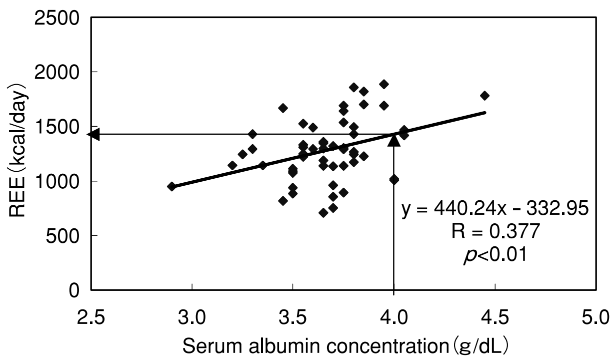

Figure 2. Relationship between REE and serum albumin concentration.
The subjects were 54 patients who measured REE. $p<0.01$

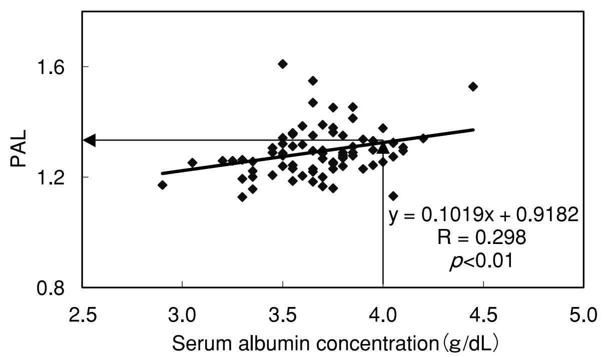

Figure 3. Relationship between PAL and serum albumin concentration
The subjects were 81 patients who determined PAL. $p<0.01$

body mass and decrease of BMR (30, 31). Ishimura, *et al.* (32) have studied the changes of body composition for up to 15 y after the initiation of hemodialysis. The patients of the study were 62.3±11.5y of age and their mean BMI was 21.5±3.3 which were similar to our subjects (59.1±10.7 y and BMI 20.7±3.0). Nutritional status of the patients improved until 3 y from the initiation of hemodialysis and then declined. They reported that fat-free mass was low in their patients. Low physical activity may be another factor of low fat-free mass in the patients. Of course the sickness itself decreases the activity, too. These indicate that both of them deteriorate and lead to a vicious circle. Low PAL (lower than 1.3) was observed in 59.2% of male and 70.4% of female subjects. These values are similar to 64% of institutionalized Japanese elderly female (n=113, 79.5±7.0 y)(13).

REE of Japanese was estimated in 3833 healthy subjects by Metavine (12, 33) using the same gas monitor used in this study. REE of the healthy subjects vs. our hemodialysis patients aged 50-69y were 1807±490 kcal per day (n=389) vs. 1291±312 kcal per day (n=18)($p<0.001$) and70y< were1757±530 kcal per day (n=187) vs. 1287±196 kcal per day (n=6)($p<0.01$), respectively, in male subjects. In female, REE of the healthy subjects vs. our hemodialysis patients aged 50-69y were 1590±390 kcal per day (n=569) vs. 1129±165 kcal per day (n=14)(p<0.001) and 70y< were 1331±411 kcal per day (n=228) vs. 1034±222 kcal per day (n=4) (N.S.), respectively. Except the female patients aged 70y or older, the subjects displayed significantly lower values compared with the healthy subjects (unpaired *t*-test). REE per weight of healthy subjects aged 50-69y was 29.6 kcal/kg per day in male and 29.9 kcal/kg per day in female. These indicate REE of our hemodialysis patients was low (Table 3).

The results of this study suggest that maintenance hemodialysis patients with poor nutritional status may have low REE. Serum albumin level of them need to be more than 4.0 g/dL. We think that energy intake of our patients need to be more than 29 kcal/kg per day based on the results (Fig. 2, 3), namely, REE (27kcal/kg per day)×0.8×PAL (1.33) with the proviso that 80% of REE is BMR (12). An increase in energy intake in such patients is difficult without improvement in both REE and appetite.

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