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QUANTITATIVE ESTIMATION OF DIETARY ENERGY DEFICIENCY AND EFFECTS OF ITS SUPPLEMENTATION ON PROTEIN NUTRITIONAL STATUS OF NONDIABETIC UREMIC PATIENTS UNDERGOING PROTEIN RESTRICTED DIETARY REGIMENS

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ABSTRACT

In chronic renal failure (CRF) patients with a reduced protein intake, if the patients' energy intake could be estimated on the basis of biochemical data together with protein intake, it would be easier to provide them with adequate dietary treatment. Thus, from the relationship among the normalized protein catabolic rate (nPCR) and the intrinsic creatinine generation rate (%GCr) both calculated on the basis of 24-hr urine creatinine, as well as the daily dietary energy intake evaluated by a skilled nutritionist, we devised the following equation to estimate the amount of dietary energy deficiency (ΔE) whose supplementation increases the %GCr of patients on protein-restricted dietary regimens to the target level (i.e., the dietary energy deficient amount). This was done by taking the %GCr of average nondiabetic hemodialysis patients of the same age and sex as a temporal target level: $\Delta E = [31.22 - 1.97\ (\%GCr)^{0.6}]/\ (nPCR)^{0.15}$. In order to examine the clinical usefulness of this equation, the daily dietary energy deficient amount calculated by the equation was supplemented with protein-free jelly. As a result, the %GCr increased from approximately three-fourths of the target level to the target level within 4 months.

Key Words: Creatinine, Low-protein diet, Nitrogen balance, Nutrition, Renal failure

INTRODUCTION

It has been reported that restricting dietary protein intake may retard the rate of progression of chronic renal failure (CRF).[1-3)] Although this possibility awakens interest in protein-restricted dietary regimens for nondialyzed CRF patients, possible malnutrition is a concern. However, some short-term studies on uremic subjects have suggested that a neutral or positive nitrogen balance can be achieved in such patients with reduced protein but sufficient energy intake (i.e., daily intake of 0.6 g/kg protein and 35 kcal/kg energy).[4)]

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Thus, in order to prevent malnutrition during protein-restricted dietary treatment, monitoring the daily dietary energy intake together with the protein intake may be necessary. However, it is not clinically practical to monitor these on the basis of nutritionists' reports.

If the patients' energy and protein intakes could be estimated on the basis of biochemical data, it would be easier to provide them adequate dietary treatment. While dietary protein intake may be estimated from the normalized protein catabolic rate (nPCR) calculated on the basis of the amount of urea excreted in the urine,[5,6] dietary energy intake cannot be estimated on the basis of serum or urine biochemical data at present.

As mentioned above, some studies on uremic subjects have suggested that a negative nitrogen balance due to reduced protein intake can be prevented by sufficient energy intake.[4] If so, there could be a mathematical relationship among protein nutritional status, daily dietary protein intake, and daily dietary energy intake. Thus, among the CRF patients on protein-restricted regimens, we determined an equation indicating such a relationship when the nPCR was taken as the index for protein intake[5,6] and the creatinine (Cr) generation rate as the index for protein nutritional status.[7] Moreover, on the basis of that equation, we attempted to devise a new equation to estimate the amount of daily dietary energy deficiency whose supplementation increases the Cr generation rate to the target level (i.e., dietary energy deficient amount.)

The usefulness of such a devised equation was examined by observing the variation in the Cr generation rate after supplementation of the daily dietary energy intake deficiency calculated by an equation with protein-free jelly.

METHODS

Measurements

1. Collection of 24-hr urine

All the patients studied here were instructed to collect their urine for 24 hr starting with the second urination in the morning of the day before the hospital visit and ending with the first urination in the morning of the day of their visit.

2. Calculation of normalized protein catabolic rate (nPCR)

The nPCR was calculated on the basis of 24-hr urine urea nitrogen by the following formula:[6]

$$\text{nPCR (g/kg/day)} = 6.25 \left[\frac{\text{24-hr urine urea nitrogen (g/day)}}{\text{ideal body weight (kg)}} + 0.031\right] \quad [1]$$

where ideal body weight was calculated by the following equation:[8]

$$\text{Ideal body weight (kg)} = 22 \times \text{Height (m)}^2 \quad [2]$$

3. Calculation of intrinsic creatinine generation rate

Muscle mass represents 4 to 6 kg of the body's total 10 to 12 kg of protein.[9] Expressed in terms of metabolizable energy, this amounts to 20,000 to 30,000 kcal, of which 70 to 80% can be utilized during periods of negative energy balance.[10] Therefore, muscle mass may be an important index of protein-energy nutritional status.[11]

On the other hand, it is known that urinary excretion of Cr is a rough index of muscle

mass.[7] This may be due to the fact that the rate of Cr release from the muscles (i.e., intrinsic Cr generation rate) is directly proportional to the muscle mass. Thus, the intrinsic Cr generation rate would reflect the protein-energy nutritional status.

In the present study, the intrinsic Cr generation rate in nondialyzed CRF patients ($GCr_{non\text{-}HD}$) was calculated by subtracting the Cr derived from food (i.e., extrinsic Cr) from the total Cr excreted in the urine and then adding the amount of Cr degraded in the gut.

4. Creatinine amount derived from food (i.e., extrinsic creatinine)

In the present study, the extrinsic Cr excreted in a patient's urine was roughly estimated by multiplying the extrinsic Cr excreted in the urine in normal volunteers by the ratio of the daily meat and fish intake after initiation of the dietary regimen relative to that before its initiation. The ratio was decided by the patient him- or herself by answering a questionnaire during every hospital visit.

5. Extrinsic creatinine amount excreted in the urine in normal volunteers

In order to estimate the extrinsic Cr generation rate, 12 normal volunteers eating regular meals [55.7 ± 8.3 kg of body weight and 54.5 ± 6.1 years in age] were hospitalized for the experiment. For the 4 days immediately before hospitalization, they were asked to stay home, not to engage in strenuous exercise, and to eat their usual meals (regular-meal period). Following hospitalization, they were served meals containing no meat or fish; the resulting reduced protein content in the meal was supplemented with eggs, cheese, soy bean curd and milk (Cr-free meal period).

The urinary excretions of urea and Cr per day during the regular-meal period were then calculated on the basis of the total amount of the respective substance excreted in the urine for the 3 days immediately before hospitalization, whereas excretions during the Cr-free meal period were calculated on the basis of the total amount of the respective substance excreted in the urine for 3 days beginning with the 6th day of hospitalization. From the urea amount excreted in the urine during the respective periods, nPCR was determined using Maroni's equation (6).

The urinary excretion of extrinsic Cr per day (E_{ext}) was calculated by the following equation:

$$E_{ext} = E_{regular} - E_{Cr\text{-}free} \quad [3]$$

where $E_{regular}$ is the urinary excretion of total Cr during the regular-meal period, and $E_{Cr\text{-}free}$ is that during the Cr-free meal period, all in units of mg/kg/day.

6. Creatinine amount degraded in the gut

Mitch et al.[12] reported that, in near end-stage renal failure, among patients whose serum Cr concentration is more than 6 mg/dl a significant amount of Cr is degraded in the gut, whereas in early-stage renal failure, among patients whose serum Cr concentration is less than 2 mg/dl virtually no Cr is degraded. According to their report, gut Cr clearance is 0.038 ± 0.008 L/kg/day. Thus, in the present study, the gut Cr clearance was assumed to be constant at 0.04 L/kg/day when the serum Cr concentration was over 6 mg/dl, and zero when the serum Cr concentration was less than 2 mg/dl. It was also assumed to increase linearly with serum Cr concentration between 2 mg/dl and 6 mg/dl.

7. Correction of intrinsic Cr generation rate of CRF by sex and age

The intrinsic Cr generation rate is acknowledged to be less in female patients than in male

patients and to decrease with age.[13,14] Therefore, when the intrinsic Cr generation rate is used for long-term observation of the patient's protein nutritional status, adjustments should be made for sex and age.

There are a few reports on equations for the relationship between Cr generation rate and age in males and females. Cockcroft et al.,[14] for example, devised equations for the relationship between the amount of total Cr excreted in the urine and age in males and females with normal renal function. A report by the Patient Registration Committee of the Japanese Society for Dialysis Therapy[13] produced equations for the relationship between the intrinsic Cr generation rate and sex or age among nondiabetic anuric maintenance hemodialysis patients. To our knowledge, however, there have been no reports to date on equations for the relationship between the intrinsic Cr generation rate and age in normal male and female subjects.

Thus, in the present study, in order to correct the intrinsic Cr generation rate of nondialyzed CRF patients by sex and age, the rate was divided by that of average nondiabetic anuric maintenance hemodialysis patients of the same age and sex (GCr_{HD}) reported by the Japanese Society for Dialysis Therapy,[13] thus obtaining the percent intrinsic Cr generation rate (%GCr).

$$\%GCr = \frac{GCr_{non\text{-}HD}}{GCr_{HD}} \times 100 \quad [4]$$

8. Intrinsic creatinine generation rate in nondiabetic anuric maintenance hemodialysis patients of the same age and sex (GCr_{HD})

The GCr_{HD} was calculated using the following equations provided by the Patient Registration Committee of the Japanese Society for Dialysis Therapy[13] in 1994. The relationship between the intrinsic Cr generation rate and the age of nondiabetic male patients was determined by analyzing the data for 48,095 patients, and that for nondiabetic female patients by analyzing the data for 35,168 patients. Both sets of patients had been on maintenance hemodialysis for more than 2 years. Here, the intrinsic Cr generation rate of a maintenance hemodialysis patient was calculated using a method reported elsewhere.[15]

[Male patients]

$$GCr_{HD} = 23.53 - 0.15\ Yr \quad [5a]$$

[Female patients]

$$GCr_{HD} = 19.58 - 0.12\ Yr \quad [5b]$$

where Yr is the age (years).

9. Evaluation of dietary energy intake by nutritionists

Patients were asked to record all food and beverages consumed over a 3-day period ending at their bedtime the night before a hospital visit. When they visited the hospital the next morning, the record was checked during an interview. Subsequently, the individual items on the records were coded and analyzed by personal computer using nutrition calculation software (My Calorie^{R}; Total Software Co., Ltd.; Kagoshima, Japan), in order to evaluate each person's daily energy intake.

Relationship among nPCR, %GCr and daily dietary energy intake evaluated by nutritionist

The %GCr may increase as either the nPCR or the daily dietary energy intake increases. Hence, the daily dietary energy intake was assumed to correlate with $(\%GCr)^{m} \times (nPCR)^{-n}$, where $m>0$ and $n>0$. The %GCr, nPCR and daily dietary energy intake evaluated by the nutri-

tionist were obtained in 19 nondialyzed nondiabetic CRF outpatients, and they were modified to fit an equation of the following form, so as to determine each constant (i.e., "a," "m" or "n").

$$E_{nutritionist} = a\ (\%GCr)^{m} \times (nPCR)^{-n} \quad [6a]$$

The patients were 10 males and 9 females. The mean (± SD) age was 56.1 ± 10.3 years. Their Cr clearance averaged 36.8 ± 9.4 ml/min/1.73 m^2, ranging from 24 to 49 ml/min/1.73 m^2. The causes of CRF were as follows: chronic glomerulonephritis (N=17), nephrosclerosis (N=1), and polycystic kidney (N=1). Patients treated with corticosteroids and/or immunosuppressive agents, or those whose urine protein was over 1.0 g/day, were not included in the study. Informed consent was obtained from each patient for their participation in the experiments.

The patients were instructed to maintain a 0.60-g/kg protein and 35-kcal/kg energy diet every day. Each patient visited the hospital once a month.

Each parameter (i.e., the nPCR, %GCr and daily dietary energy intake evaluated by a nutritionist) employed in this experiment was composed of the mean of 4 values obtained during 4 months in the protein-restricted period. The nPCR, %GCr and dietary energy intake were all obtained more than 4 months after initiation of the protein-restricted dietary regimens, assuming that the nutritional status had reached a stable level within 4 months after initiation of the regimens.

It was known that additional Cr is released from muscle during exercise.[16] Therefore, the patients were also asked not to do strenuous exercise either the day before or on the actual day of urine collection. According to the questionnaires filled out by the patients during each hospital visit, no one had engaged in strenuous exercise on those days.

Amount of daily dietary energy deficiency whose supplementation increases %GCr to target level

1. Devising of equation

The variation in the resting energy expenditure from patient to patient[4] may cause a variation in the amount of energy from patient to patient sufficient to prevent catabolism due to a protein-restricted diet. Therefore, in order to cancel the effect of such a variation in the resting energy expenditure from patient to patient, the deficient amount of the daily dietary energy intake (i.e., the amount which, if supplemented, brings %GCr up to a target level) was employed for monitoring patients' nutritional status instead of the daily dietary energy intake. Thus, the following equation, which was also described in the "Results Section," was devised to estimate the amount of daily dietary energy deficiency whose supplementation increases the %GCr of a nondialyzed nondiabetic CRF patient to the level of average nondiabetic hemodialysis patients of the same age and sex, which was the tentative target level (i.e., 100%):

$$\Delta E = E_{estimate(100)} - E_{estimate} = \frac{31.22 - 1.97\ (\%GCr)^{0.6}}{(nPCR)^{0.15}} \quad [7]$$

where ΔE is the amount of daily energy deficiency whose supplementation increases the %GCr of a nondialyzed CRF patient to the target level, $E_{estimate}$ is the estimated dietary energy intake of the patient with a given nPCR and a given %GCr (estimated by Equation [6b] described in the "Results Section"), and $E_{estimate(100)}$ is the estimated dietary energy intake of the same patient when %GCr was put at 100% but with the same nPCR level. An equation for $E_{estimate(100)}$ can be obtained by substituting the %GCr of Equation [6b] by 100%. Equation [6b] is shown in

the “Results Section.”

2. Evaluation of equation

In order to examine the clinical usefulness of Equation [7], we selected 7 other nondialyzed nondiabetic CRF outpatients who were treated with protein-restricted regimens for more than 4 months and whose %GCr was less than 90%. Informed consent was obtained from each patient for their participation in the experiments. The patients were 3 males and 4 females with a mean age of 54.0 ± 12.4 years. Their Cr clearance averaged 29.7 ± 6.9 ml/min/1.73 m^2, ranging from 22 to 39 ml/min/1.73 m^2. The cause of CRF in all patients was chronic glomerulonephritis. Patients treated with corticosteroids and/or immunosuppressive agents or those whose urine protein was over 1.0 g/day were not included in the study.

The patients had been instructed to maintain a 0.60-g/kg protein and 35-kcal/kg energy diet every day. Each patient visited the hospital once a month.

In this experiment, the daily amount of dietary energy needed for the %GCr to reach 100% (i.e., deficient amount of dietary energy intake) was first calculated using Equation [7] on the basis of nPCR and %GCr of the respective patient, each of which were the means of 4 values obtained during 4 months immediately before initiation of the experiment. The patient was then instructed to eat an amount of protein-free jelly (Makuton Jelly^R; Banyu A.C.E. Co. Ltd.; Tokyo Japan), the energy content of which was equivalent to the previously estimated deficient amount of dietary energy intake between meals each day, and was forbidden to change dietary habits thereafter. According to the manufacturer, one cup of Makuton Jelly (27.5 g; 50 kcal) contains 0.5 g of medium chain triglyceride with *n*-caproic acid and 11.4 g of carbohydrate, but no protein.

In order to evaluate the usefulness of Equation [7], variations in %GCr and nPCR were observed for 4 months following the start of this dietary energy supplementation. Analysis of variance was used to determine statistically significant variations in %GCr and nPCR following the start of the dietary energy supplementation. If a significant variation was indicated by the analysis, Scheffe’s t test was used to compare each parameter at any given time with the mean of 4 values obtained during the 4 months immediately before the start of the supplementation.

RESULTS

Extrinsic creatinine amount excreted in the urine in normal volunteers

In the present study, the urinary excretion of the extrinsic Cr was obtained by subtracting the urinary excretion of total Cr during creatine-free meal periods from that during the regular-meal periods in normal volunteers. The thus-obtained extrinsic Cr was 3.15 ± 0.90 mg/kg/day. Since there was no significant difference in the nPCR between the regular-meal period (1.13 ± 0.44 g/kg/day) and the creatine-free meal period (1.11 ± 0.43 g/kg/day), such a difference in urinary excretion of total Cr between these periods is not due to any variation in the nitrogen balance level.

Relationship among nPCR, %GCr and daily dietary energy intake evaluated by nutritionist

When the %GCr, nPCR, and daily dietary energy intake evaluated by the nutritionist, all of which were composed of the means of 4 values obtained during 4 consecutive months in the protein-restricted period, were modified to fit an equation of the form $E_{nutritionist} = a\,(\%GCr)^m \times (nPCR)^{-n}$, the following equation was obtained:

$$E_{nutritionist} = 1.97\ (\%GCr)^{0.60} \times (nPCR)^{-0.15} \quad [6b]$$

The mean error of the daily energy intake estimated by Equation [6b] from that evaluated by the nutritionist was 2.43 kcal/kg/day, with a maximum error of 4.37 kcal/kg/day.

Amount of daily dietary energy deficiency whose supplementation increases %GCr to target level

At the start of the supplementation of dietary energy deficiency, the deficiency was 4.62 ± 1.35 kcal/kg/day. The dietary energy deficiency in individual patients is indicated in Table 1 together with the %GCr and nPCR.

As shown in Figure 1, analysis of variance revealed a significant variation in the %GCr following the start of supplementation of dietary energy deficiency ($P<0.0001$), despite no significant variation in the nPCR.

Scheffe's t test indicated that the %GCr value was significantly greater at 92.0 ± 6.0% ($P<0.001$) in the 1st month, 101.5 ± 9.0% ($P<0.001$) in the 2nd month, 99.5 ± 10.6% ($P<0.001$) in the 3rd month and 100.3 ± 7.4% ($P<0.001$) in the 4th month from the start of supplementation than the mean of 4%GCr values obtained during the 4 months prior to the start of the supplementation (78.2 ± 5.9%).

The mean of 4 nPCR values obtained during 4 months prior to the start of the supplementation was 0.62 ± 0.07 g/kg/day, against 0.64 ± 0.08 g/kg/day in the 1st month, 0.62 ± 0.05 g/kg/day in the 2nd month, 0.63 ± 0.09 g/kg/day in the 3rd month and 0.64 ± 0.03 g/kg/day in the 4th month from the start of supplementation.

DISCUSSION

The present study was designed under two assumptions. One is that the nitrogen imbalance would be reflected by the variation in the intrinsic Cr generation rate, which may be an index of muscle mass.[17] The other is that the factors determining nitrogen balance would be the dietary protein intake and the dietary energy intake in nondialyzed nondiabetic CRF patients.[4]

The intrinsic Cr generation rate can be influenced by physical exercise. In the present study, however, since the patients answering the claimed not to have undertaken strenuous exercise,

Table 1 The %GCR, nPCR and energy deficiency at the start of supplementation of energy deficiency in each patient.

Patient No.	%GCR (%)	nPCR (g/kg/day)	Energy deficiency (kcal/kg/day)
1	81.1	0.73	3.86
2	79.6	0.64	4.27
3	81.1	0.61	3.97
4	86.5	0.68	2.75
5	70.4	0.57	6.45
6	70.6	0.60	6.35
7	78.2	0.54	4.69
mean ± S.D.	78.21 ± 5.86	0.62 ± 0.07	4.62 ± 1.35

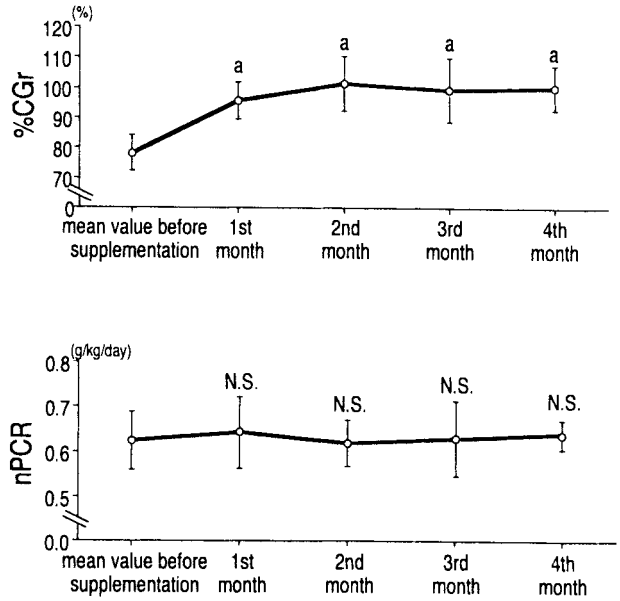

Figure 1: Variations in %GCr and nPCR following the start of supplementation of deficient amount of dietary energy intake. There was a significant increase in the %GCr following the start of supplementary regimens, despite no significant variation in the nPCR. [a)]$P<0.005$

the effects of exercises on intrinsic Cr generation rate may be neglected.

In the present study, the amount of intrinsic Cr generated was calculated by subtracting the food-derived Cr from the total Cr excreted in the urine and then adding the Cr degraded in the gut. Here, the amount of food-derived Cr excreted in the urine was estimated roughly on the basis of the extrinsic Cr generation rate in 12 normal volunteers in Japan and the ratio of the amount of meat and fish consumed during the protein-restricted dietary regimens relative to that when eating regular meals before the initiation of the regimens. The ratio of the amount of meat and fish consumed before and during the regimens was decided by each patient.

Although an approximate extrinsic Cr generation rate was obtained in the present study, the error in that rate was thought to be smaller when the extrinsic Cr amount excreted was taken into account than when it was not.

The intrinsic Cr generation rate, which may be an index of muscle mass,[7)] is reported to be lower in females than in males and decreases with age.[13,15)] Hence, that rate in a nondialyzed patient should be adjusted for age and sex, so as to be expressed as the ratio relative to that of a normal subject of the same age and sex. However, there have been no reports on the intrinsic Cr generation rate of normal subjects. Therefore, in the present study, we tentatively employed the intrinsic Cr generation rate of nondiabetic maintenance hemodialysis patients of the same age and sex instead of that of normal subjects of the same age and sex, assuming that the Cr generation rates of each would be equivalent. However, the Patient Registration Committee of the Japanese Society for Dialysis Therapy indicated that the mean %GCr tended to increase every year[18)] since 1994, thanks to the technical improvements in hemodialysis. These findings suggest that the %GCr of maintenance hemodialysis patients might be lower than that of nor-

mal persons of the same age and sex. If so, the target level of %GCr may need to be higher than 100%. A new equation to calculate the deficient amount of daily dietary energy intake can be obtained by substituting a new target level of %GCr for "$\%GCr_{estimate(100)}$" in Equation [7].

It is impossible to compare the estimated deficient amount of daily dietary energy intake with the actual deficient amount for verification of the validity of Equation [7], since there is no way to measure the latter. Nevertheless, the clinical usefulness of the equation was demonstrated in the present study. The mean %GCr increased from approximately three-fourths of the target level (i.e., 78.2 ± 5.9%) to the target level (i.e., 100.3 ± 7.4%) within 4 months by supplementing the daily dietary energy deficiency calculated by Equation [7] with protein-free jelly.

Whether or not restriction of dietary protein intake retards the progression of CRF remains controversial.[1-3,19,20] However, it is not the purpose of the present study to clarify the effectiveness of a restricted-protein diet.

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