Original Article

Muscle mass index in haemodialysis patients: a comparison of indices obtained by routine clinical examinations

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Abstract

Background. Measurement of muscle mass is useful for evaluating protein nutritional status. Various methods for estimating muscle mass in haemodialysis patients have recently been developed.

Methods. The validity of the estimate of creatinine production calculated with the creatinine kinetic model (CKM) was examined in 46 haemodialysis patients by comparing it with the actual creatinine production, this being determined from the sum of creatinine appearing in the dialysate and the estimated metabolic degradation. The correlation of various other muscle mass indices with creatinine production was also investigated in these patients.

Results. The estimate of creatinine production using CKM was significantly correlated with creatinine production calculated from the spent dialysate plus an estimate for the extra-renal creatinine degradation ($r_s = 0.90, P < 0.001$). A Bland–Altman analysis revealed that the mean prediction error for the estimate of creatinine production by CKM was $0.10 \text{ g day}^{-1}$ and the limits of agreement were $0.34$ to $-0.14 \text{ g day}^{-1}$. The cross-sectional area of the thigh muscle measured by computed tomography (CT) was also significantly correlated with creatinine production ($r_s = -0.86, P < 0.01$). In contrast, the correlations of 3-methylhistidine production measured in the spent dialysate, the mid-upper arm muscle circumference and the skeletal muscle mass estimated by an anthropometric prediction model with creatinine production were lower ($r < 0.82$).

Conclusion. Creatinine production calculated using CKM and CT measurement of thigh muscle area are valid methods for estimating muscle mass during routine clinical examinations of haemodialysis patients.

Keywords: creatinine; kinetic model; 3-methylhistidine; muscle mass; nutritional assessment

Introduction

Protein nutritional status is considered important in the care of dialysis patients, because it is closely associated with morbidity and mortality [1]. Because more than 60% of the body protein is stored in the skeletal muscles [2], the estimation of muscle mass as a somatic protein reserve may be as useful as the measurement of various serum protein concentrations, including serum albumin, prealbumin and other rapid-turnover proteins, for evaluating the protein nutritional status in a haemodialysis patient.

The daily rate of creatinine formation in normal individuals is constant and depends on the creatine-creatine phosphate pool, which is proportional to the muscle mass. Furthermore, since creatinine is almost completely excreted in the urine, daily creatinine excretion has been considered a measure of total muscle mass in the body. The creatinine excreted by patients with chronic renal failure, however, is somewhat different due to their higher extra-renal creatinine degradation. Mitch et al. have reported an estimated extra-renal creatinine clearance value of $0.038 \text{ l kg day}^{-1}$ in patients with a serum creatinine value of $>6 \text{ mg dl}^{-1}$ [3]. If we allow for the extra-renal degradation of creatinine, the dialysate of anuric patients can be used to estimate the creatinine production rate as shown by Keshaviah et al. [4]. They have reported that the rate of creatinine production based on the amount of creatinine appearing in the dialysate and on its metabolic degradation is highly correlated with the lean body mass (LBM) measured by a bio-impedance analysis or calculated from the total body water, and they have suggested creatinine production to be a good indicator of LBM. The method for collecting the dialysate, however, is cumbersome and is not routinely performed in dialysis centers. Shinzato et al. have recently reported a new method for calculating...
the creatinine production rate from the pre- and post-dialysis creatinine concentrations by means of creatinine kinetic modelling [5]. Although this method can be easily applied to the clinical setting, it has not been validated by any subsequent study.

The upper arm muscle circumference is an anthropometric parameter traditionally used for evaluating muscle mass [2]. The technique, however, is dependent on the skill of the evaluator, and is subject to errors resulting from inconsistent skin-fold thicknesses and irregular outlines of the muscles. It may also be difficult to estimate the whole-body muscle mass from the upper arm muscle circumference. As an alternative to this unreliable measurement of arm muscle circumference, several investigators have attempted to measure muscle volume by using computed tomography (CT) [6]. The fat-free muscle area on the image has been reported to show a strong association with the direct measurement of muscle volume in cadavers. We too have reported that the thigh muscle cross-sectional area measured by CT is highly correlated with the creatinine production in haemodialysis patients [7].

The amino acid 3-methylhistidine is a product of the degradation of myofibrillar protein and is not re-utilized for protein synthesis. Urinary 3-methylhistidine excretion is used, therefore, as an index of the somatic protein reserve, and has shown high correlation with muscle mass in normal individuals [8]. 3-Methylhistidine appearing in the dialysate of haemodialysis patients may therefore be used as an indicator of muscle volume.

The goal of this study is to devise a method to assess the protein nutritional status of haemodialysis patients that uses easily and repeatedly available methods in clinical practice. To this end, we examined the validity of the creatinine kinetic method for determining creatinine production by comparing it with the direct dialysate creatinine quantification method that has been adopted as the reference. In addition, several other methods that have been used for estimating muscle mass or LBM in clinical practice were compared for their correlation with creatinine production.

Subjects and methods

Subjects

Forty-six aneuric patients (31 males and 15 females) who had been undergoing haemodialysis at Miyaji Hospital (Shimizu, Japan) for > 6 months were enrolled in the study. Bed-ridden or disabled patients who might have had muscle atrophy were excluded, as were patients with diabetic nephropathy, anorexia or those who had ingested an unusual amount of meat during the week before the study. The patients were maintained on a regular haemodialysis regimen (three times a week for 4–5 h) with hollow-fibre dialysers and a bicarbonate-buffered dialysate (Kindary AF-3P, Fuso, Osaka, Japan). The blood flow rate was in the range of 150–200 ml/min, with a dialysate flow rate of 500 ml/min (each machine was calibrated before use). Blood samples were drawn at the start and end of the first dialysis session of the week. Serum or plasma was separated immediately and stored at −82°C until analysed.

Measurement of creatinine and 3-methylhistidine production

Creatinine production was determined from the sum of the creatinine present in the dialysate and the estimated metabolic degradation [3]. The spent dialysate was collected by the modified partial dialysate collection method developed by Ing et al. [9]. Briefly, a portion of the dialysate was collected through a narrow side tube which had been introduced into the dialysate drainage tube. The flow rate of the collected dialysate was limited by an adjustable clamp to 1.5–2.0 ml/min, and the dialysate was collected throughout the session. The amount of creatinine removed during the dialysis session was calculated from the creatinine concentration in the collected spent dialysate, the dialysis flow rate of 500 ml/min, the duration of the dialysis session, and the ultrafiltration volume.

During preliminary studies, we collected the dialysate from three successive dialysis sessions each for nine patients and calculated the total amount of creatinine removed during one week. The creatinine removed during each dialysis session was 36.6±2.0% for the first dialysis of the week, 33.0±1.4% for the mid-week dialysis, and 30.4±2.2% for the final dialysis of the week. Thereafter, the amount of creatinine removed per week was roughly calculated as three times the measured value from the mid-week dialysis session. The amount of creatinine removed per day was calculated as the week’s creatinine removal divided by 7. The metabolic degradation of creatinine was calculated by using the following equation [3]:

\[
\text{Degradation} = 0.38 \times \text{mean of the pre- and post-dialysis serum creatinine concentrations (mg/dl)} \times \text{body weight (kg)}.
\]

The intra-subject variability expressed as a coefficient of variation was 5.6% for this method.

3-Methylhistidine delivery into the dialysate was also determined by partial dialysate collection from the subjects, with no additional route for its metabolism being considered in this study.

Estimation of creatinine production by the creatinine kinetic model (Cr-CKM)

Based on the creatinine kinetic model developed by Shinzato et al., the creatinine production rate was estimated by using the pre- and post-dialysis creatinine concentrations at the first dialysis session of the week according to the following equation [5]:

\[
\text{The total creatinine generation rate (g/kg/day)} = C_s \left( \frac{7056}{A} + \frac{240}{72 - T_d} \right)
\]

where

\[
A = 3864 + \left( 7.8T_d + 411 \right) \ln \left( \frac{C_s}{C_r} \right) - 1.5T_d
\]

\[
- \frac{1449}{0.0190T_d + 0.999} \ln \left( \frac{C_s}{C_r} \right) - (0.00367T_d - 0.0219)
\]
where \( C_t \) (mg/dl) is the pre-dialysis creatinine concentration, \( C_0 \) (mg/dl) is the post-dialysis creatinine concentration, \( \Delta \text{BW} \) (kg) is the body weight decrease resulting from dialysis, \( \text{IBW} \) (kg) is the ideal body weight, and \( T_d \) (h) is the dialysis duration.

The intra-subject variability of Cr-CKM from six measurements over 3 months was 6.4%.

**Measurement of the thigh and abdominal muscle area by computed tomography**

CT scans of the thigh and abdominal muscle were performed during a patient’s periodic check-up. The CT scan and the measurement of creatinine production were done within 3 months of each other. Each patient was examined in the supine position with thigh muscles relaxed. Images for evaluating muscle mass were obtained at the mid-point of a line extending from the superior border of the patella to the greater trochanter of the femur, and at the level of the third lumbar spine. The thickness of a slice was 10 mm. The images were digitally scanned for analysis by a personal computer. The adipose-tissue-free thigh and abdominal muscle cross-sectional areas were measured with a planimetry program, ‘NIH-image’ (written by Wayne Rasband, US National Institute of Health). CT evaluation of muscle mass was performed by two investigators, the difference between the two evaluations being 2.4% for the thigh muscle measurements and 5.6% for the abdominal muscle measurements.

**Anthropometric measurements**

Body weight was measured before and after each dialysis; the post-dialysis body weight being taken as the dry weight. The BMI was calculated as dry weight in kilogrammes divided by the square of the height in metres. The mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSF) were measured with a tape measure and Harpenden skinfold calipers (Holtain, Crumch, UK), respectively, on the limb not used for vascular access. All the measurements on patients were performed by one skilled investigator (S.O.). The mid-upper arm muscle circumference (MUAMC) was calculated by using the following equation:

\[
\text{MUAMC} = \text{MUAC} - (\text{TSF} \times 3.14),
\]

where MUAMC, MUAC and TSF were measured in centimetres.

**Estimation of muscle mass by an anthropometric prediction model**

An anthropometric prediction model has recently been developed to estimate the total-body skeletal muscle mass in large samples of non-obese healthy subjects, and the values from this equation were reported to be strongly correlated with the reference values measured by magnetic resonance imaging [10]. The equation for this model is as follows:

\[
\text{Skeletal muscle mass} = 0.244 \times \text{body weight (kg) + 7.80} \\
\times \text{height (m) + 6.6} \times \text{sex - 0.098} \\
\times \text{age + race - 3.3},
\]

where sex = 0 for women and 1 for men, and race = -1.2 for Asians.

**Analytical procedures and statistical analyses**

Serum and spent dialysate creatinine were measured by the Jaffe reaction method with an AU-1000 automatic analyser (Olympus, Tokyo, Japan). The machine was calibrated in the 0.3–15 mg/dl range of creatinine concentration, and thus was adequate for both serum and dialysate creatinine measurements. 3-Methylhistidine in the plasma and spent dialysate was determined by the high-pressure liquid chromatography method developed by Wassner et al. [11].

Each variable is presented as the mean ± SD. Differences among groups were evaluated by an analysis of variance (ANOVA) and subsequent Bonferroni test. Repeated measures two-factor ANOVA was applied to compare the two types of creatinine production and the difference between men and women. A simple regression analysis was applied to examine the relationship between variables, while a Bland–Altman plot was used for assessing the measurement of bias, the limit of agreement and the root mean square error between two methods. Statistical significance was given to a \( P \) value of <0.05. All statistical calculations were performed with GB-STAT software (Dynamic Microsystems, Silver Spring, MD, USA).

**Results**

The patients’ characteristics and indices of muscle mass are shown in Table 1. The mean age, duration of haemodialysis, and BMI were not significantly different between the men and women, whereas height, dry weight, serum creatinine and plasma 3-methylhistidine were significantly higher in the men than in the women. The indices of muscle mass such as creatinine production (mmol/day), 3-methylhistidine generation (mmol/day), thigh muscle area, abdominal muscle area and skeletal muscle mass estimated by an anthropometric prediction model were all significantly higher in men than in the women. Repeated measures two-factor ANOVA indicated that creatinine production estimated by the creatinine kinetic model was significantly higher than the value measured from spent dialysate.

**Validation study for Cr-CKM**

The estimate of creatinine production by CKM was strongly correlated with the creatinine production determined from the spent dialysate after allowing for the extra-renal creatinine degradation (\( r = 0.90, P < 0.001 \)) (Figure 1). A Bland–Altman analysis indicated that the mean prediction error for Cr-CKM was 0.10 mg/day, the limits of agreement were +0.34 to −0.14 mg/day, and the root mean square error was 0.16 mg/day (Figure 2). The correlation coefficient in the Bland–Altman plot was insignificant (\( r = 0.24, P = \text{NS} \)).

**Correlation study for other muscle indices**

The adipose-tissue-free thigh muscle cross-sectional area measured by computed tomography was highly correlated with creatinine production measured either with the spent dialysate or estimated by the creatinine
Table 1. Patients’ characteristics and muscle mass indices

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.3 ± 8.3</td>
<td>57.5 ± 8.6</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>5.8 ± 3.6</td>
<td>5.2 ± 3.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.6 ± 7.2</td>
<td>149.6 ± 3.3</td>
</tr>
<tr>
<td>Dry weight (kg)</td>
<td>54.0 ± 7.6</td>
<td>45.8 ± 5.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.8 ± 2.1</td>
<td>19.4 ± 2.7</td>
</tr>
<tr>
<td>AMC (cm)</td>
<td>22.1 ± 2.1</td>
<td>20.1 ± 1.9</td>
</tr>
<tr>
<td>Thigh muscle area (cm²)</td>
<td>93.4</td>
<td></td>
</tr>
<tr>
<td>Abdominal muscle area (cm²)</td>
<td>113.4</td>
<td></td>
</tr>
</tbody>
</table>

Serum creatinine concentration and creatinine production are also represented by both SI and conventional units.

The cross-sectional area of a muscle also was measured at the level of the third lumbar spine. The relationships between these CT-measured muscle areas and creatinine production is summarized in Table 3, and scatter plots of these relationships are shown in Figure 3. Compared with the thigh muscle area, the abdominal muscle area had lower correlation with the creatinine production, and the correlation of the thigh plus abdominal muscle area with creatinine production also was lower than that of the thigh muscle area.

**Discussion**

In this study we examined the reliability of estimating creatinine production by the creatinine kinetic model,
and compared it with various other methods currently used in clinical practice for estimating muscle mass and creatinine production. The results indicate that estimating creatinine production by using the creatinine kinetic model is a reasonable substitute for determining creatinine production from the spent dialysate plus the estimated extra-renal creatinine degradation, and equally useful as an index of muscle mass. Among other measures of muscle mass, the cross-sectional area of the thigh muscle by CT was highly correlated (r = 0.85) with the creatinine production. In contrast, the correlation with creatinine production of the production of 3-methylhistidine (as measured in the spent dialysate, the mid-arm muscle circumference and the skeletal muscle mass estimated by an anthropometric prediction model) tended to be lower (r < 0.82).

Among the various non-invasive methods for assessing muscle mass, measuring total body nitrogen by a rapid \textit{in vivo} neutron activation analysis [12] has been considered to be the gold standard for estimating the total body protein store. However, few facilities have total body counting equipment for measuring this as yet experimental index. Double energy X-ray absorptiometry is also a useful technique for determining the lean body mass [13], but the instrument is not commonly found at haemodialysis facilities. Bioimpedance analysis is another non-invasive and inexpensive technique for measuring lean body mass, but although it can be applied easily to patients at the bedside, fluctuations in the volume status may result in an incorrect lean body mass of dialysis patients [14].

In contrast, daily creatinine production is the most popularly used index of muscle mass for the general population, and it has been shown to have a strong correlation with LBM [15]. However, determining creatinine production in haemodialysis patients is cumbersome because it requires the collection of spent dialysate. Shinzato \textit{et al.} [5] have developed a new equation to calculate creatinine production by using the pre-dialysis creatinine concentration and the estimated post-rebound creatinine concentration with the application of the method for determining the protein catabolic rate reported by Depner and Daugirdas [16]. In this equation, the post-rebound creatinine concentration is estimated from the post-dialysis creatinine concentration and the Kt/V value for creatinine. An estimate of creatinine production using the pre- and post-dialysis serum creatinine values showed the best correlation with creatinine production measured from the spent dialysate, and a Bland–Altman analysis showed that the root mean square error between these values was 0.16 g/day, suggesting the creatinine kinetic model to be acceptable for practical clinical use in estimating the creatinine production of haemodialysis patients. As shown by the mean difference, however, the value for creatinine production calculated by the creatinine kinetic model was 10% higher than that actually measured in the dialysate. This over-estimation might have been caused by the assumptions that were made for developing the creatinine kinetic method. These assumptions are that creatinine is distributed to one compartment in the body and that the ratio of the creatinine distribution volume is 0.49. Furthermore, the difference between the estimate of creatinine production by the creatinine kinetic model and the direct dialysate creatinine quantification method was more apparent in females. The creatinine kinetic method does not consider sex difference, and this might be responsible for over-estimating creatinine production in females. Since there are some differences in creatinine metabolism and body composition between males and females, it might be better for the estimate of creatinine production to be performed by different formulae for males and females.

We recognize that the application of creatinine production as a reference index of muscle mass has some limitations. First, creatinine excretion has a day-to-day variation of 20% or more even in healthy subjects [17], while creatinine should be converted from creatine at a fairly constant rate and excreted completely in the urine. Despite this problem, 24-h creatinine clearance has been used worldwide to estimate glomerular filtration rate. Secondly, the intake of creatinine in foods may be added to the intrinsically generated creatinine, so that the creatinine production
rate might be over-estimated if the subject has not eaten a meat-free diet for some time. Heymsfield et al. have demonstrated that a readjustment in the size of the creatinine pool took >1 week after changing from a meat diet to a creatinine-free diet [18]. They concluded, therefore, that the diet must remain reasonably consistent during the study. It is for this reason that we did not recommend a meat-free diet to our patients in this study and eliminated only those patients from the study who had eaten an unusual amount of meat during the week before the study. The highly significant correlation between creatinine production measured from the spent dialysate and other muscle indices might suggest that the influence of creatinine ingestion is not an important factor for evaluating the production of creatinine in our haemodialysis patients. The major reason for this might be because the Japanese haemodialysis patients had not regularly eaten much meat in their diet. Furthermore, even if muscle mass might be over-estimated as a result of extrinsic creatinine, serial measurements of creatinine production over time would show a trend for muscle mass in a subject whose diet has remained fairly constant.

CT measurement of muscle cross-sectional area could be used to make a direct assessment of muscle mass with definition of the fat–muscle interface and intramuscular adipose tissue. This method is likely to be more accurate and reliable than any other anthropometric method for evaluating muscle mass. Furthermore, there is no need to take into account the errors caused in the estimation of creatinine production by the dietary intake of creatinine and the post-dialysis rebound in the serum creatinine concentration. Another advantage of CT is that the portrait of the muscle makes it possible to identify immediately muscle atrophy. Of the muscles measured in this study, the thigh muscle showed a better correlation with creatinine production than the abdominal muscle or thigh plus abdominal muscle. A possible explanation for this may be that the limb lean tissue is more sensitive to lean tissue depletion than the trunk lean tissue, as has been shown by Woodrow et al. [19].

3-Methylhistidine, MUAMC and the skeletal muscle mass estimated by an anthropometric prediction model did not show a noteworthy association with creatinine production measured from the spent dialysate. Although the urinary 3-methylhistidine excretion has been reported to be correlated with the LBM in normal individuals, the source of 3-methylhistidine in urine is not exclusively skeletal muscles. The gut actin pool could contribute to the output of urinary 3-methylhistidine in the range of approximately 30–40% [20]. This fact may explain the poorer association of 3-methylhistidine with creatinine production in our subjects. The correlation between the anthropometric prediction model and other muscle indices also was fairly low in this study, because this prediction model might not be appropriate for application to dialysis patients and did not consider the fat mass [10]. The limitation of MUAMC as a muscle index has been reported previously [7] and does not require additional explanation.

Since the pre- and post-dialysis serum creatinine levels have usually been measured in most dialysis facilities, the determination of Cr-CKM enables us to examine retrospectively changes of muscle mass volume and protein nutritional status over a long period. This method is also suited for a large-scale cohort study to evaluate the nutritional status of haemodialysis patients. Furthermore, the cost benefit of this method is much better than other methods. On the other hand, the CT evaluation of muscle mass is superior in that the muscle architecture can be visualized directly. The cost of CT scanning is not particularly high for a one-image slice.

In summary, creatinine production estimated by the creatinine kinetic model was found to be a valid indicator of muscle mass in haemodialysis patients, and the thigh muscle area measured by CT scanning was also useful for evaluating muscle mass as well as muscle architecture. These indices of muscle mass can be applied easily for the nutritional evaluation of a haemodialysis patient.

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