Association of age with muscle mass, fat mass and fat distribution in non-diabetic haemodialysis patients

Sakae Ohkawa1, Mari Odamaki1, Naoki Ikegaya1, Ikuo Hibi2, Kunihiko Miyaji2 and Hiromichi Kumagai1

1Department of Clinical Nutrition, School of Food and Nutritional Sciences and COE Program in the 21st Century, University of Shizuoka and 2Miyaji Hospital, Shizuoka, Japan

Abstract

Background. In the general population, aging induces changes in body composition, such as sarcopenia or a relative increase in visceral fat, but it remains unclear if similar changes occur in elderly haemodialysis (HD) patients.

Methods. Age-related changes in muscle and fat mass and fat distribution in the thigh and abdomen were cross-sectionally investigated in Japanese HD patients. The thigh muscle area (TMA), thigh intermuscular fat area (IMFA), thigh subcutaneous fat area (TSFA), abdominal muscle area (AMA), abdominal visceral fat area (AVFA) and abdominal subcutaneous fat area (ASFA) were measured by computed tomography in 134 non-diabetic patients between 21 and 82 years on HD. AMA, AVFA and ASFA were also measured in 70 age-matched controls.

Results. Muscle mass, fat mass and fat distribution differed significantly with age in both HD patients and controls, without significant differences in BMI. In both male and female HD patients, TMA and AMA showed significant negative correlations with age. All measures of subcutaneous fat—including TSFA, ASFA and the triceps skinfold thickness, were inversely associated with age in the female patients. In contrast, both IMFA and AVFA showed significant positive correlations with age in both male and female patients. The increase in the AVFA/ASFA ratio with age suggests progression of visceral fat accumulation in the elderly HD patients. Controls showed similar relationships between age and muscle mass and visceral fat accumulation.

Conclusions. We found an association between age and decrease in muscle mass as well as increase in visceral and intermuscular fat in non-diabetic HD patients. Such changes may be associated with the metabolic abnormalities and increased mortality in elderly HD patients.

Keywords: computed tomography; elderly patient; intermuscular fat; nutritional status; muscle mass; visceral fat

Introduction

The proportion of elderly haemodialysis (HD) patients has increased dramatically during the last decade. These patients often suffer from nutritional problems, which would be associated with increased morbidity and mortality [1]. Previous studies have indicated that 50–68% of dialysis patients older than 65 years were judged to be malnourished by such nutritional measures as serum albumin, normalized protein nitrogen appearance, an indicator of dietary protein intake, and subjective global assessments [2]. In those studies, however, relative body weight or body mass index (BMI) was unlikely to change with aging.

In the general population, body composition, including fat mass, fat distribution and muscle mass, gradually changes with aging, even if the body weight remains unchanged [3]. Lean body mass decreases significantly, while fat mass increases and is preferentially stored in abdominal tissues. These changes might result from decreased physical activity, an imbalance between energy intake and expenditure, and altered endocrine functions. Decreased muscle mass, which is termed sarcopenia, has been reported to have prognostic implications in the general population [4] and in those with chronic obstructive pulmonary diseases [5]. Beddhu et al. [6] have also demonstrated that increased muscle mass conferred a survival advantage in HD patients with a high BMI. Sarcopenia is considered to be associated with falls, functional decline,
osteoporosis, glucose intolerance and impaired immunocompetency. Furthermore, in the elderly, these complications might be linked with bone fractures and the increased risk of infection. Visceral fat accumulation is also related to cardiovascular diseases, diabetes and metabolic disorders, complications associated with poor prognosis [7].

Using X-ray computed tomography (CT), we previously demonstrated that visceral fat tends to accumulate irrespective of the BMI, and that the visceral fat area (AVFA) is correlated with serum triglycerides and the atherogenic index in HD patients [8]. However, the changes in body composition with aging have not yet been investigated in these patients.

CT has some advantages over other methods for examining body composition. First, the visceral and subcutaneous fat masses can be independently measured, the ratio of these fat masses being recognized as a useful indicator of visceral fat accumulation [9]. Secondly, thigh muscle area (TMA), which can be measured by CT simultaneously with abdominal CT scanning, is a reliable indicator of muscle mass. This muscle area has been found to be strongly correlated with the creatinine production in HD patients [10]. Furthermore, intermuscular adipose tissue can be precisely distinguished from muscle. Thirdly, CT scanning is more available than other reliable methods for investigating body composition, such as dual energy X-ray absorptiometry and magnetic resonance imaging.

The purpose of this study was to determine by CT scanning the effect of age on body composition—specifically, on TMA, thigh subcutaneous fat area (TSFA), intermuscular fat area (IMFA), abdominal muscle area (AMA), AVFA and abdominal subcutaneous fat area (ASF A)—and also to examine the effect of age on other metabolic variables related to the changes of body composition in HD patients.

**Subjects and methods**

In all, 134 patients (85 males and 49 females), who had been on HD at Miyaji Hospital (Shizuoka, Japan) for more than 6 months, and 70 control subjects (33 males and 37 females) with normal renal function participated in this study. The control population includes the individuals who had abdominoscopy for acute illnesses, but who were found not to have serious diseases. All of the HD patients were outpatients. The patients were dialysed regularly—three times a week for 4–5 h each—with a bicarbonate-lack of physical activity. The patients were dialysed regularly—three times a week for 4–5 h each—with a bicarbonate-buffered dialysate (Kindaly AF-3P, Fuso, Osaka, Japan). All patients used hollow-fiber dialysers—72 with high-flux polyether sulfone membrane (Fresenius, Tokyo, Japan), 35 with medium-flux polymethylmethacrylate membrane (PMMA; Toray, Tokyo, Japan) and 27 with medium-flux cellulose triacetate membrane (CTA; Nipro, Osaka, Japan). The dialysate passed through a pyrogen filter before entering the dialysers. Blood flow was in the range of 150–250 ml/min, with a dialysate flow of 500 ml/min (these rates being standard in Japan). The patients had been educated by dietitians to restrict their intake of sodium, potassium and fluids, and to ingest 35 kcal/kg/day of energy and 1.2 g/kg/day of protein; however, their energy and protein intake was relatively free. Blood samples were drawn at the start of the first dialysis session of the week. Serum was immediately separated and stored at ~82°C until analysed. The study protocol was approved by the ethics committee of Miyaji hospital.

**Measurement of the muscle and fat area by computed tomography**

Axial CT images of the thigh (HD patients only) and abdomen were obtained at, respectively, the midpoint 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. Each patient was examined in the supine position with the thigh muscles relaxed. The thickness of a slice was 10 mm. The radiographic images were digitally scanned for analysis by a personal computer. The adipose-tissue-free TMA, IMFA, TSFA, femoral shaft area (FSA), AMA, AVFA and ASF A were quantified using NIH IMAGE, a public-domain planimetry program (written by Wayne Rasband, US National Institutes of Health). The ratio of TMA divided by FSA was used as the thigh muscle mass index, which was independent of body size [14].

**Anthropometric measurements**

Body weight was measured before and after each dialysis session, the post-dialysis body weight being used as the dry weight. The BMI was calculated as dry weight in kilograms divided by the square of the height in meters. Mid-arm circumference (MAC) and triceps skinfold thickness (TSF) were measured with Harpenden skinfold calipers (Holtain, Crymych, UK) on the limb not used for vascular access. The mid-arm muscle circumference (MAMC) was calculated by the following equation:

$$MAMC = MAC - (TSF \times 3.14),$$

MAMC, MAC and TSF being measured in cm.

**Analytical procedures**

Serum albumin, creatinine, urea nitrogen, total cholesterol, HDL-cholesterol and triglycerides were measured using standard laboratory techniques with an automatic analyser. Serum pre-albumin and C-reactive protein (CRP) were quantified by laser nephelometry.

The HD dose was checked by the following formula:

$$Kt/V_{\text{urea}} = -\ln(R - 0.008 \times t) + (4 - (3.5 \times R)) \times UF/W,$$

where $Kt/V$ is single-pool $Kt/V$, $R$ is the ratio of post-dialysis to pre-dialysis serum urea nitrogen, $t$ is the duration of dialysis in hours, $UF$ is the ultrafiltration in litres and $W$ is the post-dialysis body weight in kilograms [11]. The measure of dietary protein intake was the normalized protein
equivalent of nitrogen appearance (nPNA), which was calculated by the formula published by the Kidney Disease Outcomes Quality Initiative (KDOQI) HD adequacy working group [11]:

\[
\text{nPNA} \text{ (g/kg/day)} = C_0/[36.3 + 5.48(Kt/V) + 53.5/(Kt/V)] + 0.168,
\]

where \( C_0 \) is the predialysis concentration of serum urea nitrogen in milligrams per decilitre. Data collected during a beginning-of-week dialysis session were used for these calculations; nPNA was calculated once a month, and the average of 3 months is shown in the results.

**Statistical analyses**

Each parameter is presented as the mean ± SD. Differences among groups were evaluated by performing an analysis of variance (ANOVA) and subsequently the Bonferroni test or a non-parametric analysis for data having skewed distributions. Simple and multiple regression analyses were used to examine the relationships between variables. A \( P \)-value < 0.05 was considered to be statistically significant. All statistical analyses were performed with the GB-STAT software (Dynamic Microsystems, Silver Spring, MD, USA).

**Results**

The subjects’ characteristics and various nutritional indices and muscle and fat areas are listed in Table 1. Mean age was not significantly different between the HD patients and controls. BMI, serum albumin, total cholesterol and HDL-cholesterol were significantly lower, and triglycerides were higher in the HD patients than in the controls. AMA was significantly lower in the HD patients than in the controls. AVFA was also lower in the HD patients than in the controls, although statistical significance was evident only in the males. There was no significant difference in ASFA between the HD patients and the controls.

The relationships of between age and BMI, muscle mass and fat mass are shown in Figures 1–3, respectively. BMI did not differ with age in either the HD patients or controls (Figure 1). AMA showed a significantly negative correlation with age in the HD patients and controls both (Figure 2). AVFA and AVFA/ASFA each had a significantly positive correlation with age in both male and female HD patients; AVFA/ASFA also had a positive correlation with age in the controls. TMA and TMA standardized for FSA were each

<table>
<thead>
<tr>
<th>Variables</th>
<th>HD patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n = 85)</td>
<td>Females (n = 49)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>59.3 ± 11.0</td>
<td>60.9 ± 13.7</td>
</tr>
<tr>
<td>Duration of HD (mo)</td>
<td>66.6 ± 52.1</td>
<td>77.2 ± 59.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.7 ± 2.3</td>
<td>20.3 ± 2.6</td>
</tr>
<tr>
<td>PNA (g/d)</td>
<td>57.4 ± 12.5</td>
<td>51.6 ± 10.5a</td>
</tr>
<tr>
<td>nPNA (g/kg/d)</td>
<td>1.01 ± 0.19</td>
<td>1.13 ± 0.20a</td>
</tr>
<tr>
<td>Kt/Vurea</td>
<td>1.35 ± 0.13</td>
<td>1.50 ± 0.15a</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>39.5 ± 3.4</td>
<td>39.1 ± 3.1</td>
</tr>
<tr>
<td>Prealbumin (g/l)</td>
<td>0.34 ± 0.08</td>
<td>0.34 ± 0.07</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>1150 ± 212</td>
<td>990 ± 17</td>
</tr>
<tr>
<td>Urea nitrogen (mmol/l)</td>
<td>55.6 ± 8.8</td>
<td>58.0 ± 10.0</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>3.9 ± 0.8</td>
<td>4.5 ± 0.8b</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.2 ± 0.3</td>
<td>1.4 ± 0.4b</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.4 ± 0.8</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>4.9 ± 8.6</td>
<td>3.6 ± 4.7</td>
</tr>
<tr>
<td>CRP &gt;20 mg/l (%)</td>
<td>5.6</td>
<td>–</td>
</tr>
</tbody>
</table>

Computed tomographic data

<table>
<thead>
<tr>
<th>Variables</th>
<th>HD patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n = 85)</td>
<td>Females (n = 49)</td>
</tr>
<tr>
<td>AMA (cm²)</td>
<td>121.1 ± 20.8</td>
<td>81.4 ± 17.9a</td>
</tr>
<tr>
<td>AVFA (cm²)</td>
<td>81.9 ± 52.0</td>
<td>83.0 ± 43.2</td>
</tr>
<tr>
<td>ASFA (cm²)</td>
<td>97.5 ± 45.3</td>
<td>116.2 ± 66.5</td>
</tr>
<tr>
<td>AVFA/ASFA</td>
<td>0.85 ± 0.34</td>
<td>0.92 ± 0.64</td>
</tr>
<tr>
<td>TMA (cm²)</td>
<td>105.2 ± 23.0</td>
<td>76.0 ± 14.8a</td>
</tr>
<tr>
<td>TMA/FSA</td>
<td>14.1 ± 3.1</td>
<td>12.6 ± 2.3</td>
</tr>
<tr>
<td>IMFA (cm²)</td>
<td>8.3 ± 3.7</td>
<td>8.9 ± 4.8</td>
</tr>
<tr>
<td>TSFA (cm²)</td>
<td>30.8 ± 13.1</td>
<td>52.3 ± 24.8</td>
</tr>
<tr>
<td>MAMC (cm)</td>
<td>22.5 ± 1.9</td>
<td>20.2 ± 2.1a</td>
</tr>
<tr>
<td>TSF (mm)</td>
<td>6.3 ± 1.6</td>
<td>9.5 ± 3.6a</td>
</tr>
</tbody>
</table>

Mean ± SD. HD, haemodialysis; nPNA, normalized protein equivalent of nitrogen appearance; CRP, C-reactive protein; HDL, high-density lipoprotein; TMA, thigh muscle area; FSA, femoral shaft area; IMFA, intermuscular fat area; TSFA, thigh subcutaneous fat area; AMA, abdominal muscle area; AVFA, abdominal visceral fat area; ASFA, abdominal subcutaneous fat area; MAMC, mid-arm muscle circumference; TSF, triceps skinfold thickness.

a,bSignificantly different from males.

a,cSignificantly different from haemodialysis patients of the same sex.

\( a,bP < 0.01; b,dP < 0.05. \)
negatively correlated with age in the HD patients (Figure 3), while TSFA was negatively correlated with age in the female HD patients. In contrast, IMFA showed a significant positive correlation with age in both male and female HD patients. Among the fat mass data from the HD patients, IMFA was significantly correlated with AVFA in both males ($r = 0.49$, $P < 0.001$) and females ($r = 0.66$, $P < 0.001$); and the three subcutaneous fat indices were correlated with each other in both males (TSF vs TSFA, $r = 0.47$, $P < 0.001$; TSF vs ASFA, $r = 0.48$, $P < 0.001$; TSFA vs ASFA, $r = 0.70$, $P < 0.001$) and females (TSF vs TSFA, $r = 0.53$, $P < 0.001$; TSF vs ASFA, $r = 0.59$, $P < 0.001$; TSFA vs ASFA, $r = 0.74$, $P < 0.001$).

The correlations between muscle or fat masses and other clinical variables for the HD patients are shown in Table 2. It is noteworthy that nPNA and serum albumin seem to be associated with many of these indicators of body composition. A multiple regression analysis was applied to age and other clinical variables to identify which factor had the strongest relationship with muscle and fat masses. First, a forward stepwise method was applied to select principal factors among the following: age, duration of HD, nPNA, Kt/Vurea, serum albumin, pre-albumin, total cholesterol, HDL-cholesterol, triglycerides and CRP. The final model was then devised with age, nPNA, serum albumin and...
triglycerides as independent variables (Table 3). The result shows that age and nPNA are significant factors for most of the muscle and fat mass indices, even after controlling for other factors.

**Discussion**

This cross-sectional study examined the relationship between age and changes in BMI, muscle mass, fat mass and fat distribution in HD patients by using CT scanning. Muscle mass, fat mass and fat distribution were significantly correlated with age, whereas no significant association was shown between age and BMI. Muscle mass, of the thigh and abdominal muscles included, showed a significantly negative association with age in both male and female HD patients. The thigh subcutaneous fat mass and triceps skinfold thickness also had negative correlations with age in female patients. In contrast, the thigh intermuscular fat area and visceral fat area showed significant positive correlations with age in both male and female HD patients.
It is well known that lean tissue mass decreases with age throughout adult life in the general population of western countries [4] and Japan [12]; and adults lose on average 6–7% of their fat-free mass over a 20 year interval. The results of the present study suggest that a similar decline in muscle mass may occur with aging in HD patients. A previous study demonstrated that lean body mass was significantly lower in HD patients than in age-matched healthy subjects and undialysed patients with chronic renal failure [13]. Therefore, an age-related decrease in muscle mass would be a serious problem in elderly HD patients. Muscle mass is considered to be affected by many other factors apart from aging, and the effect of these factors on muscle mass may be more important than that of aging. However, the results of the multiple-regression analysis indicate that the association between age and the muscle mass indices was evident after controlling for other clinical variables. The age-related decrease in the muscle mass without any change in BMI suggests that other soft tissue or fat masses increase with aging. In fact, visceral and intermuscular fat increased with age in our HD patients. This result agrees with those of other studies showing the accumulation of visceral adipose tissue among the elderly of a general population [7]. Our result also shows that the AVFA/ASFA ratio, an indicator of visceral fat accumulation, has a positive association with age in healthy controls. We have previously reported that visceral fat tended to accumulate more in HD patients than in control subjects with comparable BMI [8], and our finding was supported by Yamauchi et al. [15]. They also demonstrated that visceral fat accumulation was associated with carotid atherosclerosis in chronic HD patients. These results indicate that large accumulations of abdominal adipose tissue in elderly HD patients might have a strong impact on their prognosis with respect to the progression of atherosclerosis, although the effect of obesity on the prognoses remains controversial in HD patients.

Leavey et al. [16] have demonstrated a clear association between greater BMI and better survival, and their result has been confirmed by those of other studies with short observation periods in US and European cohorts [17]. In contrast, we have already demonstrated overweight to be a risk factor for the long-term survival (past 12 years) in Japanese HD patients [18]. Although that study included only a small number of patients, a similar result was obtained by a larger study of Asian Americans, using the US Renal Data System (USRDS) [19], and an Oceanian study of patients undergoing peritoneal dialysis [20]. Since the 1 year survival rate has been reported to be better in patients with higher BMI than in those with lower BMI, even including Japanese HD patients [21], the negative effect of obesity on patient survival might appear only by a long-term study. A similar finding, named ‘the dialysis-risk paradox’, has been reported involving serum cholesterol: patients with higher cholesterol levels had a better one-year survival in the follow-up study, but also that high cholesterol led to increased mortality in long-term follow-up [22]. The undesirable long-term effect of obesity and hypercholesterolaemia on the mortality rate has been underestimated in the past, because HD patients have had a relatively short life expectancy. However, recent data indicate that the 10 year survival rate has been increased to over 60% in non-diabetic Japanese HD patients [21], suggesting the need to investigate survival long-term. With that in mind, the risks of visceral and intermuscular fat accumulation await to be further long-term study investigation.

Although for a long time little attention had been paid to IMFA, an adipose tissue within the fascia surrounding skeletal muscle, Goodpaster et al. [23] have presented evidence that IMFA bears some responsibility for metabolic derangements in the obese and diabetics. In that study, adipose tissue beneath the fascia or infiltrating muscle groups was associated with insulin resistance in obesity and type 2 diabetes, although such fat mass was much smaller than subcutaneous fat by which insulin resistance was not predictable. That study also suggested that the elderly with normal body weight are at risk of such metabolic abnormalities as type 2 diabetes, if they possess an inordinate amount of intermuscular or visceral fat [23]. The IMFA of HD patients was strongly correlated with AVFA, which is also known to be associated with insulin resistance. Both fat masses significantly increased with age in our study. These facts suggest that IMFA and AVFA should be similarly indicative of abnormalities of lipid and carbohydrate metabolism in elderly HD patients.

Anthropometric measurements such as BMI and MAMC provide important information about nutritional status. However, BMI does not reflect changes either in muscle mass or in any fat mass during the aging process, because it cannot differentiate between muscle mass and fat mass. MAMC is frequently used in the clinical setting for measuring muscle mass, but its accuracy is relatively poor because of problems with the method. We have previously reported that the correlation of MAMC with creatinine production ($r = 0.64$) was weaker than that of TMA with creatinine production ($r = 0.85$) [10]. The results of our present study point out the importance of separately measuring different elements of body composition for a nutritional evaluation. CT makes it possible to separately measure subcutaneous, visceral or intermuscular fat areas, of which the latter appears to more precisely reflect metabolic derangement in a patient than does the subcutaneous fat.

A limitation of the present study is its cross-sectional design, therefore, caution should be used in interpreting the observed associations. Since the elderly HD patients included in our study had been dialysed for between 13 and 212 months, the association of age with body composition should not imply that long-term HD has an aging effect. A longitudinal follow-up study would better capture the effect of aging on long-term HD patients. Such longitudinal analyses would also
eluicate the effect of changes in body composition on morbidity and mortality.

In summary, the direct measurement of thigh and abdominal muscle and fat areas by CT scanning revealed the association of age with muscle mass, fat mass and fat distribution in HD patients. Muscle mass was negatively correlated and the visceral and intermuscular fat masses were positively correlated with age, although there was no apparent association between age and BMI. An accumulation of visceral and intermuscular fat masses may be associated with the high prevalence of metabolic abnormalities in elderly patients undergoing HD, and it may affect their prognosis.

Acknowledgements. This study was supported in part by a grant from the Shizuoka Research and Education Foundation (Shizuoka, Japan).

Conflict of interest statement. None declared.

References


Received for publication: 1.04.04
Accepted in revised form: 6.10.04