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The creatinine/cystatin C ratio provides effective evaluation of muscle mass in kidney transplant recipients

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Abstract

Introduction Measuring muscle mass is an important step in detecting sarcopenia. The evaluation of sarcopenia is also important for kidney transplant recipients. Methods for estimating muscle mass have been established using computed tomography or magnetic resonance imaging, which are considered the gold standards. But these methods are invasive and costly, and there is a need for a more practical and simple method using blood samples from kidney transplant recipients.

Methods The study population was 62 patients who underwent kidney transplantation at Kansai Medical University Hospital, and were evaluated from August to October 2017. Muscle mass was measured using dual-energy X-ray absorptiometry. Serum creatinine and cystatin C levels were measured by immunoassay.

Results We analyzed 62 transplant recipients who met the inclusion criteria (20 females and 42 males, mean age of 45.6 ± 12.7 years). The creatinine/cystatin C ratio in the male group was > 1, whereas the creatinine/cystatin C ratio in the female group was < 1. Muscle mass was significantly larger in the male group than the female group. There was a significant positive correlation between the skeletal muscle index and creatinine/cystatin C ratio in the male ($r = 0.553$; $p < 0.001$) and female groups ($r = 0.675$; $p < 0.001$).

Conclusion The creatinine/cystatin C ratio is appropriate for evaluating muscle mass in kidney transplant recipients.

Keywords Muscle mass · Cystatin C · Creatinine · Kidney transplantation

Abbreviations

CT	Computed tomography
MRI	Magnetic resonance imaging
DXA	Dual energy X-ray absorptiometry
BIA	Bioelectrical impedance analysis
GFR	Estimate glomerular filtration rate
BMI	Body mass index
SMM	Skeletal muscle mass
SMI	Skeletal muscle mass index

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Introduction

In 2010, the European Working Group on Sarcopenia in Older People proposed an operational definition and diagnostic strategy for sarcopenia that have become the most widely used worldwide [1]. In 2014, the Asian Working Group for Sarcopenia (AWGS) established a consensus on the diagnosis of sarcopenia, recommending a set of approaches for the measurement of muscle mass, muscle strength, and physical performance, and different cutoff values according to data derived from Asian populations [2].

Sarcopenia, the loss of skeletal muscle mass, strength, and performance, is common among chronic kidney diseases patients, particularly the elderly, and it is associated with high mortality and morbidity [3–5]. Previous studies found a high frequency of sarcopenia in kidney transplant recipients. We also reported that age, duration of dialysis, and low physical activity are factors associated with the development of sarcopenia [6, 7]. Sarcopenia in kidney transplant recipients may also be associated with increased mortality and morbidity. Because the survival rate of renal transplantation patients has improved, assessment of muscle mass in kidney transplant recipients is now an important consideration for future clinical management.

Many methods have been developed to measure muscle mass and diagnose sarcopenia. Currently, the gold standard methods for estimating muscle mass are computed tomography (CT) or magnetic resonance imaging (MRI) [8–10]. Recently, dual-energy X-ray absorptiometry (DXA) and bioimpedance analysis (BIA) have been used to estimate muscle mass in routine practice [1, 11]. Both CT and MRI are very expensive systems that are not always available in small hospitals, clinics, and research centers. Similarly, DXA and BIA require considerable costs.

Cystatin C and creatinine are serum markers routinely used to estimate the glomerular filtration rate (GFR). Serum creatinine is a derivative of the skeletal muscle protein creatine phosphate. The production of creatinine varies with body composition such that in patients with elevated muscle mass, serum creatinine levels may underestimate the actual GFR, and in malnourished patients with low muscle mass, GFR may be overestimated by serum creatinine levels. Cystatin C is a small nonionic protein excreted by all nucleated cells. The impact of muscle mass on cystatin C production is less than for serum creatinine; therefore, circulating cystatin C levels may potentially be used to estimate the GFR without concerns about lean body mass and nutritional status.

Considering cystatin C is independent of muscle mass, we hypothesized that the discrepancy between creatinine and cystatin C may be explained by overall muscle mass. In the present study, we examined whether the creatinine/cystatin ratio provides an effective evaluation of muscle mass in kidney transplant recipients.

Methods

Patient characteristics

The study population of 62 patients underwent kidney transplantation at Kansai Medical University Hospital, and were evaluated from August to October 2017. Patients were enrolled if they were > 20 years of age, had undergone renal transplantation at least 6 months earlier, and had an estimated GFR > 30 ml/min/1.73 m^2. The recipients who have antibody- or cellular-mediated immune rejections, viral infection, and calcineurin-related renal toxicity were excluded.Previous medical history was acquired, and clinical variables including height and weight were measured. Each patients underwent DXA, and had blood collection for the measurement of serum creatinine and cystatin C levels on the same day. All recipients had no metal prostheses, which interfere with measuring muscle mass using DXA.

The Institutional Review Board of Kansai Medical University (IRB approval number: H150926) approved the study protocol, which was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. This study is registered with the University Hospital Medical Information Network (ID: UMIN000019153).

Study procedures

Height was measured to the nearest 0.5 cm via a stadiometer with barefoot patients. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Body composition was determined by whole-body DXA (QDR 4500A, Hologic Inc., Bedford, MA, USA). DXA was used to determine skeletal muscle mass (SMM). Bone mineral content, fat mass, and lean soft-tissue mass were measured separately for each part of the body, including the arms and legs. The lean soft-tissue masses of the arms and legs were almost equal to SMM. The arm and leg SMM index (SMI) were defined as the lean mass (kg) of the arms and legs, respectively, divided by height squared (m^2). Appendicular SMI was defined as the sum of the arm and leg SMIs.

The 62 transplant recipients received standard combined immunosuppression induction therapy, consisting of tacrolimus, mycophenolate mofetil, prednisone, and basiliximab (anti-CD25, on postoperative days 0 and 4). Eight recipients who received ABO-incompatible grafts were also administered rituximab (200 mg/m^2 per body surface area) 1 week before transplantation. Possible

adverse effects, including diabetes mellitus and hypertension, were monitored at every outpatient visit.

Laboratory measurements

Blood samples were obtained from the antecubital vein between 08:30 and 10:00 am, after fasting for ≥ 8 h. Graft function was evaluated based on eGFR, which was calculated from serum creatinine concentrations using the standardized conversion formula for Japanese individuals [12]. Serum cystatin C concentrations were determined by using a particle-enhanced immunoturbidimetric assay (MODULAR P analyzer, Roche/Hitachi, Indianapolis, IN). The creatinine/cystatin C ratio = serum creatinine (mg/dl)/serum cystatin C (mg/dl).

Statistical analysis

Data are presented as mean ± standard deviation. Correlations between the muscle mass assessed by DXA and the creatinine/cystatin C ratio were determined by simple linear regression analysis and Spearman's rank correlation test. Nonparametric data were analyzed with the Kruskal–Wallis test. If the results of this test were significant ($p < 0.05$). All statistical analyses were performed using Stat-View for Windows statistical software (Abacus Concepts Inc., Berkeley, CA, USA).

Results

We analyzed 62 transplant recipients who met the inclusion criteria (20 females and 42 males, mean age of 45.6 ± 12.7 years). The average observational period after transplantation was 6.9 ± 6.5 years, and the mean duration of dialysis prior to transplantation was 2.8 ± 4.0 years. Table 1 shows the age, height, body weight, BMI, serum creatinine, serum cystatin C, creatinine/cystatin C ratio, and SMI for each sex. All recipients had a mean creatinine and serum cystatin C of 1.38 ± 0.59 mg/dl and 1.29 ± 0.39 mg/dl. Therefore, many recipients had CKD patients with eGFR 60 ml/min/1.73 m^2 or less. The creatinine/cystatin C ratio in the male group was > 1, whereas the creatinine/cystatin C ratio in the female group was < 1. Muscle mass was significantly greater in the male group than in the female group.

There was a significant positive correlation between the SMI and creatinine/cystatin C ratio in both the male ($r = 0.553$; $p < 0.001$) (Fig. 1) and female groups ($r = 0.675$; $p < 0.001$) (Fig. 2).

Table 1 Clinical characteristics of the male and female groups

	Male $n = 42$	Female $n = 20$
Age	46.5 ± 13.7	45.5 ± 10.8
Height	1.69 ± 0.06	1.58 ± 0.04
Body weight	64.2 ± 12.3	50.1 ± 5.6
BMI	22.4 ± 3.6	20.1 ± 1.9
Serum creatinine	1.51 ± 0.63	1.12 ± 0.34
Serum cystatin C	1.43 ± 0.58	1.14 ± 0.31
Cr/cystatin C rate	1.06 ± 0.13	0.98 ± 0.14
SMM	19.7 ± 3.0	13.7 ± 1.75
SMI	6.90 ± 0.92	5.49 ± 0.51

Mean ± SD

Discussion

In the present study, men had a high muscle mass and the creatinine/cystatin C ratio was > 1, and females had a lower creatinine/cystatin C ratio because of less muscle mass. Both male and female kidney transplant recipients exhibited a creatinine/cystatin C ratio that was positively correlated with muscle mass.

Serum creatinine has been widely used for estimating GFR, but creatinine-based GFR estimation is largely influenced by physiological and clinical conditions that affect muscle mass [13]. Serum creatinine levels of patients with low muscle mass are usually low. Recently, cystatin C has been the focus as a new marker for GFR, because it is a low molecular weight protein with a stable production rate and is freely filtered by the glomerulus [14]. Cystatin C levels may provide a more useful estimate of GFR in patients with decreased muscle mass, because existing formulas that predict GFR take into account gender, age, and weight, but not muscle mass.

Since creatinine is secreted in some renal tubules in addition to glomerular filtration, the serum creatinine value does not increase with early renal dysfunction. Therefore, it is overestimated in renal function evaluation using serum creatinine value.On the other hand, the serum cystatin C value depends on the glomerular filtration amount and is useful as an excellent diagnostic marker for early renal dysfunction such as diabetic nephropathy. The kidney transplant recipients have only one kidney, so many are CKD stage 3. The recipients of this study also had mean serum creatinine levels of 1.38 ± 0.59 mg/dl (1.51 ± 0.63 mg/dl in men and 1.12 ± 0.34 mg/dl in females), again mostly patients with CKD stage 3a or 3b.In such cases with mild renal failure, there is a difference between serum creatinine value and cystatin C value, which is considered to reflect muscle mass. As in this study, muscle mass evaluation by creatinine/cystatin

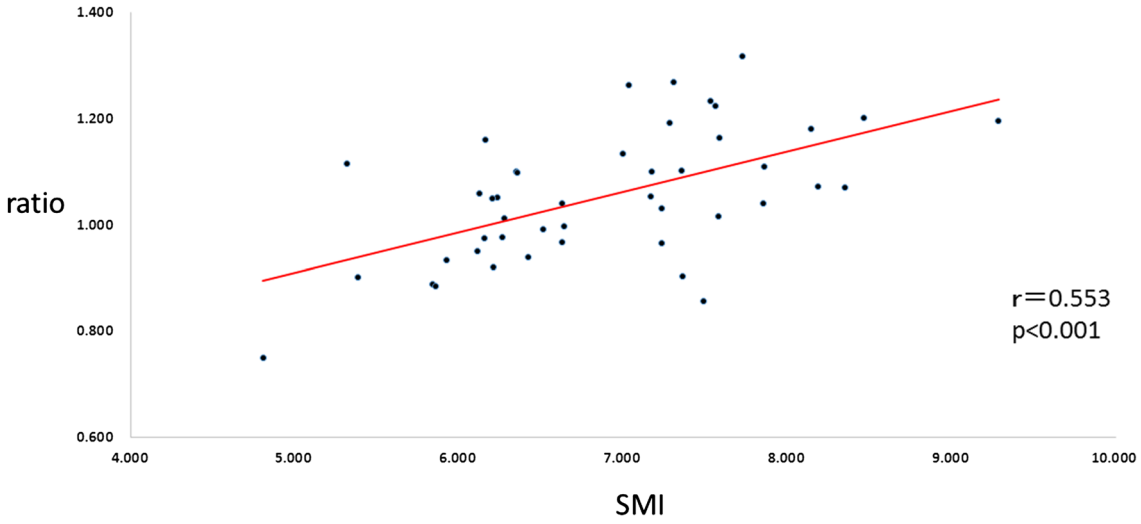

Fig. 1 Linear correlation between the skeletal muscle mass index (SMI) and creatinine/cystatin C ratio in the male group

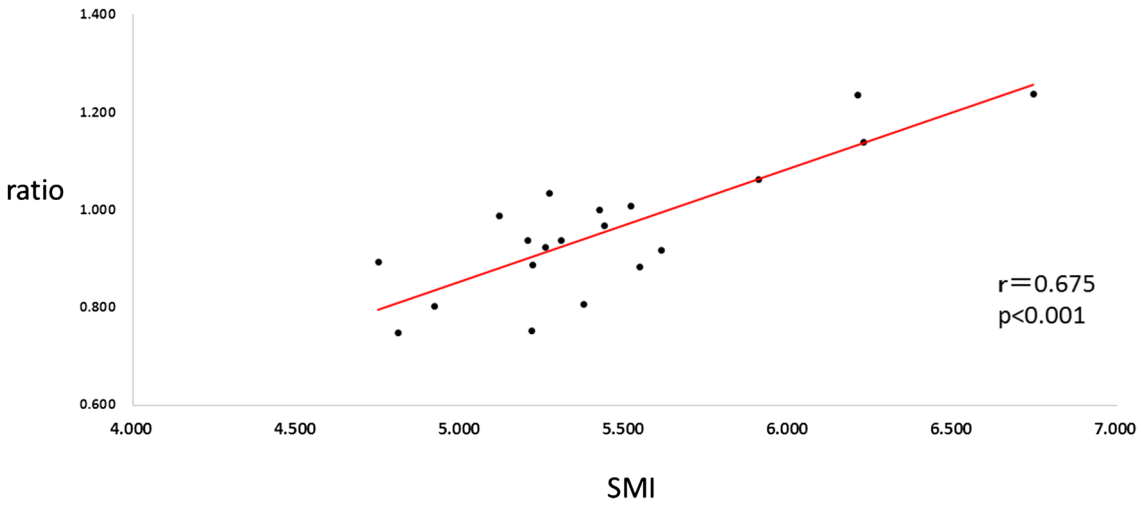

Fig. 2 Linear correlation between the skeletal muscle mass index (SMI) and creatinine/cystatin C ratio in the female group

C ratio is more effective in the case of kidney transplant recipients who have a lot of CKD stage 3.

We previously reported that the frequency of sarcopenia in kidney transplant recipients was high [6]. Furthermore, a relationship between sarcopenia and patient prognosis has been reported [15, 16], so evaluation of muscle mass has an important role in clinical practice. In the present study, we evaluated muscle mass using the creatinine/cystatin C ratio. Since the creatinine/cystatin C ratio was positively correlated with muscle mass in both male and female groups, it was suggested that the creatinine/cystatin C ratio may be appropriate for evaluating muscle mass in kidney transplant recipients who are susceptible to sarcopenia.

One advantage of using the creatinine/cystatin C ratio to measure body muscle mass is that it the reduced cost compared with MRI, CT, and DXA. Moreover, the creatinine/cystatin C ratio avoids the hazards of radiation, so it can be repeatedly measured without concern of X-ray exposure. In a recent study, Osaka et al. [17] reported that a reduced creatinine/cystatin C ratio was a surrogate marker for sarcopenia in patients with type 2 diabetes. In this study, the optimized cut-off value for the creatinine/cystatin C ratio to differentiate sarcopenia was 0.90. In addition, the creatinine-cystatin C ratio may serve as a useful predictive marker for chemotherapy-related adverse effects in patients with lung cancer [18]. Future studies should further evaluate the clinical use of the creatinine/cystatin C ratio to detect sarcopenia

in kidney transplant recipients. In addition, it may be possible to determine the effect of intervention therapy, such as exercise therapy or supplements.

The limitations of this study include its cross-sectional design and small sample-size. Furthermore, the study group consisted only of Japanese patients, possibly limiting the interpretation of the results to other ethnic groups. Therefore, the current findings should be further validated in additional patient populations. In addition, evaluation of renal function with cystatin C has limitations, and it is unsuitable for renal function evaluation in patients with estimated GFRs < 15 ml/min/1.73 m^2 [19]. Therefore, patients with an estimated GFR < 30 ml/min/1.73 m^2 were excluded in the present study.

In conclusion, the present study indicated that there was a significant positive correlation between the SMI and creatinine/cystatin C ratio in males ($r = 0.553$; $p < 0.001$) and females ($r = 0.675$; $p < 0.001$). These results suggest that the creatinine/cystatin C ratio is appropriate for evaluating muscle mass in the kidney transplant recipients.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals The Institutional Review Board of Kansai Medical University (IRB approval number: H150926) approved the study protocol, which was performed in accordance with the Declaration of Helsinki. This study is registered with the University Hospital Medical Information Network (ID: UMIN000019153).

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