Mod Rheumatol (2000) 10:230–234

ORIGINAL ARTICLE

Masato Moriguchi · Chihiro Terai · Yumi Koseki
Masashi Uesato · Naoyuki Kamatani

Renal function estimated from serum creatinine is overestimated in patients with rheumatoid arthritis because of their muscle atrophy

Received: March 17, 2000 / Accepted: July 14, 2000

Abstract We evaluated the reliability of serum creatinine concentration (Scr) to estimate renal function in patients with rheumatoid arthritis (RA). To quantify muscle volume (study 1) the lean body mass (LBM) in 25 women RA patients and 10 controls was measured using dual X-ray absorptiometry (DEXA). The 60-min creatinine clearance (Ccr60) and 60-min urinary excretion of creatinine (Ucr60) were also determined. The Ucr60 and LBM of the extremities, which were significantly correlated ($r = 0.757$, $P < 0.0001$), were lower in patients with long-standing and advanced RA than in controls. In study 2, the 24-h creatinine clearance (Ccr24) and 24-h urinary excretion of creatinine (Ucr24) were determined retrospectively in 82 women RA patients and 120 controls with normal Scr. The Ccr of long-standing and advanced RA patients was significantly lower than that of the controls, although the Scr of the long-standing RA patients was significantly lower than that of the advanced RA patients. The upper limit of the normal Scr for RA patients was calculated as being approximately 10% lower than that for controls. Thus, the renal function estimated from Scr may be overestimated in patients with long-standing and advanced RA because of their muscle atrophy.

Key words Creatinine · Rheumatoid arthritis (RA) · Lean body mass · Dual X-ray absorptiometry (DEXA)

Introduction

Renal failure has been the second or third most important cause of death in patients with rheumatoid arthritis (RA).[1–3] Renal involvement in RA patients derives from several different causes, such as drug-induced nephropathy, secondary AA-amyloidosis, rheumatoid vasculitis, or possibly nephropathy due to RA itself.[4–6] Although the frequency of subclinical renal dysfunction is relatively high in RA patients,[7] it often remains insidious until an advanced stage of renal insufficiency because of a lower serum creatinine concentration (Scr) in RA patients than in normal controls.[2,8,9] It is of critical importance to have accurate information about the renal function of RA patients because the drugs used in these patients are often excreted through the kidneys. Thus, most nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate are excreted through the kidneys, and it would be dangerous to administer them without knowing the state of renal function.

The level of creatinine clearance (Ccr) is widely used to estimate the glomerular filtration rate (GFR). However, Scr is commonly taken as an index of renal function since the measurement of Ccr is inconvenient in outpatient clinics. Previous investigators have suggested that Scr might be low in RA patients, probably due to their muscle atrophy.[8,9] However, it has not been clearly demonstrated how muscle atrophy is related to low Scr levels in RA patients. In this paper, we quantified muscle mass by measuring lean body mass (LBM) using dual X-ray absorptiometry (DEXA), and examined the relationship between low Scr and muscle atrophy in RA patients. We also evaluated the usefulness of Scr as a parameter of renal function in hospitalized RA patients with normal Scr by determining their 24-h creatinine clearance (Ccr24).

Patients and methods

Study 1: creatinine clearance and muscle volume

Patients

Twenty-five women patients with RA and 10 women controls participated in this prospective study. Men patients were excluded from this study since there were only small number of them. All the patients fulfilled American Rheumatism Association 1987 revised criteria for the classification of RA (ACR criteria).[10] "Long-standing RA" was

M. Moriguchi (✉) · C. Terai · Y. Koseki · M. Uesato · N. Kamatani
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
Tel. +81-3-5269-1725; Fax +81-3-5269-1726
e-mail: mmoriguchi@ior.twmu.ac.jp

defined as RA patients with stage III–IV by Steinbrocker's radiological progression stages[11] and a disease duration of more than 10 years. All subjects were ambulatory outpatients attending the Institute of Rheumatology, Tokyo Women's Medical University. None of the patients in the control group, which consisted of patients with osteoarthritis ($n = 3$), hyperuricemia ($n = 3$), and other miscellaneous diseases ($n = 4$), had either arthralgia or myalgia at the time of the study. None of the patients or controls had edema, varices, or tumors in the extremities. Informed consent was obtained from all the subjects who participated in this study.

Methods

Creatinine concentrations in serum and urine were measured by Jaffe's method. The 60-min creatinine clearance test (Ccr60) was done at the outpatient clinic. For Ccr60, subjects were given 500 ml water orally just before the test to ensure an adequate urine flow. Patients were instructed to discard their first urine collection at the start of the test, and then to collect their urine at 60 min and 120 min from the starting time. The time for urine collection was recorded exactly. A blood sample was obtained 60 min after the starting time. The volume of urine collected was measured accurately, and serum and urine concentrations of creatinine were determined. Ccr is obtained by the formula

$$\text{Ccr} = U \times \text{V/Scr}$$

where U is urinary creatinine concentration, V is urine flow rate, and Scr is serum creatinine concentration. If Ucr60 denotes the 60-min urinary creatinine excretion (mg/h), BSA is the body surface area (m^2), and 1.48 is the average Japanese BSA (m^2), the Ccr60 is calculated using the formula

$$\text{Ccr60 (ml/min)} = (\text{Ucr60 (mg/h)} \times 1.48\ (m^2) \times 100\ (\text{ml}))/(\text{Scr (mg/dl)} \times \text{BSA}\ (m^2) \times 60\ (\text{min}))$$

The average value of two serial determinations of Ccr60 was used.

Total body composition was measured using a scanner (Expert No. 1205, Lunar Radiation Corporation, Madison, WI, USA) as described previously.[12,13] The regional LBM, i.e., the upper limbs, trunk, and lower limbs, was obtained by dividing the figure of the body on the monitor screen of the DEXA machine. The upper limbs were separated from the trunk by a midaxillary line, and the lower limbs by a line that connected the anterior superior iliac spine with the pubic symphysis. While lean tissue in the extremities consists of mainly muscle, that of the trunk contains many other organs.

Study 2: retrospective study on creatinine clearance and serum creatinine concentration

Patients

The clinical records of 82 women RA patients and 120 women controls with normal Scr were reviewed retrospectively. All the subjects were admitted to Aoyama Hospital, Tokyo Women's Medical University, and their renal function was evaluated by Ccr24. All RA patients fulfilled the ACR criteria. The numbers of RA patients in Steinbrocker stages I, II, III, and IV were 9, 32, 16, and 25, respectively. Controls consisted of patients with cardiovascular diseases ($n = 83$), gastrointestinal diseases ($n = 35$), and other miscellaneous diseases ($n = 2$).

Methods

Ccr24 was measured in all RA patients at least twice during their period of admission, and the average value was used for analysis. Ccr24 is obtained by the formula

$$\text{Ccr24 (m./min)} = (\text{Ucr24 (mg/day)} \times 1.48\ (m^2) \times 100\ (\text{m.}))/(\text{Scr (mg/dl)} \times \text{BSA}\ (m^2) \times 1440\ (\text{min}))$$

where Ucr24 denotes 24-h urinary creatinine excretion (mg/day).

Normal concentrations of Scr for women in our institute were 0.6–1.1 mg/dl, and the lower limit of the normal range for Ccr was 70 ml/min/1.48 m^2. In this study, "normal Ccr" was defined as 60 ml/min/1.48 m^2 or more, and "decreased Ccr" as a Ccr below 40 ml/min/1.48 m^2, since GFR is known to decrease in older people,[14] and the average age of patients and controls in this study was around 60 years.

Statistics

The results are expressed as the mean ± SD, and statistical analyses were done by Student's unpaired t-test and Fisher's exact probability test. The Ucr60 and LBM of the extremities were analyzed by linear regression and the correlation coefficient. Differences with a P value of <0.05 were considered to be statistically significant.

Results

Study 1: Ccr and LBM

Table 1 shows the clinical features and the results of the analysis of total and regional LBM for RA patients and controls in study 1. RA patients were older and had a smaller body surface area than controls, but the differences were not significant. The Ucr60 with long-standing RA was significantly lower than that of controls. The Ccr with long-standing RA was also significantly lower than that of controls, but the difference in Scr between the two groups was not statistically significant.

No differences were observed either in total LBM or LBM of the trunk among the three groups. The LBM values for the extremities, especially those for legs, were significantly lower in the long-standing RA patients than in controls. However, no differences in the LBM values for upper limbs were found among the three groups. Thus, muscle atrophy was prominent in the lower extremities of patients with advanced RA.

Table 1. Clinical features and values of several parameters of subjects in Study 1

	Whole RA	Long-standing RA	Control
Number	25	8	10
Age (years)	61.2 ± 10.0	64.0 ± 7.7	56.9 ± 11.2
Body surface area (m^2)	1.43 ± 0.12	1.41 ± 0.13	1.52 ± 0.13
Disease duration (years)	7.6 ± 6.5	12.1 ± 1.6	–
CRP (mg/dl)	1.0 ± 1.4	1.7 ± 2.1	–
Scr (mg/dl)	0.83 ± 0.43	1.04 ± 0.63	0.68 ± 0.13
Ucr60 (mg/h)	30.9 ± 7.0	27.6 ± 6.1*	35.3 ± 6.8
Ccr60 (ml/min/1.48 m^2)	74.0 ± 24.9	58.6 ± 27.6*	86.9 ± 21.5
Lean body mass (kg)			
Extremities	11.1 ± 1.9	10.5 ± 1.6*	12.3 ± 1.6
Upper extremities	2.4 ± 0.6	2.3 ± 0.8	2.6 ± 0.6
Lower extremities	9.0 ± 1.2	8.2 ± 1.0*	9.7 ± 1.2
Trunk	19.7 ± 2.2	20.2 ± 1.9	20.5 ± 1.3
Total	30.8 ± 3.6	30.7 ± 2.6	32.8 ± 2.7
Steinbrocker's stage and class			
Stage I	5	0	–
Stage II	4	0	–
Stage III	8	2	–
Stage IV	8	6	–
Class I	8	3	–
Class II	17	5	–
Class III	0	0	–
Class IV	0	0	–

* $P < 0.05$ compared with long-standing RA and control (unpaired Student's *t*-test)

The correlation between Ucr60 and the LBM of the extremities measured by DEXA was significant (Fig. 1). The correlation coefficient was 0.757, and the following regression equation was obtained:

$$Ucr60 = 2.908 \times LBM_{ext} - 1.033$$

where LBM_{ext} is the LBM of the extremities expressed in kilograms.

Study 2: Ccr and Scr

The clinical features of the subjects are shown in Table 2. No significant differences in age were seen between the "whole RA" (no muscle atrophy), "long-standing RA," and control subjects. RA patients, especially those with long-standing RA, showed smaller body surface areas as compared with the control subjects. The average Scr and Ucr24 of the RA groups were significantly lower than those of the controls. There were no significant differences in Ccr24 between whole RA patients and controls. On the other hand, the level of Scr with long-standing RA was significantly lower than that of controls, although the Ccr24 of the former group was significantly lower than that of the latter.

The number of patients with decreased Ccr but normal Scr was significantly higher in both whole RA and long-standing RA patients than in controls (Table 3). These patients could be said to have a "false normal Scr." Thus, the usual normal range of Scr cannot be applied to patients with RA.

As a next step, we determined the mean and SD values of the Scr of the subjects who had normal Ccr values. As shown in Table 4, Scr values in the whole RA and long-

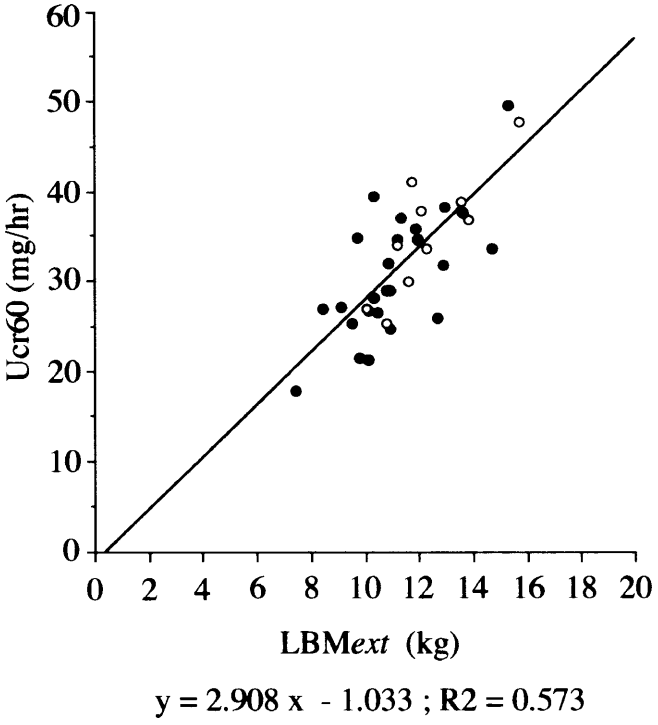

Fig. 1. Relationship between the lean body mass of the extremities (LBM_{ext}) measured using dual X-ray absorptiometry and 60-min urinary excretion of creatinine (Ucr60)in 35 subjects, including 25 patients with RA (*closed circles*) and 10 controls (*open circles*). There was a significant correlation between these parameters (correlation coefficient 0.757, $P < 0.0001$), and the following regression equation was obtained: $Ucr60 = 2.908 \times LBM_{ext} - 1.033$

Table 2. Clinical features and values of several parameters of the subjects in study 2

	Whole RA	Long-standing RA	Control
Number	82	24	120
Age (years)	57.4 ± 12.5	60.3 ± 8.4	59.5 ± 12.6
Body surface area (m^2)	1.43 ± 0.14**	1.38 ± 0.11***	1.49 ± 0.12
Disease duration (years)	8.1 ± 7.4	17.3 ± 6.4	–
Scr (mg/dl)	0.65 ± 0.16**	0.64 ± 0.20**	0.74 ± 0.16
Ucr24 (mg/day)	585 ± 191***	475 ± 147***	699 ± 200
Ucr24 (mg/day/1.48 m^2)	605 ± 198**	509 ± 152***	694 ± 199
Ccr24 (ml/min/1.48 m^2)	66.2 ± 21.2	58.3 ± 19.4*	66.0 ± 16.8
Steinbrocker's stage			
Stage I	9	0	–
Stage II	32	0	–
Stage III	16	7	–
Stage IV	25	17	–

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with whole or long-standing RA and control (unpaired Student's *t*-test)

Table 3. Number of patients with a false normal serum creatinine in whole RA, long-standing RA, and control subjects

	Whole RA ($n = 82$)	Long-standing RA ($n = 24$)	Control ($n = 120$)
Patients with normal Scr and a Ccr of ≥40 ml/min/1.48 m^2	73	20	116
Patients with normal Scr and a Ccr of <40 ml/min/1.48 m^2	9* (11.0%)	4* (16.7%)	4 (3.3%)

* $P < 0.05$ compared with whole or long-standing RA and control (Fisher's exact probability test)

Table 4. Serum creatinine levels in RA patients and controls with a normal creatinine clearance (>60 ml/min/1.48 m^2)

	Whole RA	Long-standing RA	Control
No. of patients	50	10	78
Age (years)	52.7 ± 12.2	55.7 ± 6.3	56.9 ± 13.4
Scr (mg/dl)	0.61 ± 0.13*	0.56 ± 0.16**	0.71 ± 0.14
Mean + 2SD	0.87	0.88	0.99

* $P < 0.0001$; ** $P < 0.005$ compared with whole or long-standing RA and control (unpaired Student's *t*-test)

standing RA groups were significantly lower than those in the control subjects. If the subjects with normal Ccr values were considered as having a normal renal function, the normal range of Scr for RA patients should be set at a range different from that for the control subjects. The new upper limits of normal Scr ranges should thus be defined as the mean +2 SD; that is, 0.87, 0.88, and 0.99 mg/dl for whole RA, long-standing RA, and control subjects, respectively. In other words, the upper limit of the "normal Scr range" for RA patients should be reset to a value approximately 10% lower than that for controls.

We also compared the strength of the correlation between indicators of muscle mass and various other factors in RA patients. Various parameters of RA patients, including age, body weight, height, Steinbrocker's stage, and duration of RA, were correlated significantly with LBM, Ucr60, or Ucr24. The Spearman's rank correlation test among the 82 RA patients in study 2 showed that the index of Steinbrocker's stage correlated most closely with Ucr24 (Table 5).

Table 5. Comparison of the correlation coefficients between lean body mass of extremities (LBM_{ext}) or urinary excretion of creatinine (Ucr) and various other factors of RA patients

	Study 1 ($n = 25$)		Study 2 ($n = 82$)
	LBM_{ext}	Ucr60	Ucr24
Age	−0.28	−0.46*	−0.34**
Body weight	0.58**	0.49*	0.27*
Height	0.51*	0.56**	0.15
Steinbrocker's stage	−0.52*	−0.25	−0.37***
Duration of RA	−0.44*	−0.30	−0.25*

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (Spearman's rank correlation test)

Discussion

In the first study, we showed a significant positive correlation between Ucr60 and the LBM of extremities measured by DEXA. Both of these parameters were lower in patients with long-standing RA. Physical inactivity, general waste by active inflammation, and the use of corticosteroids may lead to loss of muscle mass in RA patients. The existence of muscle atrophy is apparent in RA patients, although this muscle exhaustion with RA has not been well quantified by fully convincing methods to date. The introduction of total body DEXA has made it possible to measure bone, fat, and LBM throughout the body. Using DEXA, Westhovens et al.[15] recently demonstrated a significant decrease of LBM in all body parts as well as an increase of central fat in RA patients. They found a substantial decrease in LBM in the trunk, and the highest loss of LBM in the legs, and suggested that chronic illness (rheumatoid cachexia) rather than local disuse might be involved. In our series, there

were no differences in the LBM of the trunk, and only the LBM of the legs was significantly lower with long-standing RA, suggesting an important role of local factors in the loss of muscle mass in the extremities. The discrepancy between the two studies was most likely to be due to sample selection bias. The subjects in the study by Westhovens et al. showed a more severe functional disability (Steinbrocker's functional index 2.38–2.76) than that shown by our patients in study 1 (see Table 1). Our study 1 patients were ambulatory and reasonably well controlled, as shown by their CRP levels, although 60% of them had arthralgia affecting their knees.

Because the LBM for the trunk includes many nonmuscular organs, the LBM for the extremities, rather than the total LBM, may correlate more strongly with total body muscle mass. In fact, the correlation coefficient between Ucr60 and the LBM of the extremities was higher than that between Ucr60 and total LBM, (0.757 vs. 0.684). Therefore, we suggest that the LBM of the extremities is a better measure of the total body muscle mass than the total LBM.

In study 2, the renal function and the Ucr24 of RA patients and controls were analyzed by reviewing their clinical records. The patients with long-standing RA showed a lower Scr in spite of their diminished Ccr24 compared with controls. The Ucr24 of RA patients was also lower than that of controls. The low Ucr24 of RA patients was not only due to their small body mass, since the Ucr24 corrected for BSA was still significantly low in RA patients (see Table 2). Some of the RA patients in this study were taking NSAIDs or cimetidine, which might lower the tubular secretion of creatinine. However, if the serum creatinine level is steady, the daily urinary excretion of creatinine is equal to the daily creatinine production, and is not influenced by the action of NSAIDs or of H2-blocker because creatinine is excreted solely by the kidneys unless renal function is severely impaired.[16] The major determinant of the production of creatinine as well as the creatine pool is the total muscle mass. In addition to the total muscle mass, the dietary intake of creatine, largely in the form of meat, may influence the size of the creatine pool. However, the differences in dietary intake should have been small between the RA patients and controls since both of them took the standard food served in the hospital. Thus, the decreased Ucr24 in RA patients was most likely to be due to the decline in their muscle mass. The results of study 1 support this conclusion.

The number of subjects with a false normal Scr was very high in RA patients (see Table 3). Between 10% and 17% of RA patients with a normal Scr had moderate renal disorder ($Ccr < 40\,ml/min/1.48\,m^2$). Only 42% of the 24 patients in the long-standing RA group who had a normal Scr had a truly normal renal function. These results confirmed the presence of a subclinical renal dysfunction in RA patients.[9] False normal Scr was considered to come from low creatinine production in RA patients.

References

1. Laakso M, Mutru O, Isomaki H, Koota K. Mortality from amyloidosis and renal diseases in patients with rheumatoid arthritis. Ann Rheum Dis 1986;45:663–7.
2. Mutru O, Laakso M, Isomaki H, Koota K. Ten-year mortality and causes of death in patients with rheumatoid arthritis. Br Med J 1985;290:1797–9.
3. Suzuki A, Ohosone Y, Obana M, Mita S, Matsuoka Y, Irimajiri S, et al. Cause of death in 81 autopsied patients with rheumatoid arthritis. J Rheumatol 1994;21:33–6.
4. Sorensen AWS. The kidney function in patients with rheumatoid arthritis in relation to the commencement of the disease. Acta Rheum Scand 1964;10:11–28.
5. Helin H, Korpela M, Mustonen J, Pasternack A. Mild mesangial glomerulopathy – a frequent finding in rheumatoid arthritis patients with hematuria or proteinuria. Nephron 1986;42:224–30.
6. Helin HJ, Korpela MM, Mustonen JT, Pasternack AI. Renal biopsy findings and clinicopathologic correlations in rheumatoid arthritis. Arthritis Rheum 1995;38:242–7.
7. Boers M, Dijkmans BA, Breedveld FC, Camps JA, Chang PC, van Brummelen P, et al. Subclinical renal dysfunction in rheumatoid arthritis. Arthritis Rheum 1990;33:95–101.
8. Nived O, Sturfelt G, Westling H, White T. Is serum creatinine concentration a reliable index of renal function in rheumatic diseases? Br Med J (Clin Res Ed) 1983;286:684–5.
9. Boers M, Dijkmans BA, Breedveld FC, Mattie H. Errors in the prediction of creatinine clearance in patients with rheumatoid arthritis. Br J Rheumatol 1988;27:233–5.
10. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
11. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659–62.
12. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy X-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 1990;51:1106–12.
13. Pritchard JE, Nowson CA, Strauss BJ, Carlson JS, Kaymakci B, Wark JD. Evaluation of dual energy X-ray absorptiometry as a method of measurement of body fat. Eur J Clin Nutr 1993;47:216–28.
14. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men. A cross-sectional and longitudinal study. J Gerontol 1976;31:155–63.
15. Westhovens R, Nijs J, Taelman V, Dequeker J. Body composition in rheumatoid arthritis. Br J Rheumatol 1997;36:444–8.
16. Mitch WE, Collier VU, Walser M. Creatinine metabolism in chronic renal failure. Clin Sci 1980;58:327–35.