Table 3 SMI and handgrip strength of HD patients and control group, and surrogate markers for CKD-MBD in HD patients

	HD patients	Control group	Ratio to control (%)	*p*
SMI (kg/m^2)	4.60 ± 0.98	5.55 ± 0.81	79.19 ± 14.02	<0.01**
Male	5.10 ± 0.80	6.41 ± 0.50	79.56 ± 12.50	<0.01**
Female	3.96 ± 0.82	5.03 ± 0.40	78.71 ± 16.24	<0.01**
Grip strength (kg)	20.10 ± 7.87	33.46 ± 8.81	60.59 ± 21.85	<0.01**
Male	22.42 ± 8.78	43.00 ± 6.76	55.80 ± 1.80	<0.01**
Female	17.11 ± 5.45	27.60 ± 2.64	66.75 ± 21.08	<0.01**
Bone density (mmAl)	2.27 ± 0.49		78.63 ± 16.64	n/a
Male	2.54 ± 0.40		87.39 ± 13.15	n/a
Female	1.94 ± 0.40		67.36 ± 13.82	n/a
BAP (μg/L)	16.61 ± 8.82			
Male	15.32 ± 8.23			
Female	18.37 ± 9.58			
Intact P1NP (μg/L)	70.07 ± 39.73			
Male	59.23 ± 24.91			
Female	83.99 ± 50.81			
TRAPC5b (mU/dL)	487.34 ± 265.49			
Male	465.11 ± 285.58			
Female	515.93 ± 244.68			
Intact PTH (pg/mL)	154.03 ± 133.56			
Male	142.81 ± 70.27			
Female	168.47 ± 188.90			

HD hemodialysis, *CKD-MBD* chronic kidney disease–mineral and bone disease, *SMI* skeletal muscle index, *BAP* markers such as bone-specific alkaline phosphatase, *intact P1NP* intact procollagen type I intact N-terminal peptide, *TRACP5b* tartrate-resistant acid phosphatase 5b, *intact PTH* intact parathyroid hormone; *n/a* not available

** $p < 0.01$

Table 4 Multivariate linear regression analyses of the association of vigorous and moderate physical activity volumes and SMI and grip strength in HD patients

	SMI model ($R^2 = 0.584$)		Grip strength (model $R^2 = 0.444$)	
	β	*p*	β	*p*
Log(V and M volumes) adjusted (METs/week)	0.309	0.023*	0.231	0.131

Log(V and M volumes) adjusted: included age, sex, hemodialysis duration

HD hemodialysis, *SMI* skeletal muscle index, *log(V and M volumes)* logarithm vigorous and moderate physical activity volumes

* $p < 0.05$

Physical activity volumes

Log(V and M volumes) of the HD group (Table 2) did not differ significantly between HD days and non-HD days ($p = 0.19$).

SMI and grip strength

SMI and grip strength were significantly positively correlated with both HD ($r = 0.599$, $p < 0.001$) and control groups ($r = 0.896$, $p < 0.01$) (Table 3). After adjustment for age, sex, and HD duration, log(V and M volumes) in HD patients were positively associated with SMI ($\beta = 0.309$, $p = 0.023$) but not grip strength ($\beta = 0.231$ $p = 0.131$) (Table 4).

Bone density and bone metabolism markers

Analysis of bone density and bone metabolism markers for both groups is shown in Table 3. Statistical analysis of bone density was not performed because bone density of HD patients was compared with published data for a Japanese young to middle-aged population [21] rather than with the present study's control group. Serum bone metabolism marker levels in HD patients are also presented in Table 3. Log(V and M volumes) in HD patients were not associated with bone density or any markers of bone metabolism (BAP, intact P1NP, TRAPC5b, and iPTH) after adjustment for age, sex, and HD duration (Table 5).

Discussion

Results of the present study show that SMI and grip strength were lower in HD patients than those in healthy controls. Additionally, V and M volumes were positively associated with SMI but not grip strength, bone density, or serum bone metabolism markers. These results suggest that

Table 5 Multivariate linear regression analyses of the association of vigorous and moderate physical activity volumes and bone density and metabolic markers in HD patients

	Bone density (model $R^2 = 0.526$)		BAP (model $R^2 = 0.098$)		Intact P1NP (model $R^2 = 0.124$)		TRAPC5b (model $R^2 = 0.056$)		Intact PTH (model $R^2 = 0.181$)	
	β	p	β	p	β	p	β	p	β	p
Log(V and M volumes) adjusted (METs/week)	0.106	0.447	0.030	0.874	0.042	0.823	0.104	0.596	−0.100	0.583

Log(V and M volumes) adjusted: included age, sex, hemodialysis duration

HD hemodialysis, *BAP* markers such as bone-specific alkaline phosphatase, *intact P1NP* intact procollagen type I intact N-terminal peptide, *TRACP5b* tartrate-resistant acid phosphatase 5b, *intact PTH* intact parathyroid hormone, *log(V and M volumes)* logarithm vigorous and moderate physical activity volumes

V and M volumes are positively associated with skeletal muscle mass but not skeletal muscle strength or surrogate markers for CKD-MBD in maintenance HD patients. Skeletal muscle loss has been reported to increase the risk of fracture and decrease physical performance, and these may lead to decreased quality of life in CKD patients [3–5]. Some studies propose that skeletal muscle loss should be evaluated in terms of losses of both mass and strength as compared to those of a healthy young to middle-aged population [22, 23]. Therefore, we compared skeletal muscle loss in HD patients to that of young to middle-aged healthy subjects. Recently, several studies have demonstrated that all CKD patients, including those on maintenance HD, can benefit from exercise [13, 14]. Exercise training can improve physical capacity and reduce the risk of skeletal muscle loss [13, 14]. Additionally, although a direct cardiovascular benefit from exercise in CKD patients has not been reported, several studies have demonstrated the beneficial effects of exercise on potential mediators of cardiovascular disease, such as arterial stiffness and C-reactive protein [15, 16]. The National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines recommend assessment of patients' physical functioning and encouragement to participate in physical activity as part of a routine care plan for HD patients [24]. In this study, skeletal muscle mass and strength of HD patients were lower than those of normal controls, and V and M volumes that several guidelines recommended to use for the evaluation of exercise volume [17–19] were positively associated with skeletal muscle mass after adjustment for age, sex, and HD duration but not with skeletal muscle strength, suggesting that V and M volumes may reduce skeletal muscle loss. Taking the results of the present study together with those of previous studies, V and M volumes may influence the prognosis of maintenance HD patients. Grip strength has been reported to be closely associated with lower extremity muscle power, knee extension isometric torque, and calf muscle mass [25]. It has also been reported to be a predictor of clinical prognosis and the ability to perform activities of daily living [25, 26]. Although in the present study the grip strength of HD patients was significantly lower than that of the control group and was significantly associated with SMI, it was not associated with V and M volumes. This may be explained by V and M volumes affecting skeletal muscle mass more than they affect strength. Another possibility is that V and M volume measurement using an activity monitor with built-in triaxial accelerator technology may be more accurate for the lower extremities than for upper extremities. An understanding of the association between exercise volume and muscle strength of the lower extremities may be useful and should be investigated in future studies.

CKD-MBD has been reported to be associated with the development of cardiovascular disease and bone fractures [6–9]. However, no large clinical studies have investigated the effects of V and M volumes for CKD-MBD in HD patients. In this study, no association was observed between V and M volumes and bone density or markers of bone metabolism. These results suggest that V and M volumes may not affect CKD-MBD compared with skeletal muscle.

There are several limitations to this study. The sample sizes were small, and because this was a single-center study in Japan, results may not be applicable to HD patients in other parts of the world. SMI measured using BIA may not be comparable to that obtained using other methods, such as magnetic resonance imaging [27] or dual-energy X-ray absorptiometry [28], in determining SMI; however, BIA has been reported to evaluate body composition accurately in HD patients [29–32]. Bone biopsy was not performed to evaluate bone condition. Pharmacological treatment for CKD-MBD, for example with vitamin D, phosphorus binder, bisphosphonate, and cinacalcet, is generally prescribed for HD patients, and most patients in the present study took these medications. The effects of these drugs on CKD-MBD may thus have influenced the association between V and M volumes and CKD-MBD in the present study. Finally, the association of V and M volumes with prognosis, such as the development of cardiovascular disease, bone fracture, and all-cause mortality, was not

investigated. Hence, further large-scale studies should investigate the association between exercise habits and the prognosis of HD patients.

In conclusion, V and M volumes were positively associated with loss of skeletal muscle mass but not muscle strength or surrogate markers for CKD-MBD.

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Conflict of interest The authors declare that they have no conflicts of interest.

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Skeletal Muscle Loss Is Negatively Associated With Single-Pool Kt/V and Dialysis Duration in Hemodialysis Patients

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Abstract: We evaluated the skeletal muscle loss in hemodialysis (HD) patients by bioelectrical impedance analysis (BIA) and handgrip strength test. Thirty-four HD patients and 16 healthy subjects (control group) were measured for skeletal muscle mass normalized as the skeletal muscle mass index (SMI), calculated as skeletal muscle mass (kg)/height $(m)^2$ using a tetrapolar bioelectrical impedance plethysmograph. Handgrip strength test was also performed using a hand dynamometer in both groups. In HD patients, the associations of SMI and handgrip strength with age, sex, HD conditions, and HD parameters such as body mass index (BMI), single-pool Kt/V (spKt/V), normalized protein catabolic rate (nPCR), creatinine generation rate (CGR) and serum albumin level (Alb) were investigated. SMI of HD patients (4.58 ± 0.95 kg/m^2) was significantly lower than that of the control group (5.55 ± 0.80 kg/m^2, $P < 0.01$). The handgrip strength of HD patients (19.9 ± 7.74 kg) was also significantly lower than that of the control group (33.0 ± 8.94 kg, $P < 0.01$). In HD patients, HD duration was associated with both SMI and handgrip strength. Among HD parameters, spKt/V was negatively associated with both SMI and handgrip strength, BMI and Alb were positively associated with SMI, while nPCR and CGR were associated with neither SMI nor handgrip strength. HD duration independently contributed to skeletal muscle loss and the value of spKt/V may be affected by skeletal muscle loss in HD patients. **Key Words:** Bioelectrical impedance analysis, Handgrip strength test, Hemodialysis, Skeletal muscle loss.

Chronic kidney disease (CKD) patients show decreased maximal exercise capacity (1,2). This decrease gradually induces skeletal muscle loss. The skeletal muscle loss is also associated with whole-body protein-energy wasting (PEW), which involves a state of reduced protein and energy resources (3,4). The PEW progresses much more intensively in CKD patients in association with several factors often observed in this condition, such as nutritional deficiencies, acidosis and vitamin D deficiency (5,6). The skeletal muscle loss increases the risk of fracture and decreases quality of life. In addition, it is one of the main predictors of mortality in advanced-stage CKD patients, including hemodialysis (HD) patients (7–9). Recently, accumulated evidence has suggested that skeletal muscle loss in HD patients can be improved and prevented by appropriate nutritional intake and physical exercise training (10,11). Therefore, the detection and evaluation of skeletal muscle loss are very important for the prognosis of HD patients. It has been considered that skeletal muscle loss should be evaluated by both loss of mass and loss of strength (12,13); however, these evaluations in HD patients have not been reported yet. Therefore, we evaluated the skeletal muscle loss in HD patients by bioelectrical impedance analysis (BIA) for muscle mass and handgrip strength test for muscle strength. Furthermore, we investigated the association of skeletal muscle loss with age, sex and HD conditions (HD duration, number of times on HD and average HD time) to determine the factors contributing to skeletal muscle loss in HD patients. We also investigated

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the association of skeletal muscle loss with parameters of HD such as body mass index (BMI), single-pool Kt/V (spKt/V), normalized protein catabolic rate (nPCR), creatinine generation rate (CGR) and serum albumin level (Alb) to determine the markers of skeletal muscle loss in HD patients.

PATIENTS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki and was approved by ethics committee of Haga Red Cross Hospital. Informed consent was obtained from all patients and healthy subjects. No patients had obvious edema or an implanted pacemaker.

Subjects

Thirty-four HD patients (19 males and 15 females) were investigated in this study. Their initial nephropathy was chronic glomerulonephritis (three patients), renal sclerosis (10 patients), diabetic nephropathy (12 patients), anti-neutrophil cytoplasmic autoantibody-related glomerulonephritis (two patients), polycystic kidney disease (one patient), chronic pyelonephritis (one patient), pregnant nephropathy (one patient) or unknown etiology (three patients). All studied patients had not shown a change in their dry weight in at least one month. Sixteen healthy subjects (six males and 10 females) served as controls. Table 1 shows the baseline characteristics of HD patients and the control group.

Skeletal muscle mass and other body composition factors

Body height was measured to the nearest 1 cm. In HD patients, body weight was measured to the nearest 0.1 kg before and after an HD session. BMI was calculated as body weight/body height^2 (kg/m^2). BIA to obtain the ratios of fat, water, bone and organs was performed using a tetrapolar impedance plethysmograph (InBody S10; Biospace, Seoul, Korea) with multiple operating frequencies of 1, 5, 50, 250, 500 and 1000 kHz. Whole-body BIA measurements in HD patients were taken between the ends of the fingers and ankle with the subjects in a supine position after an HD session. The skeletal muscle mass was defined using the mass of non-skeletal muscle tissues such as fat, extracellular fluid (ECF), intracellular fluid (ICF), bone and organs. Absolute skeletal muscle mass measured by BIA was converted to percentage skeletal muscle mass and termed the skeletal muscle index (SMI). The SMI was calculated using the following formula: SMI (kg/m^2) = skeletal muscle mass (kg)/body height^2 (m^2). The ratios of fat, ECF and ICF were also calculated by the same formula and called fat index, ECF index and ICF index.

TABLE 1. *Baseline characteristics of hemodialysis (HD) patients and the control group*

Parameter	HD patients	Control	*P*
Number	34	16	
Age (years)	66.9 ± 9.62	36.9 ± 8.9	<0.01**
Gender			
Male	19	6	
Female	15	10	
Height (cm)	156.3 ± 9.42	162.5 ± 9.70	0.04*
Male	162.7 ± 6.56	172.8 ± 4.62	<0.01**
Female	148.1 ± 5.11	156.3 ± 5.58	<0.01**
Dry weight (kg)	51.4 ± 9.43	57.4 ± 10.2	0.05
Male	55.2 ± 9.14	66.0 ± 10.5	0.05
Female	46.6 ± 7.58	52.3 ± 5.74	0.04*
BMI (kg/m^2)	20.8 ± 2.57	21.6 ± 2.77	0.25
Male	20.8 ± 2.66	22.1 ± 3.66	0.42
Female	20.8 ± 2.54	21.4 ± 2.27	0.50

*$P < 0.05$; **$P < 0.01$. BMI, body mass index.

Handgrip strength test

Handgrip strength test was performed by the hand in which an arteriovenous shunt was not produced before an HD session in HD patients using a digital handgrip dynamometer (T.K.K 5401 GRIP D, Takei Science Instruments, Niigata, Japan). It was performed by the dominant hand in the control group.

Parameters of HD

spKt/V, nPCR and CGR were calculated each month by the formulae reported by Shinzato et al. (14,15). Standard laboratory tests were performed each month at the Department of Clinical Examination in Haga Red Cross Hospital. The averages of spKt/V, nPCR, CGR and the other laboratory tests were calculated during the last 12 months, or after the initial month that subjects initiated HD if the subjects had undergone HD for less than 12 months.

Statistical analysis

All data are expressed as the mean ± SD. Unpaired *t*-test was used to compare two groups. Multiple linear regression analysis was used to determine the independent variables. SPSS Statistics version 21 software (IBM, Armonk, NY, USA) was used for statistical analyses. Values of $P < 0.05$ were considered to be significant.

RESULTS

Table 1 shows the baseline characteristics of HD patients and the control group. In HD patients,

TABLE 2. *Skeletal muscle index (SMI), and fat, extracellular fluid (ECF) and intracellular fluid (ICF) indexes and handgrip strength of hemodialysis (HD) patients and the control group*

Parameters	HD patients	Control	*P*
SMI (kg/m^2)	4.58 ± 0.95	5.55 ± 0.80	<0.01**
Male	5.07 ± 0.79	6.41 ± 0.50	<0.01**
Female	3.97 ± 0.79	5.03 ± 0.40	<0.01**
Fat index (kg/m^2)	5.70 ± 2.39	4.75 ± 1.93	0.14
Male	4.72 ± 1.94	3.63 ± 2.00	0.28
Female	6.95 ± 2.38	5.42 ± 1.62	0.09
ECF index (L/m^2)	4.41 ± 0.65	4.82 ± 0.44	0.01*
Male	4.74 ± 0.61	5.23 ± 0.38	0.04*
Female	4.00 ± 0.42	4.58 ± 0.28	<0.01**
ICF index (L/m^2)	6.70 ± 0.95	7.63 ± 0.90	<0.01**
Male	7.11 ± 0.95	8.39 ± 0.92	0.02*
Female	6.17 ± 0.65	7.18 ± 0.52	<0.01**
Handgrip strength (kg)	19.9 ± 7.74	33.0 ± 8.94	<0.01**
Male	21.9 ± 8.84	43.6 ± 7.37	<0.01**
Female	17.3 ± 5.30	27.7 ± 2.64	<0.01**

*$P < 0.05$; **$P < 0.01$.

their age was 66.9 ± 9.62 years old, height was 156.3 ± 9.42 cm (male: 162.7 ± 6.56 cm, female: 148.1 ± 5.11 cm) and dry weight was 51.4 ± 9.43 kg (male: 55.2 ± 9.14 kg, female: 46.6 ± 7.58 kg). Their BMI was calculated to be 20.8 ± 2.57 kg/m^2 (male: 20.8 ± 2.66 kg/m^2, female: 20.8 ± 2.54 kg/m^2). In the control group, their age was 36.9 ± 8.9 years old, height was 162.5 ± 9.70 cm (male: 172.8 ± 4.62 cm, female: 156.3 ± 5.58 cm) and weight was 57.4 ± 10.2 kg (male: 66.0 ± 10.5 kg, female: 52.3 ± 5.74 kg). Their BMI was calculated to be 21.6 ± 2.77 kg/m^2 (male: 22.1 ± 3.66 kg/m^2, female: 21.4 ± 2.27 cm). The BMI did not differ significantly between HD patients and the control group ($P = 0.25$).

SMI and other body composition factors measured by BIA

The SMI of HD patients was 4.58 ± 0.95 kg/m^2 (male: 5.07 ± 0.79 kg/m^2, female: 3.97 ± 0.79 kg/m^2). That of the control group was 5.55 ± 0.80 kg/m^2 (male: 6.41 ± 0.50 kg/m^2, female: 5.03 ± 0.40 kg/m^2) (Table 2). The SMI of HD patients was significantly lower than that of the control group ($P < 0.01$) (Table 2). The fat index, ECF index and ICF index of HD patients were as follows: 5.70 ± 2.39 kg/m^2 (male: 4.72 ± 1.94 kg/m^2, female: 6.95 ± 2.38 kg/m^2), 4.41 ± 0.65 L/m^2 (male: 4.74 ± 0.61 L/m^2, female: 4.00 ± 0.42 L/m^2) and 6.70 ± 0.95 L/m^2 (male: 7.11 ± 0.95 L/m^2, female: 6.17 ± 0.65 L/m^2) respectively (Table 2). These parameters in the control group were as follows: fat index was 4.75 ± 1.93 kg/m^2 (male: 3.63 ± 2.00 kg/m^2, female: 5.42 ± 1.62 kg/m^2), ECF index was 4.82 ± 0.44 L/m^2 (male: 5.23 ± 0.38 L/m^2, female: 4.58 ± 0.28 L/m^2) and ICF index was 7.63 ± 0.90 L/m^2 (male: 8.39 ± 0.92 L/m^2, female: 7.18 ± 0.52 L/m^2) (Table 2). ECF index and ICF index of HD patients were significantly lower than those of the control group (ECF index: $P = 0.01$ and ICF index: $P < 0.01$). Fat index of HD patients was not significantly different from that of the control group ($P = 0.14$) (Table 2).

Handgrip strength

The handgrip strength of HD patients was 19.9 ± 7.74 kg (male: 21.9 ± 8.84 kg, female: 12.3 ± 5.30 kg) (Table 2), while that of the control group was 33.0 ± 8.94 kg (male: 43.6 ± 7.37 kg, female: 27.7 ± 2.64 kg) (Table 2). The handgrip strength of HD patients was significantly lower than that of the control group ($P < 0.01$). There were statistically significant associations between SMI and handgrip strength in both HD patients ($r = 0.591$, $P < 0.01$) and the control group ($r = 0.896$, $P < 0.01$).

HD parameters of patients

Table 3 shows the age, sex, HD conditions (HD duration, number of times on HD and average HD time) and the parameters of HD in HD patients. There were 19 males and 15 females aged 66.9 ± 9.62 years old (also shown in Table 1). Their overall HD duration was 6.29 ± 0.26 years, number of times on HD was 2.83 ± 0.45 times/week and average HD duration was 3.99 ± 0.26 h/session. The parameters of HD were as follows: BMI was 20.8 ± 2.57 kg/m^2 (also shown in Table 1), spKt/V was 1.47 ± 0.31, nPCR was 0.77 ± 0.13 g/kg/d, CGR was 83.5 ± 29.8% and Alb before an HD session was 3.61 ± 0.40 g/dL.

The associations of age, sex and HD conditions with SMI and handgrip strength in HD patients

Multivariate linear regression analyses showed that HD duration was independently negatively

TABLE 3. *Age, sex, hemodialysis (HD) conditions and parameters of HD*

Age (years)	66.9 ± 9.62
Sex	
Male	19
Female	15
Total HD duration (years)	6.29 ± 4.71
Number of HD (/week)	2.85 ± 0.44
Average HD time (h/session)	3.99 ± 0.26
BMI	20.8 ± 2.57
spKt/V	1.47 ± 0.31
nPCR (g/kg/day)	0.77 ± 0.13
CGR (%)	83.5 ± 29.8
Alb (g/dL)	3.61 ± 0.40

Alb, serum albumin level; BMI, body mass index; CGR, creatinine generation rate; spKt/V, single-pool Kt/V; nPCR, normalized protein catabolic rate.

TABLE 4. *Multivariate linear regression analyses of the association of age, sex and hemodialysis (HD) duration with skeletal muscle index (SMI) and handgrip strength in HD patients*

	SMI (Model $R^2 = 0.456$)		Handgrip strength (Model $R^2 = 0.273$)	
	β	*P*	β	*P*
Age (years old)	0.033	0.226	−0.309	0.046*
Sex	−0.486	<0.01**	−0.201	0.214
Total HD duration (years)	−0.401	<0.01**	−0.495	<0.01**
Time on HD (/week)	−0.258	0.07	−0.294	0.08
Average HD time (h/session)	−0.032	0.827	0.019	0.91

*$P < 0.05$; **$P < 0.01$.

associated with both SMI and handgrip strength (Table 4). Sex was independently associated with SMI but not handgrip strength (Table 4). Males had significantly higher SMI than females. Age was independently negatively associated with handgrip strength, but not with SMI (Table 4). Number of times on HD and HD duration were associated with neither SMI nor handgrip strength (Table 4).

The associations of HD parameters with SMI and handgrip strength in HD patients

spKt/V was negatively associated with both SMI and handgrip strength (Table 5). BMI and Alb were positively associated with SMI but not handgrip strength (Table 5). nPCR and CGR were associated with neither SMI nor handgrip strength (Table 5).

DISCUSSION

The results in the present study showed that SMI and handgrip strength of HD patients were associated with each other. In addition, they were significantly lower than those of the control group. Furthermore, multivariate linear regression analyses showed that HD duration was independently negatively associated with both SMI and handgrip strength. Among HD parameters, spKt/V was negatively associated with both SMI and handgrip strength. These results suggest that HD duration independently contributed to skeletal muscle loss and the value of spKt/V may be affected by skeletal muscle loss in HD patients.

The decrease in skeletal muscle has been shown to progress in association with aging, and PEW intensively progressed in HD patients in association with several factors observed in CKD (5,6). Skeletal muscle loss is one of the main predictors of mortality in HD patients (7–9). It has been reported that the skeletal muscle loss should be evaluated in terms of both loss of mass and loss of strength compared with those of healthy young/middle-aged populations (12,13). Therefore, we compared skeletal muscle loss in HD patients with that of healthy middle-aged subjects.

Magnetic resonance imaging and dual-energy X-ray absorptiometry (DEXA) (16,17) are established methods to evaluate skeletal muscle mass; however, they have several problems, such as being time-consuming, and involving large, expensive devices and exposure to radiation. Therefore, they cannot be readily performed at all medical

TABLE 5. *Multivariate linear regression analyses of association of hemodialysis (HD) parameters with skeletal muscle index (SMI) and handgrip strength in HD patients*

	SMI (Model $R^2 = 0.663$)		Handgrip strength (Model $R^2 = 0.184$)	
	β	*P*	β	*P*
BMI (kg/m^2)	0.316	<0.01**	0.221	0.176
spKt/V	−0.708	<0.01**	−0.457	<0.01**
nPCR (g/kg/day)	0.018	0.886	0.257	0.155
CGR (%)	0.143	0.294	0.263	0.193
Alb (g/dL)	0.294	<0.01**	0.290	0.075

*$P < 0.05$; **$P < 0.01$. Alb, serum albumin level; BMI, body mass index; CGR, creatinine generation rate; spKt/V, single-pool Kt/V; nPCR, normalized protein catabolic rate.

institutions. Instead, BIA has been reported to be a useful tool to measure body composition including muscle mass, fat mass and water volume because of its noninvasiveness, availability and simplicity. Recent developments regarding the precision of BIA devices and determination of the appropriate timing to estimate body composition in HD patients have enabled accurate measurement of the body composition in HD patients by BIA methods (18–21). Di Lorio et al. reported the usefulness of BIA for the estimation of body composition in HD patients (19). They reported that the estimation of muscle mass by multifrequency plethysmographs after an HD session was more appropriate in HD patients because extra water mass can be removed by ultrafiltration after an HD session (19). Kaysen et al. reported that skeletal muscle mass measured by multifrequency plethysmographs correlated well with isotopic methods in approximating values obtained by MRI and can be used to estimate limb muscle mass in HD patients (21). In the present study, we measured skeletal muscle mass in HD patients using multifrequency plethysmographs just after an HD session, and compared the values with those of healthy subjects in accordance with the above lines of evidence. BIA analysis revealed that SMI in HD patients was significantly lower than that in the control group. The indexes of ECF and ICF ratios of HD patients were significantly lower than those of the control group. These results may suggest that volume overload was corrected by ultrafiltration and the setting of dry weight was appropriate in HD patients in the present study.

The results of the handgrip test have been reported to be closely associated with lower-extremity muscle power, knee extension isometric torque and calf muscle area (22). They have also been reported to be a useful predictive factor for clinical prognosis and the occurrence of disability of daily living (22,23). In the present study, the handgrip strength of HD patients was significantly lower than that of the control group. In addition, it was significantly associated with SMI. These results suggest that the combination of SMI and handgrip test is useful to evaluate skeletal muscle loss in HD patients. These results also suggest that HD patients in this study had skeletal muscle loss; thus, their performance of appropriate exercise training and nutritional counseling should be promoted to increase their skeletal muscle because it has been reported that skeletal muscle loss in HD patients can be improved and inhibited by appropriate nutrition and exercise training (10,11).

Skeletal muscle loss is often observed in association with aging (12,13). It is called sarcopenia, which can be defined as the age-related (1% per year after the age of 25) loss of muscle (7,13). In the present study, multivariate linear regression analyses showed that HD duration was independently negatively associated with both SMI and handgrip strength. Sex was independently associated with SMI but not handgrip strength. Age was independently negatively associated with handgrip strength but not SMI. These results suggest that renal failure on HD may strongly independently contribute to the skeletal muscle loss in HD patients more than sex and aging.

Several parameters for evaluating HD are available, such as spKt/V for the efficacy of HD, nPCR for the nutritional state and CGR for muscle mass. Several HD guidelines have recommended that spKt/V be above 1.4 (24,25). However, it should be noted that spKt/V may be affected by not only HD efficacy but also the muscle mass of HD patients. It has been reported that spKt/V is high when the muscle mass of HD patients is low, regardless of HD efficacy (26,27). The result of spKt/V in the present study may have been affected by the decreased skeletal muscle loss in HD patients because SMI and handgrip strength were inversely associated with spKt/V. These results support the results of previous studies that spKt/V should be carefully estimated in HD patients (26,27). Taken together, not only HD conditions such as dialyzer size, blood flow and HD times but also skeletal muscle loss should be taken into consideration when spKt/V is evaluated in HD patients.

The other HD parameters such as nPCR and CGR may not be sensitive markers to evaluate skeletal muscle loss in HD patients because they were associated with neither SMI nor handgrip strength.

There are several limitations to this study. First, the sample numbers were small, and second the results of SMI measured by BIA are not comparable to those of other methods, such as MRI and DEXA (16,17). Further large-scale studies to estimate skeletal muscle loss in HD patients, including a comparison of BIA methods and DEXA methods or MRI, are needed.

CONCLUSION

Hemodialysis duration independently contributed to skeletal muscle loss and the value of spKt/V may be affected by skeletal muscle loss in hemodialysis patients.

Disclosure: The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Prevalence of colorectal carcinoma in CKD patients in pre-dialysis and during the dialysis introduction period

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Keywords Colorectal cancer · Malignant diseases · Chronic kidney disease · Past history · Dialysis introduction period

To the Editor

Chronic kidney disease (CKD) is a risk factor for malignant disease (MD), but the relationship between these aliments remains to be elucidated. Recently, Wu et al. [1] reported on the increased colorectal cancer (CRC) incidence in Taiwanese CKD patients. In Japan, there are few epidemiological data on non-dialysis CKD patients with MD. Therefore, we conducted a single-center retrospective survey to explore the previous history and the prevalence of MD in CKD patients, treated at Jichi Medical School Hospital between January 2008 and December 2013, using the dialysis-introduction database. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Jichi Medical University (epidemiology 13–95). The dialysis introduction period (DIP) was determined as being within 1 year before and after dialysis administration. Acute kidney injury cases that had quit dialysis within 2 months of its initiation were excluded. Out of 724 dialysis introduction patients [464 were male; age of dialysis introduction: 64 (mean) ± 14 (SD)], 44 cases had a previous history of MD, 55 cases had newly diagnosed MD during the DIP (Table 1) and five cases had both previously and newly diagnosed MD.

Within previously-diagnosed and newly-diagnosed MD cases, CRC ranked first in both. During the DIP, CRC tended to be diagnosed in the early stage. Furthermore, most of the CRCs were adenocarcinomas and one was a neuroendocrine carcinoma. Serum creatinine level and amount of urine protein at the time of diagnosis of pre-dialysis CRC were 1.70 ± 0.57 mg/dL and 3.3 ± 2.8 g/g creatinine, respectively. Among pre-dialysis and DIP CRC patients, none had received adjuvant chemotherapy and only one patient had taken oral alfacalcidol prior to being diagnosed with CRC.

Considering that CRC has been found to be third in terms of incidence of MD in the general Japanese male population and that the crude rate of CRC in the same population was 105.5/10 [2, 5], the prevalence of CRC in this CKD population appears to be relatively high.

Four causal associations between CKD and CRC were assumed to have occurred. One was a hypovitaminosis D and another was an abnormality of folate and homocysteine metabolism [3]. CKD has been shown to be a well-known cause of hypovitaminosis [4], and hypovitaminosis D has been found to be a principal epidemiological factor of CRC [5]. However, the significance of hypovitaminosis D and vitamin D receptor polymorphisms in CRC in CKD patients has not been investigated. Treatment-related kidney injuries including chemotherapy-induced acute tubular necrosis and cancer-associated nephropathy are also suggested causes. To understand more the relationship between CRC and CKD will likely require a multicenter

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Table 1 Previous history (PH) and incidence of malignant disease in dialysis-introduced CKD patients during the dialysis-introduction period (DIP)

Involved organs	PH (male/female)	DIP (male/female)
Colorectal	14 (13/1)	10 (9/1)
Colon	11 (10/1)	8 (7/1)
Rectum	3 (3/0)	2 (2/0)
Early	2 (2/0)	6 (5/1)
Advanced	12 (11/1)	4 (4/0)
Stomach	4 (3/1)	9 (6/3)
Liver	1 (1/0)	3 (3/0)
Lung	1 (1/0)	3 (2/1)
Kidney	9 (7/2)	5 (4/1)
Bladder	3 (2/1)	1 (1/0)
Prostate	1	4
Breast	0 (0/0)	4 (0/4)
Others	10 (3/7)	17 (6/11)
Total	44 (32/12)	55 (34/21)

prospective comparative cohort study in non-CKD and CKD populations.

Conflict of interest The authors have no conflicts of interest to declare.

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Research Article

Therapeutic Potency of Febuxostat for Hyperuricemia in Patients with Chronic Kidney Disease

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Abstract

Febuxostat is a non-purine xanthine oxidase inhibitor for which the metabolic pathway extensively differs from that for allopurinol. Since little information is available about the use of this agent in patients with chronic kidney disease (CKD), we investigated the effects of oral febuxostat for 2 months in patients with CKD, stage G3b–G5, and asymptomatic hyperuricemia. We found that the degree of serum uric acid decrease (ΔUA) after febuxostat administration was significantly larger in patients who had not been previously administered allopurinol or angiotensin receptor blockers. Furthermore, we found a significant positive correlation between ΔUA and baseline UA concentration. Finally, we found a weak negative correlation between ΔUA and baseline estimated glomerular filtration rate, suggesting that febuxostat could efficiently decrease UA levels in patients with severe renal dysfunction. These results suggest that we can prescribefebuxostat more safely and efficiently than allopurinol, for which the dosage has to be carefully reduced in patients with relatively advanced CKD.

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Keywords
- Febuxostat
- Chronic kidney disease
- Uric acid
- Xanthine oxidase inhibitor

ABBREVIATIONS

Chronic Kidney Disease; XO: Xanthine Oxidase; UA: Uric Acid; ARB: Angiotensin II Receptor Blocker; eGFR: Estimated Glomerular Filtration Rate

INTRODUCTION

Although hyperuricemia is a relatively common complication in patients with chronic kidney disease (CKD), a large body of evidence suggests that it has a pathogenic role in the progression of CKD itself [1-3]. A major obstacle when treating patients with CKD with hyperuricemia is the adverse effects caused by allopurinol, including severe dermatological diseases such as Stevens-Johnson syndrome or toxic epidermal necrosis. Therefore, it is necessary to reduce the dose of allopurinol, but this can sometimes lead to inadequate suppression of serum uric acid (UA) levels [4-6]. According to previous reports, febuxostat is highly efficacious in reducing serum UA levels in patients with CKD [7]. However, only a few reports have studied its efficacy and safety in more advanced cases of CKD [8,9].

Febuxostat, a non-purine xanthine oxidase (XO) inhibitor which recently received marketing approval, has been focused on as an alternative for the treatment of hyperuricemia in patients with CKD because it undergoes hepatic metabolism and may require less dose adjustment in association with renal function[10, 11]. However, information regarding the experience with this therapeutic agent among patients with advanced CKD is limited. In this regard, the current study investigated the effects of febuxostat in patients with relatively advanced CKD, i.e., greater than stage G3b, and hyperuricemia in terms of reduction of serum UA levels.

MATERIALS AND METHODS

Forty-nine- patients with CKD who had been prescribed allopurinol, or who had serum UA levels above 8.0 mg/dL and were not receiving anti-hyperuricemic agents, participated in the study. Estimated glomerular filtration rate (eGFR: mL/min/1.73 m^2) was calculated using the formula of the Japanese Society of Nephrology [12]. Eighty-four percent of patients (41/49) were classified in CKD stage 4 or 5 (Table 1). The subjects had to be

in a stable condition, had no history of active liver diseases or any other significant medical status, and no change in diuretics or steroid therapy within one month of study enrolment. The usual medications, such as anti-hypertensive agents, erythropoiesis-stimulating agents and phosphate binders, were continued during the study period. The exclusion criteria were as follows: age of < 20 years or > 90 years, type I diabetes mellitus or type II diabetes mellitus with poor glucose control (glycosylated hemoglobin> 9% at the start of the observation period), treatment with immunosuppressant agents, pregnancy, and any medical or surgical condition that made patients unsuitable for this study as judged by the attending physician. All patients were assigned to oral febuxostat and entered the 2-month treatment period during which the initial dose of febuxostat was 10- 20 mg orally once daily in the morning. The initial dose of febuxostat was principally determined by the attending physician. Twenty-six and 23 patients received febuxostat doses of 10, and 20 mg, respectively. In the group of allopurinol-treated patients, anti-hyperuricemic medication was changed to febuxostat according to the following guideline: If the dose of previously administered allopurinol was 50 mg/day or higher, then the dose of febuxostat was 10 mg/day or 20 mg/day, respectively.

Blood samples were obtained at the beginning and the end of febuxostat treatment. Serum levels of UA, creatinine (Cr), sodium (Na), chloride (Cl), potassium (K), calcium (Ca), inorganic phosphate (Pi), were measured. This study was performed in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Dokkyo Medical University. All patients included in the present study provided their informed consent.

The data were expressed either as the number of participants or as the percentage (%) of the study population. The remaining data were expressed as means ±standard error (SE). An analysis of variance combined with Fisher's protected least significant difference test for normal distributions, and the Kruskal–Wallis test with Dunn's method for skewed distributions were used to compare the two time points, when appropriate. To evaluate the associations between the degree of UA suppression and the baseline serum UA concentration, the previously used allopurinol dose, and prescription of angiotensin II receptor blocker (ARB), a multivariate regression analysis was performed using stepwise variable selection methods. Values of $p < 0.05$ were considered to be statistically significant. All statistical procedures including multiple regression analyses were performed using the JMP software program for Windows (SAS Institute, Cary, NC) unless otherwise stated.

RESULTS AND DISCUSSION

Current urate-lowering strategies include reducing UA production with XO inhibitors and accelerating the urinary excretion of UA by using uricosuric agents. Uricosuric agents, such as probenicid and benzbromarone, may have limited effectiveness in patients with reduced renal function [13, 14]. The purine analogue XO inhibitor, allopurinol, is widely prescribed for the treatment of hyperuricemia, but requires dose adjustment in subjects with renal impairment [4-6]. Therefore, we used febuxostat in this study, which can be used safely and efficaciously without dose adjustment, even in patients with CKD [8,9].

The demographic profiles of the 49patients included in the present study are summarized in (**Table 1**). The number of patients at each stage of CKD is also shown in (Table 1).The causes of advanced CKD included diabetic nephropathy, chronic glomerulonephritis, hypertensive nephrosclerosis, and polycystic kidney disease. All subjects were receiving the optimum tolerated medical management. Febuxostat lowered serum UA levels (Total: 8.4 ± 1.6 mg/dL, male: 8.3±1.5, and women: 8.6±1.7 mg/dL at baseline) significantly from 2 months after the initiation of treatment (**Table 2A**). When we divided the study population according to the underlying cause of CKD, the baseline and 2-month serum UA levels were as follows, respectively: diabetic nephropathy, 8.09 ± 1.85, 6.55 ± 1.24 ($p < 0.005$); chronic glomerulonephritis, 8.67 ± 1.49, 6.60 ± 1.66 ($p < 0.005$); and hypertensive nephrosclerosis, 7.97 ± 1.29, 6.40 ± 1.08 ($p = 0.22$) (Table 2B). Febuxostat was well tolerated by the patients with no withdrawals due to side effects or allergic reactions. Serum levels of sodium, potassium, chloride, calcium, inorganic phosphate, and creatinine did not change during the observation period (**Table 2A**). No patients experienced symptoms of gouty arthritis, including joint pain, swelling or redness, during the observation period.

The KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [15] states that there is insufficient evidence to support the use of anti-hyperuricemic agents for lowering serum UA in patients with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay the progression of CKD. Therefore, the appropriate dose of febuxostat among asymptomatic hyperuricemia subjects with advanced CKD has not yet been established. The current findings suggest that even relatively low doses of febuxostat, 10 mg or 20 mg, might effectively reduce serum UA levels in CKD patients to 6.5 ± 1.4 mg/dl after only 2 months of febuxostat administration.

Table 1: Demographic profiles of the patients at the start of the study.

DEMOGRAPHIC CHARACTERISTICS	
Age	57.7±16.7
Sex (male/female)	32/17
CKD STAGE	
IIIb	8
IV	22
V	19
UNDERLYING CAUSES OF CKD, N (%)	
Diabetic nephropathy	15(31)
Chronic glomerulonephritis	26(53)
Hypertensive nephrosclerosis	6 (12)
Polycystic kidney disease	2(4)
MEDICATION, N (%)	
Calcium channel antagonist(s)	35(71)
Angiotensin-converting-enzyme inhibitor	1(2)
Angiotensin receptor blocker(s)	40(81)
Thiazide-like diuretic(s)	5 (10)
Loop diuretic(s)	20(41)

Table 2A. Changes in clinical parameters between the beginning and the end of the observation period

	Total (n= 49)		Male (n= 32)		Female (n= 17)	
	BASELINE	2 MONTHS	BASELINE	2 MONTHS	BASELINE	2 MONTHS
UA(mg/dL)	8.4±1.6	6.5±1.4*	8.3±1.5	6.7±1.1*	8.6±1.7	6.2±1.9*
Na(mEq/L)	139.9±2.8	140.1±4.1	139.8±3.3	140.5±3.3	140.3±1.8	139.9±5.4
K(mEq/L)	4.7±0.7	4.7±0.6	4.7±0.7	4.7±0.6	4.7±0.6	4.7±0.6
Cl(mEq/L)	106.3±5.5	105.8±4.4	106.9±3.8	106.6±3.5	104.9±7.8	104.3±5.6
Ca(mg/dL)	9.3±0.5	9.3±0.5	9.2±0.5	9.2±0.6	9.5±0.5	9.4±0.4
IP(mg/dL)	4.1±1.3	3.9±0.9	3.9±1.3	3.7±0.9	4.3±1.1	4.1±0.9
Cre(mg/dL)	3.3±2.3	3.2±2.0	3.5±2.7	3.4±2.3	2.9±1.1	2.7±1.2
eGFR (mL/min/1.73m^2)	20.1±10.5	20.7±10.2	21.6±11.2	21.9±11.9	18.9±8.0	16.5±6.1

*: $p < 0.001$

Table 2B: Changes in clinical parameters between the beginning and end of the observation period according to the cause of chronic kidney disease.

	BASELINE		2 MONTHS	
Diabetic nephropathy	8.09 ± 1.85		6.55 ± 1.24	
Chronic glomerulonephritis	8.67	±1.49	6.60	±1.66
Hypertensive nephrosclerosis	7.97	±1.29	6.40	±1.08

*: $p < 0.005$, #: $p = 0.22$

In the patients who had received allopurinol as an anti-hyperuricemic agent before this study started, ΔUA was significantly smaller than that in the patients who did not previously receive allopurinol ($p < 0.001$, Figure 2A). This is in accordance with the findings of several previous studies showing the superiority of febuxostat over allopurinol with regard to decreasing of serum UA level in CKD patients [7,16]. When we plotted the dose of previously administrated allopurinol and ΔUA, we found a statistically significant negative correlation between them ($p= 0.0020$, Figure 2B). Furthermore, there was a significant positive correlation between ΔUA and baseline UA concentrations ($p< 0.0001$, Figure 3). Finally, we compared ΔUA in the patients with and without ARB administration. ΔUA was significantly larger in the patients not taking ARBs than in those taking ARBs ($p < 0.005$, Figure 4). It is not surprising that the magnitude of febuxostat-induced UA reduction was augmented when it was used in patients with higher serum UA. However, it was unexpected that serum UA would be suppressed more efficiently in patients not taking ARBs than in ARB-treated patients. Because there have been no previous reports investigating the efficacy of febuxostat in ARB-treated patients, its efficacy will need further confirmation in a larger number of patients.

When we focused on the relationship between ΔUA and baseline eGFR, there was a weak negative correlation but this was statistically insignificant (Figure 5). This suggests at least in part that serum concentrations of UA could be efficiently suppressed by febuxostat in patients with severe renal dysfunction.

Therefore, to evaluate whether these changes in ΔUA were independently associated with the baseline serum UA concentrations, ARB prescription, and previously used allopurinol dose, we conducted a multivariate regression analysis. The analysis showed that two parameters, the baseline serum UA concentrations and ARB prescription, were significant independent variables for the change in eGFR (Table 3), but the previously used allopurinol dose was not.

We have to consider the fact that some types of reactive oxygen species (ROS) are produced as byproducts of UA synthesis through XO [17,18]. The pharmacological nature of febuxostat is characterized by a higher bioavailability and a more potent blockade of XO activity than that achieved with allopurinol [4, 19]. Furthermore, febuxostat has been reported to have a more potent inhibitory activity than that of allopurinol against reactive oxygen synthesis [20,21]. Since serum UA levels could be used as a surrogate indicator of XO activity, the lower levels of UA attainable with febuxostat might inhibit cardiovascular events more effectively through strong ROS suppression. We recently reported that not only the serum levels of UA, but also those of 8-hydroxydeoxyguanosine, an oxidative stress marker, were significantly reduced after six months of febuxostat treatment, without adverse events [9]. Therefore we have to continue to investigate the clinical impact of lowering serum UA levels with febuxostat in patients with advanced CKD in terms of concomitantly reducing oxidative stress via the blockade of XO.

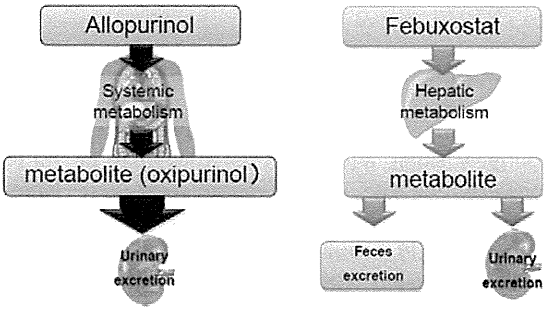

Figure 1 Allopurinol is converted to the active metabolite, oxipurinol, after systemic metabolism. Oxipurinol is mainly excreted in the urine and its serum concentration increases in patients with CKD. It is necessary to adjust the dose depending on the patients' renal function. However, febuxostat is metabolized in the liver and its inactive metabolite is excreted in feces and urine. It is not necessary to adjust the oral dose of febuxostat according to the patients' renal function.

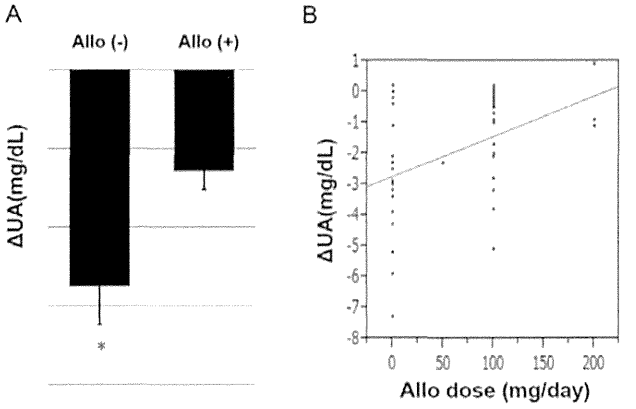

Figure 2 A. Compared to patients without prior allopurinol use, patients who received allopurinol before the beginning of this study showed a significantly smaller degree of decrease in serum UA concentration. Allo: allopurinol , *p < 0.001 versus Allo(+)
B. When we plot the dose of allopurinol and the degree of serum uric acid (UA) decrease, we observe a significant correlation between these two values (p< 0.005). The grey line in the graph is the regression line. ΔUA = -2.72 + 0.0130 x Allo dose.

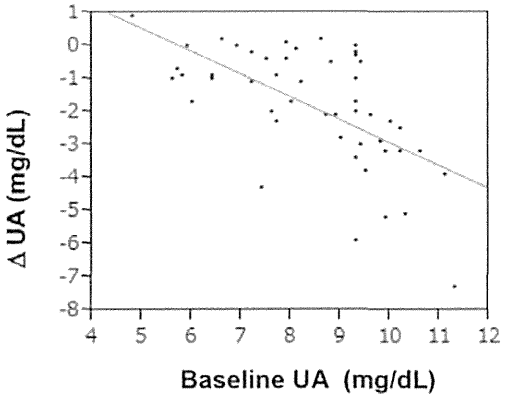

Figure 3 The higher baseline serum urci acid (UA) concentration, the larger the degree of serum UA decrease after febuxostat administration. This positive correlation was statistically significant (p < 0.0001).
The grey line in the graph is the regression line. ΔUA = 3.99 - 0.692 x Baseline UA.

Finally, the number of patients included in the present series was relatively small, and thus this study may be statistically underpowered or the clinical parameters may have been overestimated. Another limitation is the lack of data concerning the duration of allopurinol prescription. As such, our findings should be interpreted with caution. Nevertheless, our results encourage us to pursue further investigations regarding the clinical impact of lowering serum UA level with a low dose of febuxostat in patients with CKD. Obviously, more detailed studies with a larger number of subjects, and assessment of the effects of multiple factors affecting hyperuricemia, such as age, sex, and dietary habits, would shed light on the therapeutic challenges of treating asymptomatic hyperuricemia in patients with various stages of CKD.

CONCLUSION

Febuxostat is more efficacious in CKD patients with a high baseline serum UA concentration; however, its efficiency is blunted in allopurinol- or ARB-treated patients. Febuxostat was well tolerated by all patients with no withdrawals due to side effects. Febuxostat could be used efficaciously and safely even in cases of relatively advanced CKD including stages G4 and G5 over 80%.

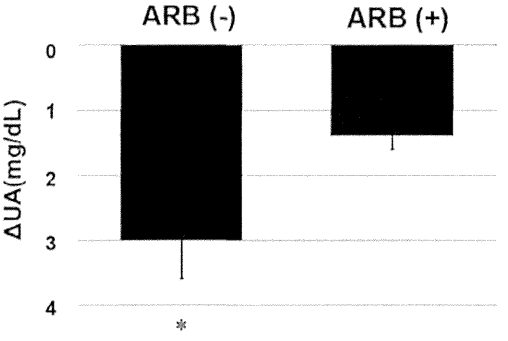

Figure 4 The degree of serum uric acid (UA) decrease after febuxostat administration was significantly larger in the patients without administration of angiotensin II receptor blocker (ARB) than in those who received ARBs. *p < 0.005versus ARB(+).

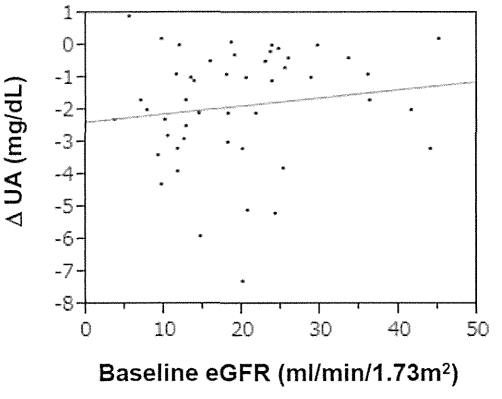

Figure 5 Baseline estimated glomerular filtration rate (eGFR) and the degree of serum uric acid (UA) decrease had a weak negative correlation but this was not statistically significant (p = 0.101). The grey line in the graph is the regression line. ΔUA = -2.48 + 0.0288 x Baseline eGFR.

Table 3: According to the result of multiple-regression analysis, the previously used allopurinol dose, baseline uric acid (UA) level, and angiotensin II receptor blocker (ARB) administration were independent variables to predict the degree of UA decrease.

	Regression coefficient	F statistic	P value
Baseline UA	-0.6	4.03	0.0000275
ARB	1.56	11.5	0.00143
Allo dose	0.00358	1.05	0.31

R^2: 0.543

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Spontaneous Spinal Epidural Hematoma as a Potentially Important Stroke Mimic

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ABSTRACT: Hemiparesis develops in response to a wide range of neurological disorders, such as stroke, neoplasms and several inflammatory processes. Occasionally, it may also occur due to a lesion located in the high cervical spinal cord. In this concise review, we describe the features of spontaneous spinal epidural hematoma, which should be included in the large list of stroke mimics. Various concerns regarding the diagnostic and therapeutic conundrums relating to the condition are also discussed.

KEYWORDS: hemiparesis, ischemic stroke mimic, spontaneous spinal epidural hematoma

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Introduction

Hemiparesis develops in response to a wide range of neurological disorders. The presence of concomitant cranial nerve signs or facial weakness generally prompts a search for cerebral etiologies such as stroke, neoplasms or inflammatory processes, while it may occasionally be due to a lesion located in the high cervical spinal cord.[1] In this concise review, we describe the features of spontaneous spinal epidural hematoma (SSEH), which is a rare cause of spinal cord compression and a neurological emergency requiring prompt diagnosis and management to prevent morbidity and mortality.[2,3] Most SSEH patients present with either paraplegia or tetraplegia; however, there are numerous descriptions about acute hemiparesis as an initial manifestation of SSEH, which may lead physicians to include an acute ischemic cerebrovascular event as a diagnostic consideration,[4] thus leading to the concept that SSEH should be included in the large list of stroke mimics. In the following sections, we also discuss various concerns regarding the diagnostic and therapeutic conundrums associated with this disease.

Epidemiology and Pathophysiology

SSEH represents a rare spinal emergency, with a frequency accounting for less than 1% of spinal epidural space-occupying lesions.[2,3] Jackson first described SSEH in a 14-year-old female in 1869,[5] and the first surgically-treated case was reported by Bain in 1897.[6] Although the introduction of neuroradiological investigations and progress in neurosurgery may lead to a sharp increase in the number of diagnoses of spinal bleeding,[7] only approximately 530 cases were included in the largest recent literature search for SSEH.[8] Holtas et al have reported their experience with 13 patients with SSEH during a nine-year period in a population of 1.49 million total patients, giving an incidence, on the basis of their population, of approximately 0.1 patient per 100,000 patients per year.[9] Most of the patients present in their 60s or 70s, but all age groups from six months[10] to late 80s have been affected, with a slight predominance of the male sex.[2,7]

Any level of the spinal canal may be involved; the location of the hematoma appears to have a bimodal distribution,

with peaks at C6 to C7 and T12,[2,8] while the level distribution has been shown to depend strongly on age. The localization of SSEH at the lower dorsal and lumbosacral segments under the age of 40 appears to be an exception.[2] The hematoma remains limited to a small number of segments (three to four).[2,11] The disease-related mortality rate ranged from 6 to 8%, and highly correlated with cervical or cervicothoracic hematomas, especially in patients with cardiovascular disease and those undergoing anticoagulant management.[2,11,12] A recent study also revealed that a long hematoma may predict a worse outcome.[13]

Although the precise pathogenesis of the disease remains to be delineated, hemorrhagic disorders due to anticoagulants, thrombolytics and anti-platelet agents, platelet dysfunction, pregnancy, vascular malformation, neoplasms and systemic diseases, such as hypertension and rheumatoid arthritis, have been considered as predisposing factors, while many cases without any known underlying cause also have been demonstrated.[2,12–14] Approximately 3% of patients are hypertensive; however, a relationship between hypertension and the development of a hematoma is considered to be marginal.[2] Nevertheless, the clinical significance of these previous findings should be evaluated carefully in terms of the fact that there is still no established definition of SSEH. A spontaneous hematoma is most often defined as a condition occurring in the absence of any traumatic event or iatrogenic procedure,[15] and thus, some of the predisposing factors described above cannot be excluded. Other authors argue that a hematoma can only be labelled "spontaneous" when it is of idiopathic origin.[16]

Regardless of the etiological background, the actual origin of spinal bleeding has been the subject of some discussion. Despite the presence of literature in support of both venous and arterial origin,[17,18] the posterior epidural venous network is believed to be the most likely source of the hematoma, due to the predominance of posterolateral hematomas, the segmental distribution of SSEH and the anatomical characteristics of the internal vertebral venous plexus, in addition to the fact that the spinal epidural veins have no valves and are thus prone to damage by changes in abdominal or thoracic pressure.[2,12,15] In a recent case series analysis, more than half of the patients with SSEH were reported to have experienced a subjective straining-associated event during the initial attack, lending even more credibility to the venous etiology theory.[14] On the other hand, Beatty and Winston made a radical argument for an arterial source of hemorrhage, at least in the cervical region, and they focused on the fact that the intrathecal pressure is higher than the venous pressure at the cervical level, which would preclude bleeding in the intrathecal space from veins.[18]

Clinical Presentation and Misleading Symptoms: Relevance to a Potentially Important Stroke Mimic

The onset of SSEH may be associated with neck or back pain radiating to the corresponding dermatome, which may sometimes be vague and ignored until the subsequent cord compression and neurological deficits arise.[13] Most patients present with paraplegia or tetraplegia,[5,11,19] while hemiparesis is considered to be a rare feature of SSEH.[11,19] Due to the rarity of the disease, no prospective series from single departments or study groups are available to date, and the international medical literature, including incidental cases from one's own department, is the only source of information for evaluating this topic.[8]

More than two decades ago, Anderson et al reported that the association with hemiparesis is low, occurring in only 6 of more than 250 reported cases.[20] However, modern radiological imaging modalities may overcome the shortfalls of clinical examinations in the management of acute spinal cord injuries, and may lead to new findings. Following the first report published on the use of magnetic resonance imaging (MRI) in the diagnosis of acute SSEH in 1987,[21] the mean incidence of such cases increased from 2.2 to 6.4 new cases per year.[22] Therefore, the precise incidence of hemiparesis among the overall patients with SSEH must be evaluated carefully. Indeed, anecdotal information regarding cases with hemiparesis as an initial presentation is still being accumulated.[4,14,19,23–33] The majority of hematomas in such cases were located within the cervical region, while four patients with hematomas that ranged from the cervical to thoracic region were also reported (Table 1). The presence of a spinal epidural hematoma was promptly diagnosed in more than half of these cases during the observation period.

Persistent neck or back pain and fluctuating neurological symptoms should result in a high index of suspicion of the illness. However, it is noteworthy that there were at least twelve patients who were suspected to have an ischemic stroke during the initial assessment,[4,23,25,27,29–33] and thus, there were four patients whose neurological manifestations were falsely attributed to ischemic cerebrovascular events who were consequently subjected to anti-coagulation with heparin,[25,27] thrombolytic treatment with a recombinant tissue plasminogen activator[29] or treatment with an anti-platelet agent as an adjunct to warfarin,[23] prior to the final diagnosis that their neurological deficits were etiologically linked to the cervical spinal epidural hematoma. In these cases, the presence of neck pain with or without shoulder pain might have been inadvertently dismissed during the initial physical assessment. Alternatively, or in addition, the occurrence of concurrent dysarthria,[29] which has been demonstrated to be a potential sign for discriminating stroke mimics from actual ischemic stroke in emergency settings,[34,35] might also have played a role in the false attribution of the illness to a cerebrovascular event.[1] The main cause of dysarthria in the patient with hemipareic SSEH described by Son et al.[29] is unclear. However, they concluded that dysarthria is a rather subjective symptom of patients with stroke, and they noted that removing the patient's dentures during the acute phase of the disease might have resulted in the slurring of speech.[29] Finally, the hemorrhagic risks associated with anticoagulants may not be equivalent to those of a

Table 1. The recently reported cases of SSEH with hemiparesis as an initial presentation.

AUTHOR (REF NO.)	AGE (YEARS)	SEX (M/F)	INITIAL PRESENTATIONS	TREATMENT FOR ISCHEMIC STROKE	LOCATION OF HEMATOMA	TREATMENT FOR SSEH	OUTCOME
Schmidley JW et al[4]	96	f	neck pain, shoulder pain, left hemiparesis	(–)	C5–C7	surgery	incomplete recovery
	81	f	neck pain, shoulder pain, right hemiparesis	(–)	C3–C6	surgery	incomplete recovery
Lobits B et al[14]	85	f	neck pain, shoulder pain, right hemiparesis	(–)	C5–C6	surgery	incomplete recovery
Marinella MA et al[19]	60	f	neck pain, left hemiparesis	(–)	C2–C6	conservative	complete recovery
Sakamoto N et al[23]	75	f	neck pain, right hemiparesis	anti-platelet treatment	C3–C4	surgery	complete recovery
Lin IY[24]	83	f	neck pain, right hemiparesis	(–)	C1–C7	surgery	died
Hsieh CF et al[25]	65	m	neck pain, right hemiparesis	anti-coagulation	C3–C5	surgery	incomplete recovery
Ishikawa E et al[26]	83	m	neck pain, left hemiparesis	(–)	C2–C6	surgery	incomplete recovery
Wang CC et al[27]	69	m	neck pain, shoulder pain, right hemiparesis	anti-coagulation	C4–C5	surgery	complete recovery
Nakanishi K et al[28]	73	f	neck pain, right hemiparesis	(–)	C3–C5	surgery	incomplete recovery
	62	m	neck pain, right hemiparesis	(–)	C6–T1	surgery	complete recovery
	60	f	neck pain, left hemiparesis	(–)	C2–C4	conservative	complete recovery
Son S et al[29]	63	m	neck pain, shoulder pain, left hemiparesis	thrombolytic treatment	C4–T2	surgery	incomplete recovery
Shima H et al[30]	84	f	neck pain, right hemiparesis	(–)	C2–C3	conservative	complete recovery
Matsumoto H at al[31]	71	f	neck pain, right hemiparesis	(–)	C2–T4	conservative	complete recovery
	54	f	neck pain, right hemiparesis	(–)	C3–T2	conservative	complete recovery
Liou KC et al[32]	60	f	neck pain, right hemiparesis	(–)	C2–C6	surgery	incomplete recovery
	58	f	neck pain, right hemiparesis	(–)	C2–C5	conservative	complete recovery
Lemmens R et al[33]	66	f	shoulder pain, right hemiparesis	(–)	C2–C7	conservative	complete recovery

thrombolytic agent and antiplatelet agent; however, a previous case presentation demonstrating the expansion of an already developing cervical spinal epidural hematoma by the addition of heparin, based on a presumptive diagnosis of a cardiac ischemic event,[36] suggests that the clinical picture of patients with SSEH mimicking an ischemic stroke might be modulated by the agents described above.

Management of SSEH

The mainstay of treatment for SSEH has been surgical evacuation, combined with prompt decompressive laminectomy. There have been several studies that have provided valuable information regarding the outcome following the surgical management of SSEH.[11–13,37,38] Based on these findings, the degree of preoperative neurological deficit and the