Table 2 Predictors of disease progression (50 % eGFR decline or ESRD requiring dialysis)

Predictors	Univariate model		Multivariate model 1[a]		Multivariate model 2[b]	
	OR (95 % CI)	*P*	OR (95 % CI)	*P*	OR (95 % CI)	*P*
GLPS (per 10 %)	1.4 (1.2–1.6)	<0.0001	1.3 (1.1–1.6)	0.001	1.3 (1.1–1.5)	0.004
MAP (per 10 mmHg)	1.5 (1.2–1.9)	0.0005	1.4 (1.1–1.8)	0.01	1.4 (1.1–1.8)	0.01
Proteinuria (per 1 g/day)	1.1 (0.9–1.3)	0.23	0.9 (0.8–1.1)	0.59	1.0 (0.8–1.1)	0.57
eGFR (per 10 mL/min/1.73 m^2)	0.8 (0.7–0.9)	0.0006	0.9 (0.8–1.1)	0.21	0.9 (0.7–1.0)	0.16
Immunosuppressive therapy	1.4 (0.7–2.7)	0.34			1.3 (0.6–3.0)	0.48
RAS blockade therapy	1.6 (0.8–3.1)	0.19			1.6 (0.8–3.6)	0.21

Univariate and multivariate logistic regression analyses to explain significant predictors of the risk of disease progression (50 % eGFR decline or ESRD requiring dialysis)

P based on the risk of disease progression

The suitability of the two models was good by Hosmer–Lemeshow test

Model 1: good suitability (χ^2: 10.22, $P = 0.25$), Model 2: good suitability (χ^2: 13.04, $P = 0.11$)

CI confident interval, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *GLPS* glomerular lesions percentage score, *HG* histologic grade; *MAP* mean arterial pressure, *OR* Odds ratio, *RAS* renin–angiotensin system

[a] Multivariate with GLPS, MAP, UP, and eGFR

[b] Multivariate with GLPS, MAP, UP, eGFR, immunosuppressive therapy, and RAS blockade therapy

Table 3 Predictors of annual eGFR decline

Predictors	Univariate models		Multivariate model 1[a]		Multivariate model 2[b]	
	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
GLPS (per 10 %)	−0.36 (0.08)	0.0001	−0.44 (0.1)	<0.0001	−0.46 (0.1)	<0.0001
MAP (per 10 mmHg)	−0.43 (0.14)	0.003	−0.46 (0.14)	0.002	−0.41 (0.15)	0.005
Proteinuria (per 1 g/day)	−0.07 (0.11)	0.50	0.12 (0.11)	0.26	0.11 (0.11)	0.30
eGFR (per 10 mL/min/1.73 m^2)	−0.01 (0.08)	0.86	−0.24 (0.09)	0.007	−0.24 (0.09)	0.008
Immunosuppressive therapy (vs. no)	−0.13 (0.43)	0.76			0.22 (0.45)	0.63
RAS blockade therapy (vs. no)	−0.73 (0.44)	0.10			−0.59 (0.42)	0.16

Univariate and multivariate linear regression analyses to explain significant predictors of annual eGFR decline. *P* based on annual decline in eGFR

β partial regression coefficient, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *GLPS* glomerular lesions percentage score, *HG* histologic grade, *MAP* mean arterial pressure, *RAS* renin–angiotensin system, *SE* standard error of mean

[a] Multivariate with GLPS, MAP, UP, and eGFR

[b] Multivariate with GLPS, MAP, UP, eGFR, immunosuppressive therapy, and RAS blockade therapy

Table 4 Correlations between outcomes and histologic grades

Histologic grade	Patients		Univariate logistic regression analysis (disease progression)		Univariate linear regression analysis (annual eGFR decline)	
	Total	Disease progression (rate)	Odds ratio (95 % CI)	*P*	β (SE)	*P*
HG 1	94	12 (12.8 %)	1.0			
HG 2 (vs HG 1)	65	21 (32.3 %)	3.3 (1.5–7.2)	0.004	−1.25 (0.44)	0.005
HG 3/4 (vs HG 1)	39	18 (46.2 %)	5.9 (2.4–14.0)	0.0001	−1.89 (0.49)	0.0002
HG 2 vs HG 3/4			1.8 (0.8–4.1)	0.16	−0.64 (0.71)	0.37

P based on the risk of disease progression (50 % eGFR decline or ESRD requiring dialysis) in univariate logistic regression analysis and on annual eGFR decline in univariate linear regression analysis

β partial regression coefficient, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *HG* histologic grade, *SE* standard error of mean

There are several differences in subjects and methods between the JHC 2013 study [12] and our study: our median follow-up period of 12.0 years was longer than that of 9.3 years in the JHC 2013 study; our cases were all adults, while the JHC 2013 study included children and adults; and we used logistic regression analysis and linear regression analysis, while the JHC 2013 study used only logistic regression analysis. Despite these differences, the results in the two studies were similar in showing a significant correlation between disease progression and HG classification. Therefore, our validation study suggests that the JHC 2013 system based on GLPS (HG) is useful for predicting the long-term renal outcome in patients with IgAN.

IgAN prognostic classifications for assessment of renal survival have been developed in several previous studies [10–12, 15–17]. The Oxford classification system was published in 2009 by an international consensus working group [10, 11]. This system includes four histological variables that were identified as histologic predictors of IgAN: mesangial hypercellularity (Mes), SG, endocapillary hypercellularity (Endo), and TA/IF. Mes, SG, and TA/IF were subsequently shown to be independent histologic predictors of renal clinical outcome in a multivariate Cox regression model and linear regression analysis. In patients who received no immunosuppressive therapy, the rate of renal function decline in patients with Endo was significantly faster than that in patients without Endo. Therefore, Endo was chosen as one of the histologic predictors. The Oxford classification is a split system classification based on statistical methodology, including validation of interobserver variability and univariate and multivariate regression analyses adjusted by variables such as MAP, UP, eGFR, immunosuppressive therapy, and RAS blockade. In the Oxford classification, prediction of disease progression (50 % eGFR decline) and annual eGFR decline is based on four histologic variables (Mes, SG, Endo, and TA/IF). These variables have high reproducibility beyond age and race (30 Japanese cases were included in the establishment of this classification). Therefore, the Oxford classification can be used worldwide. However, this classification also has some controversial aspects, since active glomerular lesions (CC and FCC) and chronic glomerular lesions (GS and FC) are not included as predictive factors, despite crescent formations and GS being shown to have prognostic value in previous IgAN studies [15–17]. This is a concern that requires further discussion in Japan and elsewhere. Katafuchi et al. [18] suggested that $\geq$10 % crescent formations in all obtained glomeruli were significantly correlated with disease progression of IgAN in Japanese patients. In addition, several previous lumped system classifications have included crescent formations as prognostic lesions. The glomerular grading systems of S. M. K. Lee et al. [15], Haas [16], and H. S. Lee et al. [17] are typical IgAN prognostic lumped classifications that generally combine GS, SS, and crescents as histological predictors. This suggests that GS and crescent formation should be included as histologic prognostic factors for IgAN, and there is a need to validate previous IgAN classifications and to develop new classifications as split or lumped systems.

In this context, the JHC 2013 was developed as a lumped system using clinicopathological data in only Japanese patients with IgAN [12]. In this classification system, five histologic lesions (CC, FCC, GS, SG, and FC) were included as histologic predictors for long-term prognosis. The association between histologic lesions and progression to ESRD was examined by multivariate logistic regression analysis, separately for patients who required dialysis <5 years after biopsy (early progressors) and those who required dialysis within 5–10 years after biopsy (late progressors). Of the histologic lesions, SG and FC were analyzed separately as independent variables, since these histologic lesions are etiologically associated with each other. Multivariate logistic regression analyses of each histologic lesion as an independent predictor in IgAN were adjusted for other histologic lesions and clinical data such as initial MAP, daily UP, and eGFR. CC, FCC, GS, SG, and FC were shown to be independent histologic variables predicting early progressors, and similarly CC, FCC and GS were predictors of late progressors.

In the JHC 2013 study [12], Mes and Endo were not significant independent predictors, while GS was a significant independent predictor with a highly significant association with IF. Therefore, in the JHC 2013 system, GS was used instead of TA/IF. GLPS can be simply calculated based on five glomerular lesions (CC, FCC, GS, SG, and FC) and the renal outcome can easily be assessed using the HG category. In our validation study, categorization into HGs by three nephrologists showed close to outstanding reproducibility (ICC, 0.78). The utility of the JHC 2013 as a pure Japanese classification of IgAN has been recognized by many Japanese doctors. Recently, Tanaka et al. [19] also developed a new scoring system for predicting disease progression of IgAN based on the Oxford classification [10, 11] to identify the subgroup of Japanese patients with IgAN at a higher risk of incident ESRD, and verified the external validity of the score in an independent cohort. In Tanaka et al., SG and TA/IF were significantly associated with a higher risk of incident ESRD. This prediction rule may also be useful in Japanese medical centers.

There were several limitations in our retrospective cohort study. Disease progression (50 % eGFR decline or ESRD requiring dialysis) was evaluated only at 10 years after renal biopsy. Only three clinical variables (MAP, UP, and eGFR) at the time of biopsy and two treatments (immunosuppressive therapy and RAS blockade) during follow-up were used as adjustments (covariates) in two multivariate regression analyses because there were no other standard time points at which clinical data was examined and no other standard treatment strategies for IgAN at the time of the study.

Future analysis of renal disease prognostic factors and development of prognostic classifications should use a prospective cohort and statistical analyses based on typical classifications and standardized histologic definitions. The efficacy of corticosteroid therapy has been proven by Pozzi et al. [20, 21]. Active treatments such as tonsillectomy and steroid pulse therapy, which Hotta et al. [22] found to have a significant impact on clinical remission of IgAN, have recently been introduced for some patients with IgAN, based on the clinical condition and histologic lesions. Therefore, the analysis of IgAN prognostic classifications needs to be adjusted for these treatments. Continued validation of prognostic classifications of IgAN is necessary to determine treatment strategies and to obtain accurate information on disease levels and courses for patients with IgAN.

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

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RESEARCH ARTICLE Open Access

Primary care physicians' own exercise habits influence exercise counseling for patients with chronic kidney disease: a cross-sectional study

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Abstract

Background: The appropriate exercise counseling for chronic kidney disease (CKD) patients is crucial to improve their prognosis. There have been few studies about exercise counseling by primary care physicians for CKD patients. We investigated primary care physicians' exercise counseling practices for CKD patients, and the association of these physicians' own exercise habits with exercise counseling.

Methods: The population of this cross-sectional study was 3310 medical doctors who graduated from Jichi Medical University from 1978 to 2012. The study instrument was a self-administered questionnaire that was mailed in August 2012 to investigate their age class, specialty, workplace, exercise habits, and practices of exercise counseling for CKD.

Results: 581 (64.8%) medical doctors practiced the management of CKD among a total of 933 responses. These 581 medical doctors were defined as CKD primary care physicians and their answers were analyzed. CKD primary care physicians' own exercise habits (frequencies and intensities) were as follows: frequencies: daily, 71 (12.1%); ≥2–3 times/week, 154 (26.5%); ≥1 time/week, 146 (25.1%); and ≤1 time/month, 176 (30.2%); intensities: high (≥6 Mets), 175 (30.1%); moderate (4–6 Mets), 132 (22.7%); mild (3–4 Mets), 188 (32.3%); very mild (<3 Mets), 47 (8.1%); and none, 37 (6.4%). The CKD primary care physicians' exercise recommendation levels for CKD patients were as follows: high, 31 (5.3%); moderate, 176 (29.7%); low, 256 (44.0%); and none, 92 (15.8%). The CKD primary care physicians' exercise recommendations for CKD patients were significantly related to their own exercise frequency ($p < 0.001$), but they were not related to their age, specialty, workplace, or exercise intensity.

Conclusions: CKD primary care physicians' exercise recommendation level for CKD patients was limited. In addition, CKD primary care physicians' own exercise habits influenced the exercise counseling for CKD patients. The establishment of guidelines for exercise by CKD patients and their dissemination among primary care physicians are needed. (University Hospital Medical Information Network Clinical Trial Registry. number, UMIN000011803. Registration date, Sep/19/2013)

Background

Chronic kidney disease (CKD) patients show gradual decline in maximal exercise capacity in accordance with the progression of their CKD stage [1,2]. Actually, CKD stage 3–5 patients have been reported to show lower peak oxygen consumption, averaging 50-80% compared with healthy subjects [3,4]. This decreased exercise capacity decreases quality of life and enhances sarcopenia, which can be defined as the age-related (1% per year after the age of 25) loss of muscle [5,6]. Several studies reported that sarcopenia progressed much more intensively in CKD patients in association with several factors often observed in CKD, such as nutritional deficiencies, acidosis, and vitamin D deficiency [7,8]. Sarcopenia is an independent predictor of low physical performance activities and fractures [9]. Recently, accumulated evidence has demonstrated that all CKD patients, irrespective of CKD stage and treatment modality, can improve their physical functioning and reduce the risk of

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sarcopenia by exercise training [10,11]. Previous studies have reported beneficial effects of resistance exercise training on muscle mass and contractile function in CKD patients [12-15]. In addition, several studies also have reported the beneficial effects of exercise on potential mediators of cardiovascular disease in CKD [12,16]. Since the prevalence of CKD has been increasing globally [17,18] and it has become a common disease globally, like cardiovascular diseases and metabolic syndrome, appropriate exercise counseling by primary care physicians as well as nephrologists for CKD patients is crucial to improve their prognosis. However, physicians reported limited medical school and residency training education about the beneficial effects of exercise, as well as inadequate guidelines for writing exercise prescriptions or referrals as barriers to exercise counseling [19,20]. Several studies reported that physicians who exercise are more likely to counsel their patients to do so as well [21,22]. However, there have been few studies about exercise counseling by primary care physicians for CKD patients. Therefore, in the present study, we investigated primary care physicians' exercise counseling practices for CKD patients. Furthermore, we also investigated the associations of primary care physicians' own exercise habits with their exercise counseling, as well as major barriers for exercise counseling for CKD patients.

Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Jichi Medical University. Since this study was analysis of anonymous self-administered questionnaire, responses were considered as consents for this study. This study was registered at University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR). The identification number is UMIN000011803.

Subjects

The population of this cross-sectional study was 3310 medical doctors who graduated from Jichi Medical University from 1978 to 2012. The medical doctors who graduate from this medical university have a 5–7-year term of duty to work in a rural area of Japan as primary care physicians. In addition, almost all medical doctors (> 80%) continue to work as primary care physicians after this term of duty.

Study instrument

The study instrument was a self-administered questionnaire. This was designed to obtain detailed information about primary care physicians' characteristics, including their age class, specialty, workplace, personal exercise habits, and management of CKD (exercise counseling practice, medical prescription pattern). The results of their medical prescription pattern will be analyzed and reported elsewhere. This study focused on the primary care physicians' exercise counseling practices for CKD patients, and the association of primary care physicians' own exercise habits with their exercise counseling for CKD. The questions that were used for analysis in the present study were as follows:

Characteristics

1. Age (24–30, 30–40, 40–50, 50–60, ≥60 years)
2. Specialty (internal medicine, surgery, general medicine, pediatrics, others)
3. Workplace: (university hospital, polyclinic hospital, hospital, clinic, others)

Personal exercise habits

1. Exercise frequency (daily, ≥2–3 times/week, ≥1 time/week , ≤1 time/month)
2. Exercise intensity (high [≥6 Mets], eg, swimming, jogging, soccer, cycling; moderate [4–6 Mets], eg, quick walking, golf; mild [3–4 Mets], eg, walking, cleaning; very mild [<3 Mets], eg, stretching, cooking; none; others)

Exercise recommendation for CKD

1. Management of CKD patients (yes, no)
2. Diseases for which you recommend exercise [multiple selection] (diabetes mellitus, hyperlipidemia, apoplexia, heart failure, arterial hypertension, others)
3. General exercise recommendations for CKD patients (high, moderate, low, others)

The next two questions were for those who chose high or moderate for the question above about general exercise recommendations for CKD patients.

1. Recommended exercise frequency for CKD patients (daily, ≥2–3 times/week, ≥1 time/week, ≤1 time/ month)
2. Recommended exercise intensity for CKD patients (high [≥6 Mets], eg, swimming, jogging, soccer, cycling; moderate [4–6 Mets], eg, quick walking, golf; mild [3–4 Mets],eg, walking, cleaning, very mild [<3 Mets],eg, stretching, cooking; others

The next question was for those who chose low or no for the above question about general exercise recommendations for CKD patients.

1. What are the barriers for exercise recommendations for CKD patients [multiple selection] (no interest,

Table 1 The characteristic of CKD primary care physicians

Age	Number (%)	Specialty	Number (%)	Workplace	Number (%)
24-30	55 (9.5)	Internal medicine	350 (60.2)	University hospital	51 (8.8)
30-40	189 (32.5)	Surgery	48 (8.3)	Polyclinic hospital	89 (15.1)
40-50	175 (30.1)	General medicine	145 (25.0)	Hospital	187 (32.1)
40-50	154 (26.5)	Pediatrics	12 (2.1)	Clinic	239 (41.1)
60≦	8 (1.4)	Others	26 (4.5)	Others	15 (2.6)
Total	**581 (100)**	**Total**	**581 (100)**	**Total**	**581 (100)**

Abbreviations: *CKD* chronic kidney disease.

inadequate knowledge on the effects of exercise, concern that exercise may impair renal function and cause complications, inadequate knowledge to prescribe exercise for CKD patients, inadequate time, others)

Statistical analysis

The associations between primary care physicians' own exercise habits (frequency and intensity) and their age class, specialty, and workplace were analyzed by multiple linear regression analysis to determine the independent variables. Values of $p < 0.01$ were considered to be significant.

Results

The survey was mailed to 3310 medical doctors, with responses being received from 933 in total (28.2%). 37 responses were excluded from this study due to their inadequacy. Among the remaining 896, 581 (64.8%) medical doctors managed CKD patients. In this study, these 581 medical doctors were defined as CKD primary care physicians and their answers to the self-administered questionnaire were analyzed.

The characteristics and exercise habits of CKD primary care physicians

The characteristics of CKD primary care physicians' age class, specialty, workplace and their exercise habits are shown in Table 1 and Table 2. Multivariable linear regression analysis showed that the CKD primary care physicians' exercise frequency was significantly associated with their age class ($p < 0.01$), but was not associated with their specialty or workplace (Table 3). Those in the older age classes were more likely to have a high exercise frequency. The CKD primary care physicians' exercise intensity was not significantly associated with their age class, their specialty and workplace (Table 3).

CKD primary care physicians' exercise counseling

The diseases for which CKD primary care physicians recommend exercise were as follows: diabetes mellitus, 562 (96.7%); hyperlipidemia, 509 (87.6%); apoplexia, 250 (43.0%); heart failure, 129 (22.2%); arterial hypertension, 408 (70.2%); and others, 61 (10.5%). Table 4 shows CKD primary care physicians' exercise counseling for CKD patients. Among CKD primary care physicians who had low and no exercise recommendations, the barriers to exercise counseling for CKD patients are shown in Table 5. Multivariable linear regression analysis showed that the CKD primary care physicians' exercise recommendations (general) for CKD patients were significantly associated with their own exercise frequency ($p < 0.001$), but they were not associated with their age, specialty, workplace, or their own exercise intensity (Table 6, Figure 1). The CKD primary care physicians who had a high exercise frequency were more likely to recommend exercise at a high frequency for CKD patients than those who had a lower exercise frequency (Figure 1). Furthermore, multivariable linear regression analysis showed among the CKD primary care physicians who had high and moderate exercise recommendations for CKD patients,

Table 2 CKD primary care physicians' exercise habits

Frequency	Number (%)	Intensity	Number (%)
Daily	71 (12.2)	High (≥6 Mets)	175 (30.1)
≥2–3 times/week	154 (26.5)	Moderate (4–6 Mets)	132 (22.7)
≥1 time/week	146 (25.1)	Mild (3–4 Mets)	188 (32.2)
≤1 time/month	176 (30.3)	Very mild (<3 Mets)	47 (8.1)
Others	32 (5.5)	None	37 (6.4)
N/A	2 (0.3)	Others	3 (0.5)
Total	**581 (100)**	**Total**	**203 (100)**

Abbreviations: *CKD* chronic kidney disease, *N/A* not available.

Table 3 Multivariate linear regression analyses of the association of age, specialty and workplace and exercise habits (frequency and intensity) in CKD primary care physician

	Exercise frequency		Exercise intensity	
	(Model $R^2 = 0.139$)		(Model $R^2 = 0.139$)	
	χ^2	p	χ^2	p
Age (years old)	38.224	*0.001	37.462	0.010
Specialty	28.470	0.028	25.553	0.181
Workplace	18.623	0.289	21.999	0.341

*$p < 0.01$.

Table 4 CKD primary care physicians' exercise counseling for CKD patient

General	Number (%)	Frequency	Number (%)	Intensity	Number (%)
High	31 (5.3)	daily	22 (10.8)	High (≥6 Mets)	1 (0.5)
Moderate	172 (29.6)	≥2–3 times/week	143 (70.4)	Moderate (4–6 Mets)	61 (30.5)
Low	256 (44.1)	≥1 time/week	25 (12.3)	Mild (3–4 Mets)	132 (66.0)
No	92 (15.8)	≤1 time/month	0 (0)	Very mild (<3 Mets)	3 (1.5)
Others	10 (1.7)	Others	13 (6.4)	None	3 (1.5)
N/A	20 (3.4)			Others	3 (1.5)
				N/A	3 (1.5)
Total	581 (100)	Total	203 (100)	Total	203 (100)

Abbreviations: *CKD* chronic kidney disease, *N/A* not available.

exercise recommendations frequency was associated with their own exercise frequency ($p < 0.01$) but not exercise intensity (Table 7, Figure 2). They were not also associated with their age class, specialty or workplace (Table 7). The CKD primary care physicians who had a high exercise frequency were more likely to recommend exercise at a high frequency for CKD patients (Figure 2). Their exercise recommendations intensity for CKD patients was not associated with their age class, specialty, or workplace, or with their own exercise frequency and intensity (Table 6).

Discussion

The results in the present study show that primary care physicians' exercise recommendation levels for CKD patients were limited because their rate of positive exercise recommendations (high recommendation: 5.4% + moderate recommendation: 30.9%) was < 40% and their rate of negative exercise recommendations was > 50% (low recommendation: 44.1% + no recommendation: 15.8%) for such patients. In addition, the CKD primary care physicians' exercise recommendation (general) for CKD patients was significantly associated with their own exercise frequencies, but not with their age, specialty, workplace or their own exercise intensity. Furthermore, in the CKD primary care physicians who had positive exercise recommendations (high and moderate) for CKD patients, their exercise frequency recommendations for CKD patients were significantly associated with their own exercise frequency; however, they were not associated with their age class, specialty, or workplace, or with their own exercise intensity, and their exercise intensity recommendations for CKD patients were not associated with their age class, specialty, or workplace, or with their own exercise frequency and intensity.

There have been few studies about exercise counseling by primary care physicians for CKD patients. To the best of our knowledge, this is the first study to report on such exercise counseling. Several studies reported that physicians who have substantial exercise habits are more likely to counsel their patients to exercise [21,22]. In the present study, we also found associations of the CKD primary care physicians' exercise frequency recommendations with their own exercise frequency.

Recently, several studies have demonstrated that all CKD patients, irrespective of their CKD stage, treatment modality, age, and functional impairment, can benefit from exercise [10-15]. Exercise including resistance exercise training can improve their physical capacity and reduce the risk of sarcopenia [10-15]. In addition, although the direct cardiovascular outcome in CKD patients due to exercise has not been reported, several studies have reported the beneficial effects of exercise on potential mediators of cardiovascular disease such as arterial stiffness, C-reactive protein, and interleukin 6 [12,16]. In terms of renal function, although there have been no large studies that clearly showed the effects of exercise on renal function, several studies have shown that exercise decreased proteinuria and glomerular sclerosis in an animal model with CKD [23,24]. The European

Table 5 Barriers for CKD primary care physicians' exercise counseling for CKD patient

Barrier	Number (%)
No interest	11 (3.2)
Inadequate knowledge on the effects of exercise	204 (58.6)
Concern that exercise may impair renal function and cause complications	113 (32.5)
Inadequate knowledge to prescribe exercise for CKD patients	234 (67.2)
Inadequate time	21 (6.0)
Others	21 (6.0)

Abbreviation: *CKD* chronic kidney disease.

Table 6 Multivariate linear regression analyses of the association of age, specialty and workplace and exercise habits of CKD primary care physician and their exercise counseling (general) for CKD patient

	Exercise recommendation general (Model $R^2 = 0.333$)	
	χ^2	p
Age (years old)	20.616	0.194
Specialty	19.744	0.232
Workplace	11.937	0.748
Exercise frequency	38.548	** < 0.001
Exercise intensity	13.055	0.875

Abbreviation: *CKD* chronic kidney disease, **p < 0.001.

Association of Rehabilitation in Chronic Kidney Disease recommends maintaining CKD patients on a fairly intense level of exercise [25]. The National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines recommend that physical functioning assessment and encouragement to participate in physical activity should be part of the routine care plan for dialysis patients [26]. However, these recommendations do not seem to have been widely adopted and have been insufficiently referred to CKD primary care physicians because positive exercise recommendations by CKD primary care physicians in the present study were limited at <40% (high recommendation: 5.4% + moderate recommendation: 30.9%), and the rate of negative exercise recommendation was > 50% (low recommendation: 44.1% + no recommendation: 15.8%) for CKD patients; however, they highly recommended exercise for patients with metabolic syndrome, such as diabetic mellitus (97.0%), hyperlipidemia (87.9%), and hypertension (70.8%). In addition, in the CKD primary care physicians who had negative exercise recommendations for CKD patients, the main reasons why these physicians did not recommend exercise for CKD patients in the present study were inadequate knowledge on the effects of exercise (59.3%) and inadequate knowledge to prescribe

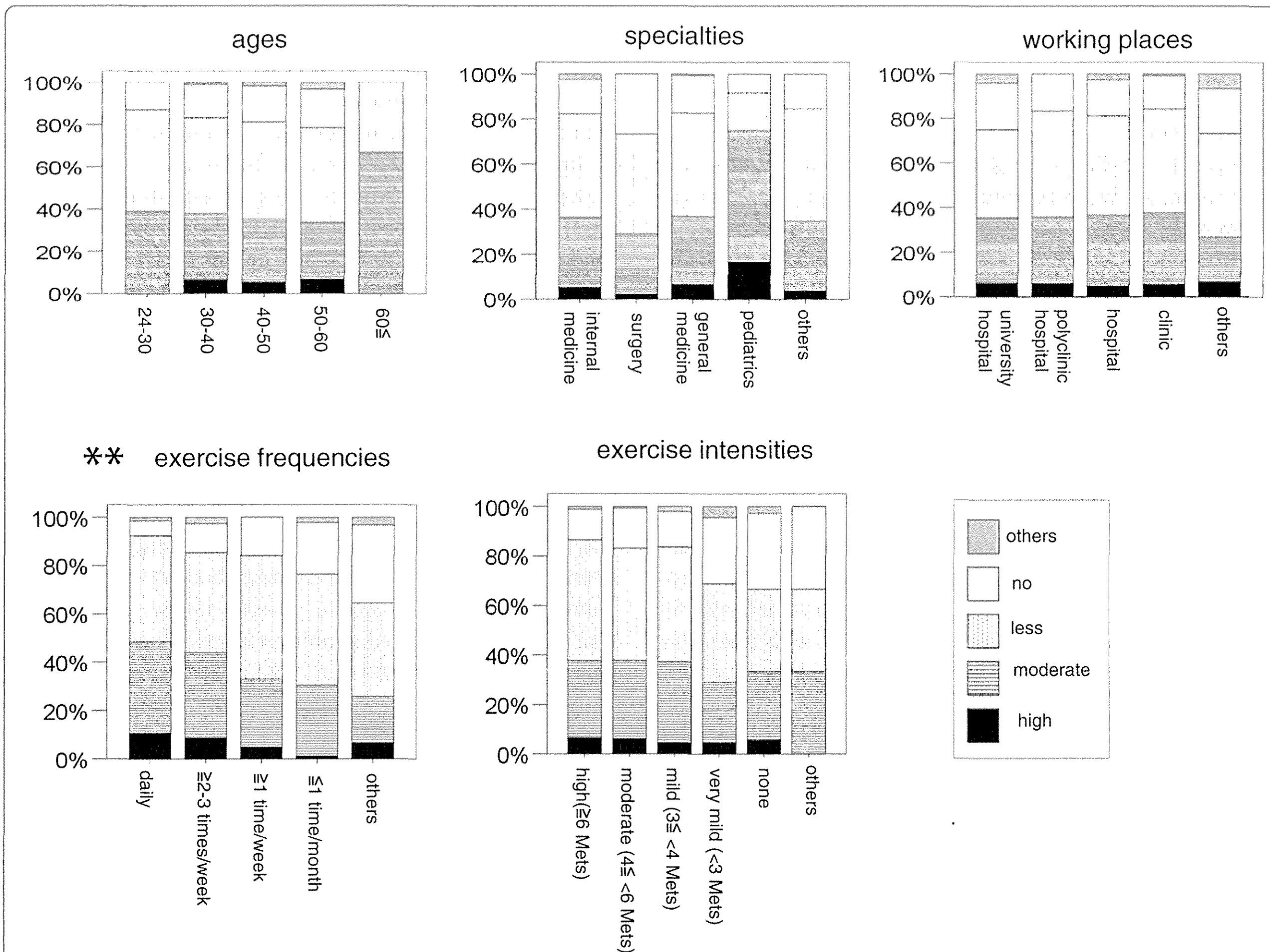

Figure 1 The associations of CKD primary care physicians' exercise recommendations (general) for CKD patients and their age class, specialty, and workplace, as well as their own exercise frequency and intensity. CKD: chronic kidney disease. **p < 0.001.

Table 7 Multivariate linear regression analyses of the association of age, specialty and workplace and exercise habits of CKD primary care physician who had who had high and moderate exercise recommendations for CKD patients and their exercise counseling (frequency and intensity) for CKD patient

	Exercise recommendation frequency (Model $R^2 = 0.333$)		Exercise recommendation intensity (Model $R^2 = 0.333$)	
	χ^2	p	χ^2	p
Age (years old)	9.137	0.691	16.973	0.387
Specialty	19.619	0.075	17.649	0.345
Workplace	19.378	0.080	12.986	0.674
Exercise frequency	28.728	*0.004	16.693	0.406
Exercise intensity	17.719	0.278	26.126	0.162

Abbreviation: *CKD* chronic kidney disease; *, $p < 0.01$.

exercise (68.7%). Each CKD patient has a different type of disease, such as cardiovascular disease, heart disease, and metabolic syndrome. These complicated conditions may contribute to difficulty in establishing clear exercise guidelines for CKD patients. Clyne reported that physicians should preferably prescribe exercise training and nephrologists or physiologists should design a program and evaluate its progress for CKD patients [25]. The cooperative planning and management of exercise for CKD patients may be useful to encourage exercise and improve their prognosis. In the management of CKD patients, appropriate pharmacological medication in CKD also very impotent. We investigated and reported medication-prescribing patterns of the primary care physicians in CKD. In that analysis, there were certain associations between the prescribing patterns of the CKD primary care physicians for CKD and their specialty and workplace (in press); however, there was no association between their prescribing patterns for CKD and their exercise habits (unpublished data).

There are several limitations in this study. First, this was cross-sectional study, which limits the generalizability of the results. Seconds, since the study instrument was a mailed self-administered questionnaire, there may be self-selection bias, and it may also contribute to low response rate (28.2%) to questionnaire. Second, the primary care physicians in this study may not be a representative population of all primary care physicians because all medical doctors in this study graduated from one medical university; however, majority of graduates of this medical university work as primary care physicians. Third, the results were from a self-administered questionnaire and were not objectively evaluated in terms of primary care physicians' personal exercise habits and exercise recommendations for CKD patients. These confounding factors in cross-sectional study might affect the results. Further studies will thus need to investigate more accurately the exercise prescription patterns for CKD patients and the exercise habits of primary care physicians using instruments such as exercise recording devices for both primary care physicians and CKD patients.

Conclusion

CKD primary care physicians' exercise recommendation level for CKD patients was limited. In addition, CKD primary care physicians' own exercise habits influenced

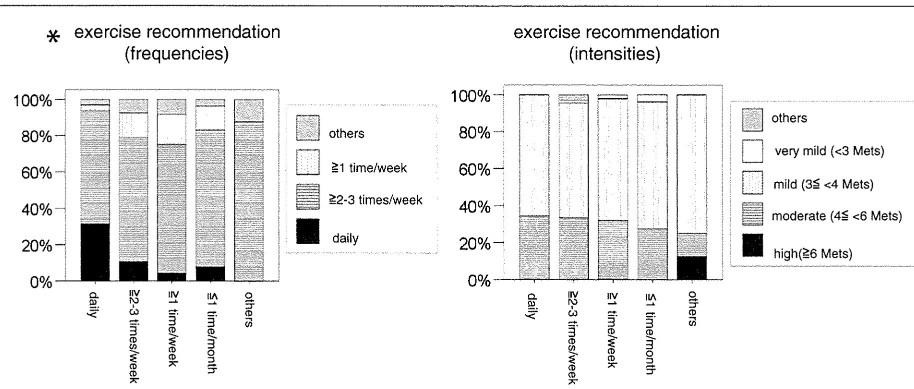

Figure 2 The associations of CKD primary care physicians' own exercise frequency and their exercise recommendations (frequency and intensity) for CKD patients. CKD: chronic kidney disease. *$p < 0.01$.

the exercise counseling for CKD patients. The establishment of guidelines for exercise by CKD patients and their dissemination among primary care physicians are needed.

Competing interests
The authors declare no competing interests.

Authors' contributions
YM participated in the design of the study and coordination, and performed the statistical analysis and drafted the manuscript. AN participated in its design. AM participated in its design and helped to carry out the statistical analysis. MO participated in its design and helped to carry out the statistical analysis. KI participated in its design. FT participated in its design. YA participated in its design. SM participated in its design. DN conceived of the study and participated in its design and coordination. EK conceived of the study and participated in its design and coordination. All authors have read and approve the final manuscript.

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ORIGINAL RESEARCH

Exercise counseling of primary care physicians in metabolic syndrome and cardiovascular diseases is associated with their specialty and exercise habits

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Background: We investigated the practice of exercise counseling of primary care physicians in metabolic syndromes and cardiovascular diseases and its association with their age class, specialty, work place, and their own exercise habits.

Subjects and methods: The subjects were 3,310 medical doctors who had graduated from Jichi Medical University in Japan. The study instrument was a self-administered questionnaire to investigate their age class, specialty, workplace, exercise habits, and exercise counseling for their patients.

Results: Overall, 839 completed responses were analyzed from a total of 933 that were received (28.2%). The primary care physicians whose specialties were internal medicine and general medicine significantly more often recommended exercise in diabetes mellitus, hyperlipidemia, heart failure, and hypertension cases than those whose specialties were surgery and pediatrics. The primary care physicians whose specialty was pediatrics recommended exercise less often in apoplexia cases than those whose specialties were internal medicine, general medicine, and surgery. Their exercise habits were positively associated with their recommendation of exercise in hyperlipidemia, heart failure, and hypertension cases; however, these associations were not observed in diabetes mellitus and apoplexia. The primary care physicians' age class and work place showed no association with their exercise recommendations in metabolic syndrome and cardiovascular diseases.

Conclusion: The primary care physicians whose specialties were internal medicine and general medicine significantly more often recommended exercise in diabetes mellitus, hyperlipidemia, heart failure, and hypertension cases. In addition, their own exercise habits were positively associated with their recommendation of exercise in hyperlipidemia, heart failure, and hypertension cases.

Keywords: primary care physician, self-administered questionnaire, exercise recommendation, metabolic syndrome, cardiovascular diseases

Introduction

Exercise counseling is very important for the prevention and inhibition of the progression of many chronic diseases, including metabolic syndrome and cardiovascular diseases.[1–6] Increased physical activity has been reported to have beneficial effects on the incidence and prognosis of these chronic diseases, as well as overall morbidity and mortality.[1–6] Primary care physicians have important roles in exercise counseling for these patients because they provide them with close and continuous care. A few studies reported primary care physicians' exercise counseling in cases of chronic disease, and suggested that their lifestyle may be associated with their exercise counseling for

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such cases.[7–11] However, primary care physicians' exercise counseling in cases of metabolic syndrome and cardiovascular diseases has not been fully reported. Therefore, we conducted a cross-sectional study to investigate the practice of exercise counseling of primary care physicians in cases of chronic diseases such as metabolic syndrome, cardiovascular diseases, and chronic kidney disease. We previously reported that primary care physicians offering exercise counseling for chronic kidney disease patients was positively associated with their own exercise habits.[12] In the present study, we performed a subanalysis of our survey to investigate the practice of primary care physicians' exercise counseling for cases of metabolic syndrome (diabetes mellitus and hyperlipidemia) and cardiovascular diseases (apoplexia, heart failure, and hypertension), and its association with their age class, specialty, work place, and own exercise habits.

Subjects and methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Jichi Medical University.

Subjects

The subjects of this cross-sectional study were 3,310 medical doctors who graduated from Jichi Medical University in Japan from 1978 to 2012. The majority of graduates of this university have been working as primary care physicians.

Study instrument

The study instrument was a self-administered questionnaire that was mailed along with an addressed and stamped envelope for reply. It was designed to investigate the primary care physicians' characteristics (age, specialty, work place, personal exercise frequency and intensity), exercise counseling for cases of metabolic syndrome and cardiovascular diseases, and management of chronic kidney disease. The parameters canvased in the questionnaire of the primary care physicians' characteristics were reported in our previous manuscript[13] and are also shown in Table 1. The question on exercise counseling for patients with metabolic syndrome and cardiovascular disease was as follows: diseases for which you recommend exercise (multiple selections allowed): 1) diabetes mellitus; 2) hyperlipidemia; 3) apoplexia; 4) heart failure; 5) arterial hypertension; and 6) others.

Exercise habits

The exercise volume (metabolic equivalents of task [Mets] × hours/week) was calculated as representing their exercise habit by multiplying their exercise frequency by their exercise intensity. The details of this calculation were reported in our previous manuscript,[13] but a brief explanation is provided here. Their exercise frequency was scored as follows: daily was given a score of 3.5 (7 days ×0.5 hours), ≥2–3 times/week was 1.25 (2.5 days ×0.5 hours), ≥1 time/week was 0.5 (1 day ×0.5 hours), and ≤1 time/month was 0.125 (0.25 days ×0.5 hours). Their exercise intensity was scored as follows: high was 6 (6 Mets), moderate was 5 (5 Mets), mild was 4 (4 Mets), very mild was 3 (3 Mets), and none was 0 (0 Met).

Table 1 The characteristics of primary care physicians

	n (%)
Age	
24–30	71 (8.5)
30–40	259 (30.9)
40–50	265 (31.6)
50–60	230 (27.4)
≥60	14 (1.7)
Total	839 (100)
Specialty	
Internal medicine	387 (46.1)
Surgery	158 (18.8)
General medicine	155 (18.5)
Pediatrics	44 (5.2)
Others	95 (11.3)
Total	839 (100)
Work place	
University hospital	97 (11.6)
Polyclinic hospital	191 (22.8)
Hospital	236 (28.1)
Clinic	273 (32.5)
Others	42 (5.0)
Total	839 (100)
Exercise frequency	
Daily	104 (12.4)
≥2–3 times/week	233 (27.8)
≥1 time/week	224 (26.7)
≤1 time/month	278 (33.1)
Total	839 (100)
Exercise intensity	
High (≥6 Mets)	264 (29.5)
Moderate (4–6 Mets)	199 (22.2)
Mild (3–4 Mets)	295 (32.9)
Very mild (<3 Mets)	68 (7.6)
Total	839 (100)

Statistical analysis

The associations between primary care physicians' exercise recommendations for patients with metabolic syndrome and cardiovascular diseases and their own age class, specialty, work place, and exercise volume were analyzed by multiple logistic regression analyses. SPSS Statistics version 21 software (IBM, Armonk, NY, USA) was used for the statistical analyses. Values of $P<0.01$ were considered to be significant.

Results

The survey was mailed to 3,310 medical doctors, with responses being received from 933 in total (28.2%). Of these, 37 responses were excluded from this study due to their inadequacy, such as a blank response for age, specialty, work place, or exercise habits. Responses marked "others" in terms of exercise frequency (n=52) and exercise intensity (n=6) were excluded from the analyses to evaluate the exercise volume because they could not be scored.[13] The remaining 839 medical doctors' responses to the self-administered questionnaire were analyzed.

The primary care physicians' age class, specialty, work place, and own exercise habits

The analyzed primary care physicians' age class, specialty, work place, and exercise habits are shown in Table 1. Their exercise volume was calculated (average ± standard deviation) to be 21±5.67 (Mets × hours/week).

Exercise counseling by primary care physicians for patients with metabolic syndrome and cardiovascular diseases

The proportions of those recommending exercise among the total primary care physicians for patients with metabolic syndrome and cardiovascular diseases were as follows (number of primary care physicians who recommend exercise/total): diabetes mellitus, 758/839 (90.3%); hyperlipidemia, 659/839 (78.5%); apoplexia, 325/839 (38.7%); heart failure, 150/839 (17.9%); and arterial hypertension, 517/839 (61.6%).

The association between the exercise counseling by primary care physicians for patients with metabolic syndrome and cardiovascular diseases and their age class, specialty, work place, and own exercise habits

Multiple logistic regression analyses showed that the primary care physicians whose specialties were internal medicine and general medicine significantly more often recommended exercise than those whose specialties were surgery and pediatrics, in cases of diabetes mellitus ($P<0.01$), hyperlipidemia ($P<0.01$), heart failure ($P<0.01$), and arterial hypertension ($P<0.01$) (Table 2). It was also shown that the primary care physicians whose specialty was pediatrics less often recommended exercise in apoplexia cases than those whose specialties were internal medicine, general medicine and surgery ($P<0.01$) (Table 2). Their own exercise habits were also positively associated with their recommendation of exercise in cases of hyperlipidemia ($P<0.01$), heart failure ($P<0.01$), and hypertension ($P<0.01$); however, these associations were not observed in diabetes mellitus and apoplexia patients (Table 2). Their age class and work place showed no significant association with their exercise counseling (Table 2).

Discussion

The results in the present study showed that the exercise recommendation level of primary care physicians for patients with metabolic syndrome was high. In contrast, their exercise recommendation level for hypertension cases was moderate, while those for cases of apoplexia and heart failure were low. Furthermore, the primary care physicians whose specialties were internal medicine and general medicine significantly more often recommended exercise than those whose specialties were surgery and pediatrics, for patients with metabolic syndrome and cardiovascular diseases. Their exercise habits were also positively associated with their recommendation of exercise in cases of hyperlipidemia, heart failure, and hypertension; however, their age class and work place showed no significant association with their exercise counseling for patients with metabolic syndrome and cardiovascular diseases.

Exercise counseling is very important in chronic diseases such as metabolic syndrome and cardiovascular diseases because exercise can improve physical capacity and prevent disease progression.[1–6] Primary care physicians have a pivotal role in terms of exercise counseling for these patients because they manage them at the front line. Several studies reported that patients want to receive physical activity counseling from their primary care physicians.[14,15] In addition, it was suggested that counseling by primary care physicians could contribute to improve patients' exercise habits.[16]

Previous studies have also suggested that physicians' own lifestyle may influence their lifestyle counseling for patients.[7–11] Abramson et al reported that physicians who exercise regularly are more likely to counsel patients on the merits of exercise.[9] They also reported that pediatricians and geriatricians counsel fewer patients about exercise than family practitioners and internists.[9] Wells et al also reported

Table 2 Multivariate logistic regression analyses to investigate the relationships of the diseases for which primary care physicians recommend exercise and their age, specialty, work place, and own exercise volume

	Exercise recommendation		OR	95% CI	*P*-value
	(yes)	(no)			
Diabetes mellitus					
Age					
24–30	67	4	1	ref	ref
30–40	241	18	0.7	0.21–2.29	0.55
40–50	234	31	0.47	0.15–1.51	0.2
50–60	202	28	0.4	0.12–0.133	0.13
≥60	14	0	N/A	N/A	N/A
Specialty					
Internal medicine	376	11	1	ref	ref
Surgery	130	28	0.14	0.07–0.31	*<0.01
General medicine	151	4	0.97	0.30–3.11	0.95
Pediatrics	30	14	0.06	0.03–0.15	*<0.01
Others	71	24	0.11	0.05–0.25	*<0.01
Work place					
University hospital	83	14	1	ref	ref
Polyclinic hospital	167	24	1.15	0.54–2.45	0.72
Hospital	221	15	2.03	0.89–4.66	0.09
Clinic	256	17	1.55	0.66–3.62	0.31
Others	31	11	0.69	0.25–1.92	0.48
Exercise volume[a]	N/A	N/A	1.04	0.98–1.09	0.15
Hyperlipidemia					
Age					
24–30	56	15	1	ref	ref
30–40	210	49	0.88	0.57–2.30	0.71
40–50	202	63	0.93	0.44–1.76	0.72
50–60	181	49	0.69	0.45–1.90	0.84
≥60	10	4	0.69	0.17–2.80	0.6
Specialty					
Internal medicine	336	51	1	ref	ref
Surgery	97	61	0.26	0.16–0.41	*<0.01
General medicine	139	16	1.16	0.63–2.13	0.64
Pediatrics	27	17	0.23	0.12–0.46	*<0.01
Others	60	35	0.29	0.17–0.51	*<0.01
Work place					
University hospital	73	24	1	ref	ref
Polyclinic hospital	133	58	0.75	0.41–1.35	0.33
Hospital	191	45	1.13	0.62–2.06	0.69
Clinic	234	39	1.21	0.65–2.27	0.55
Others	28	14	0.71	0.30–1.68	0.44
Exercise volume[a]	N/A	N/A	1.02	1.02–10.9	*<0.01
Apoplexia					
Age					
24–30	21	50	1	ref	ref
30–40	95	164	1.46	0.82–2.63	0.2
40–50	102	163	1.66	0.92–2.99	0.09
50–60	100	130	1.93	1.06–3.51	0.03
≥60	7	7	2.45	0.75–8.05	0.14
Specialty					
Internal medicine	167	220	1	ref	ref
Surgery	57	101	0.76	0.51–1.13	0.17
General medicine	69	86	1.09	0.74–1.61	0.66
Pediatrics	3	41	0.09	0.03–0.31	*<0.01
Others	29	66	0.66	0.40–1.10	0.11

(*Continued*)

Table 2 (*Continued*)

	Exercise recommendation		OR	95% CI	*P*-value
	(+)	(−)			
Work place					
University hospital	36	61	1	ref	ref
Polyclinic hospital	60	131	0.8	0.47–1.34	0.39
Hospital	104	132	1.3	0.79–2.15	0.31
Clinic	113	160	1.04	0.63–1.71	0.89
Others	12	30	0.68	0.30–1.04	0.35
Exercise volume[a]	N/A	N/A	1.01	0.98–1.04	0.45
Heart failure					
Age					
24–30	9	62	1	ref	ref
30–40	48	211	1.64	0.75–3.60	0.22
40–50	48	217	1.61	0.73–3.55	0.24
50–60	42	188	1.51	0.68–3.39	0.31
≥60	3	11	2.11	0.46–9.62	0.34
Specialty					
Internal medicine	95	292	1	ref	ref
Surgery	11	147	0.23	0.12–0.45	*<0.01
General medicine	33	122	0.8	0.50–1.27	0.34
Pediatrics	2	42	0.14	0.03–0.60	*<0.01
Others	9	86	0.34	0.16–0.73	*<0.01
Work place					
University hospital	15	82	1	ref	ref
Polyclinic hospital	25	166	0.85	0.42–1.75	0.67
Hospital	48	188	1.22	0.63–2.35	0.56
Clinic	57	216	1.01	0.53–1.95	0.97
Others	5	37	0.75	0.24–2.31	0.61
Exercise volume[a]	N/A	N/A	1.04	1.01–1.07	*<0.01
Hypertension					
Age					
24–30	39	32	1	ref	ref
30–40	170	89	1.6	0.90–2.82	0.11
40–50	154	111	1.12	0.63–1.97	0.71
50–60	144	86	1.23	0.69–2.21	0.49
≥60	10	4	2.09	0.55–7.91	0.28
Specialty					
Internal medicine	274	113	1	ref	ref
Surgery	69	89	0.34	0.23–0.52	*<0.01
General medicine	114	41	0.99	0.64–1.52	0.95
Pediatrics	16	28	0.22	0.12–0.44	*<0.01
Others	44	51	0.37	0.22–0.61	*<0.01
Work place					
University hospital	53	44	1	ref	ref
Polyclinic hospital	101	90	0.95	0.57–1.59	0.84
Hospital	138	98	1.01	0.61–1.68	0.96
Clinic	201	72	1.67	1.00–2.81	0.05
Others	24	18	1.25	0.57–2.75	0.58
Exercise volume[a]	N/A	N/A	1.05	1.02–1.08	*<0.01

Notes: [a]The relationship between exercise recommendation and their own exercise volume. *$P<0.01$.
Abbreviations: CI, confidence interval; ref, reference; N/A, not available; OR, odds ratio.

that primary care physicians whose specialty was surgery counseled less about lifestyle factors including exercise than those with a nonsurgical specialty, even after controlling for differences in health related attitudes and personal habits.[7] Recently, Hung et al reported that nonsmoking physicians were more likely to perform lifestyle intervention, and those who exercised at least one day per week were more likely to recommend limiting alcohol use in their patients with hypertension.[11] In the present study, we found the primary care physicians whose specialties were internal medicine and general medicine highly recommended exercise compared with those whose specialties were surgery and pediatrics in cases of diabetes mellitus, hyperlipidemia, heart failure, and arterial hypertension. In addition, the primary care physicians whose specialty was pediatrics recommended exercise less often in cases of apoplexia. In addition, the primary care physicians' own exercise habits were positively associated with their recommendation of exercise for patients with hyperlipidemia, heart failure, and hypertension. These results are consistent with previous studies.[7,9,11] In the present study, primary care physicians less often recommended exercise in cases of apoplexia, heart failure, and arterial hypertension than in diabetic mellitus and hyperlipidemia. These results may show that primary care physicians have difficulty providing exercise counseling and exercise prescription for cases of heart failure, apoplexia, and arterial hypertension because these diseases have large variations from a mild stage to a severe stage. Further studies will need to clarify why primary care physicians recommended exercise less often for cases of apoplexia, heart failure, and arterial hypertension than for diabetic mellitus and hyperlipidemia. Since there were several differences in primary care physicians' exercise counseling for cases of cardiovascular disease and metabolic syndrome in terms of their specialty and own exercise habits in the present study, it was suggested that there should be greater recognition and implementation of exercise guidelines for cases of metabolic syndromes and cardiovascular diseases by primary care physicians, regardless of their specialty and own exercise habits.

There are several limitations in this study. First, since the study instrument was a mailed questionnaire, there may have been self-selection bias. Second, it should be noted that the results of this study were not obtained by objective evaluation of the actual exercise counseling performed by primary care physicians. Further study will need to investigate actual exercise counseling, such as counseling time and detailed content, by primary care physicians. Third, the exercise volume of primary care physicians in this study did not reach the levels recommended in several sets of guidelines, as we previously reported.[13] The low exercise volume of primary care physicians in the present study may thus have affected the results.

In conclusion, the exercise recommendation level of primary care physicians in this study was high for cases of metabolic syndrome, but low for cardiovascular diseases. The primary care physicians whose specialties were internal medicine and general medicine significantly more often recommended exercise in cases of diabetes mellitus, hyperlipidemia, heart failure, and hypertension. In addition, their own exercise habits were positively associated with their recommendation of exercise in cases of hyperlipidemia, heart failure, and hypertension.

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Disclosure

The authors declare no conflicts of interest.

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NEPHROLOGY - ORIGINAL PAPER

Positive association of vigorous and moderate physical activity volumes with skeletal muscle mass but not bone density or metabolism markers in hemodialysis patients

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Abstract
Purpose To determine whether vigorous and moderate physical activity volumes are associated with skeletal muscle loss and chronic kidney disease–mineral and bone disorder (CKD-MBD) in hemodialysis (HD) patients.
Methods Skeletal muscle index (SMI) was measured using a bioelectrical impedance plethysmograph, and grip strength using a hand dynamometer, in 32 HD patients and 16 healthy controls. In HD patients, bone density was measured using digital image processing, and serum bone metabolism markers were measured as surrogate markers for CKD-MBD. Vigorous and moderate physical activity volumes of HD patients were measured using an activity monitor for 1 week, and associations between vigorous and moderate physical activity volumes and SMI, grip strength, and surrogate markers for CKD-MBD were investigated.
Results SMI of HD patients (4.60 ± 0.98 kg/m^2) was significantly lower than that of controls (5.55 ± 0.80 kg/m^2, $p < 0.01$). Grip strength of HD patients (19.9 ± 7.74 kg) was also significantly lower than that of controls (33.0 ± 8.94 kg, $p < 0.01$). In HD patients, vigorous and moderate physical activity volumes were significantly positively associated with SMI ($\beta = 0.309$, $p = 0.023$) but not grip strength ($\beta = 0.231$, $p = 0131$) after adjustment for age, sex, and HD duration. They were not associated with bone density ($\beta = 0.106$, $p = 0.470$) or any markers of bone metabolism.
Conclusions Vigorous and moderate physical activity volumes were positively associated with skeletal muscle mass but not skeletal muscle strength or surrogate markers for CKD-MBD.

Keywords Physical activity volume · Skeletal muscle mass · Bone density · Bone metabolism markers · Hemodialysis

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Introduction

Chronic kidney disease (CKD) patients demonstrate loss of skeletal muscle mass and strength that is associated with several factors often observed in this condition, such as vitamin D and other nutritional deficiencies and acidosis [1, 2]. Skeletal muscle loss has been shown to increase the risk of fractures and decrease quality of life in CKD patients [3–5]. Chronic kidney disease–mineral and bone disorder (CKD-MBD) is another common complication of CKD that involves biochemical abnormalities in serum calcium, phosphorus, bone resorption, bone formation, and bone density and linear growth [6–10]. CKD-MBD also produces cardiovascular abnormalities, such as vascular calcification, as consequences of these biochemical abnormalities [9], and therefore is considered to be associated with the development of cardiovascular disease and bone abnormalities, both resulting in decreased quality of life [6–9, 11, 12]. This evidence strongly suggests that inhibition of skeletal muscle loss and control of CKD-MBD are crucial to improving the prognosis of CKD.

Accumulating evidence suggests that all CKD patients, regardless of CKD stage and treatment modality, can benefit from exercise [13, 14]. Previous studies have reported that exercise improved physical functioning and reduced skeletal muscle loss and benefitted potential mediators of cardiovascular disease, which is closely related to CKD-MBD [15, 16]. However, few studies have reported the association between actual exercise volume and skeletal muscle loss and CKD-MBD in CKD patients. We previously evaluated skeletal muscle loss in CKD with maintenance hemodialysis (HD) patients (in press). In this study, we objectively measured vigorous and moderate physical activity volumes (V and M volumes), which several guidelines have recommended to use to evaluate exercise volume using an activity monitor in HD patients [17–19]. We then investigated the association between V and M volumes and skeletal muscle mass via bioelectrical impedance analysis (BIA), and muscle strength via handgrip strength testing, in the HD patients from our original study. We also investigated the associations between V and M volumes and surrogate markers for CKD-MBD, such as bone density determined using a digital image processing (DIP) method and bone metabolism markers [bone-specific alkaline phosphatase (BAP)], intact procollagen type I intact N-terminal peptide (intact P1NP), tartrate-resistant acid phosphatase 5b (TRACP5b), and intact parathyroid hormone (iPTH) in the same HD patients.

Table 1 Baseline characteristics of HD patients and the control group

Parameters	HD patients	Control group	*p*
Number	32	16	
Age (years)	67.0 ± 9.91	36.9 ± 8.90	<0.01**
Gender			
Male	18	6	
Female	14	10	
Height (cm)	156.2 ± 9.53	162.5 ± 9.70	0.04*
Dry weight (kg)	51.3 ± 9.72	57.4 ± 10.2	0.05
Body mass index (kg/m^2)	20.7 ± 2.59	21.6 ± 2.77	0.25
Total HD duration (years)	6.36 ± 4.84		
Number of HD (week^{-1})	2.94 ± 0.25		
Average HD time (h/session)	3.98 ± 0.27		
Initial nephropathy			
Chronic glomerulonephritis	4		
Diabetic nephropathy	12		
Renal sclerosis	10		
Polycystic kidney disease	1		
ANCA-associated GN	1		
Chronic pyelonephritis	1		
Unknown	3		
Blood analysis	2		
Calcium	9.09 ± 0.67		
Phosphate	5.00 ± 0.85		

HD hemodialysis, *ANCA* antineutrophil cytoplasmic autoantibody

** $p < 0.01$; * $p < 0.05$

Patients and methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Haga Red Cross Hospital. Informed consent was obtained from all patients. No patient had obvious edema or an implanted pacemaker. The present study represents a sub-analysis of our previous study, which investigated skeletal muscle loss in HD patients.

Subjects

Thirty-four HD patients undergoing maintenance HD at the Haga Red Cross Hospital dialysis center were investigated in the previous study. One patient was transferred to the hospital and one patient received renal transplantation. Therefore, 32 HD patients (18 males, 14 females) were investigated in the present study. Initial nephropathies of the study group were chronic glomerulonephritis in four patients, diabetic nephropathy in 12, renal sclerosis in 10, antineutrophil cytoplasmic autoantibody-related glomerulonephritis in one, polycystic kidney disease in one, chronic pyelonephritis in one, and unknown etiology in three. No patient had shown a change in dry weight in at least 1 month. Sixteen healthy subjects (6 males, 10 females; age, 36.9 ± 8.90 years) served as controls to evaluate skeletal muscle mass and strength. Baseline characteristics of HD patients and the control group are shown in Table 1.

Physical activity volume

Physical activity volume was measured for 1 week by asking all enrolled HD patients to behave normally while using an activity monitor with built-in triaxial accelerator technology (Calorism AM121; Tanita Co., Ltd., Tokyo, Japan). Using this activity monitor, vigorous [above 6 Metabolic Equivalents of Task (METs)] and moderate (3–6 METs) physical activity intensities [20] were assessed. Vigorous and moderate physical volumes (V and M volumes) were then calculated by multiplying physical activity intensity by physical activity duration.

Skeletal muscle index

Body weight was measured to the nearest 0.1 kg before and after an HD session. Body mass index (BMI) was calculated as body weight/body height^2 (kg/m^2). BIA was performed to obtain the ratios of fat, water, bone, and organs using tetrapolar impedance plethysmography (InBody S10; Biospace, Seoul, Korea) with multiple operating frequencies of 1, 5, 50, 250, 500, and 1,000 kHz. Whole-body BIA measurements in HD patients were taken between the tips of the fingers of one hand and the ipsilateral ankle with the subjects lying supine after an HD session. Skeletal muscle mass was determined using the mass of non-skeletal muscle tissues such as fat, extracellular fluid, intracellular fluid, bone, and organs. Absolute skeletal muscle mass measured by BIA was converted to percentage skeletal muscle mass and termed skeletal muscle index (SMI), which was calculated using the following formula: SMI (kg/m^2) = skeletal muscle mass/body height^2. SMI ratio was calculated as a percentage of mean SMI of the control group.

Grip strength test

Grip strength testing was performed prior to an HD session, on the hand without an arteriovenous shunt, using a digital handgrip dynamometer (T.K.K. 5401 Grip D; Takei Science Instruments Co., Ltd., Niigata, Japan). It was performed on the dominant hand in the control group. The ratio of grip strength was calculated as a percentage of mean grip strength for the control group.

Bone density

Bone density was measured in HD patients at the midshaft of the 2nd metacarpal using the DIP method on posteroanterior radiographs of the hand and an aluminum step wedge. The measured bone density was expressed as the thickness of an aluminum equivalent (mmAl) showing corresponding X-ray absorption. The ratio of bone density was expressed as a percentage of that published for a Japanese young to middle-aged population [21].

Markers of bone metabolism

Serum BAP, intact P1NP, TRACP5b, and iPTH levels in HD patients were measured by a commercial laboratory (SRL, Tokyo, Japan) using chemiluminescent enzyme immune assay, radioimmunoassay, enzyme immunoassay, and electrochemiluminescent assay, respectively.

Table 2 HD patients' vigorous and moderate physical activity volumes

Log(V and M volumes) (Ex/week)	1.08 ± 0.58
Male	1.08 ± 0.63
Female	1.07 ± 0.55
Log(V and M volumes) on HD days (Ex/day)	0.22 ± 0.46
Male	0.25 ± 0.53
Female	0.18 ± 0.36
Log(V and M volumes) on non-HD days (Ex/day)	0.18 ± 0.67
Male	0.24 ± 0.67
Female	0.11 ± 0.68

HD hemodialysis; *Ex* exercise, *Log(V and M volumes)* logarithm vigorous and moderate physical activity volumes

Statistical analysis

All data except for physical activity volume are expressed as mean ± standard deviation (SD) after confirmation by Kolmogorov–Smirnov analysis that they were normally distributed. Because physical activity volume did not show a normal distribution, it was converted to a logarithm, which was confirmed by Kolmogorov–Smirnov to be normally distributed. Unpaired t test was used to compare the means between HD and control groups for age, height, body weight, BMI, SMI, and grip strength. Associations between SMI and grip strength in HD and control groups were investigated using the Pearson's correlation coefficient. Unpaired t test was also used to compare the means of log(V and M volumes) on an HD day and a non-HD day in the HD group. Multiple linear regression analysis was used to determine independent variables in order to investigate associations between V and M volumes and SMI, grip strength, bone density, and metabolic markers in the HD group. SPSS Statistics version 21 software (IBM, Armonk, NY, USA) was used for statistical analyses, and $p < 0.05$ was considered statistically significant.

Results

Table 1 shows baseline characteristics of HD and control groups, including age, sex, physical characteristics, nephropathy, and laboratory data. The medications for CKD-MBD taken by study patients included vitamin D (25 patients), phosphorus binder (30 patients), cinacalcet (four patients), and bisphosphonate (one patient). BMI did not differ significantly between HD and control groups ($p = 0.25$).