Physical Activity and Renal Function Declines in Patients with Chronic Kidney Disease

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ABSTRACT

Objectives: Physical activity was suggested to decline as the stage of chronic kidney disease (CKD) advances. This study aimed to examine the impact of physical activity on developing CKD independent of comorbidity.
Methods: Among 305 CKD patients (stages 3–5) who had been treated at the outpatient care of our department at the University of the Ryukyus Hospital and who participated in the physical activity survey, 208 were finally enrolled in this study after applying the exclusion criteria. The patients' amounts of physical activity were assessed using the International Physical Activity Questionnaire Short Version. The changes in estimated glomerular filtration rate (eGFR) were retrospectively examined according to the quartile of baseline physical activity time for 36 months.
Results: The physical activity times were 25.7, 21.4, and 12.2 min/day in stages 3, 4, and 5, respectively. Diabetes mellitus and lower hemoglobin level were significantly associated with lower physical activity. Patients with the lowest quartile of physical activity showed greater decline in eGFR. Multivariate regression analysis revealed that the lowest quartile of physical activity was significantly associated with greater decline in eGFR independent of confounding factors.
Conclusions: Lower physical activity might be independently associated with greater decline in renal function among CKD patients. *Ryukyu Med. J., 40 (1~4) 9~16, 2021*

Key words: Physical activity, Renal Function, Decline, Chronic Kidney Disease

Introduction

Patients with chronic kidney disease (CKD) are at high risk for developing end-stage kidney disease (ESKD). Thus, effective treatments are needed to retard the progression of CKD[1, 2)]. Several comorbidities including hypertension and diabetes and lifestyle factors including smoking are associated with developing CKD[3, 4)]. Additionally, lower physical activity was suggested to be a potential risk factor for developing CKD[5)].

However, CKD patients are prone to a state called protein energy wasting, in which muscle protein and other proteins are hypercatabolized, resulting in decreased endurance due to abnormal mitochondrial function[6, 7)]. Moreover, various comorbid conditions including cardiovascular disease, renal anemia[8)], and neurological impairment[9)] might be associated with declined physical function[10, 11)] and physical activity level[12)] in CKD patients. Since such factors are also associated with developing CKD, the independent impact of low physical activity on CKD development remained to be determined. Therefore, this study aimed to investigate whether the amounts of physical activity were associated with greater decline in renal function independent of confounding factors in CKD patients.

Materials and methods

Participants

This study included 305 CKD patients (stage 3, 4, or 5) who were self-sufficient in outpatient care after discharge from the Third Department of Internal Medicine of the University of the Ryukyus Hospital and who participated in the physical activity survey between November 2011 and November 2013. The study participants who were excluded from the study

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were as follows: maintenance dialysis patients, patients who did not respond adequately to the questionnaire, patients aged <35 years, patients taking steroids, and patients who were difficult to follow up. Finally, 208 patients were included in the analysis (Fig. 1).

Procedure

The patient background characteristics at the time of enrollment were investigated, including age, sex, body mass index (BMI), systolic blood pressure (BP), diastolic BP, ankle-brachial pressure index (ABI), and pulse wave velocity (PWV); risk factors; comorbidities; laboratory data including hematuria, estimated glomerular filtration rate (eGFR), and levels of creatinine (Cr), hemoglobin (Hb), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), blood glucose, HbA1c, and urinary protein (UP); prescription drugs; and physical activity.

Assessment of physical activity

The short version of the International Physical Activity Questionnaire (IPAQ) was used to survey the amount of physical activity in accordance with the guidelines for physical therapy[13-15]. Physical activity according to the IPAQ is defined as "high-intensity," which is physically demanding and considerably disrupts breathing; "moderate intensity," which is slightly strenuous and causes slight breathlessness; "walking activity," which is walking for >10 minutes in a row; "sitting activity," which is not during sleep time; and "rest time," when the patient is in the supine position with the head in the normal position. In this study, information on the mean weekly physical activity time and frequency directly from patients were collected, and the total time of high-intensity, moderate-intensity, and walking activities (physical activity time [PAT]) was used as a measure of physical activity. Furthermore, the PATs in groups I, II, III, and IV were less than those in the first quartile (11.8 min/day), more than those in the first quartile (11.8 min/day) and less than those in the second quartile (25.7 min/day), more than those in the second quartile (25.7 min/day) and less than those in the third quartile (59.7 min/day), and higher than those in the third quartile (59.7 min/day), respectively.

Outcome

Changes in eGFR were examined according to the quartile of physical activity from November 2011 to November 2015.

Research design and ethical considerations

The research design used was a cross-sectional observational study. The study was conducted with the approval of the ethics committee at the University of the Ryukyus (approval No. 1678). Moreover, this study has also complied with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical Research Involving Human Subjects.

Statistical analyses

One-way analysis of variance (ANOVA) and the Kruskal–Wallis test were used to compare continuous variables among the three groups. For multiple comparisons, the Steel–Dwass test was used. For comparisons of frequencies, the chi-square or Fisher exact probability test was performed and corrected using the Bonferroni method. A multivariate logistic regression analysis was used to determine the factors which were associated with PAT. Adjustments were made based on age, sex, eGFR, urine protein, hypertension, diabetes, cerebral cardiovascular disease, and chronic heart failure. A stepwise method was used for variable selection. To reduce the effect of multicollinearity in the multivariate logistic regression analysis, high correlation coefficients were checked

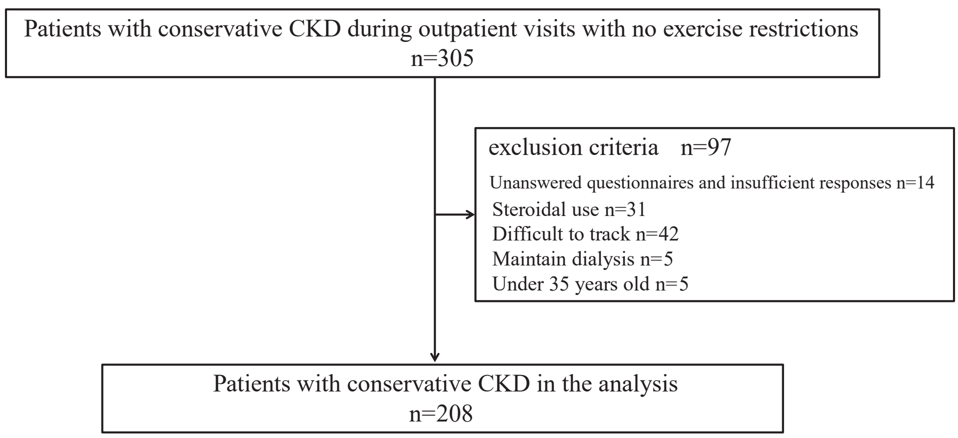

Fig. 1 **Flow chart of the study**

with each other beforehand, and one of them was used as the explanatory variable. PAT was divided into four quartiles and was analyzed for trends in %ΔeGFR using one-way ANOVA and the Steel–Dwass test for comparisons among the four groups and for multiple comparisons, respectively. A multiple regression analysis was used to determine the association of PAT with subsequent changes in eGFR adjusted with potential confounding factors. All analyses were performed using the JMP 15 software (SAS Institute). Continuous data are expressed as means +/− SDs or medians (interquartile ranges). For all analyses, a P value of <0.05 was statistically significant.

Results

Of the 305 outpatients with CKD, 208 (118 men and 90 women; age, 68.1 ± 10.6 years; stage 3: 165 [79%]; stage 4: 35 [17%]; and stage 5: 8 [4%]) who met the criteria for inclusion in the study were followed up for up to 36 months.

Baseline clinical background and physical activity levels according to CKD stage

ABI; smoking history; eGFR; levels of Cr, Hb, HDL-C, UA, UP, ezetimibe, and calcium antagonist; and renin inhibitor and diuretic use were found to be significantly different between the three groups. The PATs were 25.7 min/day (12.2–65.0 min/day), 21.4 min/day (12.9–42.9 min/day), and 12.2 min/day (0–28.2 min/day) in stages 3, 4, and 5, respectively, with no significant difference, although it tended to decrease as the stage progressed (Table 1).

Table 1 **Clinical characteristics of patients by CKD stages**

Characteristic	Total CKD (*n*=208)	CKD 3 (*n*=165)	CKD 4 (*n*=35)	CKD 5 (*n*=8)	p-Value
Physical examination data					
Age (yr)	68.1±10.6	68.1±10.4	69.3±11.5	64.8±11.7	0.5417
Men, *n* (%)	118(56.7)	78(47.3)	10(28.6)	2(25.0)	0.0726
BMI (kg/m^2)	24.9±3.52	25.0±3.55	24.5±3.23	25.3±4.28	0.6999
Systolic BP (mmHg)	127±17.4	126±16.7	127±16.7	132±17.9	0.7259
Diastolic BP (mmHg)	70.4±11.5	71.0±11.7	68.4±10.9	67.0±9.01	0.3342
ABI	1.08 [1.00-1.14]	1.08 [1.01-1.13]*	1.04 [0.87-1.16]*	1.21 [1.19-1.26]	0.0028
PWV (cm/sec)	1770 [1498-2015]	1764 [1455-1977]	1872 [1565-2224]	1753 [1569-1939]	0.2275
Underlying diseases, *n* (%)					
Hypertension	181(87)	140(84.9)	33(94.2)	8(100)	0.1722
Diabetes	63(30)	48(29)	11(31.4)	4(50)	0.4480
Dyslipidemia	138(66)	112(67.9)	21(60)	5(62.5)	0.6512
Smoking history	63(30.7)	40(24.7)	18(51.4)†	5(62.5)†	0.0011
Comorbidity, *n* (%)					
Cerebral cardiovascular disease	94(45)	70(42)	19(54)	5(63)	0.2663
Ischemic heart disease	44(21)	35(21.2)	7(20)	2(25)	0.9516
Cerebrovascular accident	45(22)	32(19.4)	10(28.6)	3(37.5)	0.2632
Peripheral Arterial Disease	23(11)	16(9.7)	7(20)	0(0)	0.1255
Chronic heart failure	10(4.8)	6(3.6)	4(11.4)	0(0)	0.1194
Laboratory values					
eGFR (ml/min per 1.73 m^2)	43.0±13.6	48.8±7.88	23.0±4.57	11.7±2.98	<0.0001
Creatinine (mg/dl)	1.40±0.86	1.07±0.24	2.25±0.56†*	4.48±1.48†	<0.0001
Hemoglobin (g/dl)	13.5±1.84	13.9±1.65	12.1±1.48†*	10.5±1.08†	<0.0001
Cholesterol (mg/dl)	178±33.3	181±34.4	158±17.1†*	170±37.1†	0.0750
LDL-C (mg/dl)	96.8±25.6	98.9±25.6	90.0±25.7	85.4±19.9	0.1000
HDL-C (mg/dl)	52.5±14.3	54.5±14.3	45.1±10.3	43.8±16.7	0.0004
Triglycerides (mg/dl)	148±71.0	146±70.8	157±72.7†	151±74.9†	0.7224
Uric acid (mg/dl)	6.20±1.39	6.10±1.33	6.37±1.53	7.59±1.45	0.0090
Blood glucose (mg/dl)	111±33.0	109±32.7	116±33.6	111±38.6	0.5848
HbA1c (%)	6.10±0.90	6.07±0.85	6.20±1.23	6.40±0.61	0.5785
Urine protein (−/±/+/2+/3+)	97/30/32/25/15	91/24/26/11/4	6/5/5/13/6	0/1/1/1/5	<0.0001
Hematuria (−/±/+/2+/3+)	123/35/25/13/3	102/23/19/10/2	18/8/5/3/1†	3/4/1/0/0†	0.3263
Forms of activity, *n* (min/day)					
total physical activity time	25.7 [11.8-59.7]	25.7 [12.2-65.0]	21.4 [12.9-42.9]	12.2 [0-28.2]	0.2037
leisure time physical activity	38.6 [25.7-68.6]	34.3 [25.7-68.6]	51.4 [25.7-85.7]	34.3 [10.7-105]	0.3840
Prescription drugs, *n* (%)					
Statin	181(87)	140(84.9)	33(94.2)	8(100)	0.1274
Ezetimibe	8(3.9)	5(3.0)*	1(2.9)*	2(25)	0.0065
Ca antagonist	127(61)	95(58)†	24(69)*	8(100)	0.0338
RAS inhibitor	170(82)	135(82)	29(83)	6(75)	0.8723
ACE inhibitor	48(23)	38(23)	8(23)	2(25)	0.9911
Angiotensin II Receptor Blocker	142(68)	111(67)	25(71)	6(75)	0.8170
Renin inhibitor	15(7.2)	5(3.0)	8(23)†	2(25)†	<0.0001
Anti-aldosterone drug	42(20)	31(19)	9(26)	2(25)	0.6129
Diuretic	77(37)	52(32)*	18(51)*	7(88)	0.0009

Values are mean ± SD or median (IQR).
The values were obtained using one-way analysis of variance and the Kruskal–Wallis test.
The cerebral cardiovascular diseases included ischemic heart disease, cerebrovascular accident, and peripheral arterial disease. The RAS inhibitors used were ACE inhibitor and angiotensin II receptor blocker. BMI : body mass index, BP : blood pressure. ABI : ankle-brachial pressure index. PWV : pulse wave velocity, eGFR : estimated glomerular filtration rate, LDL-C : low-density lipoprotein cholesterol, HDL-C : high-density lipoprotein cholesterol.
* Compared with CKD stage 5 † Compared with CKD stage 3

Association between physical activity time and clinical parameters

Multivariate logistic regression analysis revealed that Hb levels and diabetes mellitus were significantly associated with PAT, respectively: an odds ratio (OR) of 1.2843, 95% confidence interval of 1.0194–0.6370, p=0.0373; and OR of 0.4601, 95% confidence interval of 0.2154–0.9826, p=0.0449.

Association of physical activity time with changes in eGFR

CKD patients with the lowest quartile of PAT (<11.8 min/day) showed a greater decline in eGFR than the others (Fig. 2). Multivariate regression analysis revealed that shorter physical activity time was associated with greater decline in eGFR independent of confounding factors during the observational period (Table 2)

Discussion

This study found that the amount of physical activity decreased as CKD stages developed. The lowest quartile of physical activity at baseline was associated with greater decline in eGFR independent of confounding factors during the observational period.

Previous studies[12] reported that patients with advanced stage of CKD had significantly lower physical activity levels than those patients at higher CKD stages. Similarly, in this study, CKD patients were found to show shorter physical activity time as

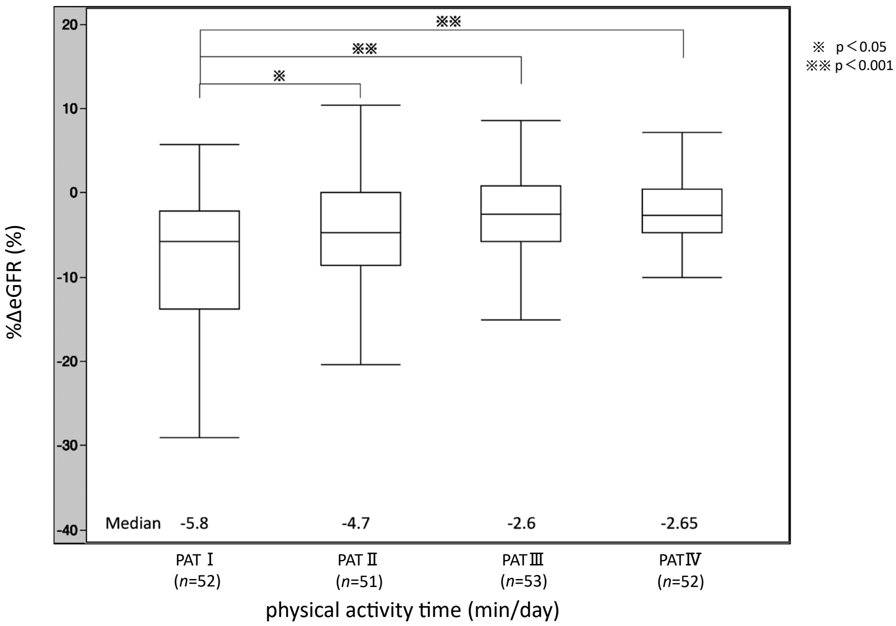

Fig. 2 **%changes in eGFR according to the quartile of physical activity time**

PAT: physical activity time. eGFR: estimated glemerular filtration rate
The values were obtained using one-way analysis of variance and the Kruskal-Wallis test.
The PATs in groups I, II, III, and IV were less than those in the first quartile (11.8min/day), more than those in the first quartile and less than those in the second quartile (25.7min/day), more than those in the second quartile and less than those in the third quartile (59.7min/day), and higher than those in the third quartile, respectively.

Table 2 **Association of changes in eGFR with clinical parameters**

	Model 1		Model 2		Model 3	
	β	p-Value	β	p-Value	β	p-Value
physical activity time (min/day)	0.2141	0.0019	0.2033	0.0035	0.1729	0.0114
Age (yr)	0.0362	0.5945	0.0608	0.3784	0.0101	0.8816
Gender (Men)	−0.1269	0.0636	−0.1432	0.0389	−0.0488	0.4955
Hemoglobin (g/dl)			0.1356	0.0534	0.0634	0.4332
Diabetes			0.0047	0.9461	−0.0508	0.471
Urine protein (−/±/+/2+/3+)					−0.3794	<0.0001
Systolic BP (mmHg)					0.002	0.7774

Model 1: physical activity time, Age, Gender
Model 2: Model 1 + Hemoglobin, Diabetes
Model 3: Model 2 + Urine protein, Systolic BP
BP: blood pressure

the CKD stage progressed. Frailty was commonly seen in middle-aged and elderly CKD patients compared with healthy individuals, [16] and lower limb functions such as comfort walking speed, timed up-and-go test, and 6-minute walking distance are reduced by at least 30%. Additionally, Japanese CKD patients were reported to have a 20%–30% reduction in grip strength and 10%–15% reduction in knee extension strength as compared with healthy subjects[17]. These results suggest that CKD patients may have lower physical activity levels as the CKD stage progresses due to organic and functional deterioration in peripheral muscle tissue.

The most important finding of this study was that the lowest physical activity time was associated with greater decline in eGFR independent of risk factors for developing CKD. Similar to the findings of this study, a large population-based longitudinal study also showed that lower physical activity was associated with rapid renal function decline compared to a higher physical activity[5]. Moreover, small pilot studies showed aerobic exercise had favorable effect on renal function[18, 19]. These findings suggested that low physical activity may accelerate renal function decline. Some mechanisms underlying the association of low physical activity and greater renal function decline might relate to its effects on comorbidities such as blood pressure, obesity, glucose, and lipid abnormality. Additionally, experimental studies suggested that some myokine which are secreted from the muscle through muscle contractions (physical activity might have an important role in such association)[20-22].

This study showed that Hb levels were associated with the amount of physical activity in the CKD patients. Anemia, one of the most common complications of CKD, generally develops as a result of decreased endogenous erythropoietin production. Anemia was an independent risk factor of poor exercise tolerance[23-25]. Anemia may affect both the oxygen transport and utilization for exercise tolerance and may cause physical activity limitations.

In this study, diabetes was associated with lower physical activity. Diabetes mellitus is caused by impaired insulin secretion and resistance, which prevents the tissues from adequately using carbohydrates, resulting in insufficient ATP production even with oxygen supply. Diabetic patients have decreased muscle mass, decreased percentage of type 1 fibers with high aerobic capacity, decreased oxidative enzymes, and decreased muscle capillary density, resulting in decreased oxygen utilization capacity[26]. Moreover, previous reports have indicated that diabetic patients have decreased muscle strength[27, 28], balance function due to sensory neuropathy[28, 29], and gait speed[30] and that CKD in patients with diabetes mellitus may have a significant effect on physical activity.

This study has several limitations. First, it included single-center cases and a small sample size. Second, sex-related differences were not fully considered. Age and sex have been reported to affect physical activity[31]. Third, physical activity was assessed using a questionnaire. The IPAQ, which was used in this study, has been confirmed as reliable and valid in previous studies[13-15]. The questionnaire method is less accurate than measuring the amount of activity because its content depends on the subject's memory. On the other hand, the advantage of the questionnaire method is that the details of the behavior can be grasped if the memory is accurate, and it is inexpensive and simple. Lastly, this study could not determine the causality of low physical activity for decline in renal function. Although a few studies suggested a favorable effect of exercise in maintaining renal function, the other study failed to show such potential benefit[32]. Further studies including large-scaled interventional studies are warranted to address this issue.

In conclusion, physical activity reduces as CKD stages advance. Low physical activity was associated with greater decline in renal function independent of comorbidities among patients with CKD stages 3–5.

Disclosure

The authors have no conflict of interest to declare related to this study.

References

1) Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. Suppl.3 : 1–150, 2013.
2) Japan Society of Nephrology (ed.): CKD Practice Guide 2012, pp. 1–7, Tokyo Igaku-sha, Tokyo, 2012.
3) Iseki K., Kohagura K., Sakima A., Iseki C., Kinjo K., Ikemiya Y., Takishita S. : Changes in the demographics and prevalence of chronic kidney

disease in Okinawa, Japan(1993 to 2003). Hypertens Res 30(1)：55–62, 2007.
4) Nagata M., Ninomiya T., Doi Y., Yonemoto K., Kubo M., Hata J., Tsuruya K., Iida M., Kiyohara Y.：Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population：the Hisayama Study. Nephrol Dial Trans-plant 25(8)：2557–2564, 2010.
5) Robinson-Cohen C., Katz R., Mozaffarian D., Dalrymple L.S., Boer I., Sarnak M., Shlipak M., Siscovick D., Kestenbaum B.：Physical activity and rapid decline in kidney function among older adults.Arch. Intern. Med. 169：2116–2123, 2009.
6) Tamaki M., Miyashita K., Wakino S., Mitsuishi M., Hayashi K., Itoh H.：Chronic kidney disease reduces muscle mitochondria and exercise endurance and its exacerbation by dietary protein through inactivation of pyruvate dehydrogenase, Kidney international 85：1330–1339, 2014
7) Tamaki M., Hagiwara A., Miyashita K., Wakino S., Inoue H., Fujii K., Fujii C., Sato M., Mitsuishi M., Muraki A., Hayashi K., Doi T., Itoh H. : Improvement of physical decline through combined effects of muscle enhancement and mitochondrial activation by a gastric hormone Ghrelin in male 5/6Nx CKD model mice, Endocrinology 156：3638–3648, 2015.
8) Tsubakihara Y., Nishi S., Akiba T., Hirakata H., Iseki K., Kubota M., Kuriyama S., Komatsu Y., Suzuki M., Nakai S., Hattori M., Babazono T., Hiramatsu M., Yamamoto H., Bessho M., Akizawa T. : 2008 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. Ther Apher Dial Jun 14(3)：240–75, 2010.
9) Fahal I.H.：Uraemic sarcopenia: aetiology and implications. Nephrol Dial Transplant 29(9)：1655–1665, 2014.
10) Hiraki K., Yasuda T., Hotta C., Izawa K., Morio Y., Watanabe S., Sakurada T., ShibagakiY., Kimura K.：Decreased physical function in pre-dialysis patients with chronic kidney disease. Clin Exp Nephrol 17(2): 225–231, 2013.
11) Saito M., Ando M., Kamiwaki R., Ono A., Ishii N., Morotomi N., Nagayama M., Takanashi S., Itoh H.：Safety and effectiveness of rehabilitation after cardiac surgery based on chronic kidney disease (CKD) stage classification. Cardiac Rehabilitation 16(2): 202–206, 2011.
12) Odden M.C., Whooley M.A., Shlipak M.G.：Association of chronic kidney disease and anemia with physical capacity: the heart and soul study. J Am Soc Nephrol 15：2908–2915, 2004.
13) Paul H.L., Duncan J.M., Lam T.H., Sunita M.S.：Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. Behav Nutr Phys Act 8. Oct 21；8：115, 2011.
14) Tomioka K., Iwamoto J., Saeki K., Okamoto N.：Reliability and validity of the International Physical Activity Questionnaire (IPAQ) in elderly adults: the Fujiwara-kyo Study. J Epidemiol 21(6)：459–465, 2011.
15) Cleland C., Ferguson S., Ellis G., Hunter F.R.：Validity of the International Physical Activity Questionnaire (IPAQ) for assessing moderate-to-vigorous physical activity and sedentary behaviour of older adults in the United Kingdom. BMC Med Res Methodol Dec 22；18(1)：176, 2018.
16) Roshanravan B., Khatri M., Robinson C.C., Levin G., Patel V.K., Boer H.I., Seliger S., Ruzinski J., Himmelfarb J., Kestenbaum B.：A prospective study of frailty in nephrology-referred patients with CKD. Am J Kidney Dis 60(6)：912–921, 2012.
17) Onde Y., Hiraki K., Horita C., Izawa K., Sakurada T., Shibagaki Y., Kimura K.：Comparison of muscle strength values and the mean values of healthy subjects in patients with chronic kidney disease in the conservative period. Physical Therapy 44：401–407, 2017.
18) Pechter U., Ots M., Mesikepp S., Zilmer K., Kullissaar T., Vihalemm T., Zilmer M., Maaroos J.：Beneficial effects of water-based exercise in patients with chronic kidney disease. Int. J. Rehabil. Res. 26：153–156, 2003.
19) Aoike D.T., Flavia Baria F., Kamimura M.A., Ammirati A., Marco Túlio de Mello & Lilian Cuppari.：Impact of home-based aerobic exercise on the physical capacity of overweight patients with chronic kidney disease. Int. Urol. Nephrol. 47：359–367, 2015.
20) Karstoft K., Pedersen B.K.：Skeletal muscle as a gene regulatory endocrine organ. Curr. Opin. Clin. Nutr. Metab. Care. 19：270–275, 2016.
21) Pedersen B.K.：The diseasome of physical inactivity-and the role of myokines in muscle-fat cross talk.J. Physiol. 587：5559–5568, 2009.
22) Rondon-Berrios.H., Wang.Y., William E., Mitchcorresponding author.：Can muscle–kidney crosstalk slow progression of CKD? J. Am. Soc. Nephrol. 25：2681–2683, 2014.

23) Klip T.I., Jankowska A.E., Enjuanes C., Voors A.A., Banasiak W., Bruguera J., Rozentryt P., Polonski L., Veldhuisen J.D., Ponikowski P., Comin C.J., Meer.V.P.：The additive burden of iron deficiency in the cardiorenal-anaemia axis：scope of a problem and its consequences. Eur. J. Heart Fail. 16, 655–662，2014.
24) Anker D.S., Colet C.J., Filippatos G., Willenheimer R., Dickstein K., Drexler H., Lüscher F.T., Bart B., Banasiak W., Niegowska J., Kirwan A.B., Mori C., Rothe E.B., Pocock J.S., Wilson P.P., Ponikowski P., FAIR-HF Trial Investigators.：Ferric carboxymaltose in patients with heart failure and iron deficiency. N. Engl. J. Med. 361, 2436–2448，2009.
25) Ponikowski P., Veldhuisen J.D., Colet C.J., Ertl G., Komajda M., Mareev V., McDonagh T., Parkhomenko A., Tavazzi L., Levesque V., Mori C., Roubert B., Filippatos G., Ruschitzka F., Anker D.S., CONFIRM-HF Investigators.：Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur. Heart J. 36, 657–668，2015.
26) Kubota T., Hara K., Kadowaki T.：How to diagnose sarcopenia. Insulin Resistance and Skeletal Muscle, Modern Physician. 31: pp1316–1318, Emerging Medicine Press, 2011.
27) Andersen H., Nielsen S., Mogensen E.C., Jakobsen J.：Muscle Strength in Type 2 Diabetes. Diabetes 53：1543–1548，2004.
28) Nomura T., Ikeda Y., Suehiro M., Nishigami T., Nakao S., Ishida K.: Relationship between one-legged standing balance and knee extension strength in patients with type 2 diabetes mellitus. Diabetes Mellitus 49: 227–231, 2006.
29) Boucher P., Teasdale N., Courtemanche R., Bard C., Fleury M.：Postural stability in diabetic polyneuropathy. Diabetes Care.18：638–645 , 1995.
30) Martinelli A.R., Mantovani A.M., Nozabieli A.J., Ferreira D.M., Barela J.A., Camargo M.R., Fregonesi C.E.,：Muscle strength and ankle mobility for the gait parameters in diabetic neuropathies. The Foot. 23: 17–21，2013.
31) Shigeta S.：Resistance training for patients with internal disorders Resistance training for patients with renal disease. Physiotherapy 32(6):519–528, 2015.
32) Greenwood S.A., Koufaki P., Mercer T.H., MacLaughlin H.L., Rush R., Lindup H., O'Connor E., Jones C., Hendry.B.M, Macdougall I.C., Cairns.H.S.：Effect of exercise training on estimated GFR, vascular health, and cardiorespiratory fitness in patients with CKD: a pilot randomized controlled trial. Am. J. Kidney Dis.(65),425–434, 2015.