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Original article

Relationship between physical activity and fatigability in patients with diabetic kidney disease: A pilot study

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ABSTRACT

【Background and objectives】Recently, efforts have been made to preserve the kidneys of patients with chronic kidney disease. Among them, patients with diabetic kidney disease (DKD) are attracting attention due to the high rate of dialysis use. Physical activity in patients with DKD is associated with renal function; thus, frequent physical activity is recommended. This requires an analysis of factors related to physical activity to clarify the targets of physiotherapy interventions. Therefore, the purpose of this pilot study was to elucidate factors of physical function related to physical activity in patients with DKD.

【Methods】Patient demographics, physical activity, knee extension strength, and fatigability were evaluated in a cross-sectional manner. Physical activity was evaluated for total physical activity-International Physical Activity Questionnaire (TPA-IPAQ) (kcal/week) using the IPAQ-short version. Knee extension strength and fatigability were evaluated using a muscle function evaluation exercise device. Fatigability was calculated as the rate of the decrease in torque during a dynamic fatigue task.

【Results】26 patients were enrolled in this study and 23 patients (n = 14 men, mean age 56.4 ± 6.3 years) were included in the analysis. As a result of analysis, physical activity was negatively correlated with fatigability alone (r = -0.416, p = 0.049).

【Discussion】This study suggests that fatigability is associated with decreased physical activity, which may also lead to decreased renal function in patients with DKD. Further research on factors related to physical activity, including an analysis of fatigability, is needed to develop exercise management programs to protect kidney functionality.

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Introduction

Recently, chronic kidney disease (CKD) was regarded as a new national disease in Japan. Patients with CKD who require hemodialysis have a poor quality of life (QOL) and a high mortality rate[1-3]. Therefore, efforts are needed to protect the kidneys of patients with CKD.

Among the types of CKD, diabetic kidney disease (DKD) caused by diabetes is the most common form in patients receiving dialysis, accounting for more than 40% of the total cases in Japan[4]. Furthermore, DKD has been reported to have a higher incidence of and mortality rate associated with myocardial infarction than patients with CKD with non-diabetic primary diseases[5]. In patients with DKD, renal dysfunction is caused by metabolic disorders induced by hyperglycemia and hypertension caused by renin–angiotensin–aldosterone system activation[6]. Such patients have increased renin secretion, proteinuria, and risk of renal failure. Furthermore, in recent years, physical activity has been identified as a factor related to decreased renal function[7]. In a meta-analysis of patients with diabetic nephropathy, it was reported that physical activity is associated with increases in the glomerular filtration rate and decreases in the urinary albumin creatinine ratio and the rate of microalbuminuria[8]. Patients with DKD typically have decreased physical activity before the introduction of dialysis[9], and renal rehabilitation guidelines recommend maintaining high physical activity levels[10]. Therefore, it is necessary to analyze the factors related to physical activity and clarify the target of therapeutic interventions. Previous studies have reported that low hemoglobin levels, high blood pressure, and muscle wasting affect physical activity in patients with CKD[11,12]. Additionally, it is necessary to pay attention to fatigability in patients with DKD. "Fatigue" is a common and important symptom among patients with DKD[13]. Fatigue is defined as a disability symptom limited by the interaction between fatigability and the perceptions of fatigue[14,15]. Fatigability is generally defined as "The decline in an objective measure of performance over a discrete period of time" [14] and is excellent at capturing patient fatigue objectively. As an index of fatigability, the rate of decrease of maximal isometric contractions (MVIC) during continuous exercise load is widely used. It has been reported that fatigability is associated with physical activity in healthy adults[16], which is clinically important. The more fatigability a person is, the more likely he or she is to experience a decrease in physical activity because the same level of exercise requires a higher energy expenditure[17]. Thus, even in patients with DKD, fatigability may affect physical activity levels.

Until now, factors related to physical activity in patients with DKD are unknown, and no studies have focused on fatigability. The purpose of this pilot study was to analyze the factors that influence physical activity in patients with early DKD.

Methods

1. Participants

Participants were recruited from outpatients in the Department of Endocrinology and Metabolism, at Hamamatsu University Hospital. Participants were included in the study if they were patients with DKD with an estimated glomerular filtration rate (e-GFR) of at least 30 mL/min/1.73m^2 and they had type 2 diabetes as their primary disease. Additionally, included participants were aged 40-65 years and independently walking. Participants were excluded if the study protocol could not be performed due to severe comorbidities such as lung, orthopedic disease, or cerebrovascular accident. Those with unreliable primary outcome fatigability results were excluded from the statistical analysis. Informed consent, including an acknowledgement that participation was voluntary, was obtained in writing before testing. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Hamamatsu University School of Medicine Clinical Research Ethics Committee (acknowledgment number: 20-002) and the International University of Health and Welfare Research Ethics Committee (acknowledgment number: 19-Io-167).

2. Outcome measures

This was a cross-sectional study. The following demographic characteristics were evaluated: age, sex, height, weight, obesity index, and diabetic history. We also examined blood and urinalysis test results for serum hemoglobin, serum creatinine, serum urea nitrogen, hemoglobin A1c and microalbuminuria.

Physical activity was assessed using the Japanese version of the International Physical Activity Questionnaire (IPAQ) short version. General physical activity undertook per week (total physical activity-IPAQ; TPA-IPAQ) was calculated based on the responses from interviews and used as an indicator of physical activity. In diabetic patients, the validity has been confirmed between the amount of physical activity calculated by the IPAQ and the physical activity meter[18].

Knee extension strength and fatigability were evaluated using a muscle function evaluation exercise device (SAKAImed, BIODEX System3). An experimental protocol (Figure 1) was performed with reference to previous studies to evaluate knee extension strength and fatigability[16]. The experimental protocol comprised a baseline and a dynamic fatigue task (DFT). Subjects performed maximal isometric contractions (MVIC) and maximal voluntary concentric contractions (MVCC) in knee extension exercises. At baseline, MVIC was performed three times, and thereafter MVCC was performed 15 times consecutively once every 3 s at a load of 20% of the maximum torque value measured using the MVIC. Next, for the DFT, once every 3 s, 30 MVCCs and one MVIC were paired as one set, and this was continued for three sets. MVIC calculated the measured value in torque (Nm), which is a quantity (moment) expressed as the product of the force and distance. Participants were strongly, verbally encouraged to achieve maximal force during all MVICs and peak velocity during all MVCCs throughout the protocol. The knee extension strength was calculated by dividing the torque value measured at baseline by the body weight. Additionally, fatigability was defined as the rate of decrease in the torque value measured by the third set of MVICs from the torque value measured using the baseline value. This evaluation was performed by three people, one doctor and two physical therapists skilled in measurement.

In the evaluation of fatigability, which was the primary outcome, those who did not have a reduced torque value and those who were identified as outliers based on the interquartile range using the calculation method were excluded because the reliability of the evaluation results were low.

3. Statistical analysis

The means and standard deviations of patient demographics, physical activity, knee extension strength, and fatigability were calculated. The normality of each variable was confirmed using the

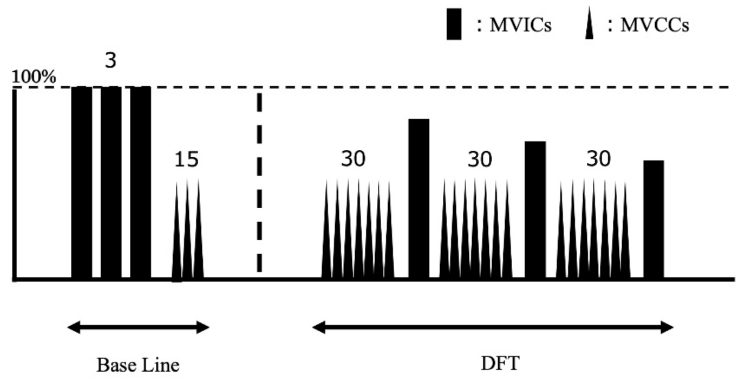

Figure 1. Protocol for evaluation of knee extension strength and fatigability

Experimental protocol. The maximal voluntary isometric contractions (MVICs), the maximal voluntary concentric contractions (MVCCs) are represented by black squares, black triangles respectively.

Shapiro-Wilk test. The Spearman's rank correlation coefficient was calculated to investigate the relationship between physical activity and patient demographics, knee extension strength, and fatigability. The significance level was set to less than 5%. IBM SPSS Statistics Ver25 was used for statistical analysis.

Results

26 patients were enrolled in this study and 23 patients (n = 14 men, mean age 56.4 ± 6.3 years) were included in the analysis. 3 patients were excluded; 1 patient who refused consent, 1 patient who had severe cerebral infarction, and 1 patient whose results were unreliable.

According to patient characteristics and physical function evaluation data, the average history of the presence of diabetes was 15.9 ± 9.6 years. Overall, 18 and 3 patients had 2nd and 3rd stage diabetic nephropathy; there was 2 atypical cases with no obvious albuminuria/proteinuria or conspicuous decrease in renal function. Other complications identified were diabetic neuropathy (n = 7), simple diabetic retinopathy (n = 4), and pre-proliferative diabetic retinopathy (n = 2) (Table 1 and Table 2).

As a result of analyzing the relationship between physical activity and each measured index that has been reported to be associated with physical activity in previous studies, no significant correlation was found between physical activity and age, body weight, hemoglobin, and knee extension strength. In contrast, a significant negative correlation was found between physical activity and fatigability ($r = -0.416$, $p = 0.049$) (Table 3).

Discussion

The results of this study suggest that fatigability may be related to the physical activity in patients with DKD.

The purpose of this pilot study was to analyze the factors that influence physical activity in patients with early DKD and thus, it was necessary to include patients with early stage DKD. As a result, we targeted patients with DKD with an e-GFR of at least 30 mL/min/1.73m^2. According to a report by the Japanese

Table 1. Clinical and demographic characteristics of the included patients

Variables	Values (n = 23)
Age (years)	56.4 ± 6.3
Males (%) / Females (%)	14 (61) / 9 (39)
Height (cm)	166.1 ± 10.3
Body weight (kg)	71.9 ± 15.8
BMI (kg/m²)	25.8 ± 4.5
Smoking habits (%)	
Never smokers	15 (65)
Ex-smokers	5 (22)
smokers	3 (13)
Duration of DM (years)	15.9 ± 9.6
Nephropathy stage※ (%)	
Stage 2	18 (78)
Stage 3	3 (13)
Atypical	2 (9)
Diabetic neuropathy (%)	7 (30)
Diabetic retinopathy (%)	
NDR	17 (74)
SDR	4 (17)
PPDR	2 (9)
eGFR (mL/min/1.73 m^2)	69.7 ± 22.2
Cre (mg/dL)	0.9 ± 0.3
Hb (g/dL)	14.4 ± 2.1
HbA1c (%)	7.9 ± 1.3

BMI = body mass index; NDR = no diabetic retinopathy; SDR = simple diabetic retinopathy; PPDR = pre proliferative diabetic retinopathy; eGFR = estimated glomerular filtration rate; Cre = serum creatinine; Hb = serum hemoglobin; HbA1c = hemoglobin A1c

※Japanese classification of diabetic nephropathy

Date are expressed as mean ± SD or number of patients with percentage in parenthesis.

Society of Nephrology, the number of patients with CKD increased sharply after the age of 40 years, and the average age of all dialysis-introduced patients was 69 years[19]. Furthermore, it has been reported that there is a significant difference in fatigability between young and elderly individuals[16]. Thus, to minimize the effect of age, patients aged 40-65 years were targeted in this study.

Table 2. Physical functionality of the included patients

Variables	Values (n = 23)
Physical activity (kcal/week)	2999.0 ± 3265.5
Knee extension strength (Nm/kg)	1.9 ± 0.6
Fatigability (%)	28.5 ± 13.1

Date are expressed as mean ± SD.

Table 3. Relationship between physical activity and patient attributes, knee extension strength, and fatigability

	Physical activity	
Variables	Correlation coefficient	*p*-Value
Age	0.340	0.112
Body weight	-0.325	0.131
Hb	-0.167	0.447
Knee extension strength	0.010	0.962
Fatigability	-0.416	0.049*

Hb = serum hemoglobin

Spearman's rank correlation coefficient were calculated between physical activity and age, Body weight, Hb, knee extension strength, and fatigability.

* $p < 0.05$

Previous studies have reported that in addition to physical characteristics such as age and weight, muscle strength and hemoglobin concentration are involved in physical activity[11,12,20]. However, this study found that only fatigability was associated with physical activity. Patients with DKD have reduced physical activity[9], and many experience fatigue[13]. A study investigating symptoms in patients with CKD before the transition to dialysis reported that approximately 80% of patients had fatigue[13]. Patients with DKD in this study also had higher fatigability than healthy subjects. In a previous study evaluated fatigability using the same method, the fatigability of healthy old adults participated (71.3 ± 6.3 years old) was 21.1 ± 9.2%, while the fatigability of patients with DKD (56.4 ± 6.3 years old) in this study, who were younger than them, was 28.5 ± 13.1%[16]. Additionally, it has been clarified in healthy subjects and patients with cancer that the amount of physical activity is affected by fatigue[16,21]. To the best of our knowledge, this is the first study to report on this finding among patients with DKD, making it novel. Patients with DKD have decreased NO production capacity due to increased oxidative stress and impaired L-arginine production[22]. This reduces muscle microvascular blood flow, which reduces oxygen uptake in skeletal muscle and lowers the lactate acidosis threshold[23]. Furthermore, it is thought that fatigability is easily caused by a decrease in calcium ion sensitivity in myofibrils and a decrease in calcium ion release ability in sarcoplasmic reticulum. It has also been reported that the complication diabetic neuropathy may affect fatigability[24]. Reduces muscle microvascular blood flow, impaired intracellular calcium ion concentration regulation in myofibrils, and diabetic neuropathy are symptoms unique to patients with DKD[25,26]. Increased fatigability is also thought to increase oxygen uptake at the same intensity and decrease physical activity[27]. Therefore, we concluded that fatigability is related to physical activity in patients with DKD.

Previously, it was a belief that physical activity in patients with renal impairment should be limited, but in recent years, active exercise therapy has been recommended for patients with stable DKD. In the renal rehabilitation guidelines published in Japan, it is recommended to use a pedometer to set a specific target number of steps and then increase the amount of physical activity[10]. The increase in physical activity not only improves the patient's physical function, but also contributes to the protection of the kidneys. And when the goal is to improve physical activity in patients with DKD, it is necessary to focus on fatigability in addition to the previously identified factors as a therapeutic target for rehabilitation.

This study has some limitations and caveats. First, the sample size was small. Only 23 cases were examined; thus, studies including a larger number of cases will be required in the future. Second, physical activity was evaluated using the IPAQ-Short Version. This tool evaluates physical activity measured by the physical activity meter; however, it may not be possible to reflect the amount of physical activity for a short period of time (i.e. within 10 min). To obtain higher accuracy, it is necessary to re-evaluate this using a physical activity meter. Third, the age of the subjects in this study was limited, so the results may not reflect those of elderly DKD patients and others. Fourth, to the best of our knowledge, it is unclear whether the subjects in this study were consistent with the amount of physical activity of DKD patients in general, so caution should be exercised in generalizing the results of this study to patients with DKD of the same age. Fifth, we did not take into account the effect of diabetic neuropathy. In this study, seven patients with diabetic neuropathy were included. Although they were mild cases who did not interfere with daily life, we cannot deny the possibility that diabetic neuropathy may have affected their fatigability as reported in previous studies[24]. Finally, we investigated the relationship with physical activity using a correlation analysis; however, we were not able to determine a causal relationship between the variables. In the future, longitudinal studies should be conducted to confirm these findings.

In conclusion, fatigability is a characteristic symptom of patients with diabetic nephropathy and may be related to physical activity. Additionally, fatigability can also lead to decreased renal function in patients with DKD. Further research on factors related to physical activity, including an analysis of factors that cause fatigability, is needed to develop interventions for maintaining renal function.

Conflict of Interest

There are no conflicts of interest.

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