Exercise Time according to Intensity among Patients with Diabetic Nephropathy in the Pre-nephropathy Stage

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[Abstract]

Background: In patients with diabetic nephropathy, exercise is one way to suppress progression of the disease. Though exercise is important beginning in the early stages, m any investigative reports have covered various disease stages. The present study therefore examined exercise time according to intensity only in patients with early diabetic nephropathy and investigated its relationship to renal function. **Methods:** The study subjects were patients with a diabetic nephropathy stage classified as pre-nephropathy. The renal function indicators used were serum creatinine (Cr), estimated glomerular filtration rate (eGFR), urinary albumin/creatinine ratio (urine A/C ratio), and urinary L-type fatty acid-binding protein. For exercise time according to intensity, the Japanese version of the International Physical Activity Questionnaire (short version) was used to survey weekly exercise times for walking and moderate- and high-intensity exercise. The relationships between the exercise time for each intensity and renal function were studied using Spearman's rank correlation coefficient. **Results:** There were eight subjects (mean age, 64.9 ± 12.7 years) with a mean Cr of 0.75 ± 0.17 mg/dL, mean eGFR of 72.1 ± 14.1 mL/min/1.73m^2, and mean urine A/C ratio of 9.7 ± 7.5 mg/gCr. Mean exercise times for walking and moderate- and high-intensity exercise were 296.9 ± 312.8 min/week, 41.3 ± 93.6 min/week, and 81.3 ± 187.9 min/week, respectively. Walking time showed a correlation with age ($r = 0.810$, $p = 0.015$) and with urine A/C ratio ($r = 0.714$, $p = 0.047$), while high-intensity exercise time showed a correlation with Cr ($r = 0.784$, $p = 0.021$). **Conclusion:** The present study showed that although patients with diabetic nephropathy in the pre-nephropathy stage had shorter moderate- and high-intensity exercise times, their walking times were longer than those of healthy individuals.

Keywords: diabetic nephropathy, pre-nephropathy stage, exercise time

1. Background

Diabetic nephropathy is one of the causative diseases of chronic renal failure. In Japan, it is the single greatest cause of new introduction of dialysis and is increasing year by year[1]. The five-year survival rate after dialysis has been introduced is approximately 60%. The disease poses a significant burden in terms of healthcare economics[2].

Diabetic nephropathy is classified based on the level of urinary protein excretion and the glomerular filtration rate into a pre-nephropathy stage, an early nephropathy stage, an overt nephropathy stage, a renal failure stage, and a dialysis treatment stage[3]. A large-scale 20-year report on patients with diabetic nephropathy due to type 2 diabetes showed that the annual mortality rate in patients with pre-nephropathy, early nephropathy, and overt nephropathy was 1.4%, 3.0% and 4.6%, respectively, showing that as the nephropathy stage advances, the mortality rate rises[4].

In recent years, it has been shown that exercise is effective for improving renal function in diabetic nephropathy. Araki et al reported that an improvement in hemoglobin A1c (HbA1c) and systolic blood pressure due to appropriate treatment of patients with early

nephropathy not only suppressed progression of the disease but also improved renal function from the early nephropathy stage to the pre-nephropathy stage[5]. Ito et al reported that long-term aerobic exercise in rats increased their nitric oxide levels and relieved oxidative stress and glycative stress, thereby mitigating their renal impairment[6].

In patients with diabetes, exercise therapy forms the core of non-drug therapy with exercise being effective for weight loss, mitigating hyperglycemia, mitigating hyperlipidemia, and improving insulin sensitivity. Diabetes guidelines recommend not only performing exercise therapy centered on aerobic exercise, but also increasing physical activity in all areas of daily life. Physical activity in patients with diabetes is effective for correcting blood sugar levels and preventing complications, and it is important to establish an exercise habit at an early stage of the disease[7].

In patients with diabetic nephropathy, daily physical activity is also regarded as important for blocking progression of the disease and preventing complications. However, almost no reports address physical activity in patients with diabetic nephropathy.

The purpose of the present study is therefore to examine physical activity times according to intensity in patients with diabetic nephropathy in the pre-nephropathy stage, which is before renal dysfunction becomes overt.

2. Methods

1) Subjects

Outpatients with diabetic nephropathy with stable symptoms who visited Minami Sapporo Hospital between June and August 2016 and underwent microalbumin testing and whose diabetic nephropathy was classified as being in the pre-nephropathy stage were enrolled in this study. Those having cognitive dysfunction were excluded.

The present study is a retrospective observational study and was performed in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects and with the Declaration of Helsinki.

2) Methods

Medical records were reviewed to obtain data on height, body weight, body mass index (BMI), hemoglobin (Hb), HbA1c, and urine test values. Estimated glomerular filtration rate (eGFR), serum creatinine (Cre), urinary albumin/creatinine ratio (urine A/C ratio), and liver-type fatty acid-binding protein (L-FABP) were used as indicators of renal function.

Exercise times according to intensity were assessed using the Japanese version of the International Physical Activity Questionnaire (IPAQ) (short version)[8]. The IPAQ (short version) is a self-reported evaluation that investigates the number of days where at least 10 minutes of walking, moderate-intensity exercise, and/or

Table 1: Patient backgrounds

Case	Sex	Age	Height (cm)	Weight (kg)	BMI (kg/m^2)	Hb (g/dL)	HbA1c (%)	Serum Cr (mg/dL)	eGFR ($mL/min/1.73m^2$)	Urine A/C ratio (mg/gCr)	L-FABP (μg/gCr)
A	F	70	1.62	64.3	24.5	13.1	7.3	0.65	67.2	13.8	0.82
B	M	57	1.70	58.9	20.3	13.3	5.6	0.64	99.1	9.3	5.10
C	F	41	1.70	122.4	42.4	14.6	8.0	0.61	84.8	3.1	4.40
D	M	64	1.75	88.8	29.1	14.1	5.7	0.81	74.1	3.2	0.82
E	F	67	1.57	66.1	26.8	13.5	7.3	0.63	71.1	16.2	0.85
F	F	86	1.55	52.3	21.8	14.1	7.0	0.65	64	23.3	4.50
G	M	66	1.63	74.9	28.2	13.7	6.4	0.96	61	6.2	2.30
H	M	68	1.73	87.4	29.2	13.1	6.8	1.04	55.4	2.7	2.00
Mean		64.9	1.66	76.9	27.8	13.7	6.8	0.7	72.1	9.7	2.6
Standard deviation		12.7	0.07	22.5	6.8	0.5	0.8	0.2	14.1	7.5	1.8

BMI: body mass index, Hb: hemoglobin, Cr: creatinine, eGFR: estimated glomerular filtration rate, urine A/C ratio: urine albumin creatinine ratio; , L-FABP: urinary liver-type fatty acid-binding protein

high-intensity exercise is performed and the exercise time according to intensity per week was determined using the duration per day. In a prior study, the moderate-intensity exercise time per week in healthy individuals was approximately 306 minutes, while the high-intensity exercise time was approximately 138 minutes[9]. The IPAG has also been confirmed to be reproducible among diabetic patients.

3) Statistical methods

Spearman's rank correlation coefficient was used to study relationships between exercise times at each exercise intensity and with each of the indicators. The statistical software used was SPSS ver. 19 (from SPSS Japan), and the level of significance was set at 5%.

3. Results

Table 1 shows the patient backgrounds. Mean age was 64.9 ± 12.7, and mean BMI was 27.8 ± 6.8 kg/m^2. HbA1c exceeded the target value of 6.0% in six individuals and was at or above 8.0% in one individual. The mean eGFR and urine A/C ratio were 72.1 ± 14.1 mL/min/1.73m^2 and 9.7 ± 7.5 mg/gCr, respectively.

Fig. 1 shows the lengths of time that walking, moderate-intensity exercise, and high-intensity exercise were performed per week. Mean walking time was 296.9 ± 312.8 min/week, mean moderate-intensity exercise time was 41.3 ± 93.6 min/week, and mean high-intensity exercise time was 81.3 ± 187.9 min/week.

Table 2 shows the relationships between each of the indicators and the exercise time according to intensity. Walking time showed a correlation with age ($r = 0.810$, $p = 0.015$) and urine A/C ratio ($r = 0.714$, $p = 0.047$), while high-intensity exercise time showed a correlation with Cr ($r = 0.784$, $p = 0.021$).

4. Discussion

The present study is the first to investigate physical activity exclusively among patients with diabetic nephropathy in the pre-nephropathy stage.

A report on physical activity time among healthy individuals from Hagströmer et al stated that for exercise time according to intensity as assessed with the IPAQ, the mean moderate-intensity exercise time was 5.1 ± 6.9 hours/week and the mean high-intensity exercise time

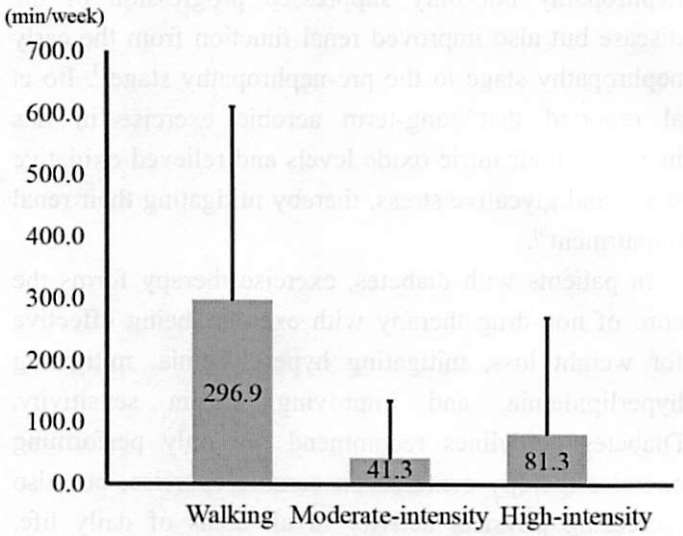

Fig. 1: Exercise time by intensity

was 2.3 ± 4.4 hours/week[10]. The moderate- and high-intensity exercise time found in the present study were lower than these values.

Inoue et al used a self-reported assessment table to study walking time in healthy individuals and reported that the mean walking time per week was 209 ± 185 minutes[11]. The mean weekly walking time in patients with diabetic nephropathy in the pre-nephropathy stage in the present study was 296.9 ± 312.8 min, which is greater than that reported by Inoue et al. According to the official guidelines for the IPAQ, walking is estimated to be 3.3 metabolic equivalents (Mets), moderate-intensity exercise to be 4 Mets, and high-intensity exercise to be 8 Mets[8]. Guidelines on exercise in diabetics recommend aerobic exercise but not high-intensity exercise. The patients in the present study were being seen for outpatient care and were receiving guidance on exercise, which may explain their short high-intensity exercise time and longer walking time.

In addition, the present study showed that walking time was related to age and to A/C ratio.

For walking among healthy individuals, it has been shown that the mean for ages 20 to 64 is 7,436 steps, with a mean of 6,389 steps for ages 65 to 74 and 4,015 steps for ages 75 and older showing that the number of steps decreases with age[12]. In a study on community-dwelling elderly women, Koizumi et al calculated a regression formula with (steps) = 22,487 –

Table 2: Relationship between exercise time by intensity and each indicator

	Walking time		Moderate-intensity exercise time		High-intensity exercise time	
	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value
Age	0.810	0.015 *	-0.027	0.949	-0.153	0.717
BMI	-0.452	0.260	-0.355	0.389	0.255	0.542
Hb	-0.229	0.586	0.373	0.363	-0.330	0.425
HbA1c	0.192	0.649	-0.576	0.135	-0.707	0.050
Serum Cr	0.156	0.713	0.082	0.846	0.784	0.021*
eGFR	-0.357	0.385	0.327	0.429	-0.396	0.332
Urine A/C ratio	0.714	0.047 *	0.218	0.604	-0.626	0.097
L-FABP	-0.476	0.233	0.082	0.847	-0.013	0.976

* $p < 0.05$

BMI: body mass index, Hb: hemoglobin, Cr: creatinine, eGFR: estimated glomerular filtration rate, urine A/C: urine albumin creatinine ratio, L-FABP: urinary liver-type fatty acid-binding protein

212 × (age)[13]. These reports are consistent with the results of the present study.

The urine A/C ratio is one of the indicators for patients with diabetic nephropathy[3]. Having a high urine A/C ratio is indicative of the possibility of decreased renal function. Being in the pre-nephropathy stage, all patients in this study were within the reference values; however, during their outpatient visits they received guidance on the need for aerobic exercise in order to prevent progression of their renal dysfunction, and it is possible that those with worse renal function had longer walking times.

The present study also showed that high-intensity exercise time was related to serum Cr. However, serum Cr is not reflective of renal function alone because it also varies depending on muscle mass[14]. Cr is generated within the muscles thus greater muscle mass means the serum Cr will be higher. Serum Cr in the results of the present study were within reference values and showed no relationship with other indicators of renal function. Therefore, it is possible that those with longer high-intensity exercise times also had greater muscle mass and, therefore, there was a relationship observed between serum Cr values and high-intensity exercise times. However, muscle mass was not actually assessed in the present study, so further investigation is needed.

The present study has several limitations. Firstly, physical activity is said to also be affected by environment[11]. However, environmental factors were not investigated in the present study. Future research that includes environmental factors is necessary. Secondly, the sample size was small making it impossible to run multiple regression analysis. A larger sample size is needed to clarify what factors affect physical activity.

The present study investigated exercise time according to intensity in patients with diabetic nephropathy in the pre-nephropathy stage. We found that patients with diabetic nephropathy in the pre-nephropathy stage had shorter moderate- and high-intensity exercise times and longer walking times than healthy individuals and their renal function was unrelated to exercise times according to intensity.

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