Extended sedentary time increases the risk of all-cause death and new cardiovascular events in patients with diabetic kidney disease

Hajime Tamiya, BS[1)]; Yuma Tamura, PhD[1)]; Syusuke Mochi, BS[1)]; Yusuke Akazawa, BS[1)]; Yumi Mochi, BS[1)]; Nobuyuki Banba, MD, PhD[2)]; Yuki Nakatani, MD, PhD[2)]; Megumi Hoshiai, MD[3)]; Asuka Ueno, MD[3)]; Moeko Nagao, MD[3)]; Takashi Tomoe, MD[3)]; Masato Onozaki, MD[3)]; Atsuko Uema, MD[3)]; Atsuhiko Kawabe, MD[3)]; Takushi Sugiyama, MD[3)]; Takanori Yasu, MD, PhD[3)]

1) Department of Rehabilitation, Dokkyo Medical University Nikko Medical Center, Nikko, Tochigi, Japan

2) Department of Diabetes and Endocrinology, Dokkyo Medical University Nikko Medical Center, Nikko, Tochigi Japan

3) Department of Cardiovascular medicine and Nephrology, Dokkyo Medical University Nikko Medical Center, Nikko, Tochigi, Japan

Short title: Sedentary time for diabetic kidney disease

*__Correspondence__: Dr. Takanori Yasu

Department of Cardiovascular Medicine & Nephrology, Dokkyo Medical University Nikko Medical Center 632 Takatoku Nikko, Tochigi 321-2593, Japan

Tel: 81-288-76-1515; fax: 81-288-76-1030

E-mail: tyasu@dokkyomed.ac.jp

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IRB information

This study was performed according to the principles of the Declaration of Helsinki and was approved by the institutional ethics committee of Dokkyo Medical University Nikko Medical Center (approval number: Nikko 27001).

Abstract

Background

Sedentary behavior may be an independent risk factor for cardiovascular events. This study aimed to clarify the effects of extended sedentary time in patients with diabetic kidney disease (DKD) on the risk of all-cause death and new events.

Methods and Results

A prospective cohort study was performed over 39 months. The study included 173 patients with DKD who completed the International Physical Activity Questionnaire (IPAQ) (101 men; mean age, 71±11 years); 37 patients (21.4%) were diagnosed with cardiovascular disease. New events were defined as all-cause death, cerebral stroke, or cardiovascular disease (CVD) requiring hospitalization or commencing hemodialysis (HD). Data were analyzed using a multivariate Cox proportional hazard regression model with variables, including sedentary time. There were 34 cases of new events during the observation period, including 4 cases of stroke, 20 cases of CVD, 4 cases of HD implementation, and 6 cases of death. Hazard ratio (HR) calculations for the new event onset group identified sedentary time as a significant independent variable. The independent variable that was identified as a significant predictor of new events was sedentary time (60 min/day; HR: 1.23, 95% CI: 1.05–1.45, p=0.012).

Conclusion

Extended sedentary time increased the risk of new cardiovascular or renal events and/or all-cause death in patients with DKD.

Keywords

All-cause death, cardiovascular events, diabetes mellitus, kidney disease, sedentary time

Introduction

Decreased physical activity has been shown to cause various adverse health effects.[1] In recent years, extended sedentary time has been reported to increase the risk of cardiovascular disease (CVD) and all-cause mortality, independent of physical activity.[2] In 2015, 422.7 and 17.92 million cases of CVD and CVD deaths, were estimated respectively.[3,4] Risks of all-cause and CVD mortality were significantly higher in those with diabetic kidney disease (DKD) and diabetic retinopathy; however, DKD was more strongly associated with excess risk.[5]

Sedentary behavior, defined as any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents (METs) while in a sitting or reclining postures, such as watching TV or using a computer,[6] can be objectively measured using an accelerometer[7] or subjectively measured using a questionnaire.[8-10] Rather than equating increased physical activity with decreased sedentary time, intervention strategies are needed to individually address each factor.

In addition, in a meta-analysis on the effects of sedentary time, extended sitting time was associated with a 14% increase in cardiovascular disease risk and a 24% increase in all-cause mortality risk.[11] Due to reports such as these, efforts are being made globally to reduce time spent in a sitting position. In the American Diabetes Association's 2016 guidelines, a specific recommendation to keep sitting time restricted to 90 minutes per day, regardless of the amount

of physical activity, was included for the first time.[12] Extended sedentary time among patients with diabetes has been associated with lower high-density lipoprotein-cholesterol (HDL-C)[13] and other metabolic disorders.[14] Furthermore, extended sedentary time has been reported among patients with DKD, a complication of diabetes[15]; however, risks of associated event are unclear.

DKD is the leading underlying cause of hemodialysis (HD). Similarly, diabetes mellitus is a strong independent risk factor for CVD,[16,17] and the onset of CVD is often a trigger for HD initiation. Therefore, preventing the onset of CVD is critical in delaying the progression of DKD and in preventing HD. This study aimed to clarify the effects of extended sedentary time in patients with DKD on the risk of all-cause death and new cardiovascular events.

Methods

Study population

Patients included 173 DKD outpatients who completed the International Physical Activity Questionnaire (IPAQ). Inclusion criteria included patents with DKD ≥20 years old, who provided written informed consent to participate in this study. Exclusion criteria were patients with dementia, type 1 diabetes mellitus, and severe infection. Similarly, patients who had sustained serious trauma, had severe impaired liver function (either pre- or postoperatively) or

were otherwise deemed unsuitable for the clinical study by investigators were excluded. The study design was a prospective single-center cohort study performed during a follow-up period from September 2013 to December 2016 (Fig 1). This study was performed according to the principles of the Declaration of Helsinki and was approved by our Institutional Ethics Committee (approval number: Nikko 27001).

IPAQ

A short form of the IPAQ (IPAQ-short) was used in this study to evaluate the physical activity and sedentary time.[10,18,19] IPAQ estimates were obtained verbally and face-to-face with each participant by trained physical therapists. The study participants were instructed to think about the time spent sitting at work, at home, while doing course work, and during leisure time. They were asked to estimate in total the number of hours and minutes per day spent sitting during a weekday and a weekend day.[10] In addition to obtaining sitting times, participants were similarly asked to complete a band graph of their activity levels throughout the day, from which their total sedentary time per day was subsequently calculated (Fig 2). Separate estimates were made for a weekday and a weekend day, and the average amount of time spent sitting per day (time/day) was used. Physical activity was equally assessed separately for weekdays and

weekends, and these estimates were used to calculate the amount of physical activity per week (kcal/week). The physical-activity quantity was based on intensity and type components, with types such as, indoor and outdoor, as well as frequency (days/week) and length of time (min/day) of locomotor-activity that lasted at least 10 minutes. METs were calculated and applied to each activity. The MET intensities used to score the IPAQ were vigorous (8 METs), moderate (4 METs) and walking (3.3 METs; www.ipaq.ki.se). Using the definition for a MET as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ) $*kg^{-1}*h^{-1}$, 1 MET was considered a resting metabolic rate obtained during quiet sitting.[20] The physical-activity quantity (kcal/week) was calculated from the IPAQ data and weight.[21]

Clinical measurements

Primary evaluation items were new CVD and stroke events, HD initiation, and all-cause death hazard ratios (HR). New CVD included acute myocardial infarction, angina pectoris requiring revascularization, and heart failure requiring admission. During the follow-up period, subjects who experienced a new CVD or stroke event requiring hospitalization were placed on HD; those who died were grouped into the new event onset group, and all other subjects were classified as the control group. The definition of CVD included myocardial infarction, ischemic heart

disease, heart failure, peripheral arterial disease, and arrhythmia. This information was collected from electronic health records and recorded, along with the amount of time before event onset.

Secondary evaluation items were blood pressure, lipid metabolism, estimated glomerular filtration rates (eGFR), urinary albumin/creatinine (Alb/Cre) ratio, DKD stage, hemoglobin A1c (HbA1c) level, hemoglobin level, physical activity, and sedentary time at the start of the observation period. These evaluation item data were collected from outpatient examinations or inpatient blood test and urinalysis results. Furthermore, the nephropathy stage was classified using the eGFR and Alb/Cre ratio.[22]

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normality of distribution of continuous variables. Data were presented as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. Baseline comparisons were conducted using the independent t-test, Mann–Whitney U test, chi-squared test, and Fisher's exact test.

The analysis was cut off at the first event that occurred from the start of the observation period. We assessed the univariate association between baseline sedentary time and other baseline characteristics with new CVD and stroke events, HD initiation, and all-cause death. Cox

multivariate regression analysis of baseline characteristics with $p<0.05$ in the univariate analysis was conducted to yield the HR for new cardiovascular or renal events and/or all-cause death. The cutoff value of the sedentary time for the onset of new events was calculated from the ROC curve. The cutoff value was selected as the point with the highest sensitivity and specificity. The participants were classified into low and high sitting time groups based on the sitting time selected by the ROC curve. Cumulative survival rates for the onset of new events between the two groups during the observation period were illustrated by Kaplan–Meier curves and compared using the log-rank test.

In patients with CKD, the HR has been reported to be 0.59 (range: 0.35–0.98) for the light-intensity activity group as compared to that for the sedentary group.[23] In this study, the sample size was calculated according to the report by Beddhu et al.[23] and the formula of Dupont and Plummer.[24] With a significance level of 0.05, a power of 80%, and median event duration of 24 months, the required sample size was 162 cases.

SPSS version 25 (IBM Corp., Chicago, IL) was used for statistical analyses. The significance of a two-tailed p-value was set at <5%.

Results

The clinical characteristics of the study participants (mean age, 71±11 years) are summarized in Table 1 (DKD stage I: 41 cases [23.7%], II: 96 cases [55.5%], III: 26 cases [15%], IV: 8 cases [4.6%], V: 2 cases [1.2%]). Fifty-two participants (30.1%) were working, 20 (11.6%) were ex-smokers, and 37 (21.4%) had established CVD. The mean physical activity was 1,850.4 kcal/week, with a mean of 460 min/day of sedentary time.

There were 34 cases of new events during the observation period. These new events were as follows: 4 cases of stroke, 20 cases of CVD, 4 cases of HD implementation, and 6 cases of death (Table 2). In the comparison of the backgrounds of the two groups, significant differences in age, medical history, diabetes duration, and DKD stage were observed (Table 1). Additionally, the blood test and urinalysis values of the new event onset group indicated significantly lower hemoglobin, HDL-C, and low-density lipoprotein (LDL)-C levels and lower eGFR. Similarly, the sedentary time was significantly higher in the new event onset group. In the univariate analysis, new cardiovascular or renal events and/or all-cause death were significantly associated with age, diabetes duration (years), history of CVD, hemoglobin, HDL-C, LDL-C, eGFR, Alb/Cre ratio, and sedentary time (Table 3). The baseline characteristics with $p<0.05$ in the univariate analysis were used to calculate the HR for new cardiovascular or renal events and all-cause death. HR calculations by Cox multivariate regression analysis for the new event onset group identified sedentary time as a significant independent variable (Table 3). Each

1-hour increase in sedentary time per day increased the risk of a new event by 23% (HR: 1.23, 95% CI: 1.05–1.45, p=0.012). Area under the ROC curve (AUC) was 0.741 (p<0.0001). The cutoff value of the sedentary time for the onset of a new cardiovascular or renal event and/or all-cause death was 525 min/day, with a sensitivity and specificity of 0.706 and 0.669, respectively (Fig 3). Cumulative survival rates for new events in the low and high sedentary time groups during the observation period were 0.903 and 0.649 for the low- and high-value groups, respectively; this was significantly lower in the high-value group (Fig 4, p<0.0001).

Discussion

To the best of our knowledge, this is the first study that showed that extended sedentary time increases the risk of new cardiovascular or renal events and/or all-cause death in patients with DKD.

Interestingly, a recent meta-analysis showed that the detrimental effects of a sedentary lifestyle are influenced by chronic disease; furthermore, sedentary behavior in combination with diabetes, hypertension, or high body mass index was associated with an increased all-cause mortality risk.[25] In recent years, extended sedentary time has been shown to cause metabolic syndrome in patients with diabetes,[13,14] and efforts are being made to reduce sedentary time.

The peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) controls exercise-related muscle function and muscle plasticity, suppresses a broad inflammatory response, and mediates the beneficial effects of exercise.[1] However, in those with diabetes, the expression of PGC-1α in the liver has been reported to be continuously increased, resulting in gluconeogenesis promotion and hyperglycemia progression.[26] Additionally, the function of PGC-1α in skeletal muscles becomes diminished and insulin resistance is increased.[27] An increase in PGC-1α in the vascular endothelium as a consequence of hyperglycemia leads to vascular endothelial dysfunction and reduced angiogenic ability.[28] Based on these facts, it can be suggested that PGC-1α plays an important role in systemic organs, particularly in the pathological condition of diabetes.[29] This observational study was approached with the hypothesis that the same adverse effects occur in DKD patients with diabetes as an underlying condition. The reduced muscular contraction that accompanies sedentary behavior leads to the decreased activity of PGC-1α, lipoprotein lipase, and GLUT4.[1,30] This increases the onset of metabolic abnormalities such as hyperglycemia, dyslipidemia, metabolic syndrome, and insulin resistance,[27] resulting in the gradual progression of arteriosclerosis.

There are reports on vascular endothelial damage, such as an increase in PGC-1α in the vascular endothelium resulting from hyperglycemia[28] and a decrease in the popliteal artery shear

rate and flow-mediated dilation due to temporary rest.[31] Therefore, chronic sedentary behavior in those with DKD may be a major factor that leads to vascular endothelial dysfunction.

Subsequently, energy consumption and muscle mass gradually decrease with chronic sitting habits, leading to a vicious cycle of sitting time prolongation. The effects of numerous factors, such as the aforementioned, supposedly combine to increase the risk of cardiovascular disease and all-cause death.

Carotid artery echo and flow-mediated dilation are important for evaluating functional and morphological changes in blood vessels caused by arteriosclerosis. The intima–media thickness obtained by carotid artery echo is closely associated with stroke[32] and CVD risk,[33] and it is reported that improving FMD by 1% also reduces CVD risk by 13%.[34] Therefore, the severity of arteriosclerosis may have an effect in this study as well, but this result cannot be mentioned. To prove these hypotheses, it must be necessary to investigate the relationship between sedentary time and arteriosclerosis or vascular endothelial function using the intima–media thickness or flow-mediated dilation in the future.

In the present study, hemoglobin was not extracted as a significant independent variable (HR: 0.80, p=0.054); nevertheless, we believe that hemoglobin is an important indicator in DKD. Previous studies reported that lower hematocrit levels increased mortality in patients with a

history of myocardial infarction[35] and severe heart failure.[36] In patients with CKD stages 3 and 4, anemia and hypertension are important factors in cardiac hypertrophy, which is the background of heart failure.[37] Such cardiac hypertrophy has been shown to increase CVD mortality, and the CKD merger equally increases CVD mortality.[38] Thus, anemia not only complicates CKD but also worsens its prognosis.

A recent meta-analysis by Ekelund et al. showed a clear dose–response relationship between accelerometer-measured physical activity and all-cause mortality and revealed that higher levels of total physical activity (at any intensity) and less time spent being sedentary are associated with a substantially reduced risk of premature mortality, with evidence of a nonlinear dose–response pattern in middle-aged and older adults.[39] Another recent meta-analysis by Qiu et al. reported an independent association between physical activity and better outcomes with respect to physical function and aerobic capacity in patients with renal failure.[40]

The IPAQ was used to assess sedentary time. Supposedly, the IPAQ is easily biased as it relies on the recall ability of the participant. Therefore, objectivity was maintained by employing a direct interview method with a physiotherapist and calculating the sedentary time through written graphs. In recent reports, the visual analog scale (VAS) was equally used to increase the precision of questionnaires.[41] Physical activity assessed by IPAQ shows a high correlation with accelerometer data,[18,19,39,42] and the IPAQ sitting items have adequate reliability and validity for

women and men (n=289) from three countries.[10] In addition, the IPAQ is used in large-scale annual surveys because of its superior cost-effectiveness compared to activity monitors.[43]

This study showed that extended sedentary time caused adverse health effects in patients with DKD. According to previous studies, the average sedentary time for Japanese patients was approximately 420 min/day, indicating the longest sedentary time among the surveyed countries.[44] The average sedentary time of the new event onset group was 570 min/day, which was considered relatively long.

A meta-analysis report on sitting time in 54 countries observed that sitting time was responsible for 3.8% of all deaths (433,000/year); therefore, eliminating the sitting time could extend the life expectancy by 0.2 years.[45] Efforts to decrease sedentary time among patients with DKD may be an important treatment strategy. However, modification of lifestyle and behavior patterns is not simple; similarly, there have been reports that sedentary behavior remained unchanged even in strict intervention studies.[46] Rather than aiming to indiscriminately decrease the sedentary time, it is critical that future research simultaneously incorporates a qualitative analysis of the factors causing or contributing to the sedentary behavior (e.g., whether the subject is capable of moving or wants to move but could not). Reports of sedentary time among CKD patients have shown that increased physical activity is more important than decreased sedentary time in reducing CKD risk among male patients[47] and that replacing sitting with a 2

minute-light walk each hour can reduce the risk of death by approximately 40%.[23] These studies demonstrate the necessity of adopting an approach that involves decreasing the sedentary time and increasing physical activity.

There are several limitations to this study. First, the sample size was limited to a single-center cohort analysis. Second, physical-activity quantification was assessed by specially trained physical therapists using the IPAQ-short questionnaire. However, assessment by IPAQ (subjective data) may not be accurate in elderly patients with mild cognitive impairment. Finally, the disease mechanisms could not be assessed based on the study methods and results obtained. Lipoprotein lipase inactivity due to extended sedentary time may be the underlying mechanism of disease development.[30]

Conclusion

Extended sedentary time increases the risk of new cardiovascular or renal events and/or all-cause death in patients with DKD. These results suggest that decreasing the sedentary time in patients with DKD may reduce cardiovascular events and all-cause death and may postpone HD initiation.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Table 1. Patient characteristics

	Overall (n=173)	No event group (n=139)	New event onset group (n=34)	p-value
Age (years)	71±11	70±11	75±10	0.016[*1]
Male (%)	101 (58)	81 (58)	20 (59)	0.953[3]
BMI (kg/m^2)	25.8±4.4	26.1±4.2	24.7±5.0	0.027[*1]
Diabetes duration (years)	10.0±8.9	8.8±7.5	14.9±11.5	0.005[*2]
Job (%)	52 (30.1)	48 (34.5)	4 (11.8)	0.009[*3]
DKD stage (%)				
I	41 (23.7)	34 (24.5)	7 (20.6)	0.119[*3]
II	96 (55.5)	85 (61.2)	11 (32.4)	0.002[*3]
III	26 (15.0)	17 (12.2)	9 (26.5)	0.026[*3]
IV	8 (4.6)	3 (2.2)	5 (14.7)	0.002[*3]
V	2 (1.2)	0	2 (5.9)	0.004[*3]
Past history (%)				
Stroke	20 (11.6)	17 (12.2)	3 (8.8)	0.578[*3]
CVD	37 (21.4)	22 (15.8)	15 (44.1)	0.001[*4]
Medication (%)				
Insulin injection	40 (23.1)	29 (20.9)	11 (32.4)	0.154[*3]
β-blocker	12 (6.9)	6 (4.3)	6 (17.6)	0.006[*3]
RAS-I	64 (37.0)	47 (33.8)	17 (50.0)	0.190[*3]
Statin	91 (52.6)	73 (52.5)	18 (52.9)	0.965[*3]
SBP (mmHg)	136.3±14.8	136.6±14.1	135±14.8	0.583[*2]

DBP (mmHg)	74.6±11.1	75.4±10.2	71.4±11.0	0.064*2
HbA1c (%)	7.2±1.1	7.2±1.1	7.3±1.0	0.580*2
Hb (mg/dL)	13.5±1.7	13.8±1.4	12.4±2.0	<0.0001*2
TG (mg/dL)	130.1±72.5	132.9±73.2	118.6±66.9	0.304*1
HDL-C (mg/dL)	52.0±13.7	53.3±14.1	46.7±10.0	0.012*1
LDL-C (mg/dL)	94.5±23.0	96.5±22.8	86.7±21.7	0.032*2
eGFR (mL/min/1.73 m^2)	63.3±20.0	65.9±17.7	53.0±24.9	0.002*2
Urinary Alb/Cre ratio	292.7±605.3	210.1±424.0	618.8±1045.6	0.159*1
PA (kcal/week)	1850.4±3041.0	2032.2±3130.3	1107.2±2496.2	0.112*1
Sedentary time (min/day)	460.0±160.7	433.2±146.2	567.4±169.5	<0.0001*1

Data are presented as mean ± standard deviation or as number (%).

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; RAS-I, renin–angiotensin system inhibitor; SBP, systolic blood pressure; TG, triglyceride; Alb/Cre, albumin/creatinine.

*1: Mann–Whitney U test

*2: Student's t test

*3: Chi-squared test

*4: Fisher's exact test

Table 2. Details of new onset events

	New event onset group (n=34)
Event (%)	
Stroke	4 (11.8)
Cerebral hemorrhage	3
Cerebral infarction	1
CVD	20 (58.8)
Heart failure	8
Ischemic heart disease	4
Myocardial infarction	3
Arrhythmia	2
Peripheral arterial disease	3
HD	4 (11.8)
Death	6 (17.6)

CVD, cardiovascular disease; HD, hemodialysis.

Recurrent disease is not included.

Table 3. Hazard ratios for new cardiovascular or renal events and/or all-cause death

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value*[1]	HR	95% CI	p-value*[1]
Age (years)	1.04	1.01–1.08	0.042	1.00	0.96–1.06	0.727
BMI	0.93	0.85–1.01	0.088			
Diabetes duration (years)	1.06	1.03–1.09	<0.0001	1.02	0.98–1.06	0.216
Stroke*[2]	1.44	0.44–4.71	0.547			
CVD*[2]	0.28	.014–0.55	<0.0001	0.64	0.29–1.41	0.264
RAS-I	0.55	0.28–1.08	0.082			
SBP (increase by 10 mmHg)	0.94	0.75–1.19	0.612			
HbA1c level	1.08	0.82–1.42	0.606			
Hb level	0.69	0.58–0.81	<0.0001	0.80	0.64–1.00	0.054
TG (increase by 10 mg/dL)	0.97	0.92–1.02	0.273			
HDL-C (increase by 10 mg/dL)	0.68	0.50–0.92	0.011	0.75	0.53–1.06	0.097
LDL-C (increase by 10 mg/dL)	0.87	0.76–0.99	0.045	0.96	0.82–1.11	0.562
eGFR (decrease by 10 mL/min/1.73 m^2)	1.36	1.14–1.61	<0.0001	1.03	0.80–1.33	0.817
Alb/Cre ratio (increase by 50)	1.03	1.02–1.05	<0.0001	1.01	0.98–1.03	0.570
PA (increase by 100 kcal/day)	0.98	0.96–1.00	0.100			
Sedentary time (increase by 60 min/day)	1.39	1.20–1.61	<0.0001	1.23	1.05–1.45	0.012

Alb/Cre ratio, albumin/creatinine ratio; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; SBP, systolic blood pressure; TG, triglyceride.

*1: Cox regression analyses were performed; variables with $p<0.05$ in the univariate analysis were introduced using the forced entry method in the multivariate analysis.

*2: Stroke and CVD variables were included as part of past medical history.

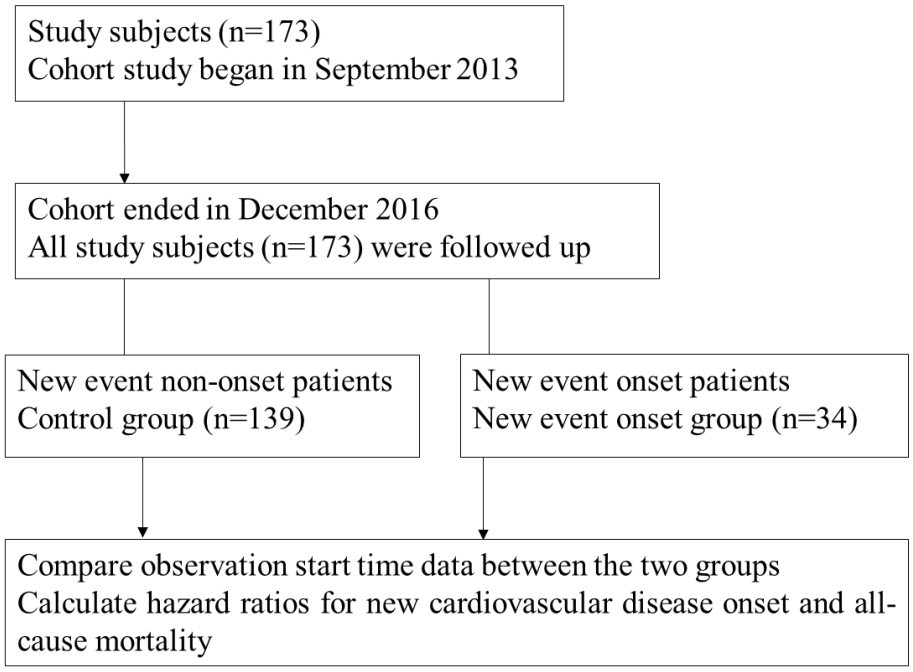

Figure 1. Study flowchart

Subjects included 173 DKD outpatients registered at our hospital who completed the International Physical Activity Questionnaire (IPAQ). This prospective single-center cohort study was performed from September 2013 to December 2016. Following study completion, subjects were classified into two groups: patients with new cardiovascular events that required hospitalization and patients without events (non-onset). Baseline clinical background data were compared between the groups, and hazard ratios were calculated for new cardiovascular disease onset and all-cause mortality.

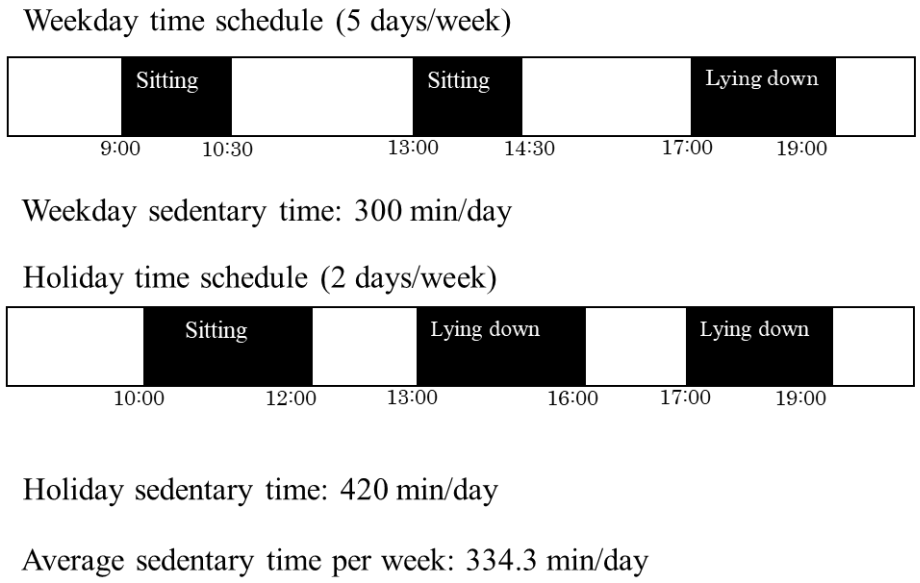

Figure 2. Sedentary time calculation method

Subjects created an all-day time schedule with a physiotherapist. Black bar represents the sedentary period. Sedentary time is calculated as the total number of hours that did not involve physical activity, from the time the subjects woke until when they went to sleep. Driving time is excluded from the sedentary time.

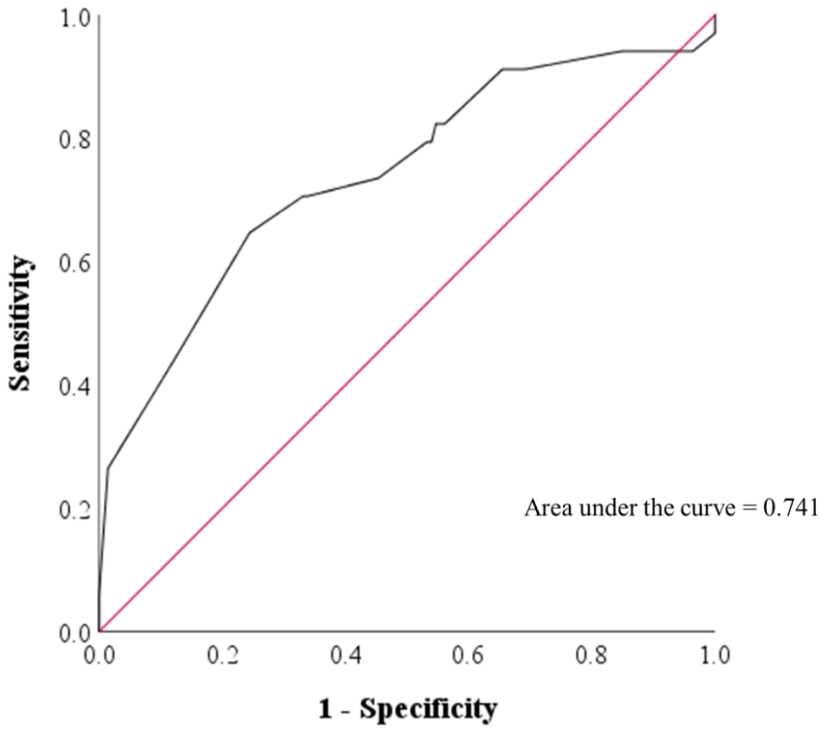

Figure 3. ROC curve for sedentary time on new event onset (myocardial infarction, ischemic heart disease requiring revascularization, heart failure event requiring admission, stroke, and hemodialysis initiation)

Area under the curve (AUC) is 0.741 ($p<0.0001$). Cutoff sedentary time is 525 min/day (sensitivity, 0.71; specificity, 0.67).

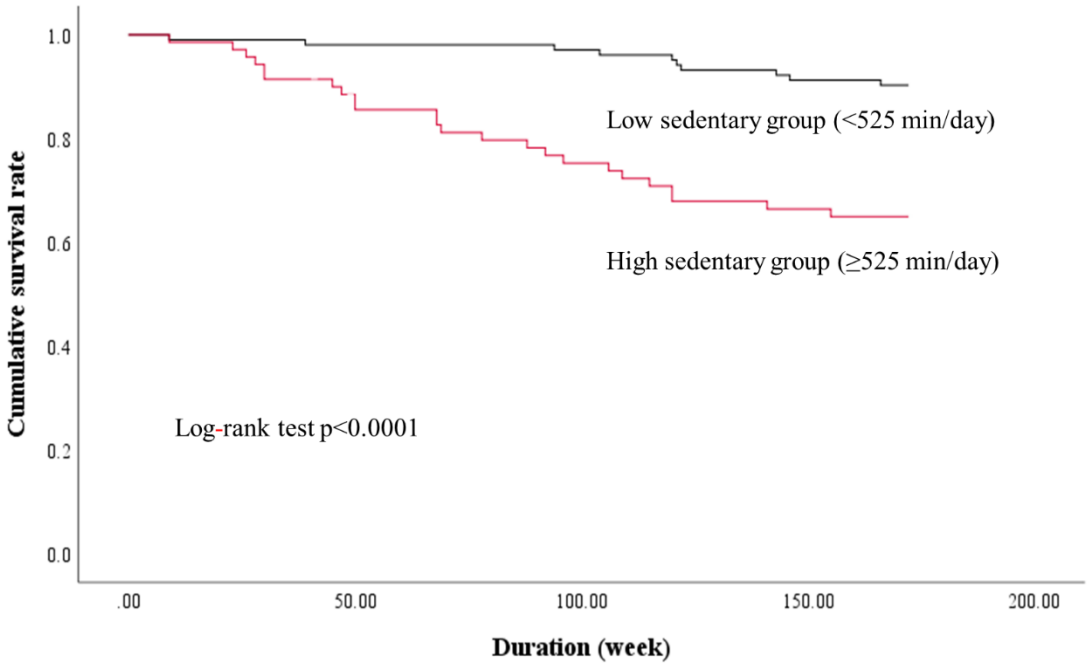

Figure 4. Kaplan–Meier curves for composite cardiovascular or renal events and/or death (myocardial infarction, ischemic heart disease requiring revascularization, heart failure event requiring admission, stroke, and hemodialysis initiation) stratified by baseline sedentary time. The high sedentary group (≥525 min/day) showed significantly lower cumulative survival rate without new events than the low sedentary group (<525 min/day)