

## Relationship between Sedentary Behavior and All-cause Mortality in Japanese Chronic Hemodialysis Patients: A Prospective Cohort Study

Shuhei Hishii<sup>a,b\*</sup>, Nobuyuki Miyatake<sup>a</sup>, Hiroyuki Nishi<sup>c</sup>, Akihiko Katayama<sup>d</sup>,  
Kazuhiro Ujike<sup>c</sup>, Kiichi Koumoto<sup>c</sup>, Hiromi Suzuki<sup>a</sup>, and Hiroo Hashimoto<sup>c</sup>

<sup>a</sup>Department of Hygiene, Faculty of Medicine, Kagawa University, Miki 761-0793, Japan,

<sup>b</sup>Medifit-plus Co., Ltd, Takamatsu 760-0029, Japan, <sup>c</sup>Innoshima General Hospital, Onomichi, Hiroshima 722-2323, Japan,

<sup>d</sup>Faculty of Social Studies, Shikokugakuin University, Zentsuji, Kagawa 765-8505, Japan

We investigated the relationship between sedentary behavior and all-cause mortality in patients undergoing hemodialysis. A total of 71 patients (39 men, 32 women, aged  $72.1 \pm 11.7$  years) were enrolled in this longitudinal study. Their sedentary behavior was measured using a tri-accelerometer that provides relative values per daily wearing time. We classified the sedentary behavior time into 2 groups (under the median: short-sedentary behavior (SB) group; over the median: long-SB group) and compared the groups' clinical parameters. We compared the groups' survival rates by using Kaplan-Meier curves and the log-rank test, and we performed multivariate analyses by a Cox-proportional hazard model to evaluate the relationship between the sedentary behavior and the survival rate. Twenty patients (28.2%) died during the observation period. The survival rate of the short-SB group was significantly higher than that of the long-SB group. Sedentary behavior was thus an important factor for all-cause mortality even after adjusting for confounding factors by a Cox-proportional hazard model. Sedentary behavior is closely linked to all-cause mortality, especially total days and non-hemodialysis days, and reducing sedentary behavior may be beneficial to reduce the all-cause mortality of patients on chronic hemodialysis.

**Key words:** sedentary behavior, hemodialysis, mortality, physical activity

In Japan, both the number of chronic hemodialysis patients and the average age of such patients are increasing (The Japan Society for Dialysis Therapy, <http://docs.jsdt.or.jp/overview/pdf2017/p015.pdf>, accessed on Sep. 15, 2018). Although the survival rate of chronic hemodialysis patients is improving due to recent medical advances (<http://docs.jsdt.or.jp/overview/pdf2014/p029.pdf>, accessed on Sep. 15, 2018), the patients' prognosis is still poor [1,2]. Improvements in the quality of life (QOL) and all-cause mortality are thus considered to be important for

patients on chronic hemodialysis.

Sedentary behavior, defined as physical activity of  $\leq 1.5$  metabolic equivalents (METs) in a reclining or sitting posture [3], is well known to be closely linked to all-cause mortality [4-13]. In patients on chronic dialysis, nutrition [14], physical activity [15-17], physical function [18], muscle mass [19], muscle strength [19,20], and metabolic syndrome [21] have been reported to be associated with all-cause mortality. However, to our knowledge, the relationship between sedentary behavior and all-cause mortality in Japanese hemodialysis patients has not been established. In our

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\*Corresponding author. Phone: +81-87-891-2465; Fax: +81-87-891-2134  
E-mail: s16d726@stu.kagawa-u.ac.jp (S. Hishii)

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prior investigations of patients on chronic hemodialysis, the patients' physical activity was closely associated with their health-related quality of life (HRQOL) [22, 23]. In a cross-sectional study, sedentary behavior was found to be an important factor for HRQOL independent of physical activity [24].

We thus conducted the present longitudinal study to evaluate the relationship between sedentary behavior and all-cause mortality in Japanese patients on chronic hemodialysis, and our analyses revealed that the sedentary behavior in this cohort was closely linked to the patients' all-cause mortality.

## Patients and Methods

**Patients.** Among 183 patients on chronic hemodialysis at our hospital, a total of 71 patients (39 men and 32 women; aged  $72.1 \pm 11.7$  years; duration of hemodialysis,  $88.2 \pm 87.7$  months) voluntarily enrolled in this longitudinal study conducted from 2013 to 2018. The 71 enrolled patients met the following criteria: (1) they underwent chronic hemodialysis at Innoshima General Hospital, Onomichi, Japan, between September 2013 and September 2018; (2) they underwent measurements of their physical activity including sedentary behavior using a tri-accelerometer as part of a previous study [24]; and (3) they provided written informed consent to participate in the present study.

Ethical approval for the present study was obtained from the ethical committee at Innoshima General Hospital, Onomichi, Japan (H25-2-27, H26-1-23, H26-12-16, H27-12-25, H28-12-9, and H29-12-4).

**Clinical parameters and measurements.** We evaluated the following clinical parameters as described previously [24]: sex; age (years); height (cm); body weight (dry weight) (kg); duration of hemodialysis (months); body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) (calculated as  $\text{body weight (kg)} / [\text{height (m)}]^2$ ); and the date and reason for dialysis cancellation. We used the patients' clinical records to determine their values of albumin (g/mL), fasting blood glucose (mg/mL), triglyceride (mg/dL), HDL-cholesterol (mg/dL), and hemoglobin (g/dL) as blood sample data, and diabetes mellitus (DM), hypertension, hyperlipidemia, low back pain (*i.e.*, osteoarthritis), and knee pain (*i.e.*, osteoarthritis) as complicating diseases. Details of low back pain and knee pain could not be evaluated.

The patients' physical activity (including sedentary

behavior) was measured using a tri-accelerometer (Active style Pro: HJA-350IT; Omron, Kyoto, Japan) as described previously [24]. We evaluated the patients' sedentary behavior as the relative values (%) per daily wearing time, and based on the results we categorized the patients into two groups: a short-sedentary behavior (SB) group (under the median SB value) and a long-SB group (over the median). We defined the days that the patients underwent hemodialysis treatment as the hemodialysis days, and the other days as the non-hemodialysis days, and we defined "total days" as the sum of hemodialysis days and non-hemodialysis days.

**Statistical analysis.** Data are expressed as the mean  $\pm$  standard deviation (SD). We compared the clinical parameters between the short-SB and long-SB groups by using the unpaired *t*-test and chi-square test, where  $p < 0.05$  was considered to be significant. We obtained Kaplan-Meier curves and used the log-rank test to compare the survival rates of the short- and long-SB groups. We performed a multivariate analysis and Cox-proportional hazards regression analysis to evaluate the relationship between the survival rate and sedentary behavior to adjust for confounding factors. The statistical analyses were performed using JMP 13.0 software (SAS, Cary, NC, USA).

## Results

The clinical profiles of the enrolled 71 patients on chronic hemodialysis are summarized in Table 1. The average age at the first hemodialysis was  $61.6 \pm 14.9$  years. The reason for the hemodialysis was diabetic nephropathy in 22 patients (31.0%). The average duration of the patients' sedentary behavior was  $74.0 \pm 13.6\%$  total days,  $74.7 \pm 14.1\%$  hemodialysis days, and  $73.4 \pm 14.3\%$  non-hemodialysis days (Table 2). A total of 20 patients (28.2%) died during the follow-up period. The causes of death were sudden death ( $n=3$ ), pneumonia ( $n=2$ ), cerebral infarction ( $n=2$ ), heart failure ( $n=2$ ) and others ( $n=11$ ). The average follow-up period was  $3.0 \pm 1.7$  years.

We compared the clinical parameters between the short- and long-SB groups of patients on chronic hemodialysis (Table 3). There were significant differences in the sex, age, height, body weight, duration of hemodialysis, and history of diabetes mellitus between the short-SB and long-SB groups defined based on total

days. When the groups were defined based on the hemodialysis days, there were also significant between-group differences in the sex, age, body weight, and low back pain. When they were defined based on non-hemodialysis days, the sex, age, height, and history of diabetes mellitus in the short-SB group were signifi-

cantly different from those in the long-SB group.

The cumulative survival rate of the 71 patients was 91.6% at 1 year, 79.3% at 3 years and 59.8% at 5 years. The survival rate of the short-SB group was significantly higher than that of the long-SB group by survival analysis (total days,  $p=0.028$ ; hemodialysis days,  $p=0.016$ ; non-hemodialysis days,  $p=0.024$ ). The hazard ratio was 2.83 (95% confidence interval [CI]: 1.11-7.32) for

**Table 1** Clinical characteristics of patients on hemodialysis

|                                      |              |
|--------------------------------------|--------------|
| Women                                | 32 (45.1%)   |
| Age (years)                          | 72.1 ± 11.7  |
| over 65 years                        | 56 (78.9%)   |
| Height (cm)                          | 155.5 ± 9.3  |
| Body weight (dry weight) (kg)        | 53.7 ± 10.7  |
| Body mass index (kg/m <sup>2</sup> ) | 22.1 ± 3.4   |
| Duration of hemodialysis (months)    | 88.2 ± 87.7  |
| <b>Blood sample</b>                  |              |
| Albumin (g/mL)                       | 3.8 ± 0.4    |
| Fasting blood glucose (mg/dL)        | 136.1 ± 46.3 |
| Triglyceride (mg/dL)                 | 111.6 ± 72.3 |
| HDL-cholesterol (mg/dL)              | 55.3 ± 17.2  |
| Hemoglobin (g/dL)                    | 11.1 ± 0.9   |
| <b>Complicating disease</b>          |              |
| Diabetes mellitus                    | 30 (42.2%)   |
| Hypertension                         | 66 (92.9%)   |
| Hyperlipidemia                       | 33 (46.5%)   |
| Low back pain                        | 27 (38.0%)   |
| Knee pain                            | 14 (19.7%)   |

Values are shown as mean ± SD or *n* (%)

**Table 2** Physical activity in patients on hemodialysis

|                              | Mean ± SD   | Minimum | Maximum |
|------------------------------|-------------|---------|---------|
| <b>Total days</b>            |             |         |         |
| SB (%)                       | 74.0 ± 13.6 | 32.2    | 95.4    |
| LPA (%)                      | 24.4 ± 12.6 | 0.1     | 55.6    |
| MVPA (%)                     | 1.8 ± 2.4   | 0.0     | 15.1    |
| <b>Hemodialysis days</b>     |             |         |         |
| SB (%)                       | 74.7 ± 14.1 | 31.4    | 94.2    |
| LPA (%)                      | 23.7 ± 13.1 | 0.1     | 56.3    |
| MVPA (%)                     | 1.8 ± 2.4   | 0.0     | 15.9    |
| <b>Non-hemodialysis days</b> |             |         |         |
| SB (%)                       | 73.4 ± 14.3 | 32.8    | 96.5    |
| LPA (%)                      | 25.0 ± 13.2 | 0.1     | 57.9    |
| MVPA (%)                     | 1.8 ± 2.6   | 0.0     | 14.5    |

SB: Sedentary behavior, ≤ 1.5 Metabolic equivalents (METs)

LPA: Light intensity physical activity, 1.6–2.9 METs

MVPA: Moderate-to-vigorous intensity physical activity, 3.0 METs ≤

**Table 3** Comparison of clinical parameters between short-SB and long-SB in patients on hemodialysis

| Variables                            | Total days      |                |                | Hemodialysis days |                |                | Non-hemodialysis days |                |                |
|--------------------------------------|-----------------|----------------|----------------|-------------------|----------------|----------------|-----------------------|----------------|----------------|
|                                      | Short-SB (n=35) | Long-SB (n=36) | <i>p</i> value | Short-SB (n=35)   | Long-SB (n=36) | <i>p</i> value | Short-SB (n=35)       | Long-SB (n=36) | <i>p</i> value |
| Women (%)                            | 22 (62.9%)      | 10 (27.8%)     | <b>0.003</b>   | 20 (57.1%)        | 12 (33.3%)     | <b>0.044</b>   | 22 (62.9%)            | 10 (27.8%)     | <b>0.003</b>   |
| Age (years)                          | 68.3 ± 1.9      | 75.7 ± 1.9     | <b>0.007</b>   | 69.2 ± 1.9        | 74.8 ± 1.9     | <b>0.042</b>   | 68.3 ± 1.9            | 75.7 ± 1.9     | <b>0.007</b>   |
| Height (cm)                          | 153.1 ± 1.5     | 157.9 ± 1.5    | <b>0.027</b>   | 154.0 ± 1.6       | 157.0 ± 1.5    | 0.164          | 153.2 ± 1.5           | 157.8 ± 1.5    | <b>0.032</b>   |
| Body weight (dry weight) (kg)        | 50.2 ± 1.7      | 57.0 ± 1.7     | <b>0.007</b>   | 50.8 ± 1.8        | 56.4 ± 1.7     | <b>0.027</b>   | 51.9 ± 1.8            | 55.4 ± 1.8     | 0.180          |
| Body mass index (kg/m <sup>2</sup> ) | 21.4 ± 0.6      | 22.8 ± 0.6     | 0.088          | 21.4 ± 0.6        | 22.8 ± 0.6     | 0.093          | 22.0 ± 0.6            | 22.2 ± 0.6     | 0.831          |
| Duration of hemodialysis (months)    | 111.1 ± 14.4    | 65.9 ± 14.2    | <b>0.029</b>   | 99.1 ± 14.8       | 77.6 ± 14.6    | 0.304          | 108.1 ± 14.6          | 68.9 ± 14.3    | 0.059          |
| Albumin (g/mL)                       | 3.8 ± 0.1       | 3.8 ± 0.1      | 0.833          | 3.7 ± 0.1         | 3.8 ± 0.0      | 0.578          | 3.8 ± 0.1             | 3.7 ± 0.1      | 0.241          |
| Fasting blood glucose (mg/dL)        | 126.1 ± 7.7     | 145.9 ± 7.6    | 0.071          | 126.8 ± 7.7       | 145.2 ± 7.6    | 0.094          | 128.9 ± 7.8           | 143.2 ± 7.7    | 0.193          |
| Triglyceride (mg/dL)                 | 100.1 ± 12.2    | 122.8 ± 12.0   | 0.188          | 112.5 ± 12.3      | 110.7 ± 12.1   | 0.917          | 106.2 ± 12.3          | 116.8 ± 12.1   | 0.539          |
| HDL-cholesterol (mg/dL)              | 59.0 ± 2.9      | 51.7 ± 2.8     | 0.075          | 57.0 ± 2.9        | 53.6 ± 2.9     | 0.417          | 58.2 ± 2.9            | 52.4 ± 2.9     | 0.155          |
| Diabetes mellitus                    | 10 (28.6%)      | 20 (55.6%)     | <b>0.021</b>   | 12 (34.3%)        | 18 (50.0%)     | 0.180          | 10 (28.6%)            | 20 (55.6%)     | <b>0.021</b>   |
| Hypertension                         | 31 (88.6%)      | 35 (97.2%)     | 0.154          | 32 (91.4%)        | 34 (94.4%)     | 0.620          | 31 (88.57%)           | 35 (97.2%)     | 0.154          |
| Hyperlipidemia                       | 15 (44.1%)      | 18 (50.0%)     | 0.622          | 16 (47.1%)        | 17 (47.2%)     | 0.989          | 15 (44.1%)            | 18 (50.0%)     | 0.622          |
| Low back pain                        | 12 (35.3%)      | 15 (41.7%)     | 0.584          | 9 (26.5%)         | 18 (50.0%)     | <b>0.043</b>   | 12 (35.3%)            | 15 (41.7%)     | 0.584          |
| Knee pain                            | 7 (20.6%)       | 7 (19.4%)      | 0.905          | 8 (25.5%)         | 6 (16.7%)      | 0.473          | 6 (17.7%)             | 8 (22.2%)      | 0.632          |

SB: Sedentary behavior, ≤ 1.5 Metabolic equivalents (METs)

Bold values indicated statistically significant ( $p < 0.05$ )

Values are shown as the mean ± SD or *n* (%)

Sedentary behavior was classified into two groups (under median: short-SB, over median: long-SB).

the total days, 2.98 (95%CI: 1.21-8.03) for the hemodialysis days, and 2.79 (95%CI: 1.13-7.49) for the non-hemodialysis days (Fig. 1).

We also observed significant differences in the moderate-to-vigorous intensity physical activity (MVPA:  $\geq 3.0$  METs) between the younger patients (<65 years) and the older group ( $\geq 65$  years) only on non-hemodialysis days. There were also significant differences in both sedentary behavior and low-intensity physical activity (LPA: 1.6-2.9 METs) between the diabetic and non-diabetic patients for only the non-hemodialysis days. Finally, using the Cox-proportional hazard model after adjusting for confounding factors including age and history of diabetes mellitus, we observed that the clinical impact of sedentary behavior on the survival rate was notable, excluding adjustments for sex and age in hemodialysis days (Table 4).

## Discussion

This is the first study to investigate the relationship between sedentary behavior evaluated by a tri-accelerometer and all-cause mortality in Japanese patients on chronic hemodialysis, and our analyses demonstrated that sedentary behavior was an important factor for all-cause mortality, especially as measured over total days or non-hemodialysis days.

Concerning the association between sedentary behavior and mortality, too much sitting was reported to be a factor in 3.8% of the all-cause mortality in 54 countries [25]. Another study reported that Japanese people engage in longer sitting times compared to individuals in all other studies examined as measured by the International Physical Activity Questionnaire (IPAQ) [26]. Among Japanese subjects in primary industry, sedentary behavior was reported to be closely associated with mortality [11]. However, there is no prior study

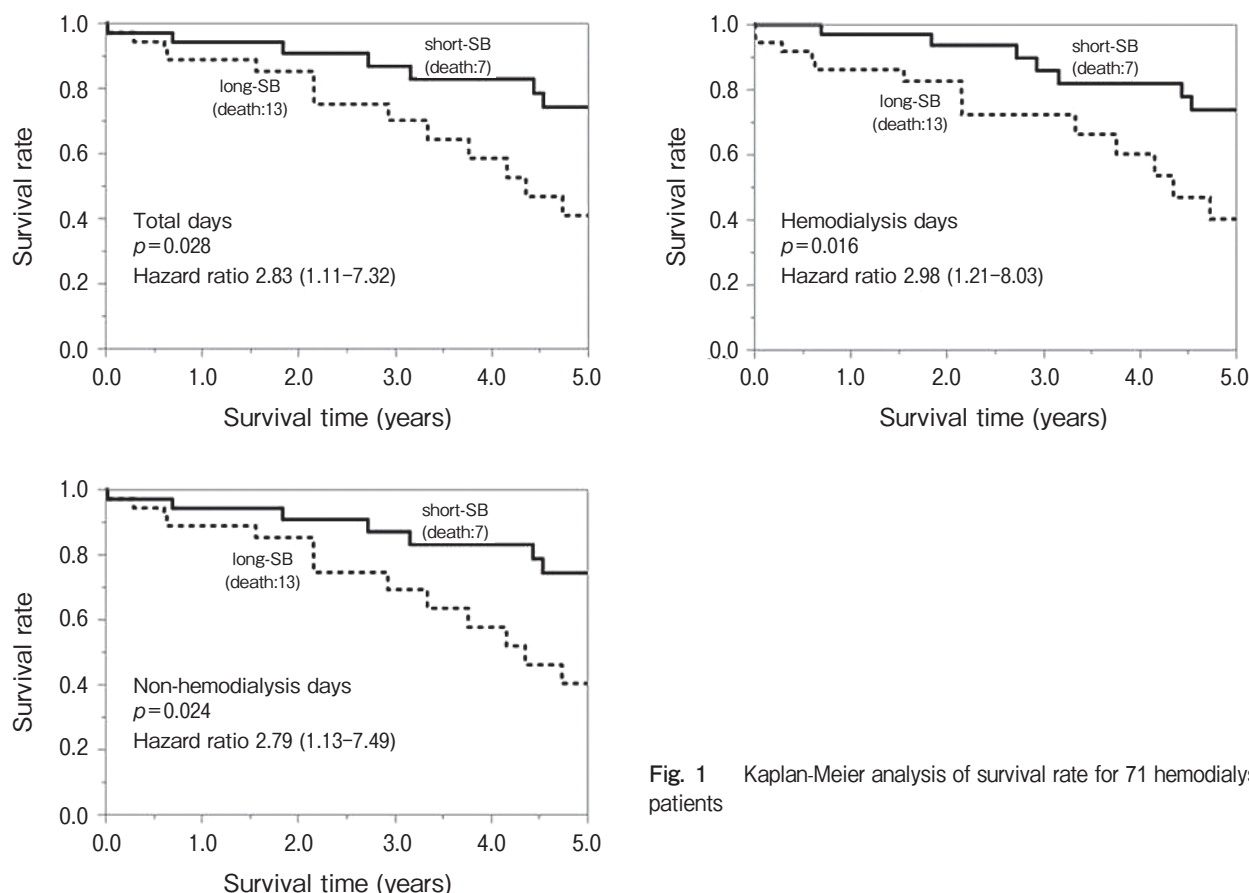


Fig. 1 Kaplan-Meier analysis of survival rate for 71 hemodialysis patients

**Table 4** Multivariate analysis for hemodialysis patients' survival rate (Cox-proportional hazard model)

| Independent variables             | $\beta$ | 95% CI<br>(Lower, Upper) | <i>p</i> value |
|-----------------------------------|---------|--------------------------|----------------|
| <b>Total days</b>                 |         |                          |                |
| SB (%)                            | 0.0427  | 0.0051, 0.0843           | <b>0.025</b>   |
| Sex                               | 0.5967  | -2.3438, -0.2076         | <b>0.017</b>   |
|                                   |         | Goodness of Model Fit    | $\rho=0.001$   |
| SB (%)                            | 0.0439  | 0.0044, 0.0857           | <b>0.029</b>   |
| Age (years)                       | 0.0380  | -0.0060, 0.0088          | 0.093          |
|                                   |         | Goodness of Model Fit    | $\rho=0.004$   |
| SB (%)                            | -0.0001 | 0.0157, 0.0929           | <b>0.005</b>   |
| Duration of hemodialysis (months) | 0.0531  | -0.0053, 0.0045          | 0.976          |
|                                   |         | Goodness of Model Fit    | $\rho=0.018$   |
| SB (%)                            | 0.0490  | 0.0105, 0.0896           | <b>0.012</b>   |
| Albumin (g/mL)                    | -0.7619 | -2.0691, 0.5182          | 0.250          |
|                                   |         | Goodness of Model Fit    | $\rho=0.009$   |
| SB (%)                            | 0.0500  | 0.0106, 0.0921           | <b>0.012</b>   |
| History of diabetes mellitus      | -0.1020 | -0.5852, 0.3685          | 0.670          |
|                                   |         | Goodness of Model Fit    | $\rho=0.016$   |
| <b>Hemodialysis days</b>          |         |                          |                |
| SB (%)                            | 0.0355  | -0.0018, 0.0779          | 0.063          |
| Sex                               | 0.6223  | 0.1329, 1.1950           | <b>0.012</b>   |
|                                   |         | Goodness of Model Fit    | $\rho=0.002$   |
| SB (%)                            | 0.0358  | -0.0023, 0.0784          | 0.066          |
| Age (years)                       | 0.0424  | -0.0013, 0.0922          | 0.058          |
|                                   |         | Goodness of Model Fit    | $\rho=0.009$   |
| SB (%)                            | 0.0454  | 0.0078, 0.0868           | <b>0.017</b>   |
| Duration of hemodialysis (months) | -0.0010 | -0.0053, 0.0045          | 0.974          |
|                                   |         | Goodness of Model Fit    | $\rho=0.052$   |
| SB (%)                            | 0.0407  | 0.0030, 0.0826           | <b>0.034</b>   |
| Albumin (g/mL)                    | -0.8422 | -2.1141, 0.4004          | 0.189          |
|                                   |         | Goodness of Model Fit    | $\rho=0.022$   |
| SB (%)                            | 0.0408  | 0.0028, 0.0836           | <b>0.035</b>   |
| History of diabetes mellitus      | -0.1764 | -0.6503, 0.2859          | 0.453          |
|                                   |         | Goodness of Model Fit    | $\rho=0.040$   |
| <b>Non-hemodialysis days</b>      |         |                          |                |
| SB (%)                            | 0.0430  | 0.0069, 0.0833           | <b>0.018</b>   |
| Sex                               | 0.5871  | 0.0915, 1.1642           | <b>0.019</b>   |
|                                   |         | Goodness of Model Fit    | $\rho=0.001$   |
| SB (%)                            | 0.0450  | 0.0068, 0.0850           | <b>0.021</b>   |
| Age (years)                       | 0.0362  | -0.0075, 0.0861          | 0.107          |
|                                   |         | Goodness of Model Fit    | $\rho=0.003$   |
| SB (%)                            | 0.0536  | 0.0175, 0.0918           | <b>0.003</b>   |
| Duration of hemodialysis (months) | -0.0001 | -0.0054, 0.0045          | 0.971          |
|                                   |         | Goodness of Model Fit    | $\rho=0.012$   |
| SB (%)                            | 0.0500  | 0.0128, 0.0890           | <b>0.008</b>   |
| Albumin (g/mL)                    | -0.7460 | -2.0800, 0.5647          | 0.271          |
|                                   |         | Goodness of Model Fit    | $\rho=0.006$   |
| SB (%)                            | 0.0516  | 0.0130, 0.0922           | <b>0.008</b>   |
| History of diabetes mellitus      | -0.0679 | -0.5553, 0.4066          | 0.779          |
|                                   |         | Goodness of Model Fit    | $\rho=0.011$   |

CI, Confidence interval; SB, Sedentary behavior,  $\leq 1.5$  Metabolic equivalents (METs). Bold values indicate statistically significant ( $p < 0.05$ ).



reporting the relationship between sedentary behavior and mortality in Japanese patients on chronic hemodialysis. Our earlier cross-sectional study revealed a significant relationship between sedentary behavior and HRQOL after adjusting for age, sex, duration of hemodialysis, and history of diabetes mellitus [24].

Concerning the relationship between sedentary behavior and all-cause mortality, there are reports that muscle weakness is strongly associated with an increased mortality risk [19, 20]. A study using electromyography showed no activity of the quadriceps muscle while the subjects were seated [26], and other reports showed that sedentary behavior had a negative effect on lipid metabolism [27, 28] and insulin sensitivity [29]. Moreover, sedentary behavior is reported to be associated with cardiovascular disease [30, 31]. These multiple factors of sedentary behavior may contribute to the increase in all-cause mortality observed in several studies.

The effects of exercise on patients with chronic kidney disease have been described previously [32], and renal rehabilitations such as exercise intervention improved the life-prognosis of patients undergoing hemodialysis [33, 34]. Renal rehabilitation is thus recommended as an effective means to improve the life prognosis in patients undergoing hemodialysis (Japanese Society of Renal Rehabilitation, <https://jsrr.jimdo.com/> accessed March 8, 2019). Most dialysis patients are elderly, and their physical activity level is low [24, 35-37]. It can be difficult to increase the physical activity of patients on chronic hemodialysis. Although in the present study there was no significant relationship between sedentary behavior and all-cause mortality after adjusting for sex and age for the patients' hemodialysis days, a reduction of sedentary behavior especially on non-hemodialysis days may improve the all-cause mortality of patients on chronic hemodialysis in clinical practice. The lying down for approximately 4-hr that is required on hemodialysis days may affect the relationship between sedentary behavior and the all-cause mortality on hemodialysis days.

Our study has several potential limitations. The sample size was small ( $n = 71$ ) and the investigation was conducted at only one hospital because of the difficulty evaluating of the physical activity of chronic hemodialysis patients [38]. In addition, the patients' sedentary behavior on their hemodialysis days might not have been accurately evaluated due to the approximately 4-hr

period of lying down during the hemodialysis. Finally, we assessed sedentary behavior on only 2-3 hemodialysis days for each patient.

These results suggest that reducing sedentary behavior, especially on patients' non-hemodialysis days, may reduce the all-cause mortality in clinical practice. Further studies using larger samples and including multiple hospitals and prospective intervention studies to improve sedentary behavior are needed for Japanese patients on chronic hemodialysis.

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