Lifestyle Behaviors and Clinical Outcomes in Idiopathic Pulmonary Fibrosis

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Keywords

Physical activity · Exercise capacity · Mortality · Exacerbations

Abstract

Background: Lifestyle behaviors are not well-characterized in idiopathic pulmonary fibrosis (IPF). **Objectives:** To assess the association between lifestyle behaviors and clinical outcomes in patients with IPF. **Methods:** A total of 34 IPF patients (median age 68 years) were assessed for daily sitting and weekly walking times using the International Physical Activity Questionnaire by in-person interview at baseline, and they were followed up for up to 40 months. Cox proportional hazard analysis was conducted for cardiorespiratory-related hospitalizations and mortality as outcomes. **Results:** Fifty percent of all patients were hospitalized, and 32% died during the follow-up period. Sitting and walking times were associated with hospitalizations and mortality in IPF. Compared to patients who reported a sitting time of <5 h/day, patients who sat 5 to <10 and ≥10 h/day experienced an increased risk of 2.4 and 5.8 (p trend = 0.036) for hospitalization and of 4.6 and 21.2 (p trend = 0.018) for mortality, respectively. Compared to patients walking <100 min/week, patients with a walking time of 100 to <150 and ≥150 min/

week were associated with a 49 and 74% reduced risk for hospitalizations (p trend = 0.022) and a 62 and 86% reduced risk for mortality (p trend = 0.018), respectively. The risk for mortality was further reduced with a combination of shorter sitting and extended walking times. **Conclusions:** Shorter daily sitting and longer weekly walking times were associated with reduced hospitalization and mortality risks in patients with IPF. These findings suggest a clinical importance of assessing lifestyle behaviors in a comprehensive evaluation and prognostication of IPF patients. The results underscore potential clinical benefits of reducing sedentary behaviors among IPF patients; however, this warrants further investigation.

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Introduction

Sitting and walking, common human behaviors, have been found to be associated with clinical outcomes [1–4]. Population-based studies show that over half of the average individual's waking hours involve sedentary activities – mainly prolonged sitting, such as watching televi-

Trial registration: Clinicaltrials.gov ID: NCT01499745.

sion and using the computer [5]. The importance of physical activity and the risk of sedentary behaviors were underscored by the World Health Organization in 2010, identifying physical inactivity as the 4th leading risk factor for global mortality [4]. Prolonged sitting time has also recently been acknowledged as an independent risk factor for an increased incidence rate of many chronic diseases, hospitalizations, and mortality [2, 3]. These observations have been confirmed among chronic respiratory disease patients, where physical inactivity and sedentary behaviors have been associated with poorer outcomes, including higher mortality risk [6, 7]. However, physical inactivity and sedentary behaviors have not been extensively studied in patients with idiopathic pulmonary fibrosis (IPF). The few available data demonstrate that inactivity and sedentary lifestyle were associated with more severe disease conditions and poorer survival in these patients [8–11].

IPF is a chronic, progressive interstitial lung disease (ILD) presenting substantial morbidity, mortality, and poor prognosis with a median survival of 2–5 years from the time of diagnosis [12–14]. IPF patients tend to be more sedentary and less physically active compared to age-matched healthy individuals [9, 14, 15]. Nevertheless, the current guidelines for IPF do not consider lifestyle behaviors, such as inactivity and prolonged sitting time, as prognostic risk factors [12]; thus, these are rarely assessed in clinical practice. Assessing and treating sedentary behaviors are potentially clinically significant for IPF, especially for many patients experiencing severe signs and symptoms during exercise and struggling to meet the physical activity guidelines [16]. Since, sedentary behaviors were suggested as major risk factors for adverse events among the general population [2–4, 17], exploring the prognostic role of these among patients with IPF seems to be clinically important for prevention and may enhance the prognostication of IPF patients. The aim of the current study was to assess the association between daily sitting and weekly walking times with hospitalizations and mortality in patients with IPF.

Methods

Subjects and Setting

This observational prospective study was conducted at Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel, in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the hospital and registered in clinicaltrials.gov (NCT01499745). Written informed consent was obtained from each patient prior to participation. Patients were included if diagnosed with IPF according to the accepted clinical-

radiological criteria of the American Thoracic Society/European Respiratory Society (ATS/ERS) and if they had been clinically stable during the previous 3–6 months [12]. Exclusion criteria were: severe comorbid illnesses, unstable cardiac disease, and any neurological or orthopedic contraindications for exercise testing. The current study was a secondary analysis of our exercise rehabilitation study [18].

Power analysis using a difference in the 6-min walk distance (6MWD) revealed that 30 patients had to be included in this study, with an additional 10% to compensate for expected dropouts as reported in a previous ILD training study [19]. Thirty-eight IPF patients treated at the Pulmonary Institute were screened for eligibility, and 34 patients were recruited in a consecutive manner between January and December 2012. In the current study, the patients' baseline data were used to determine the prognostic value of lifestyle behaviors for hospitalizations and mortality. We have previously reported that at 30-months' and at 40-months' follow-up, group allocation did not affect survival in this group of patients; however, the sample size was underpowered to detect significant changes [20, 21]. All patients were assessed as follows.

Sitting and Walking Time Assessment

The self-report, 7-day, short-form International Physical Activity Questionnaire (IPAQ) was used for all patients [22, 23]. Each patient underwent an in-person interview by a well-trained researcher specializing in physical activity. The IPAQ was used for the evaluation of sitting and walking times based on the patients' self-report to specific questions on weekly walking time and average daily sitting time [23, 24]. During the interview, these questions were explained and understanding was verified. We have previously reported on the association between total physical activity and mortality in IPF [25]. The current study addressed the specific sitting and walking components in association with hospitalizations and mortality, data that are original and have not been reported elsewhere.

Pulmonary Function, Cardiopulmonary Exercise Testing, 6MWD, and Body Fat Percentage

Pulmonary function tests were performed according to standard techniques recommended by the ATS/ERS guidelines (nSPIRE, Zan 530, Oberthulba, Germany) [26–28] and were presented as percent of predicted (% predicted) values of the European Community for Coal and Steel [29]. Cardiopulmonary exercise test was performed according to established guidelines on an electromagnetically braked cycle ergo-meter (Ergoline- 800S) using breath-by-breath respiratory gas exchange (nSPIRE, ZAN 600, Oberthulba, Germany) [30–33]. The 6-min walk test was conducted according to the ATS guidelines in a 35-m corridor at the pulmonary unit within the hospital [34]. Body fat percentage was assessed using Lange skin-fold caliper (Beta technology, Santra Cruz, CA, USA) on 4 anatomical sites (biceps, triceps, suprailiac, and subscapular) as previously proposed and validated by Durnin and Womersley [35]. A detailed description of these procedures can be found in our previous reports [18, 20, 36].

Hospitalizations and Mortality Ascertainment

The hospital's computed medical records system was used for capturing cardiorespiratory-related hospitalizations and all-cause death as outcomes. The records were carefully reviewed by a qualified research coordinator who was otherwise blinded to all test

results and other study information. The vital status of each patient was ascertained as of March 2015. Patients were considered as censored if they were free from events at the end of follow-up.

Statistical Analysis

The statistical analyses were conducted using SPSS v.23 software (IBM, Chicago, IL, USA). The significance level was set at $p < 0.05$. Demographics, clinical and physiological data of the participants are presented as median (range). Categorical variables are presented in absolute values (%) of the group. Cox proportional hazard models were analyzed in age-adjusted and multivariate models, adjusted for age, FVC %predicted, and DLCO %predicted for cardiorespiratory hospitalizations and mortality outcomes. Kaplan-Meier curves were constructed for sitting and walking times with mortality and hospitalizations outcomes.

Cutoff points <5 , 5 to <10 , and ≥ 10 h/day were used for sitting times, and cutoff points <100 , 100 to <150 , and ≥ 150 min/week were used for walking times [2, 3]. Patients who underwent lung transplants were considered as fatalities in the statistical analysis, as has been previously reported [37, 38]. An exploratory analysis using Spearman's correlation coefficient was performed for sitting and walking times with 6MWD, peak oxygen consumption (VO_2 peak), and body fat percentage [39].

Results

Demographics and general characteristics data are presented in Table 1. Nine percent of the patients were using pirfenidone at baseline, while 24% used the drug during the follow-up period. There were no other changes in IPF medications during the study period.

Median sitting and walking times were 8.5 h/day (2–15) and 110 min/week (0–630). During a median follow-up of 34.9 (5.2–40) months, 17 (50%) cardiorespiratory hospitalizations and 11 (32.4%) deaths occurred. Two patients who were at end-stage IPF underwent lung transplantation, and were considered as fatalities in the analysis. In an age-adjusted model, sitting and walking times were associated with hospitalizations and mortality in IPF. Compared to patients who reported a sitting time <5 h/day, patients who sat 5 to <10 and ≥ 10 h/day experienced an increased risk of 2.4 (95% confidence interval [CI] [1.1–5.5]) and 5.8 (95% CI [2.2–8.4]; p trend = 0.036) for hospitalization and 4.6 (95% CI [1.3–16.3]) and 21.2 (95% CI [4.1–32.6]; p trend = 0.018) for mortality, respectively. Compared to patients who walked <100 min/week, walking times of 100 to <150 and ≥ 150 min/week were associated with a 49% (95% CI [0.28–0.91]) and a 74% (95% CI [0.1–0.64]; p trend = 0.022) reduced risk for hospitalizations and a 62% (95% CI [0.16–0.88]) and a 86% (95% CI [0.03–0.53]; p trend = 0.018) reduced risk for mortality, respectively (Table 2).

Table 1. Baseline demographic characteristics and variables of the study population ($n = 34$)

Age, years	68 [50–81]
Male/Female	22 (65)/12 (35)
Body mass index	29 [22–37]
Time since diagnosis, years	1 [0.1–15]
Patients with smoking history	20 (59)
Pack/year	27 [0–112]
Supplemental oxygen users	
Rest	4 (12)
Exertion	9 (26)
Co-morbidities	
Pulmonary hypertension according to echocardiography	13 (38)
Coronary arterial disease	14 (41)
Systemic hypertension	24 (71)
Chronic obstructive pulmonary disease to emphysema	8 (24)
Type 2 diabetes	13 (38)
Osteoporosis	5 (15)
Medications	
Corticosteroids	23 (68)
Pirfenidone	3 (9)
Beta blockers	13 (38)
Modified Medical Research Council – dyspnea scale (0–4)	
0	1 (3)
1	14 (41)
2	8 (24)
3	10 (29)
4	1 (3)
Pulmonary function	
FVC, % predicted	68 [37–109]
FEV ₁ , % predicted	70 [35–124]
TLC, % predicted	64 [35–99]
DLCO, % predicted	50 [23–91]
Lifestyle factors and exercise capacity	
Sitting time, h/day	8.5 [2–15]
Walking time, min/week	110 [0–630]
6MWD, m	505 [130–749]

Values are presented as median [range] or number (%). FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; DLCO, diffusion capacity for carbon monoxide; TLC, total lung capacity; 6MWD, 6-min walking distance.

In the multivariate models, no significant associations were found between walking and sitting times with mortality and hospitalizations. Kaplan-Meier curves confirmed the association between lesser sitting time, extended walking time, and reduced hospitalizations and mortality rates (Fig. 1, 2). The risk for mortality was further reduced when lesser sitting and longer walking times

Fig. 1. Cumulative hazard and survival curves of sitting time in idiopathic pulmonary fibrosis patients. **a** Risk for hospitalization. **b** Survival probability.

Fig. 2. Cumulative hazard and survival curves of walking time in idiopathic pulmonary fibrosis patients. **a** Risk for hospitalization. **b** Survival probability.

Table 2. Age-adjusted Cox hazard ratios in patients with idiopathic pulmonary fibrosis

	HR (95% CI)	
	mortality	hospitalizations
<i>Sitting time</i>		
<5 h/day	1 (Reference)	1 (Reference)
5 to <10 h/day	4.6 (1.3–16.3)	2.4 (1.1–5.5)
≥10 h/day	21.2 (4.1–32.6)	5.8 (2.2–8.4)
<i>p</i> trend	0.018	0.036
<i>Walking time</i>		
<100 min/week	1 (Reference)	1 (Reference)
100 to <150 min/week	0.38 (0.16–0.88)	0.51 (0.28–0.91)
≥150 min/week	0.14 (0.03–0.53)	0.26 (0.1–0.64)
<i>p</i> trend	0.024	0.022

HR, hazard ratio; CI, confidence interval.

were combined (Fig. 3). Sitting and walking times were significantly correlated with each other and with 6MWD, VO_2 peak, and body fat percentage (Table 3).

Discussion

The current study sought to evaluate the association between lifestyle behaviors and clinical outcomes among patients with IPF. The results demonstrated that a shorter daily sitting time and a longer weekly walking time were associated with a reduced risk for hospitalization and mortality in the age-adjusted model (Fig. 1, 2). However, after further adjusting for FVC and DLCO, the models were no longer significant, probably due to the small sample size and low number of death cases for the multivariate model [40–42]. The combination of shorter sitting and extended walking times showed an additional reduced risk for mortality (Fig. 3), which was also sup-

ported by a significant correlation between both variables (Table 3). Moreover, sitting and walking times were correlated with established prognostic markers (Table 3) that strengthen their prognostic value [12, 32, 34, 43–45]. These data emphasize the utility and valuable role of assessing lifestyle behaviors in a comprehensive risk stratification setting to enhance prognostication of IPF patients. The findings underscore the potential clinical benefits of decreasing sitting time and increasing walking time for reducing the risk of hospitalizations and mortality in IPF, a topic that should be explored more extensively in future studies.

The results of the current study provide novel evidence with respect to the association between lifestyle behaviors and adverse events in IPF. This study is the first to demonstrate an association between daily sitting time, weekly walking time, and risk of hospitalizations and mortality in patients with IPF. The findings are consistent with established data on the association between sitting time, physical activity, and incidence of chronic diseases and mortality in the general population [2, 3, 46]. Our observations also support previous studies of lifestyle behaviors and clinical outcomes in chronic obstructive pulmonary disease and patients with IPF [9–11, 47, 48].

In this regard, Wallaert et al. [9] and Leuchte et al. [11] demonstrated among IPF patients a reduced mortality risk with a higher number of daily steps taken and with a self-report of higher daily activity, respectively [9, 11]. Similarly, our group previously reported better survival in individuals with moderate and high compared to low physical activity levels among IPF patients [25]. While, Atkins et al. [10] found only a trend towards an association between sedentary behaviors and mortality at 1 and 2 years' follow-up in IPF patients. Taken together, the current and previous studies suggest active lifestyle and reduced sedentary behaviors have a potential prognostic value for patients with IPF, and future large prospective cohorts should address these using both objective and subjective measures.

Possible mechanistic explanations can be related to the fact that physical inactivity and sedentary lifestyle are well-established all-cause, cardiovascular, and respiratory mortality risk factors [2–4, 7, 48, 49]. Regular engagement in physical activity and reduced sedentary behaviors were reported as beneficial for decreasing the incidence rate of many health conditions and slowing the progression of chronic diseases [3, 4, 50]. Recently, the ATS and ERS documented that inactivity among chronic respiratory disease patients is associated with poorer outcomes including higher mortality risk [6]. These reports

Fig. 3. Combined hazard ratios of sitting and walking times in idiopathic pulmonary fibrosis patients. The results demonstrate relative risks and 95% confidence intervals.

Table 3. Spearman's correlations between lifestyle behavioral and physiological variables in patients with idiopathic pulmonary fibrosis

	Sitting time (min/day)		Walking time (min/week)	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
6MWD (m)	–0.36	0.038	0.47	0.005
Body fat (%)	0.56	0.001	–0.38	0.028
VO ₂ peak (mL/kg/min)	–0.37	0.029	0.57	<0.001

The correlations between sitting and walking times was $r = -0.61$ and $p < 0.001$. 6MWD, 6-min walking distance.

were confirmed with findings in IPF patients on the association between low activity and poorer survival [9, 11, 25]. In addition, sitting and walking times, as we observed in the current study, were inversely correlated, providing preliminary evidence of their combined protective benefits against adverse events in IPF (Table 3, Fig. 3). Furthermore, sitting and walking times were also correlated with objective measures of exercise capacity (6MWD and VO₂peak) and body fat percentage (Table 3). The latter parameters are established prognostic markers among the general population as well as in patients with IPF [4, 21, 38, 43–45, 51–54]. It is possible that a higher exercise capacity and a lower body fat percentage may play a dominant role in the ability to be more active and less sedentary. The enhanced cardio-metabolic health and physio-

logical state might provide survival benefits that were mediated by extended walking times and shorter sitting times in patients with IPF. However, this needs to be ascertained in future research.

The strengths of the current study include: the prospective collection of the data, using an established physical activity questionnaire (IPAQ) [22–24, 55], which has been previously utilized among patients with IPF [36, 56]. An additional strength of the study is that sitting and walking times were collected using an in-person interview, a method that possibly overcomes some self-report bias. Walking and sitting times are easily, quickly, and inexpensive to assess, and can be evaluated by nonspecifically trained staff; thus, they have a potential practical implication in clinical and research settings.

Our study also has several limitations. First, we had a relatively small sample size, although the number of participants in our cohort is comparable to previous studies on the prognostic role of physical activity and lifestyle behaviors in IPF [9, 10]. Second, sitting and walking times were collected using a subjective self-report, while accelerometers or other electronical motion devices were not used in the current study. However, self-report of physical activity and sedentary behaviors are well-accepted sensitive tools in epidemiological studies and show good prognostic value [2, 3, 11]. Third, although the results consistent with previous observations [9, 11], approximately two-thirds of the patients were receiving corticosteroids for cough and exacerbation control, which potentially might induce muscle myopathy and affect physical activity levels. However, in ILD and IPF patients, corticosteroids have not been reported as limiting factors

during exercise [57, 58]. Finally, as is the case for all epidemiological studies, the findings provide an association between risk factors and an outcome, cause and effect relationship cannot be drawn.

In summary, the study demonstrated original findings on the association between lifestyle behaviors and adverse events in patients with IPF. In the age-adjusted models, a prolonged daily sitting time and a shorter weekly walking time were associated with increased hospitalizations and mortality risks in IPF, although in the multivariate model, these associations were no longer significant. The results suggest a prognostic utility of assessing lifestyle behaviors and considering sitting and walking times as potential modifiable risk factors in IPF. The study underscores possible clinical benefits of reducing sedentary behaviors for decreasing risk of adverse events in IPF. Further research is warranted to confirm these findings using objective measures of lifestyle behaviors in a large sample size.

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Financial Disclosure and Conflicts of Interest

None of the authors has any conflict of interest to declare. No funding was received for this study.

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