Original Article

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Association between Telomere Length and Idiopathic Pulmonary Fibrosis: A Case-Control Study

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Background: Given the poor survival of patients with idiopathic pulmonary fibrosis (IPF), it is necessary to investigate the effect of telomere length on this disease and on treatments that improve it; therefore, the purpose of the present study was to investigate the relationship between telomere length and IPF.

Materials and Methods: In our case-control study, 144 participants, including 72 IPF patients admitted to Masih Daneshvari Hospital and 72 healthy controls, were selected. Blood tests were done for all subjects. Telomere length was measured using quantitative real-time PCR. The results were analyzed using SPSS version 22 software.

Results: The mean telomere length in the IPF group was 0.94±0.06, which was significantly lower than that of the control group (0.97±0.03) (P<0.001). Also, there was no significant correlation between telomere length with 6-minute walk test (6MWT) (r=-0.126, P=0.296), saturated oxygen (SpO_2) (r=-0.204, P=0.088), transfer factor of the lung for carbon monoxide (TLCO) (r=-0.049, P=0.687), total lung capacity (TLC) (r=-0.028, P=0.819), FEV_1/FVC (r=-0.018, P=0.884), forced vital capacity (FVC) (r=0.022, P=0.858), body mass index (BMI) (r=0.014, P=0.908), and forced expiratory volume in 1 second (FEV_1) (r=0.096, P=0.425).

Conclusion: The results of the present study showed that IPF is an accelerated-aging disease because the telomere length index, which reflects oxidative damage, cellular turnover, and aging, is significantly reduced in these patients compared with healthy individuals of the same age.

Keywords: Idiopathic Pulmonary Fibrosis; Telomere; Telomere Length

INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of disorders with variable causes, clinical manifestations, radiographic patterns, and histological appearances that seriously affect the lung parenchyma. ILDs have more than 100 distinct characteristics (1). IPF is one of the ILD subtypes. IPF is a progressive condition in which normal lung parenchyma is gradually replaced by an abnormal extracellular matrix, resulting in impaired lung function (2). This disease is chronic and irreversible (3-6), with a poor prognosis (7, 8) which mainly affects older adults (9). IPF typically progresses within approximately three years from the time of diagnosis (10, 11). This disease most commonly presents with new-onset symptoms such as shortness of breath, cough, and fatigue (12, 13).

Telomeres are G-rich hexanucleotide repeats (TTAGGG) located at the ends of eukaryotic chromosomes, typically ranging from 4 to 15 kb in length (14). Telomeres maintain chromosomal stability by preventing

chromosome ends from being recognized as double-strand breaks and protecting them from nucleotide loss and degradation (15). DNA polymerase cannot completely replicate chromosomes, leading to telomere shortening with each cell division (16). Since telomeres do not contain genes, a certain amount of shortening can be tolerated in somatic cells, but when this process shortens telomeres to a critical extent, it leads to genomic instability, cellular exhaustion, and aging (17).

Telomerase is a ribonucleoprotein enzyme composed of two main components (TERT and TERC) and is responsible for adding TTAGGG repeat units to the ends of chromosomes (18, 19). This enzyme is typically absent in somatic cells or present only at very low and undetectable levels; however, it is expressed to varying degrees during cellular differentiation in germline cells, stem cells, and cancer cells (20). Telomere length (TL) is a biomarker closely associated with aging (21). Previous observational studies have suggested that shortened TL predicts increased risk and poor prognosis in pulmonary fibrosis (22, 23).

A study demonstrated that TERT or TERC mutations occur in approximately 15% of familial and 2% of sporadic IPF cases. Carriers of these heterozygous variants had significantly shorter telomeres and decreased telomerase activity (24). In a related study, researchers examined 73 probands from the Vanderbilt Familial Pulmonary Fibrosis Registry and reported that six individuals (8%) had heterozygous mutations in TERT or TERC (25).

Idiopathic pulmonary fibrosis (IPF) represents a growing clinical concern due to its increasing incidence. The underlying pathophysiology remains poorly understood, and no definitive therapeutic options are currently available. Furthermore, IPF carries a poor prognosis, with most patients experiencing progressive functional decline and mortality within three to five years of diagnosis. Telomere shortening may contribute to the underlying pathophysiology of IPF, and its investigation could provide valuable insights into both diagnostic approaches and potential therapeutic strategies. Therefore, this study aimed to determine the relationship between telomere length and idiopathic pulmonary fibrosis.

MATERIALS AND METHODS

This case–control study was conducted among patients with idiopathic pulmonary fibrosis who were referred to Masih Daneshvari Hospital. The eligibility criteria were explained to all participants, and written informed consent was obtained before enrollment. The study was initiated following approval by the Ethics Committee of Shahid Beheshti University of Medical Sciences (ethical approval No: IR.SBMU.MSP.REC.1400.579). Based on findings from previous studies, the required sample size was estimated at 144 participants, comprising 72 patients with IPF and 72 healthy controls. The two groups were matched for age, sex, and body weight. The inclusion criteria for the IPF group were referral to Masih Daneshvari Hospital in Tehran; a confirmed diagnosis of IPF based on clinical and radiological findings, high-resolution computed tomography (HRCT), and, when indicated, lung biopsy; and willingness to participate in the study and provision of informed consent. Dissatisfaction with participating in the study was considered an exclusion criterion.

Then all participants from both groups were sent to the laboratory to have their peripheral blood samples taken. All samples were transferred to the laboratory under cold chain conditions. The whole blood sample was divided into 2 to 3 sterile screw-cap tubes under a Class II Biosafety Cabinet and kept in a freezer at -70 °C until nucleic acid extraction. Nucleic acid was extracted from clinical samples using commercial kits according to the manufacturer's instructions. The samples were purified using the Invitek®spin DNA Mini Kit (Germany Co.). The extracted DNA was stored in a freezer at -20°C until use in downstream reactions.

To evaluate the physical condition of the extracted DNA, its quality was determined by amplifying fragments of the human globin gene using the SYBR Green real-time PCR method.

After confirming the quality and determining the concentration of the extracted DNA, telomere length was measured using real-time quantitative PCR (qPCR). The sequence of primers used was as follows:

Tel-1F 5'-CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT-3'

Tel-2R 5'-GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT-3'

After confirming the quality and determining the concentration of the extracted DNA, the target single-copy gene was quantified using real-time quantitative PCR (qPCR). The sequence of primers used was as follows:

Single-1F 36B4F, 5'-CAGCA AGTGGGAAGGTGTAATCC-3

Single-2R 36B4R, 5'-CCCATTCTATCATCAACGGGTACAA-3'

Telomere length was measured by quantitative real-time PCR as described by Cawthon (26).

The telomere repeats copy number (T) to single-gene copy number(S) ratio was calculated using the comparative Ct method.

Positive controls (DNA extracted from a healthy individual) and negative controls (double-distilled water [DDW] plus master mix) were included in each PCR run. PCR amplification was performed using a Bio-Rad real-time PCR system (Bio-Rad Laboratories, USA). Information on telomere length and other characteristics of the study participants was recorded using a standardized checklist. The collected variables included age, sex, height, weight, and body mass index (BMI). Also, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, total lung capacity (TLC), diffusing capacity or transfer factor of the lung for carbon monoxide (TLCO), and oxygen saturation (SpO_2) were evaluated and recorded through spirometry and pulse oximetry.

The normality of the data distribution was assessed using the Kolmogorov–Smirnov test. Based on the results of the normality assessment, Pearson's correlation coefficient was used to evaluate the associations between the variables. A paired sample t-test was used to compare the quantitative variables between the two groups and to investigate the relationship between telomere size and IPF and other variables. Linear regression was used. All statistical tests were performed using SPSS version 22, and a p-value<0.05 was considered significant.

RESULTS

The means of variables in the case group were as follows: age 65.50±10.53, height 162.48±8.54, weight 70.52±11.34, body mass index 26.75±4.64, FEV_1 2.40±0.55, FVC 3.04±0.69, FEV_1/FVC 0.79±0.07, TLC 5.52±1.27, TLCO 7.30±1.12, SpO_2 91.32±2.41, 6MWT 330.0±96.40, T 23.46±2.53, S 25.0±2.65, and telomere/single (T/S) 0.94±0.06. Also, 69.4% (n=50) of the case group and 66.66% (n=48) of the control group were men.

The mean telomere length in the IPF group was 0.94±0.06, which was significantly lower than that of the control group (0.97±0.03) (P<0.001) (Figure 1). The mean telomere lengths were 0.93 ± 0.059 in men and 0.94 ± 0.048 in women, with no statistically significant difference between the two groups (P = 0.863).

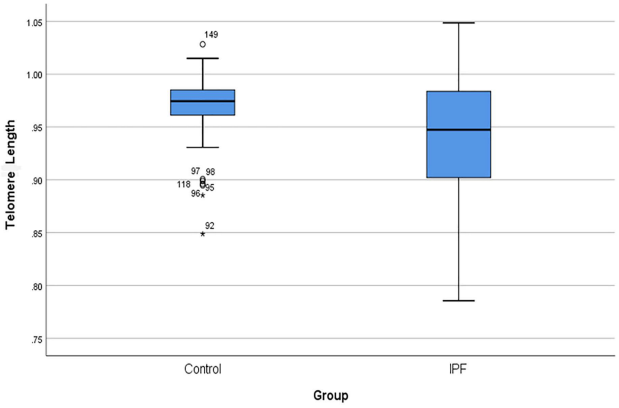

Figure 1. Comparison of the telomere length mean between the two groups

The results of the correlation between telomere length and other numerical variables are shown in Table 1. Based on these results, there was no significant correlation between telomere length with 6MWT (r=-0.126, P=0.296), SpO_2 (r=-0.204, P=0.088), TLCO (r=-0.049, P=0.687), TLC (r=-0.028, P=0.819), FEV_1/FVC (r=-0.018, P=0.884), FVC

(r=0.022, P=0.858), BMI (r=0.014, P=0.908), and FEV_1 (r=-0.096, P=0.425). Also, there was no significant correlation between these variables and telomere length based on the regression model (Table 2).

Table 1. Correlation between telomere length and other numerical variables

Variables	R	P-value
BMI	0.014	0.908
FEV_1	-0.096	0.425
FVC	0.022	0.858
FEV_1/FVC	-0.018	0.884
TLC	-0.028	0.819
TLCO	-0.049	0.687
SpO_2	-0.204	0.088
6MWT	-0.126	0.296

* P-value was calculated using the Pearson correlation coefficient test at 95% CI level

** BMI: body mass index, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, TLC: total lung capacity, TLCO: transfer factor of the lung for carbon monoxide, SpO_2: oxygen saturation, and 6MWT: 6-minute walk test

Table 2. Correlation between telomere length and other numerical variables

Variables	B	P-value	β
BMI	1.148	0.907	3.151
FEV_1	-0.939	0.416	0.391
FVC	-0.178	0.733	0.837
FEV_1/FVC	-0.202	0.308	0.817
TLC	-0.336	0.550	0.715
TLCO	-0.965	0.682	0.381
SpO_2	-8.766	0.079	0.001
6MWT	-215.879	0.285	0.000

* P-value was calculated using the Pearson correlation coefficient test at 95% levels of CI

** BMI: body mass index, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, TLC: total lung capacity, TLCO: transfer factor of the lung for carbon monoxide, SpO_2: oxygen saturation, and 6MWT: 6-minute walk test

DISCUSSION

The present study showed that telomere length was shorter in IPF patients than in non-IPF patients.

Consistent with our study, Sadr et al. (27) reported that telomere length was shorter in patients with chronic obstructive pulmonary disease (COPD) than in smokers and non-smokers, regardless of age, gender, spirometric variables, BMI, and smoking history. In a study on telomere shortening in circulating leukocytes of patients with chronic obstructive pulmonary disease, Savale et al. (28) stated that the ratio of average telomere length in patients with COPD is significantly lower than that of smokers or non-smoker controls. Tsuji et al. (29) investigated cellular aging in the alveolar epithelium of patients with pulmonary emphysema and reported that telomere length in type II alveolar epithelial cells was significantly shorter than that in control subjects. However, contrary to these results, Müller et al. showed that telomere length in cultured parenchymal fibroblasts of patients with emphysema was not different from that of the control group (30).

Zhu et al. investigated the causal relationship between genetically determined leukocyte telomere length (TL) and the risk of chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) in an Asian population. Their Mendelian randomization study, utilizing nine single-nucleotide polymorphisms, found a significant inverse causal association between leukocyte TL and both COPD (P=0.01) and ILD (P=0.001). This suggests that shorter leukocyte telomere length may causally increase the risk of developing these respiratory diseases (31).

In a study investigating telomerase mutations and telomere shortening in Chinese patients with idiopathic pulmonary fibrosis (IPF), Dai et al. (32) identified six novel mutations in telomerase-related genes that had not previously been reported in patients with sporadic IPF. Also, shorter telomeres and mild thrombocytopenia can be related to telomerase mutations and sporadic IPF, which are consistent with the results of the present study. Also, in the same year, Dai et al. (33) investigated the relationship between telomere length and the survival of IPF patients. They found that the telomere length was significantly shorter in IPF patients than in the control group of the same age, and it was also shown that short telomere length is independently associated with very poor survival in IPF patients, which is consistent with the current research. The results of the study by Cronkhite et al. (34), Stuart et al. (35), and Snetselaar et al. (36) were also consistent with the present study.

Snetselaar et al. investigated telomere length (TL) across various interstitial lung diseases (ILDs), finding it significantly shorter in all ILD cases compared to controls. Idiopathic pulmonary fibrosis (IPF) and familial interstitial pneumonia (FIP) with TERT mutations (FIP-TERT) exhibited the shortest telomeres, suggesting an innate telomere-biology defect, while FIP with SFTP mutations (FIP-SFTP) had longer telomeres, indicating acquired shortening. This distinction between innate and acquired telomere shortening highlights the varying roles of telomere biology in ILD (37).

Liu et al. investigated the relationship between peripheral blood leukocyte telomere length (PBL-TL) and the progression of systemic sclerosis-associated interstitial lung disease (SSc-ILD). They observed that SSc patients with ILD had significantly shorter PBL-TL compared to those without ILD. Crucially, their findings demonstrated that shorter PBL-TL was associated with an increased risk for lung function deterioration (38).

Povedano et al. (39) investigated the therapeutic effects of telomerase in mice with pulmonary fibrosis caused by lung damage and short telomeres. It was suggested that telomerase activation may be an effective treatment for pulmonary fibrosis induced or associated with short telomeres. It was stated by Diaz de Leon et al. (40) that the telomere length of TERT mutation carriers decreases in an age-dependent manner and becomes shorter with successive generations of mutation inheritance. Family members lacking TERT mutations have a shorter-than-average mean telomere length, suggesting epigenetic inheritance of shortened telomeres in the absence of inherited TERT mutations. The results of this study showed that a subset of pulmonary fibrosis, such as congenital dyskeratosis, bone marrow failure, and liver disease, represents a "telomeropathy" caused by germline mutations in telomerase and characterized by short telomere length. Family members in kindreds who do not inherit TERT mutations have shorter telomere length than controls, suggesting epigenetic inheritance of a shorter parental telomere length set point.

Stock and Renzoni emphasize that rare genetic mutations in telomere-related genes (TRGs), such as TERT and TERC, lead to extremely short telomeres and are linked to more rapidly progressive fibrotic interstitial lung diseases (ILDs). These mutations promote cellular senescence, genotoxic stress, and impair the regenerative potential of alveolar type II cells. Critically, shorter telomere length (TL) in idiopathic pulmonary fibrosis (IPF) and fibrotic hypersensitivity pneumonitis (HP) is associated with worse survival and an increased risk of harm from immunosuppressive therapies (41). Ruiz et al. elaborate on how telomere shortening (TS) drives cellular dysfunction in lung diseases, specifically highlighting its role in the risk and progression of IPF and COPD. TS promotes cellular senescence and genotoxic stress, impairing immune cell efficacy and fostering an inflammatory microenvironment. In IPF, TS is linked to mutations in telomere maintenance complexes, increased epithelial cell apoptosis, and a worse prognosis for patients with familial pulmonary fibrosis. In COPD, TS is caused by inflammation and oxidative stress from external factors, leading to mitochondrial damage, hyperactivation of the inflammasome, and elevated proinflammatory cytokines (42).

Ito and Barnes (43) stated that telomere length as a biomarker of replicative capacity can be a reflection of biological aging, accelerated aging, and age-related diseases. Telomere shortening has been attributed to the phenomenon of the end replication problem in previous studies. In their study titled "Telomere as a Biomarker of Chronic Oxidative Stress", Houben et al. (44) stated that since one RNA primer remains in each daughter strand, DNA polymerase is not able to fully replicate chromosomes. The last primers are removed by the 5'-3' exonuclease, but the DNA polymerase is not able to fill one of the gaps because there is no 3'-OH available to add a nucleotide to it. As a result, a small region at the end of the chromosome remains uncopied, so that the length of the human somatic cell chromosome is shortened by 20 to 200

bp in each division. Telomere length is shortened to a certain extent and reaches a point called the Hay-Flick limit, and that is the time when cell division is arrested, and the phenomenon of cell senescence or apoptosis may occur. If this shortening and telomere loss continue as a result of mutation, it may reach the critical point where the cells are not able to survive (45).

Jacobs et al. (46) reported that telomere shortening may result in cell-cycle arrest, cellular death, or an increased risk of tumor development and progression.

Tomos et al. studied telomere length (TL) in fibrotic interstitial lung diseases (f-ILDs) with a usual interstitial pneumonia (UIP) pattern and Idiopathic Pulmonary Fibrosis acute exacerbation (IPF-AE). Their research highlighted that IPF-AE patients had significantly shorter TL compared to stable Idiopathic Pulmonary Fibrosis (47). Also, Jang et al. showed that people with short telomeres are at a higher risk of lung cancer, especially small-cell lung cancer (48). Telomere length can be a predictor of replicative capacity. Telomeres also play an essential role in maintaining chromosomal integrity and stability; therefore, progressive telomere shortening is closely associated with repeated cycles of cell proliferation. Telomere length is also considered a predictive marker of aging (49). However, telomere length is also affected by environmental factors other than aging. In this regard, a large difference between the telomere length of monozygotic twins was reported in another study (50).

There were no statistically significant gender-related differences between patients and controls in terms of telomere length. In a study by Sadr et al. (27), telomere length was shorter in both male and female patients with COPD, with no significant difference in telomere length between the two sexes. Although Savale et al. (28) observed a slightly shorter telomere length in men than in women of the healthy controls. However, this difference could be due to the smaller sample size of women in the present study. The present study also showed no relationship between telomere length and BMI in patients or the control group. Consistent with the results of the present study, no relationship between BMI and telomere length was found in the studies by Sadr et al. (27) and Savale et al. (28). In contrast, Valdes et al. (51) and Cui et al. (52) found a relationship between telomere shortening and obesity in women.

Data analysis of our study showed no significant relationship between telomere length and 6-minute walk test (6MWT), SpO_2, TLCO, TLC, FEV_1/FVC, FVC, and FEV_1 parameters. These results were consistent with the studies by Sadr et al. (27) and Savale et al. (28) that reported no relationship between telomere shortening and changes in spirometry variables such as FEV_1, FVC, and FEV_1/FVC. Dressen et al. (53) reported an association between IPF status and telomere length. In the present study, the patients had relatively similar disease severity, which may explain the weak correlation observed between telomere length and spirometric parameters.

CONCLUSION

The findings of the present study suggest that IPF is associated with accelerated biological aging, as the telomere length index—a marker reflecting oxidative damage, cellular turnover, and cellular aging—was significantly lower in patients with IPF than in age-matched healthy individuals.

Conflict of Interest

There is no conflict of interest to declare.

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