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Significant Shortening of Leukocyte Telomere Length in Korean Patients with Bipolar Disorder 1

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Objective: Telomere shortening has been seen in major psychiatric disorders, including major depressive disorder. However, only a few small studies have examined this in bipolar disorder (BD). We compared the telomere length in patients with BD1 or BD2 with that in matched healthy controls.
Methods: We included 215 patients with BD (128 BD1, 87 BD2) and 204 age- and sex-matched healthy controls. Relative telomere length was determined by quantitative polymerase chain reaction. The patients and controls were compared separately for age groups, sex, and BD subgroups (BD1 and BD2).
Results: We found significant telomere shortening in patients with BD1 ($p < 0.001$), but not in patients with BD2. In male patients with BD1, the 30−39 year age group had significant shortening of telomere length than controls ($p = 0.01$). Female patients with BD1 in the 19−29-year age group had significantly shortened telomeres compared to the controls ($p < 0.01$).
Conclusion: Our results suggest a significant reduction in telomere length in BD1. Telomere shortening would be a potential biomarker for BD.

KEY WORDS: Bipolar disorder; Female; Biomarker; Telomere.

INTRODUCTION

In humans, telomeres are composed of multiple copies of the non-coding nucleotide sequence TTAGGG. Telomeres protect chromosome ends against DNA loss and become shorter with each cell division due to incomplete telomere replication [1]. Telomeres can be rebuilt by telomerase by adding small DNA fragments to the lagging DNA strand during mitosis. Telomere length is determined by both innate genetic factors and epigenetic influences [2]. Telomere shortening occurs with repeated cell division and reflects cell aging. It is influenced by many biological process, including exposure to inflammation [3] or oxidative stress, persistently raised stress hormones, and the availability of telomerase [4]. Telomere shortening causes cell damage and malfunction and is associated with many medical conditions, including major psychiatric illnesses such as schizophrenia, bipolar disorder (BD), and major depressive disorder [5,6].

A possible biological mechanism for the association between telomere length and psychiatric illness has been suggested: the regeneration of neural stem and progenitor cells could be reduced by cell death due to telomere shortening [7]. Another hypothesis is that aged immune cells secrete pro-inflammatory cytokines, which cause inflammation and then trigger oxidative stress and telomere shortening [8]. A recent meta-analysis and reviews confirmed that major depressive disorder shows accelerated aging and shortening of telomere length in peripheral blood cells [6].

However, only a few papers have examined BD. Here,

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we report additional evidence of a possible association between BD and telomere length.

METHODS

We enrolled 128 patients with BD1, 87 with BD2, and 204 healthy age- and sex-matched controls with informed consent. The participants were recruited from the psychiatric outpatient departments of Eulji Meical Center and other university hospitals in Seoul, Korea. Each patient was diagnosed by consensus by at least two psychiatrists based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Patients with a traumatic brain injury, intellectual disability, current substance-related disorder, neurocognitive disorder, or psychiatric disorder due to another medical condition were excluded. Through a matching process using a pool of control subjects previously developed by our study group, age- and sex-matched controls were selected for the BD1 and BD2 groups. Relative telomere length (T/S ratio) was determined by quantitative polymerase chain reaction (qPCR) with considering previous study [9]. In brief, the quantification cycle (Ct) of the telomeric region and the Ct of a single-copy gene (*36B4*) were assessed via the telomeric and single-copy gene specific qPCR. To check PCR efficiency, we drew a standard curves for each age group, which were created by serial dilutions of age matched control DNAs. Telomere length assay for all samples were performed in triplicate. Detailed information is provided in the Supplementary Table 1 (available online).

The three groups were compared using an analysis of variance and an analysis of covariance to control age and sex. To adjust for the effects of aging on telomere length, comparisons were done for each age group. This study protocol was approved by the ethics committee of Nowon Eulji Medical Center, Eulji University (IRB# 2016-08-009).

RESULTS

There was a significant difference in telomere length among the BD1, BD2, and control groups ($p < 0.001$). *Post-hoc* analysis found that the BD1 patients had significantly shorter telomeres than the healthy controls, while the BD2 patients did not differ from the controls. There was a significant difference between BD1 and BD2. In a subgroup analysis by sex, both males and females had a significant difference among the three groups ($p = 0.003$ for males, $p < 0.001$ for females). *Post-hoc* analysis found that BD1 patients differed significantly from BD2 patients and healthy controls. The telomere length was shortest in BD1 and longest in the controls (Table 1). In an analysis of age groups, females with BD1 who were aged 19−29 years had the most significant telomere shortening ($p < 0.01$). Although the telomere shortening in males with BD1 who were aged 19−29 years was not significant ($p = 0.09$), it tended to be shorter. Instead, males with BD1 who were aged 30−39 years had significantly shorter telomeres than matched controls ($p = 0.01$). BD2 patients who were aged 19−29 years did not show any significant telomere shortening compared to the healthy controls (Table 2).

DISCUSSION

We found a significant telomere shortening for BD1 as

Table 1. Comparison of telomere length among the BD1, BD2, and control groups

Sex	Diagnosis	Number	Mean	SD	F (adjusted F)	p value (adjusted p value)
Total	BD1	128	0.677	0.836	9.821 (13.55)[a]	< 0.001 (< 0.001)[a]
	BD2	87	1.026	0.945		
	Control	204	1.029	0.573		
Male	BD1	68	0.847	1.005	1.88 (6.07)[b]	0.155 (0.003)[b]
	BD2	40	1.179	1.147		
	Control	101	0.994	0.59		
Female	BD1	60	0.483	0.536	18.301 (18.10)[b]	< 0.001 (< 0.001)[b]
	BD2	47	0.896	0.719		
	Control	103	1.063	0.558		

BD1, bipolar disorder 1; BD2, bipolar disorder 2; SD, standard deviation.
[a]Adjusted by sex and age. [b]Adjusted by age.

Table 2. Comparison of telomere length between patients and controls according to age

Diagnosis	Sex	Age group (yr)	Number	Control	Patient	*p* value
BD1	Male	Total	68	0.94 ± 0.54	0.85 ± 1.00	0.01
		19−29	29	0.56 ± 0.22	0.44 ± 0.38	0.09
		30−39	18	1.07 ± 0.71	0.73 ± 0.38	0.01
		40−49	13	1.17 ± 0.43	0.98 ± 0.88	0.19
		> 50	8	1.40 ± 0.21	2.41 ± 1.96	0.21
BD1	Female	Total	60	1.18 ± 0.65	0.48 ± 0.54	< 0.01
		19−29	42	1.22 ± 0.70	0.37 ± 0.43	< 0.01
		30−39	4	0.62 ± 0.24	0.32 ± 0.15	0.15
		40−49	4	0.99 ± 0.41	0.55 ± 0.12	0.15
		> 50	10	1.30 ± 0.53	1.01 ± 0.80	0.17
BD2	Male	Total	40	1.11 ± 0.67	1.18 ± 1.15	0.43
		19−29	25	0.65 ± 0.24	0.82 ± 0.63	0.94
		30−39	9	1.77 ± 0.47	1.99 ± 1.67	0.63
		40−49	6	1.86 ± 0.55	1.47 ± 1.41	0.36
		> 50	0	NA	NA	NA
BD2	Female	Total	47	0.90 ± 0.33	0.90 ± 0.72	0.53
		19−29	38	0.93 ± 0.32	1.00 ± 0.72	0.62
		30−39	1	1.4	1.93	NA
		40−49	4	0.69 ± 0.23	0.31 ± 0.07	0.02
		> 50	4	0.73 ± 0.37	0.26 ± 0.17	0.04

Values are presented as number only or mean ± standard deviation.
BD1, bipolar disorder 1; BD2, bipolar disorder 2; NA, not available.

a whole as well as both in males and females separately. This result is consistent with a recent meta-analysis, which found a significantly shorter leukocyte telomere in BD [10]. In male group, most subjects were in 19−29 and 30−39 age groups and 30−39 age group showed significant telomere shortening than control group. Female 19−29 age group had most subjects and showed significant difference from control group. No gender difference was found in our study.

An effect of disease on telomere length was observed especially in young subjects, but not older subjects. Similarly, in major depressive disorder, the results were usually negative in elderly patients, probably because there was no control for vascular pathologies or late-life medical conditions [11]. We did not include those information, either. In another study, contrary to our results, significant reductions in telomere length were found in both early and late BD [12]. Besides inconsistencies of findings, insufficient and different number of samples in each age group in our study made it difficult to consider the age as a crucial factor in determining leukocyte length in BD. Further studies with enough sample size for the whole range of age and controlling for physical conditions including vascular pathologies are needed.

We could not find significant shortening of leukocyte telomere length in BD2. Contrasting our results, there was a study reported a trend to telomere shortening in BD2 [13]. As the published studies have been relatively small and rarely have differentiated BD1 and BD2, it is difficult to speculate specific reasons why BD1 and BD2 are different in telomere length at this point. Since BD2 has different clinical features from BD1, more studies on this issue would contribute to finding biological difference between BD1 and BD2.

Several studies revealed a wide range of cognitive disturbances during acute mood episodes and significant impairment in declarative memory during remission [14]. BD is thought to be associated with fronto-limbic-subcortical circuit abnormalities, and functional imaging studies suggest that abnormal hippocampus activation related to emotional, attentional, and memory tasks in BD [15]. Hippocampal morphology was associated with telomere length [16,17] and hippocampal volume and delayed recall was positively associated with telomere length. A shorter telomere length reflected a smaller hippocampal volume and more impaired delayed recall [18]. Recently, it is suggested that telomere shortening could represent a mechanism that moderates the proliferative capacity of human hippocampal progenitors, which may subsequently impact on human cognitive function and

psychiatric disorder pathophysiology [19]. However, it is unclear whether telomere shortening is a risk factor or the result of cumulative exposure to disease [20]. For example, Henje Blom *et al.* [21] suggested that shortening of telomere length and reduction of hippocampal volume are already present in early-onset major depressive disorder from a study with adolescent depression patients.

The limitations of this study should be considered when interpreting our results. First, since our data did not include clinical information other than the psychiatric diagnosis, we could not analyze the dose-response relationship for the degree of telomere shortening and severity of BD such as lifetime duration of the mood disorder, duration of a poorly or untreated mood disorder, number of episodes of mood disorder, and treatment response. Second, there are many potential confounders in the interpretation of telomere length. In peripheral blood, leukocyte age varies. Theoretically, this causes varying leukocyte telomere lengths. In addition, methods to measure telomere length are not stable. Third, more variables such as early and recent life adversity, psychological resiliency, lifestyle factors, and latent active viral infection [22-25] other than age, sex can influence leukocyte telomere length. We could not control them in this study. Fourth, we should consider psychiatric comorbidities such as anxiety and substance use disorder [26,27], as well as medical illnesses [28,29]. Heavy alcohol use itself is associated with telomere shortening [30], and psychiatric medications can influence telomere length [31,32]. Since we could not collect other clinical information, we could not analyze the influence of environmental factors, psychiatric and medical comorbidities, or psychiatric treatment.

Here, we have added more evidence of a positive association between BD1 and telomere shortening. Additional studies with more subjects covering all ages and studies that explore the clinical meaning of telomere shortening are necessary.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization, Funding: Soon Ae Kim, Eun-Jeong Joo. Data acquisition and analysis: Yong Min Ahn, Soon Ae Kim. Writing—original draft: Eun-Jeong Joo. Writing—review & editing: Eun-Jeong Joo, Yong Min Ahn, Mira Park, Soon Ae Kim.

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