Telomere Length in Major Psychiatric Disorders: Is There Any Relationship Between Telomere Length and Oxidative Stress?

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Abbreviations

ALT	Alternative lengthening of telomeres
$ApoE_2$	Apolipoprotein E_2
BD	Bipolar disorder
BD II	Bipolar disorder type II
BD I	Bipolar disorder type I
BMI	Body mass index
CHD	Coronary heart disease
COPD	Chronic obstructive pulmonary disease
DST	Dexamethasone
ECT	Electroconvulsive therapy
ELISA	Enzyme-linked immunosorbent assay
GST mu	Glutathione S-transferase
HAM-A	Hamilton anxiety score
HAM-D	Hamilton depression score
MAOA	Monoamine oxidase A
MD	Major depression
NYHA	New York Heart Association
PCR	Polymerase chain reaction
PCR-RFLP	PCR – restriction fragment length polymorphism

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PTSD	Posttraumatic stress disorder
ROS	Reactive oxygen species
STMN1	Encoding stathmin
SZ	Schizophrenia
TERT	Encoding the catalytic subunit of the telomerase
TL	Telomere length

1 Introduction

Telomeres are located at both ends of each chromosome and are composed of a repetitive DNA sequence (TTAGGG repeats) and associated proteins (shelterin – protein complex). They have a very important vital function for cell biology by preserving the information in their genome. In particular, this consists in protection of the genome from nucleolytic degradation, unnecessary recombination, and interchromosomal fusion (assurance of proper positioning of chromosomes during replication), as well as repair (protection of the chromosome end from being recognized as DNA double-strand breaks by the DNA damage response mechanisms).

During each cell division, a small segment of telomeric DNA is lost leading to the reduction of telomere length (TL). Although this is a normal physiological process, it can result in cell senescence and/or apoptosis when TL reaches a critical limit (Donate and Blasco 2011; Shammas 2011; Martínez and Blasco 2010).

TL can be restored by the enzyme telomerase (ribonucleoprotein reverse transcriptase); however, the majority of cells and tissues (except of stem cells, germ cells, and regenerating tissues) has very low telomerase activities. TL could be maintained by the other alternative mechanism (ALT – alternative lengthening of telomeres) where telomeres use other telomeric DNA as a template for DNA synthesis (Neumann et al. 2013; Muntoni et al. 2009). However, these mechanisms are not efficient at maintaining TL, and consequently telomere erosion occurs with age in numerous somatic tissues. Thus, TL or its shortening could be recognized as a predictive factor of the life span of cells and organisms and the age-related reduction of body's ability to regenerate in response to action of damaging factors (Donate and Blasco 2011; Shammas 2011) and even individual death (Cawthon et al. 2003).

Numerous factors associated with lifestyle, nutrition, and coexistent diseases can predispose to accelerate TL shortening and be responsible for negative effect on individual subject life span and state of health. Among them are lack of exercise, obesity, cigarette smoking, alcohol abuse, exposure to air pollutants, cardiovascular diseases, and diabetes, and these issues have recently been largely reviewed and discussed elsewhere (Donate and Blasco 2011; Paul 2011; Price et al. 2013). On the other hand, plasma levels of vitamin A and D and habitual tea drinking (ingestion of tea polyphenols) were positively associated with TL (Paul 2011). Since venous blood is more easily accessible than most other tissues, majority of these data were derived from cross-sectional studies focused on TL of peripheral blood leukocytes.

Chronic oxidative stress and inflammation are implicated in speeding up the aging process. Numerous studies with cell cultures and animal models proved faster

TL shortening under conditions of oxidative stress. Due to its high content of guanines and inefficient repair of single-strand breaks, telomeric DNA is highly sensitive to damage by reactive oxygen species (Petersen et al. 1998; Oikawa et al. 2001; Oikawa and Kawanishi 1999). Moreover, increased levels of pro-inflammatory cytokines, especially tumor necrosis factor alpha (TNF-α), that are frequently accompanied with oxidative stress can decrease the telomerase activity (Beyne-Rauzy et al. 2004, 2005) and oxidative damage to the bases of telomeric DNA accumulated over the life span of cells (Kawanishi and Oikawa 2004). Therefore, TL could be a biomarker of chronic oxidative stress (Houben et al. 2008).

Systemic and cerebral oxidative stress has been demonstrated in the major psychiatric disorders like schizophrenia (SZ), major depression (MD), and bipolar disorder (BD). Although these issues are discussed elsewhere in this book, it is necessary to mention that patients suffering from SZ, MD, and BD had elevated circulating levels of products deriving from oxidative damage to lipids, proteins, and DNA and decreased plasma antioxidant defense (Kim and Andreazza 2012; Ng et al. 2008; Maes et al. 2011; Yao and Reddy 2011; Bitanihirwe and Woo 2011), and analysis of postmortem obtained brain specimens revealed increased content of oxidative stress markers (Gawryluk et al. 2011a; Michel et al. 2011a; Che et al. 2010; Andreazza et al. 2010; Wang et al. 2009).

Moreover, these groups of patients are prone to diseases associated with aging (e.g., diabetes, cardiovascular diseases) and reveal tendency to have shorter natural life span than the general population. Therefore, researches executed a dozen or so clinical studies (in the vast majority cross-sectional) on blood leukocyte TL in these major psychiatric disorders during the last few years. This chapter will review the results of these studies with special attention to intensity of systemic and brain oxidative stress.

2 Telomere Length in Blood Leukocytes and Brain Samples of Patients with Schizophrenia

Table 1 summarizes the results of cross-sectional studies on TL in patients with SZ. These studies mostly compared TL in DNA isolated from blood leukocytes between SZ patients and matched controls (Kao et al. 2008; Yu et al. 2008; Fernandez-Egea et al. 2009; Mansour et al. 2011). In one of them the additional group of patients with type I bipolar disorder (BD I) was investigated (Mansour et al. 2011). Only one report was based on postmortem brain samples (gray matter of cerebellum) obtained from patients suffering from SZ, BD, MD, and controls where TL was analyzed by quantitative PCR (Zhang et al. 2010). Concerning the TL in blood leukocytes, two reports revealed telomere shortening in SZ subjects (Kao et al. 2008; Fernandez-Egea et al. 2009). One study found this difference limited to SZ patients who were poor responders to the treatment versus healthy matched controls. However, good responders did not differ from controls (Yu et al. 2008).

On the other hand, Mansour et al. on the basis of investigation of relatively large group of subjects (Table 1) did not find any significant differences in the leukocyte TL between SZ group, BD I patients, and controls (Mansour et al. 2011).

Table 1 Cross-sectional studies on telomere length in patients with schizophrenia

Aim of the study	Study description	Main results and [ref]
Do SZ patients have shorter telomeres than unaffected controls?	51 SZ patients, 24 unaffected family members, and 52 unaffected unrelated subjects. TL determined with quantitative PCR in DNA isolated from blood lymphocytes. Analyses were adjusted for age and sex	Patients with SZ had significantly shorter mean TL than controls. Current antipsychotic dose and estimated lifetime antipsychotic dose did not correlate with TL (Kao et al. 2008)
Do SZ patients have shorter TL than controls? Does response to the treatment affect TL in SZ group?	68 SZ patients (34 good responders and 34 poor responders to the treatment) and 76 age-matched healthy controls. DNA isolated from blood and TL measured with Southern blot. Analyses were adjusted for age and sex	Poor responders had shorter TL than good responders and healthy controls. Good responders did not differ from controls (Yu et al. 2008)
Do patients with SZ and other related disorders have shortened TL and increased pulse pressure?	41 subjects with nonaffective psychosis (27 with SZ, 9 schizophreniform disorder, 2 brief psychotic disorder, 2 delusional disorder, 1 psychosis not otherwise specified), 41 demographics-, smoking-, BMI- and resting heart rate-matched control subjects. DNA telomere content (that is highly correlated with TL) was determined in blood leukocytes (DNA hybridization with end-labeled telomere-specific oligonucleotide)	The psychosis group had significantly decreased mean telomere content versus controls. Men and women with nonaffective psychosis had similar telomere content. Pulse pressure was significantly higher in psychosis group than in controls (Fernandez-Egea et al. 2009)
Do SZ and BD I patients have shortened TL? Is TL a mediating factor between inbreeding and increased risk for BD I and SZ?	60 SZ patients, 108 subjects with BD I, and 168 controls. TL determined with quantitative PCR in DNA extracted from blood. The inbreeding coefficient/consanguinity rate estimated from family history data and after genotyping Short Tandem Repeat Polymorphisms among cases and controls. Analyses were adjusted for age and sex	BD I versus controls ($n=114$) and SZ versus controls ($n=60$) – no significant difference in TL. No significant associations between TL and consanguinity estimated with the two methods (Mansour et al. 2011)
Is TL altered in brains of patients with major psychiatric disorders (SZ, BD, and MD)?	DNA extracted from postmortem brain samples (gray matter of cerebellum) of 46 SZ patients, 46 BD, and 15 MD patients and 48 controls for TL determination with quantitative PCR	No difference of TL in the gray matter of cerebellum was noted in SZ, BD, and MD group compared to controls. No differences between psychiatric disorders groups were also found. Age, gender, medication, and drug used had no effect on TL (Zhang et al. 2010)

BD bipolar disorder, *BD I* bipolar disorder type I, *BMI* body mass index, *MD* major depression, *PCR* polymerase chain reaction, *SZ* schizophrenia, *TL* telomere length

In agreement with this report, no difference of TL in the gray matter of cerebellum was noted in SZ, BD, and MD patients compared to controls. Similarly, no differences in brain TL were found between these three groups of psychiatric disorders (Zhang et al. 2010).

In conclusion, studies on the TL in blood leukocytes of SZ patients are not fully conclusive. More studies involving larger patients groups and matched controls are required. Longitudinal studies on telomere shortening in the course of SZ along with the effect of antipsychotic treatment are necessary.

2.1 Discordance Between Telomere Length and Oxidative Stress in Brain Tissue of Patients with Schizophrenia and Other Major Psychiatric Disorders (Bipolar Disorder, Major Depression)

The aforementioned results on TL in brain samples are more than somewhat surprising since numerous studies proved occurrence of oxidative stress in some regions of brain tissue (postmortem samples) in patients with SZ, BD, and MD:

(a) Samples of prefrontal cortex from patients with SZ and BD revealed downregulation of uncoupling protein 2 (involved in controlling the mitochondrial production of ROS) mRNA levels (Gigante et al. 2011).
(b) Samples of prefrontal cortex of patients with SZ, MD, and BD had decreased concentrations of reduced, oxidized, and total glutathione (Gawryluk et al. 2011a). Moreover, the levels of glutathione peroxidase and the mu isoenzyme of glutathione S-transferase (GST mu) were decreased in MD and SZ brain samples evaluated with immunoblotting technique (Gawryluk et al. 2011a, b).
(c) There was an increased activity of prooxidant enzyme xanthine oxidase in the brain tissue (samples of thalamus and putamen) of patients with MD (Michel et al. 2011a). However, decreased activity was noted in SZ brain specimens (Michel et al. 2011b).
(d) Samples of hippocampus of patients with SZ, BD, and MD had increased content of 8-hydroxy-guanosine, a marker of RNA oxidative damage (Che et al. 2010).
(e) Samples of prefrontal cortex of BD patients had increased levels of oxidized proteins (carbonylated proteins) and 3-nitrotyrozine. Elevated 3-nitrotyrosine was also observed in SZ brain tissue (Andreazza et al. 2010).
(f) Anterior cingulate brain sections from BD and SZ subjects (but not from MD patients) had elevated content of 4-hydroxynonenal, a major product of lipid peroxidation (Wang et al. 2009).

Since oxidative stress predisposes to increased telomere erosion, one may expect the shortening of TL in brain specimens of patients with SZ and other major psychiatric disorders (MD, BD). However, brain specimens from patients with SZ, BD, and MD did not reveal telomere shortening in comparison to control samples (Zhang et al. 2010). Similar results (no significant difference in TL) were noted by other studies with postmortem brain specimens (dorsolateral prefrontal cortex) obtained from depressive patients and matched controls (Teyssier et al. 2011). Moreover, there was no difference in expression of genes involved in the oxidative-stress response and repair between brain samples from both studied groups (Teyssier et al. 2011) (Table 3). These findings suggest that telomere erosion did not occur in brain cortex despite the presence of distinct features of brain oxidative stress.

On the other hand, it cannot be excluded that telomere damage and oxidative stress occur in the brain; simply these phenomena could be limited to other brain regions than those studied so far.

Therefore, further studies analyzing additional brain regions in respect of telomere dysfunction, DNA damage, and intensity of oxidative stress in the course of SZ as well as other major psychiatric disorders are necessary.

3 Telomere Length in Blood Leukocytes and Brain Samples of Patients with Major Depression and Bipolar Disorder

Much more cross-sectional studies have been executed on the telomere shortening in MD and BD patients. These involved larger patients groups and were not only focused on comparison of the TL in DNA extracted from blood leukocytes between patients with mood disorders and matched controls (Tables 2 and 3) but also looked for an association between TL and various clinical variables such us disease severity and duration, treatment effect, intensity of oxidative stress, inflammatory response and perceived stress, and the monoamine oxidase A (MAOA) promoter and apolipoprotein E_2 ($ApoE_2$) polymorphism (Lung et al. 2007; Hartmann et al. 2010; Wikgren et al. 2012; Wolkowitz et al. 2011). Out of 7 reports that compared the leukocyte TL in patients with mood disorders (MD and BD) and matched controls, two described telomere shortening in BD patients (Simon et al. 2006; Elvsashagen et al. 2011) and six in MD patients (Lung et al. 2007; Hartmann et al. 2010; Wikgren et al. 2012; Simon et al. 2006; Garcia-Rizo et al. 2012), respectively. Only one study did not report significant shortening of TL in patients with MD (Wolkowitz et al. 2011). However, patient subgroups with cumulative duration of depression $\geq$9.2 years had significantly shorter telomeres than the control subjects (Wolkowitz et al. 2011). TL was inversely correlated with the ratio of plasma F2-isoprostanes (biomarkers of lipid peroxidation) to vitamin C and positively with the circulating vitamin C levels in MD patients (Wolkowitz et al. 2011). TL was also inversely associated with the stress measured with the self-report questionnaire (Wikgren et al. 2012).

However, TL in MD did not correlate with MAOA promoter and $ApoE_2$ polymorphism (Lung et al. 2007) and neither with disease severity, duration of illness, and number of hospital stays (Hartmann et al. 2010) nor with lymphocyte count (Garcia-Rizo et al. 2012). On the other hand, the load of short telomeres in DNA isolated from the blood mononuclear cells positively correlated with the high number of previous depressive episodes in bipolar disorder type II (BD II) patients (Elvsashagen et al. 2011).

These results obtained with well-defined MD and BD patients groups clearly show the occurrence of some processes that are responsible for the telomere shortening in blood DNA of these patients.

Oxidative stress could be responsible for enhanced telomere erosion in the course of MD. However, only one study was devoted to the analysis of the association

Table 2 Cross-sectional studies on telomere length in patients with major depression and bipolar disorder – part I

Aim of the study	Study description	Main results and [ref]
Effect of MAOA promoter and $ApoE_2$ polymorphisms on TL in MD patients	253 unrelated patients with MD, 411 controls with similar age and sex distribution. Southern blot for TL determination in DNA isolated from blood, PCR-RFLP for $ApoE_2$ genotypes, PCR with specific intronic oligonucleotide primers for MAOA promoter polymorphisms. Multiple linear and hierarchical regression analyses, structural equation model	The TL of patients with MD was shorter than that of the controls. No interaction between the MAOA promoter polymorphism, $ApoE_2$ polymorphism, and TL in MD (Lung et al. 2007)
Do MD or BD patients have shorter telomeres than age-matched healthy subjects?	44 patients with chronic mood disorders (15 MD, 14 BD no anxiety, 15 BD plus anxiety), 44 controls with similar age and sex distribution. Southern blot for TL determination in DNA extracted from leukocytes. Linear multiple regression analyses with adjustment for age, gender, and smoking	TL was significantly shorter in the whole group of mood disorders than in the controls. TL did not differ between the three mood disorder subgroups (Simon et al. 2006)
Do disease severity and treatment affect TL in MD patients?	54 patients with MD (20 patients low-dosed, 16 high-dosed, 18 patients additionally treated with ECT) and 20 healthy age-matched controls. HAM-D for evaluation of the disease severity. Southern blot for TL determination in DNA isolated from blood	The mean TL was significantly shorter in MD group. Each subgroup had similar TL but shorter than that of controls. No differences were between smokers and nonsmokers and males and females in MD group
		There was no significant association between TL and the disease severity, duration of illness, and number of hospital stays (Hartmann et al. 2010)
Evaluation of the load of short telomeres and mean TL and their relationships with illness duration and lifetime number of depressive episodes in BD II patients	28 BD II patients and 28 age-, sex-, and education-matched healthy controls. High-throughput quantitative fluorescence in situ hybridization for measurement of short telomeres (percentage of telomeres <3 kb) and mean TL in isolated peripheral blood mononuclear cells. Multiple regression analyses with adjustment for age, body mass index, and smoking	The load of short telomeres was higher in BD II patients than in controls (15.04 % versus 13.48 %, $p=0.04$). Mean TL did not differ significantly between groups. There was a strong association between the load of short telomeres and a high number of previous depressive episodes (Elvsashagen et al. 2011)
Is there any relationship between TL and biological and psychological facets of stress in MD patients and controls?	91 patients with recurrent MD (aged 21–87 years), 451 controls (aged 25–81 years) without dementia, mental retardation, and severe psychiatric disorders. Quantitative PCR for TL determination in DNA from leukocytes. Four self-report questionnaires for assessment of symptoms of depression, anxiety, and perceived stress. Weight-adjusted very-low-dose DST suppression test for assessment biological stress. Multiple linear regression models with adjustment for confounders	TL was shorter in MD patients versus controls. Short TL was associated with a hypocortisolemic state (low post-DST cortisol and high percentage of cortisol reduction after the DST) in both groups. TL was also inversely associated with stress measured with questionnaire (Wikgren et al. 2012)

$ApoE_2$ apolipoprotein E_2, *BD* bipolar disorder, *BD II* bipolar disorder type II, *DST* dexamethasone, *ECT* electroconvulsive therapy, *HAM-D* Hamilton depression score, *MAOA* monoamine oxidase A, *MD* major depression, *PCR* polymerase chain reaction, *PCR-RFLP – PCR* restriction fragment length polymorphism, *TL* telomere length

Table 3 Cross-sectional studies on telomere length in patients with major depression and bipolar disorder – part II

Aim of the study	Study description	Main results and [ref]
Do MD patients have shorter leukocyte TL than age-matched healthy subjects? Is there association between telomere shortening and lifetime depression exposure, intensity of oxidative stress, and inflammation?	18 MD patients, 18 age-, sex- and ethnicity-matched controls. Both groups were free of any medications, acute illnesses, and infections. HAM-D for evaluation of the disease severity. Quantitative PCR for TL determination in DNA extracted from blood. Measurement of circulating vitamin C, F2-isoprostenes, and IL-6. Multiple regression analyses with adjustment for age, sex, body mass index, and smoking	TL did not differ in MD subjects compared to the controls. MD patients ($n=10$) with cumulative duration of depression ≥9.2 years had significantly shorter telomeres than control group. TL inversely correlated with F2-isoprostanes/vitamin C ratio and IL-6 in MD group. Vitamin C positively correlated with TL in MD and control groups (Wolkowitz et al. 2011)
Do depressive patients have shorter TL and increased expression level of nine major genes of the stress response and repair systems in occipital and dorsolateral prefrontal cortex of the brain, respectively?	Total RNA extracted from postmortem dorsolateral prefrontal cortex and DNA from occipital cortex of 24 depressive subjects (13 with MD, 11 with depression associated with psychotic characteristics) and 12 sex-, age-, ethnicity-, and mean brain pH-matched 12 control subjects with no psychiatric disorder. Quantitative PCR for TL, combination of reverse transcription with quantitative PCR for expression (level of transcripts) of genes of superoxide dismutase 1 and 2, catalase, glutathione peroxidase1, 8-oxoguanine DNA glycosylase, nei-like1, methionine sulfoxide reductase A, telomere repeat-binding factor 2 and C-FOS	TL and expression of analyzed genes did not differ between the whole group of depressive subjects and MD subgroup and controls (Teyssier et al. 2011)
Do antidepressant-naïve patients with MD have shorter TL than healthy controls?	15 newly diagnosed, antidepressant-naïve MD patients, 70 matched healthy control subjects. DNA telomere content (that is highly correlated with TL) was determined in blood leukocytes (DNA hybridization with end-labeled telomere-specific oligonucleotide). Two-hour oral glucose tolerance test, blood cell count	MD group had a significantly decreased telomere content, lower lymphocyte count, and greater 2-h glucose concentration, compared with control subjects Telomere content did not correlate with lymphocyte count (Garcia-Rizo et al. 2012)
Is there association between depression and leukocyte TL in a population-based study?	Cohort of 2,225 subjects with depressive current symptoms evaluated with the Center for Epidemiological Studies Depression scale. TL measured with real-time PCR in leukocyte DNA extracted from frozen buffy coat samples. Statistical analysis adjusted for age, sex, body mass index, systolic and diastolic blood pressure, and Framingham risk score	Depressive symptoms, elevated depressive symptoms, and probable depressive disorder were each associated with longer leukocyte TL in unadjusted linear regression models. In all adjusted models depressive symptoms were not significantly associated with TL (Shaffer et al. 2012)
Assessment of the association between TL and psychological well-being in patients with chronic heart failure	890 patients with chronic heart failure (NYHA class II–IV). TL determined with real-time PCR in leukocyte DNA. Psychological well-being measured by set of questionnaires: the RAND-36 (perceived mental health), the Center for Epidemiologic Studies Depression scale (depressive symptoms), and the DS14 (type D personality)	Lower perceived mental health was associated with shorter TL. TL was not associated with depressive symptoms and presence of type D personality. Adjustment for age, sex, the severity of heart failure (NYHA class, left ventricular ejection fraction, estimated glomerular filtration rate), presence of COPD, diabetes, and history of stroke did not change these results (Huzen et al. 2010)

COPD chronic obstructive pulmonary disease, *HAM-D* Hamilton depression score, *MD* major depression, *NYHA* New York Heart Association, *PCR* polymerase chain reaction, *TL* telomere length

between TL and markers of oxidative stress in MD (Wolkowitz et al. 2011). Although this study concluded to a positive correlation between telomere erosion and intensity of oxidative stress, the sample size ($n=18$) was too low to solve this issue conclusively (Table 3).

Surprisingly, two large cross-sectional studies did not confirm negative effect of depression on TL (Shaffer et al. 2012; Huzen et al. 2010). In a population-based survey that involved 2,225 apparently healthy participants, no association between the leukocyte TL and depressive symptoms as well as TL and probable depressive disorder was found (Shaffer et al. 2012). Similarly, analysis of TL and psychological well-being in 890 patients with chronic heart failure did not reveal any significant association with the depressive symptoms (Huzen et al. 2010). However, no subject had syndromal MD in these studies. Therefore, the intensity and cumulative duration of depressive symptoms could be too low to exert negative effect on the leukocyte TL.

Only one study was executed with postmortem brain samples (dorsolateral prefrontal cortex) of MD patients and matched controls. Neither TL nor the expression of genes involved in the antioxidant defense and repair differed between MD group and controls (Teyssier et al. 2011) (Table 3). These results are analogous to those obtained with postmortem brain samples of patients with SZ discussed in previous subsection.

4 Prospective Studies on Telomere Length in Patients with Mood Disorders

Scanty data exist on association between the TL and the further development of mood disorders and on effect of the current mood disorders on the TL shortening over subsequent time. Moreover, studies reporting these associations involved observation of subjects that did not suffer from MD (and other mood disorders) as the underlying disease (Table 4).

In one study patients suffering from coronary heart disease (CHD) were screened for the presence of coexisting MD, and the TL in their blood leukocytes was measured at baseline and after 5 years (Hoen et al. 2011). Although at baseline CHD patients with current MD had shorter TL than those without MD, the MD group did not reveal a higher rate of telomere shortening over 5-year follow-up. These facts suggest that presence of MD cannot be used as a predictive factor of telomere shortening in patients with CHD (Hoen et al. 2011). As underlined by the authors, this study had some limitations, and the two most important, in my opinion, are the following: groups may differ in the CHD severity, and leukocyte telomerase activity may affect telomere shortening and be responsible for negative results of this study (Hoen et al. 2011). Therefore, it is open to question whether the coexistent MD can accelerate the telomere erosion in CHD patients.

A second study on association between the rate of telomere shortening and the poor mental well-being and poor self-rated health in community-dwelling elderly men also revealed negative results (Rius-Ottenheim et al. 2012) (Table 4).

Table 4 Prospective studies on association between telomere length and mood disorders

Aim of the study	Study description	Main results and [ref]
Association between TL and depression in patients with CHD over a 5-year period	TL measured with quantitative PCR in DNA isolated from blood leukocytes in 952 patients with CHD at baseline and 608 of them after 5-year follow-up. Computerized Diagnostic Interview Schedule used for assessment of presence of MD in CHD patients at baseline. Statistical analyses adjusted various sociodemographic variables	CHD patients with current MD had shorter TL than those without depression at baseline. Current MD did not predict subsequent telomere shortening in CHD patients over 5-year follow-up (Hoen et al. 2011)
Whether accelerated telomere shortening is associated with poor mental well-being and poor self-rated health in community-dwelling elderly men	203 men (mean age 78 years) from Netherlands, 123 men (mean age 84 years) from Greece. Depressive symptoms, dispositional optimism, global cognitive function, feelings of loneliness assessed with battery of tests, and questionnaires. TL measured with quantitative PCR in leukocyte DNA extracted from buffy coat samples. Seven-year follow-up with 75 Dutch subjects. Multivariate models for adjustment for potential confounders (sociodemographic, lifestyle, morbidity parameters)	Leukocyte TL was not associated with measures of mental well-being and self-rated health, neither in the Dutch nor in Greek participants. The rate of leukocyte telomere shortening over 7-year follow-up was not associated with changes in different measures of mental well-being and self-rated health (Rius-Ottenheim et al. 2012)
Is shorter TL a predisposing factor to the development of trauma-related MD and PTSD in rape victims?	64 female rape survivors assessed within 2 weeks from the rape incident (baseline) and after 3 months (follow-up) for resilience or the development of trauma-related MD and PTSD with set of questionnaires and scales. TL measured with quantitative PCR in DNA extracted from blood	No significant association was observed between TL and resilience and the development of MD at both baseline and after 3 months. There was a significant association between TL and PTSD. Victims with PTSD had significantly shorter TL than those without PTSD (Malan et al. 2011)
	Analysis for effect of possible confounding factors (age, ethnicity, and the level of education)	

CHD coronary heart disease, *PCR* polymerase chain reaction, *MD* major depression, *PTSD* posttraumatic stress disorder, *TL* telomere length

However, a third study presented partially positive results. This study involved a group of female rape survivors investigated within 2 weeks from the rape incident and after 3-month follow-up. TL in blood DNA measured at baseline was associated with the development of posttraumatic stress disorder. Victims presenting with posttraumatic stress disorder had shorter TL than those free of this abnormality. On the other hand, TL did not associate with the presence of trauma-induced MD either at baseline or after 3-month follow-up (Malan et al. 2011).

Description of these studies and their results clearly shows that there is a great need of prospective longitudinal studies involving patients suffering from MD, SZ, or BD and matched controls to evaluate the effect of major psychiatric disorders on the rate of telomere shortening.

5 Telomerase Activity and Expression of Genes Involved in DNA Repair in Patients with Schizophrenia and Major Depression

Since the TL in blood leukocytes of patients with SZ and MD was shorter in comparison to the matched healthy controls, one may assume that this may be related to decreased telomerase activity in these cells. Moreover, it cannot be excluded that the rise in telomerase activity may counteract this negative process, perhaps, related to the systemic oxidative stress.

This was investigated in the group of patients with MD and SZ and resulted in opposite outcomes (Table 5). Telomerase activity in subjects with SZ did not differ significantly from that found in the group of their unaffected relatives (Porton et al. 2008) and even was lower when compared to the reference group composed of unaffected relatives and unrelated controls (Porton et al. 2008). This suggests the reduction of telomerase activity in blood lymphocytes in SZ. On the other hand, no correlation between the TL and telomerase activity in lymphocytes of SZ patients was noted (Porton et al. 2008). Similarly, TL did not correlate with the telomerase activity in other immune cells (T lymphocytes, blood mononuclear cells) isolated from healthy subjects (Pan et al. 1997; Iwama et al. 1998). Therefore, it seems that suppression of telomerase activity cannot be a culprit of decreased TL in leukocytes of SZ patients.

In contrast to these results, medication-free MD patients had elevated telomerase activity in blood mononuclear cells in comparison to the unaffected controls (Wolkowitz et al. 2012). No significant correlation was noted between the TL and telomerase activity in these patients likewise to SZ group. Moreover, telomerase activity in mononuclear cells did not correlate with various markers of oxidative stress (plasma concentrations of F2-isoprostanes, 8-hydroxydeoxyguanosine, and vitamin C) and inflammation (interleukin-6 and C-reactive protein levels) both in MD subjects and controls (Wolkowitz et al. 2012). Therefore, it is difficult to judge whether the rise of telomerase activity is a defensive mechanism against the oxidative stress observed in the course of MD.

Another study that involved female MD patients and matched controls studied the expression of the set of gene encoding products that are implicated in and being markers of processes of the telomere dysfunction and repair (STMN1, encoding stathmin; TERT, encoding the catalytic subunit of the telomerase), the aging and senescence ($p16^{ink4a}$ encoded by the CDKN2A locus), the oxidative stress and DNA repair (OGG1 – encoding 8-oxoguanine-DNA glycosylase1), the response to anxiety and psychogenic stress (FOS gene, DUSP-1 gene), and the inflammatory response (Il-6 gene) in blood leukocytes. Although TL did not differ between MD women and controls, there was significant overexpression of OGG1, P16ink4a, and STMN1 genes in the MD group. These results suggest the occurrence of DNA damage and the telomere dysfunction probably due to oxidative stress in leukocytes of female MD patients (51).

While the results seem interesting, the major limitation of these studies is the low number of analyzed patients. Therefore, they are not conclusive and require confirmation in further studies involving larger groups of patients.

Table 5 Studies on telomerase activity and expression of genes involved in telomere dysfunction, DNA repair, and cell senescence in patients with schizophrenia and major depression

Aim of the study	Study description	Main results and [ref]
Comparison of telomerase activity in lymphocytes between patients with SZ and unaffected relatives and unrelated controls	53 patients with SZ, 31 their unaffected first-degree family members, 59 unrelated controls. Telomerase activity measured with real-time PCR-based assay in lymphocytes isolated from peripheral blood	No significant difference in telomerase activity between patients with SZ and their unaffected relatives. Patients with SZ had decreased telomerase activity when compared to all unaffected individuals (control + family) (Porton et al. 2008)
Comparison of telomerase activity in blood mononuclear cells between MD patients and unaffected controls	20 medication-free patients with MD and 18 controls. Plasma oxidative stress and inflammation markers (F2-isoprostanes, 8-hydroxydeoxyguanosine, ascorbic acid, interleukin-6, C-reactive protein) at baseline. Telomerase activity measured with combination of PCR and ELISA (commercial kit) in peripheral blood mononuclear cells at baseline and in 15 MD patients after 8-week treatment (open-label) with sertraline. The HAM-D for assessment of pre- and posttreatment symptom severity Analyses were corrected for age and sex	Baseline telomerase activity was significantly higher in MD patients than in controls. Antidepressant treatment did not affect mean telomerase activity. MD patients with lower pretreatment telomerase activity and with greater increase in telomerase activity during treatment showed superior antidepressant responses. Telomerase activity did not correlate with oxidative stress and inflammation markers in both groups (Wolkowitz et al. 2012)
Comparison of expression of genes implicated in telomere dysfunction, DNA repair, and biological aging between female patients with MD and matched controls	17 female MD patients and 16 control women matched for age, BMI, physical activity, and alcohol consumption. Real-time quantitative PCR for gene expression (p16INK4a, STMN1, OGG1, TERT, FOS, DUSP1, IL-6) and TL in blood leukocytes. HAM-D and HAM-A for assessment of the disease severity. Analyses adjusted for sociodemographic variables	Three genes (OGG1, P16ink4a, STMN1) were significantly overexpressed in MD patients. Expression of p16INK4a and STMN1 correlated with anxiety scores in the MD group. Mean TL did not differ between groups (Teyssier et al. 2012)

BMI body mass index, *ELISA* enzyme-linked immunosorbent assay, *HAM-A* Hamilton anxiety score, *HAM-D* Hamilton depression score, *MD* major depression, *PCR* polymerase chain reaction, *SZ* schizophrenia, *TL* telomere length

6 Concluding Remarks

Patients with MD and BD revealed shortened TL in blood leukocytes as evaluated in cross-sectional studies. Results obtained with the groups of SZ patients are not fully conclusive but also suggest telomere shortening in this disease. Numerous dietary (intake of plant polyphenols and vitamins), demographic, socioeconomic factors, and pathological conditions can affect the rate of telomere erosion in

leukocytes. Therefore, it is very difficult to select homogeneous patient group (with respect to comorbidities and lifestyle) and precisely matched controls. Although the statistical analyses of these studies included the adjustment for some confounding factors, it is not easy to completely eliminate the risk of bias especially when the size of patient group is low.

In the case of blood leukocytes, measurement of the TL reflects their replicative history.

Thus, any factor (e.g., infection, inflammation) that can enhance these cells' turnover will lead to the TL shortening and induce bias. This implicates that apart from current confounding factors, also past confounding factors can affect the results of the TL determination in blood leukocytes.

In light of this, previous reports showing prenatal exposure to influenza virus as a risk factor for adult SZ (Limosin et al. 2003; Izumoto et al. 1999), and the positive association of psychological stress with the number of upper respiratory tract infections in the subjects with chronic fatigue syndrome (Faulkner and Smith 2008), seem interesting.

It should be pointed out that early life stress (childhood adversity) is negatively associated with the TL in adult life (Price et al. 2013; Kiecolt-Glaser et al. 2011; Kananen et al. 2010), which also complicates interpretation of the results of cross-sectional studies.

There are no conclusive data on the association between intensity of systemic oxidative stress and the telomere shortening in blood leukocytes of patients with these three major psychiatric disorders. Moreover, postmortem brain samples of these patients (SZ, MD, BD) did not reveal any TL shortening, although they had elevated markers of oxidative stress. This dissonance between the TL of blood leukocytes and brain tissue is somewhat surprising since in other diseases (e.g., diabetes, autoimmune diseases, cardiovascular diseases, stroke) the reduced leukocyte TL correlated with the telomere shortening in target organs and tissues (Price et al. 2013).

Bearing this in mind, only well-planned longitudinal studies with monitoring of the blood leukocyte TL and the intensity of systemic oxidative stress will definitely solve the question whether SZ, MD, and BD are associated with accelerated telomere shortening and whether the oxidative stress belongs to the main factors responsible for this process.

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