

Common mental disorders and association with telomere length (Review)

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Abstract. Telomeres are repeated 5'-TTAGGG-3' sequences at the end of chromosomes, which maintain genomic stability. Their length is related to a number of diseases that affect humans. Apart from cancer, cardiovascular diseases, diabetes and other, telomere length has been associated with chronic diseases. Chronic mental illness includes various types of mental disorders with the most common being depression, schizophrenia and stress-anxiety. The aim of this review is to summarize the current state of knowledge on the role of telomeres in these disorders and to compare telomere length variations in patients receiving medication and patients not taking treatment. Most studies report reduced telomere length in patients suffering from mental disorders, compared to the general population. Since the factors that can affect telomere length are various, more experiments and investigations are required to understand the general impact of different factors on telomere length.

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1. Introduction

Telomeres are chromatin structures at the end of chromosomes, composed of tandem repeats of the sequence 5'-TTAGGG-3',

and protect chromosomes from degradation and recombination (1). Telomeres are also coated with a protein complex, which consists of a group of proteins: telomere repeat-binding factor 1 (TRF1) and 2 (TRF2), which interact with nuclear protein 2 (TIN2); repressor activator protein 1 (Rap1); tripeptidyl-peptidase 1 (TPP1); and protection of telomere 1 (POT1), and are also known as shelterin proteins (2,3). These are packed into a compact T-loop structure to prevent the DNA repair machinery from recognizing and processing telomeres during the repairing double-stranded DNA breaks (3).

Telomere length decreases with each cell division due to incomplete replication of linear chromosomes. High proliferating cells produce telomerase, an enzyme that acts as a reverse-transcriptase, and is responsible for catalyzing the addition of nucleotides using an RNA template. However, telomerase activity is not sufficient to prevent telomere shortening (4,5). When telomere length becomes critically short, proliferation is arrested, and the risk of apoptosis is increased (6-8). Therefore, telomeres and telomerase activity have been characterized as biomarkers of cellular aging (9,10).

A growing number of studies have linked shorter telomeres to health behaviors, such as smoking, and aging and age-related diseases including cancer, coronary heart (cardiovascular) disease, and diabetes (11-16). In addition, previous findings have shown a correlation between telomere length and depression, stress, schizophrenia, drug abuse and Alzheimer disease (17-21).

The aim of this review is to indicate the association between telomere length and mental illnesses such as depression and schizophrenia, and evaluate the potency of telomere length as biomarker of early aging.

2. Depression

Depression is not only a brain disorder, but a condition affecting the whole body (22). This is due to the fact that increased psychological and chronic stress has been associated with accelerated aging, telomere length shortening and the psychopathological characteristics of major depressive disorders (23-25).

In addition, the complex mechanisms of hypothalamic pituitary adrenal axis, brain-derived neurotrophic factor, oxidative

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or inflammatory stress, excitotoxicity, neurosteroids, mitochondrial DNA, leukocyte telomere length and telomerase are biochemical mediators of cell dysfunction or damage and have been linked to major depressive disorder (26,27). Moreover, symptoms of depression are related to oxidative stress and inflammation (22). They reduce telomerase activity (22,28) and decrease levels of neurotrophic factors (29,30), but increase apoptosis (6,7) and reduce stem cell proliferation (31).

Depression is partly heritable and the severe and early-onset forms of depression may have a higher heritability than other forms of depression (32). Over the last few decades, several studies have identified an association between bipolar disorders and diseases that cause accelerated aging, including cardiovascular diseases (33). Thus, it has been hypothesized that depression symptoms may lead to accelerated aging by decreasing telomere length (22,34).

Simon *et al* investigated the relationship between mood disorders and telomere length and found that telomeres were significantly shorter in patients with mood disorders overall, and in patients with major depressive disorders (34). This finding was confirmed by Wolkowitz *et al* who reported that the biological age of patients with depression was 10 years older compared to their chronological age (22). The mechanism of aging caused by depression includes increased rates of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which result in unspecific damage of intracellular compartments including cell membranes, organelles, DNA and telomeres (35,36). In a more recent study, Verhoeven *et al* demonstrated that individuals with major depression had shorter telomeres compared to the control group, and that severity and duration of the disorder were inversely correlated to telomere length (37). In that study, no association between psychotropic medication use and telomere length was reported (37). In this regard, Elvsåshagen *et al* observed no differences in telomere length of patients with or without use of medicines for depression (38). One year later, Needham *et al* came to contradict the results by Verhoeven *et al* (37) with his experiment where young adults, who suffered from severe depression and used antidepressants, had statistically significant shorter telomere length than those who were not under treatment (39).

Lung *et al* and Philips *et al* have shown shorter telomeres in depressive patients populations, but the levels of decrease changed with age (40,41). Telomere length was higher in the youngest group, depending on the duration of the disorder and the severity of symptoms, while men and women with depression (using or not antidepressants) had similar lengths (40). This similarity between men and women was also confirmed by Wikgren *et al* (42), who observed significant shorter telomere length in patients with depression, and by Hartmann *et al* (43) who also found notably shorter telomeres compared to the control group, as the dose of antidepressants increased (independent from duration and severity of disease).

In addition, severe depressive symptomatology, as indicated by being medically treated either in a clinical setting or by psychotropic medication, has been associated with shorter telomere length even in early adulthood, as described by Needham *et al* (39). However, less severe forms of psychopathology were not correlated with telomere length.

In the studies of Wolkowitz *et al*, Simon *et al*, Wikgren *et al* and Hartmann *et al*, it was shown that telomere shortening

occurred only in patients with a long lasting (10-30 years) depression disorder (22,34,42,43). Thus, the increased load of short telomeres in the patient group may represent 13 years of accelerated aging. Similarly, the reduction in mean telomere length among patients is equivalent to 11 years of accelerated aging (38).

It is worth mentioning that mixed results in depression and telomere studies may be due in part to the presence of potentially uncontrolled confounding factors such as variably assessed medical illness and life stressors; however, not all studies with positive results failed to control for multiple confounding variables (44). Thus, the lifetime of the illness cannot explain the prognosis of major depressive disorders, due to heterogeneity of treatment response and self-resilience against the stress, both factors of leukocyte telomere length shortening (45).

3. Schizophrenia

Schizophrenia is a complex neurodevelopmental disorder characterized by mental dysfunction in multiple domains of the brain (46). Previous studies have shown lower telomere length in patients with schizophrenia and paranoid schizophrenia compared to control groups (47,48). Patients suffering from paranoid schizophrenia, who were under anti-psychotics medication had slightly decreased leukocyte telomere length. In addition, telomere length analysis of paranoid schizophrenic patients revealed that response to treatment influences telomere length with poor responders having the shorter telomeres (49). By contrast, other authors have shown that the poor responders had the shortest terminal restriction fragments (TRFs) which was inversely associated with age. Furthermore, Fernandez-Egea *et al* (19), who included both men and women, showed that the whole psychosis group had decreased telomere content compared to the control group and that both men and women had the same telomere content. However, when patients and controls were analyzed separately men showed a higher extent of telomere length shortening than women that was affected by age (50).

At this point, it is important to mention that both typical and atypical antipsychotics affect leukocyte functioning (51,52). In particular, according to Leykin *et al* (51), clozapine and haloperidol inhibited *in vitro* leukocyte mitosis stimulation by phytohemagglutinin in 50% of treated patients, and suppressed the production of the interleukins analyzed. Accordingly, *in vitro* experiments using clozapine and haloperidol separately and above the therapeutic dosage, resulted in decreased telomerase expression in leukocytes of healthy individuals' (53). Furthermore, Rao *et al* (54) showed that leukocyte telomere length was markedly shortened in patients with schizophrenia who presented poor response to antipsychotics. Although the exact mechanism remains to be unraveled, these findings are most probably linked to high levels of oxidative stress.

In contrast to the above, Savolainen *et al* concluded that patients who were under medication had longer telomere length than healthy subjects and two possible mechanisms might be involved (55). Firstly, antipsychotics can function in a way that prevents oxidative stress and its effects, protecting telomeres from erosion and leading to longer telomeres. Secondly, psychotropic medications are correlated with the

Wnt/ β -catenin pathway, which increases telomerase expression by activating TCF4 (56,57). However, these results need to be interpreted with caution, because the study population included mixed patients suffering from severe mental or substance abuse disorder, hospitalized at some point from 1969 onwards. Thus, the health state of these patients was not assessed at the time of the study and bias of survival cannot be excluded. In addition, baseline telomere length measurements were not included, probable administration of polypharmacy treatment, having protective effect on telomere, and methodology limitations may explain these findings.

Schizophrenia is a brain disorder linked to several genetic and environmental factors that play an important role in the development of the disorder (58). This was one of the reasons which led to the characterization of schizophrenia as a syndrome of accelerated aging (59-61). Nevertheless, it is worth mentioning that the disorder itself and its development are associated with increased physiological changes in the organism, which are correlated with normal aging. Such changes include hyperlipidemia, decreased bone density, insulin resistance, cortical atrophy, thinning and wrinkling of the skin and hair, increased blood pressure and decrease in muscle mass (61). In addition, oxidative stress is one of the factors of telomere shortening and given the fact that oxidative stress is really high in this type of schizophrenia, this could increase telomere erosion as demonstrated in some reports of schizophrenic patients with shorter telomers (62,63).

It has been previously shown that oxidative stress can cause mitochondrial dysfunction and altered brain metabolism in schizophrenia, suggesting that increased oxidative stress may exist in poor responders with chronic schizophrenia (64). This is supported by a study showing that oxidative DNA damage was 10-fold higher in post-mortem hippocampi of elderly patients with 'poor-outcome' schizophrenia (65). Thus, it becomes apparent that oxidative stress plays a major role in this disorder, and the possible cause of oxidative stress in schizophrenia may be the reduction in antioxidant capacity and elevated levels of oxygen-free radicals (66-68).

However, further studies are needed to establish the status and the role of oxidative stress in the pathogenesis of schizophrenia, in good and poor responders with chronic schizophrenia, and to evaluate the association of telomere length with this disorder. Of note, the effect of psychiatric medication on telomere shortening should be considered with caution, since all antipsychotics act in the central nervous system and most studies measured telomere length in leukocytes DNA.

4. Stress-anxiety

Psychological stress is commonly observed in modern society and a high percentage of individuals suffer from high levels of anxiety. Early or recent in life, chronic exposure to psychosocial stressors, has been associated with numerous diseases including obesity and abnormal fat deposition, metabolic syndrome, cardiovascular disease, systemic inflammation, and dendritic shortening in the hippocampus and prefrontal cortex (69). Chronic stress can lead to overeating, co-elevation

of cortisol and insulin, suppression of certain anabolic hormones and this can promote systemic inflammation and oxidative stress (69).

The abovementioned biochemical environment, leads to telomere length shortening and cell senescence. Previous studies have shown that telomeric DNA can be damaged by oxidative stress (70,71). Leukocyte telomere length is a well-studied indicator of cellular aging and it is influenced by age, sex, health behaviors such as smoking (72), genetic predisposition (73) and psychosocial factors, including mental health (74). Verhoeven *et al* suggest that anxiety disrupts the hypothalamic-pituitary axis and immune function, and increases oxidative stress, leading to telomere damaging (75). A number of studies have examined the relationship between anxiety, chronic stress and telomere length. Hoen *et al* found a significant association between high anxiety levels and telomere shortening (76). The results from a meta-analysis study by Malouff and Schutte showed a weak but significant association between high anxiety and shorter telomeres in 19,424 participants. Those authors suggest that anxiety may lead to shorter telomeres which could lead to a shorter lifespan (77). In line with these findings, Mathur *et al* (78), who examined the association between perceived stress and telomere length found a weak but statistically significant relationship between increased psychological stress and decreased telomere length, but they suggest that this association may be stronger with known major stressors. Malouff and Schutte also supported that according to the literature, long-term chronic stress may have a larger cumulative effect (77).

In addition, Wang *et al* studied the differences in telomere length between primary health care patients with anxiety or stress, and they observed that telomere length was significantly shorter in patients compared to the controls. They also examined the association between telomere length and baseline characteristics in these patients and they observed shorter telomere length in male, overweighted, and elderly participants. Finally, they examined the potential effects of the 8-week treatments with a mindfulness-based therapy on telomere length and they demonstrated that telomere length remained unchanged (79).

Taken together, it can be assumed that individuals with an anxiety disorder or perceived stress might be at greater risk of telomere shortening. However, future intervention studies on the impact of antidepressant treatment on telomere length are to further clarify the role of anxiety on telomere length changes.

5. Discussion

The majority of the studies included in the present review have identified increased telomere erosion in patients suffering from one of the aforementioned disorders (schizophrenia, depression, stress-anxiety).

Schizophrenia, depression and stress-anxiety are closely related. In fact, patients with chronic symptoms of schizophrenia, experience intense stress because of the disorder and have decreased telomere length due to the combination of the two conditions (54). The same effect has been observed in the case of depression and stress. Phillips *et al* found that the effects of depressive symptoms on telomere length are

limited, and can only be detected in younger groups in which the impact of the individual's age on telomere length decrease is less strong (41). These findings oppose the concept that the effects of stress are expected to increase and accumulate in older ages. Based on this, it is expected that the effects of the disease are stronger in older ages, because early age of illness seems to have contrary effects on prognosis. Therefore, it is necessary to define a certain time interval before evaluating the effects of any disease on telomere length and biological age, in order to have relevant results including any factor that may influence these results.

However, there are some limitations in most studies. Variables including sex, age, BMI, the individual's lifestyle and health condition, should be considered to produce statistically significant results. Finally, other morbidities (such as cancer, diabetes and cardiovascular disease, unaware medical illness) might confound differences in leukocyte telomere length between cases and controls (80-82).

To conclude, more experiments and investigations should be carried out to understand the general impact of different factors on telomere length.

Competing interests

D.A. Spandidos is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

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