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Leukocyte telomere length in patients with schizophrenia: A meta-analysis

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ABSTRACT

Schizophrenia has been suggested as a syndrome of accelerated aging. Telomere length (TL) decrease is considered one biological marker associated with age and can be accelerated by pathological characteristics present in schizophrenia. Several studies evaluated TL in schizophrenia, but the results are still controversial. The aim of this study was to conduct a meta-analysis of the existing results of TL in leukocytes of individuals with schizophrenia compared to healthy controls. A search was performed in PubMed, using the keywords 'telomere schizophrenia' and 'telomere psychosis'. We included data from original articles that measured TL in leukocytes of human patients with schizophrenia and healthy control subjects. 45 articles were found, but only 7 met our criteria. Telomere length of controls was not statistically different from that of patients with schizophrenia ($p = 0.07$). Crossvalidation with the leave-one-out method resulted in a significant model ($p = 0.03$) in which TL of individuals with schizophrenia is smaller than control (SMD = 0.38; 95% CI = [0.05, 0.72]). We also propose a biological pathway through which schizophrenia could promote telomere erosion and how antipsychotics might compensate this loss. There are few studies made on this subject with diverse methodology and heterogeneous sample. Some articles did not consider other possible influences on TL. Overall our results suggest that TL is decreased in schizophrenia. Although this is consistent with the idea of accelerated aging, schizophrenia is a complex disease and there are several factors that influence TL that should be controlled in future studies.

1. Introduction

It is believed that schizophrenia is a multifactorial disorder, in which environmental factors (e.g., alcohol and drugs abuse, pre-birth infections and maternal malnutrition) and genetic variants contribute to its development (Tsuang, 2001). The disease has an unknown etiology and pathogenesis, but several anatomical, biochemical and genetic abnormalities have been identified.

Recently, some authors have suggested that schizophrenia might be a syndrome of accelerated aging (Kirkpatrick et al., 2008; Papanastasiou et al., 2011; Anthes, 2014; Okusaga, 2014; Shivakumar et al., 2014). Kirkpatrick et al. (2008) base this hypothesis in the fact that patients with schizophrenia share lifelong profile of cognitive impairment and pattern of mortality with elderly people. Beyond that, some risk factors for well-established aging-related disorders are also risk factors for schizophrenia. Additionally, physiological changes seen in aging would occur prematurely in schizophrenia. Okusaga (2014) complements this hypothesis proposing that increased oxidative stress (OS) and chronic inflammation, both present in schizophrenia, may be the basis of accelerated aging. Other age-related metabolic changes, such as increased risk for diabetes mellitus, increased pulse pressure, decreased levels of testosterone, decreased brain volume and bone mass also appear at an early age in schizophrenia (Papanastasiou et al., 2011; Shivakumar et al., 2014). Although these findings may support the hypothesis of accelerated aging, there are other factors associated with the disease that could also contribute to the abnormalities: higher prevalence of smokers (de Leon and Diaz, 2005), poor medical care (Mittal et al., 2014) and the use of antipsychotics (Savolainen et al., 2012), for example.

In this scenario, the study of telomere length (TL) in schizophrenia remains a relevant issue to be investigated. Telomeres consist in repeated non-coding sequences at the end of each chromosome (TTAGGG), capped with binding proteins. Human telomeres are normally 15–20 kb long and progressively shorten in each cell division, functioning as a "biological counter" of the number of divisions (Shay and Wright, 2007). Reduction in telomere length is related to the aging process and it is believed that when it reaches a minimum value, cell senescence is triggered (Kipling, 2001; Herbig et al., 2004). However it is now known that different pathologies can influence TL. Cardiovascular

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diseases, metabolic syndrome, diabetes, atherosclerosis, smoking, some psychiatric disorders, for instance, are related to decreased telomere length (Eitan et al., 2014).

TL is determined by the balance between mechanisms that shorten its size and mechanisms that lengthen it. The enzyme telomerase stabilizes the number of repeated sequences by adding new TTAGGG blocks at the end of chromosomes, repairing the telomeres, which are constantly eroded in its absence (Eitan et al., 2014).

Telomerase consists of a RNA subunit; telomerase RNA (TER) component, which contains the template for DNA synthesis; and a protein subunit, which functions as a reverse-transcriptase (TERT), catalyzing the addition of nucleotides using a RNA template.

Telomerase regulation is complex and involves multiple layers of control for both TER and TERT subunits: transcriptional, post translational, alternative isoforms, recruitment to telomere and processivity at telomeric end (Cifuente-Rojas and Shippen, 2012).

Besides DNA replication, oxidative stress (OS) is the main mechanism responsible for the direct shortening of telomeres. It has been described that 8-oxo-7,8-dihydro-2′-deoxyguanosine, the product of oxidation of guanosine by the hydroxyl radical, is formed in greater amounts in DNA containing telomere sequence than in DNA containing non-telomere sequence. This specific damage may exacerbate telomere shortening (Kawanishi and Oikawa, 2004). OS has been shown to be increased in schizophrenia (reviewed in Bošković et al., 2011), which could lead to faster telomere erosion.

The literature regarding the association between telomere and schizophrenia is still elusive.

Fernandez-Egea et al. (2009) and Kao et al. (2008) suggested that TL is decreased in the disease, whereas Nieratschker et al. (2013) found longer telomeres in patients with schizophrenia than in healthy people. Mansour et al. (2011) and Zhang et al. (2010) found no difference between patients and control. Yu et al. (2008) and Kota et al. (2014) detected reduced telomeres in patients who did not respond to treatment, while good responders and control were not statistically different. Malaspina et al. (2014) found no significant differences between cases and control, but showed that paternal age is associated with longer TL in male and shorter in female patients.

Therefore, the presence of increased OS status and the possibility of being an accelerated aging disorder might justify the link between telomeres and schizophrenia. Due to the poor replicability of the studies in the literature, a meta-analysis is necessary to help conclude or refute the hypothesis of rapid telomere erosion in schizophrenia.

2. Methods

The Pubmed database was searched for articles published until January 2015, with the keywords: “telomere schizophrenia” and “telomere psychosis”. After removing the duplicates, articles were screened to select those with TL measurement in leukocytes of schizophrenia patients. The number of controls and patients, the average and standard deviation of TL were extracted from each article independently by two researchers or, when unavailable, requested from authors.

Results from the different articles were aggregated with standardized mean differences (SMD) with positive values favoring the control group. A random-effects model fit via restricted maximum likelihood was used to account for heterogeneity and studies were weighted on their inverse-variance. Analyses were conducted on R Statistical Software version 2.15.3, using the metafor package 1.9-5 (Viechtbauer, 2010) and confidence level was set at 5%. Model was crossvalidated with the leave-one-out method.

3. Results

45 articles were found within our search, but only 7 satisfied our inclusion criteria (i.e. had TL measurement data of leukocytes from schizophrenia and control subjects), which are shown in Table 1.

The initial model included data from all 7 articles (Fig. 1) and showed no difference in TL between patients and control subjects (SMD = 0.34; p = 0.074).

However, crossvalidation, showed that the Nieratschker et al. (2013) study is responsible for most of the heterogeneity of the model and excluding its results in a significant model (p = 0.027) in which telomere length in individuals with schizophrenia is smaller than control (SMD = 0.43; 95% CI = [0.05, 0.82]).

4. Discussion

We believe that there is enough evidence to support the hypothesis of diminished telomere length in schizophrenia (Fig. 2). Our cross validated model showed a significant reduction in TL in schizophrenia when compared to healthy controls. The articles considered in this model pooled treated and drug-naive patients, as well as patients who do or do not respond to treatment in the schizophrenia group (Kao et al., 2008; Yu et al., 2008; Fernandez-Egea et al., 2009; Mansour et al., 2011; Kota et al., 2014; Malaspina et al., 2014). On the other hand, Nieratschker et al. (2013) reported increased TL in schizophrenia; this work had the largest sample composed only of treated patients. Also, Yu et al. (2008) and Kota et al. (2014) showed that TL reduction occurred only in patients with a bad response to treatment. Those results reinforce the hypothesis of treatment influence on TL (Fig. 3). Also, the studies did not consider several variables that could influence TL, such as oxidative state, antipsychotics use, other morbidities, smoking and paternal age.

Table 1
Seven studies performed telomere length measurement in patients with schizophrenia and controls. This table describes the methodology used for the analysis of TL and a summary for each article.

	Method	Control	Schizophrenia	Conclusion
		N (mean ± SD)	N (mean ± SD)	
Kota et al. (2014)	qPCR	73 (1.05 ± 0.6)	71 (0.79 ± 0.69)	Bad responders have shorter telomere than control; telomere length of good responders equals control's telomere length
Malaspina et al. (2014)	qPCR	20 (1.80 ± 0.65)	53 (1.91 ± 0.74)	No difference in telomere length between schizophrenia and control
Nieratschker et al. (2013)	qPCR	519 (1.30 ± 0.32)	539 (1.36 ± 0.38)	Telomere length in schizophrenia is larger than control
Mansour et al. (2011)	qPCR	60 (0.87 ± 0.26)	60 (0.89 ± 0.3)	No difference in telomere length between schizophrenia and control
Fernandez-Egea et al. (2009)	FISH	41 (100.9% ± 15.20%)	41 (93.10% ± 12.10%)	Telomere content in patients with schizophrenia is shorter than control
Kao et al. (2008)	qPCR	76 (1.51 ± 0.33)	51 (1.14 ± 0.3)	Telomere length in schizophrenia is diminished compared to control
Yu et al. (2008)	Southern Blot	76 (8.91 ± 1.36)	68 (8.14 ± 0.93)	Bad responders have shorter telomere than control; telomere length of good responders equals control's

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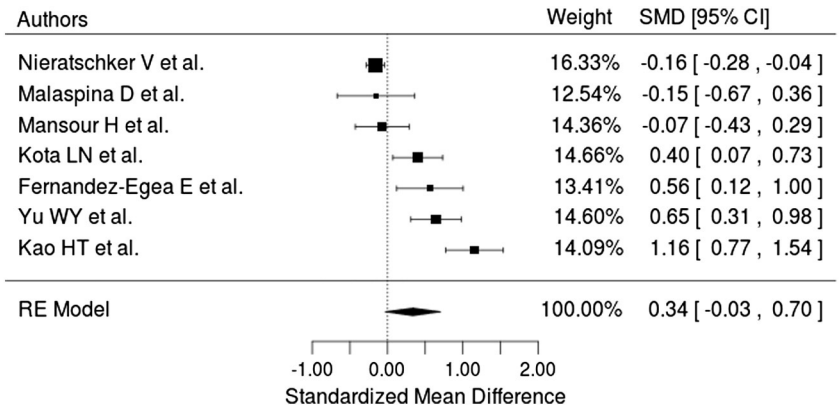

Fig. 1. Meta analysis of leukocyte TL in patients with schizophrenia and healthy controls, data presented as SMD [95% CI].

4.1. Oxidative state

Considerable evidence supports an augmented OS state in schizophrenia. This is evidenced by altered levels of lipidic markers and antioxidant defense and by relative efficacy of antioxidant treatment complementary to antipsychotics (Bitanihirwe and Woo, 2011; Bošković et al., 2011). OS is one possible mechanism for increased telomere attrition in the disease, as proposed in all articles considered in the meta-analysis. This finding is consistent with the accelerated aging hypothesis as well as with our results. Okusaga (2014) proposed that chronic inflammation in schizophrenia leads to increased OS, which explains metabolic changes similar to what occurs in elderly people. Telomere shortening might be triggered by the same mechanism.

4.2. Antipsychotic use

Antipsychotics act by blocking D2 or 5-HT2A receptors, which interfere in the function of protein kinase B (Akt)/glycogen synthase kinase 3 beta (GSK3β)/β-catenin pathway (Beaulieu and Gainetdinov, 2011). This pathway is involved in the regulation of telomerase expression through activation of TCF4, enabling telomerase expression (Hoffmeyer et al., 2012; Stower, 2012) (Figs. 2–3).

This pathway has been associated with schizophrenia in a few studies. Some results suggest increased activity of GSK3β, and decreased activity of Akt1 in the frontal cortex and lymphocytes of individuals with schizophrenia (Emamian et al., 2004) (Fig. 2). Furthermore, the work of Bousman et al. (2013) confirmed the increased activity of GSK3β

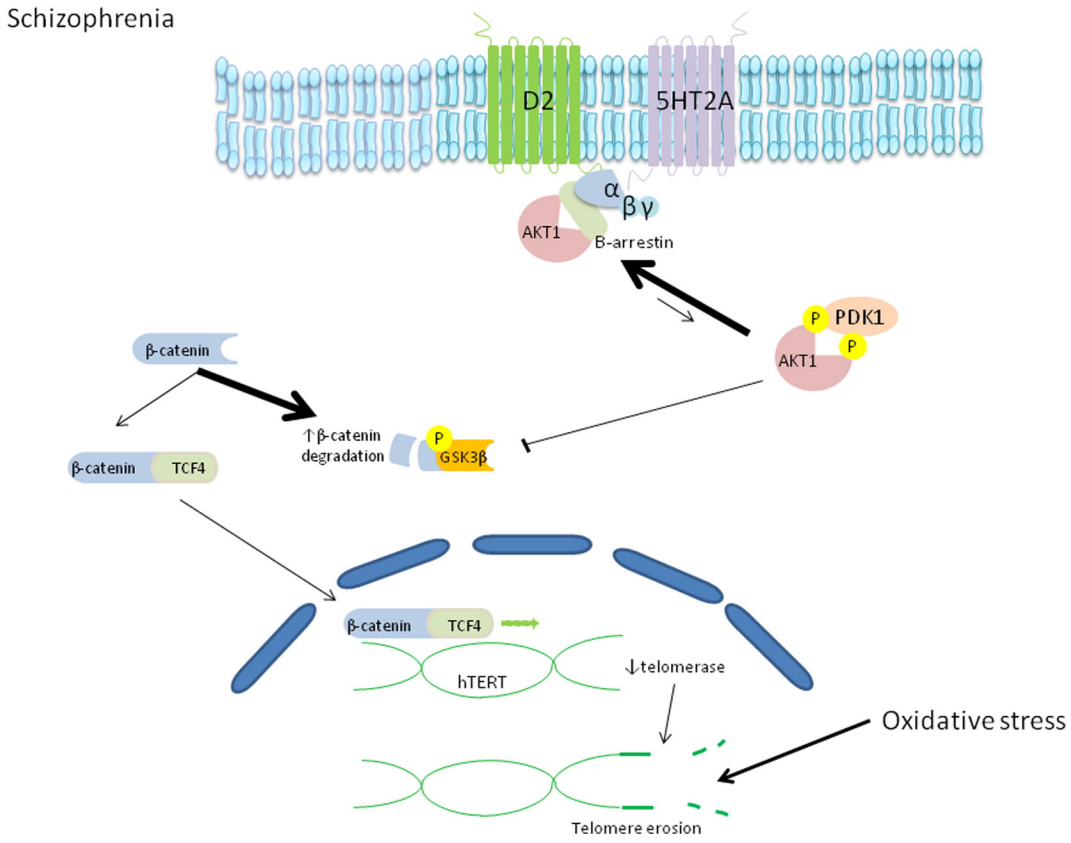

Fig. 2. In schizophrenia, activity of protein kinase B (AKT1) is reduced and activity of glycogen synthase kinase 3 Beta (GSK3B) is augmented, leading to increased β-catenin degradation. Consequently, less hTERT is transcripted. Moreover, there is evidence for increased oxidative damage in schizophrenia. The combination of oxidative damage and diminished telomerase activity causes telomere erosion. The line width represents the pathway activity.

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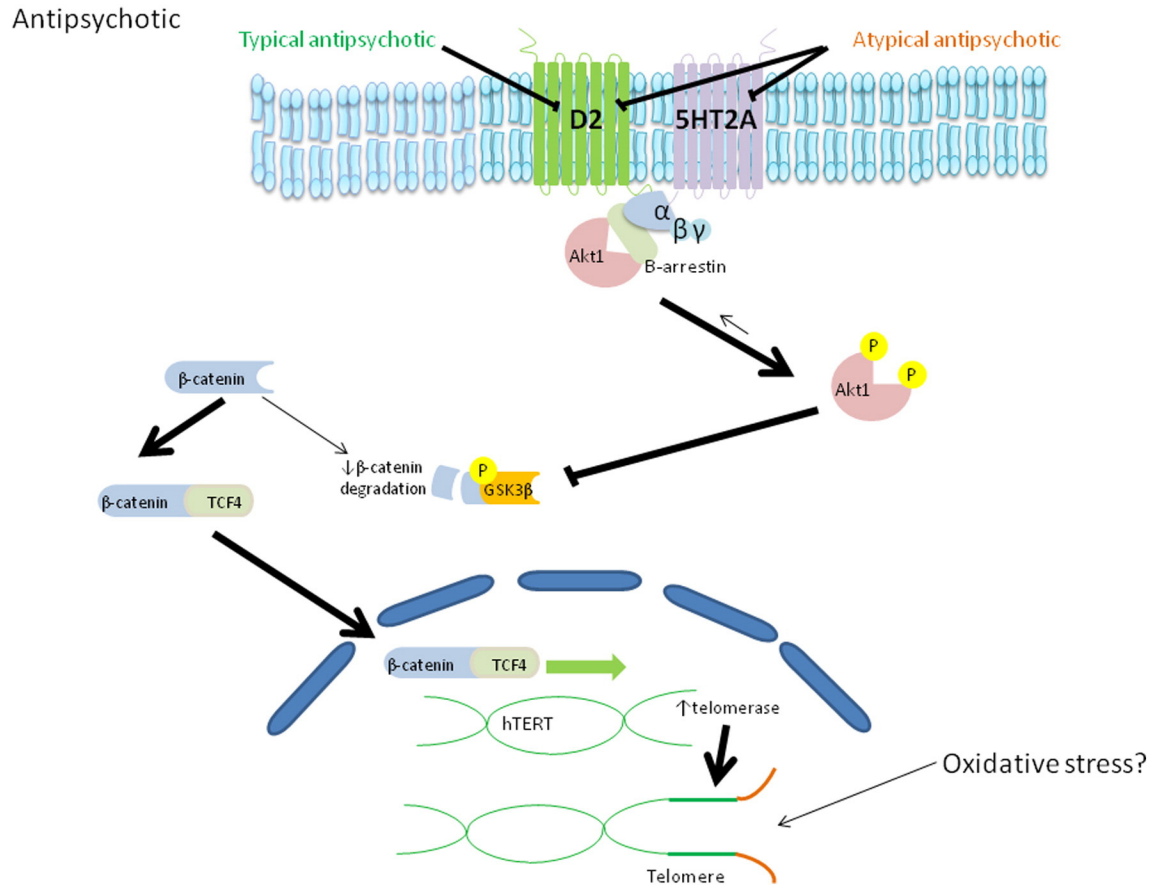

Fig. 3. Typical antipsychotics block D2 receptor, inhibiting Protein Kinase B (AKT1) deactivation. Increased activity of AKT1 inhibits β-catenin degradation, allowing the expression of hTERT and increasing activity of telomerase. Atypical antipsychotics inhibit D2 and 5HT2A receptors, enhancing the inhibition of the AKT1/GSK3B pathway. All this would lead to increased activity of telomerase and consequently telomere elongation. The line width represents the pathway activity.

and showed a trend of decreased TCF4 activity associated with negative symptoms. Porton et al. (2008) found reduced telomerase activity in individuals with schizophrenia when compared to control. This evidence supports the hypothesis of telomere attrition proposed (Fig. 2).

According to Li and Jope (2010), some antipsychotics are able to increase the serine-9-phosphorylated form of GSK3β (inactive form) in the mouse or human brain. Because atypical antipsychotics block both D2 and 5-HT2A receptors, the result on telomerase expression may be enhanced, possibly permitting telomere elongation (Fig. 3).

Most studies measured the telomere length in DNA from leukocytes. However, both typical and atypical antipsychotics alter leukocyte functioning (Leykin et al., 1997; Müller et al., 2012). According to Leykin et al. (1997), clozapine and haloperidol inhibited in vitro leukocyte mitosis stimulation by phytohemagglutinin in 50% of treated patients and suppressed the production of the interleukins analyzed. In addition, Porton et al. (2008) reported decreased telomerase expression in *healthy* individuals' leukocytes in vitro using clozapine and haloperidol separately and above the therapeutic range (Porton et al., 2008).

4.3. Metabolic syndrome

Besides direct antipsychotic effects on the receptors mentioned, people with schizophrenia have other diseases that may influence TL. Metabolic syndrome, which is a known side effect of pharmacological therapy more pronounced with atypical antipsychotics use, includes weight gain, high blood pressure and increased risk for type 2 diabetes mellitus (Maayan and Correll, 2010). However, some studies suggest that metabolic dysregulation is independent of the medication used in treatment: the relationship between schizophrenia and type 2 diabetes mellitus is known since the 19th century, before the antipsychotics discovery (Bushe, 2004).

Metabolic syndrome is a pro inflammatory state (Emanuela et al., 2012) and increases OS systemically (Roberts and Sindhu, 2009), probably leading to telomere erosion. Satoh et al. (2008) showed that OS in patients with coronary arterial disease and metabolic syndrome was higher than in those without metabolic syndrome. The work also revealed decreased telomere length in patients with coronary arterial disease and metabolic syndrome, when compared with those without metabolic syndrome. The OS and TL were negatively correlated. Therefore, the results found in the study with schizophrenia individuals might be a consequence of the metabolic dysregulation, rather than the psychiatric disorder itself.

4.4. Smoking

Some studies used in the meta-analysis suggest that increased prevalence of smokers among schizophrenia cases may be a confounding factor for diminished telomere length (Fernandez-Egea et al., 2009; Mansour et al., 2011; Nieratschker et al., 2013; Kota et al., 2014; Malaspina et al., 2014). However, a recent 10-year-follow-up study showed that the rate of telomere shortening is unrelated to smoking and other lifestyle factors, despite the existence of this relation in some cross-sectional analyses (Weischer et al., 2014).

All studies included in this meta-analysis used cross-sectional data. As observed, this type of study is not the best to evaluate the rate of telomere erosion. Long term studies evaluating TL in individuals with schizophrenia are necessary.

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4.5. Paternal age

Paternal age has been associated with TL in several longitudinal studies, with large cohorts (Kimura et al., 2008; Prescott et al., 2012). Malaspina et al. (2014) showed that advanced paternal age conferred longer telomeres to male individuals with schizophrenia, whereas the effect in the female offspring was the opposite. Furthermore, advanced paternal age is a risk factor for developing schizophrenia. According to Nieratschker et al. (2013), telomere length may be a biomarker of paternal age at the time of conception and not directly causing the disease.

5. Conclusion

Our study did not reveal any significant differences in TL between individuals with schizophrenia and healthy subjects. However, the evidence suggests an association of shortened TL with schizophrenia and that this condition might be reverted with treatment. There are few studies regarding this problem and most did not consider other important factors which have been associated with TL modification in schizophrenia such as: smoking status, metabolic syndrome and other comorbidities, antipsychotic treatment and paternal age. In addition, all of the studies considered in this meta-analysis were cross-sectional, which can not reveal telomere erosion rate. More and better controlled long term studies are required to unveil the telomere biology in schizophrenia.

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Contributors

All authors designed the study and wrote the protocol. Authors Polho and Kerr managed the literature searches and analyses. Authors dos Santos and Kerr undertook the statistical analysis, and author Polho wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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