Journal of Psychiatric Research 76 (2016) 84–93

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Shortened telomere length in patients with depression: A meta-analytic study

Pao-Yen Lin [a, b, *, 1], Yu-Chi Huang [a, 1], Chi-Fa Hung [a]

[a] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[b] Center for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

ARTICLE INFO

Article history:
Received 4 September 2015
Received in revised form
24 January 2016
Accepted 29 January 2016

Keywords:
Depression
Meta-analysis
Stress
Telomere

ABSTRACT

Background: Accelerated telomere shortening is associated with stress-related cell damage and aging. Patients with depression have been shown to have shortened life expectancy and to be associated with multiple age-related systemic diseases. Previous studies have examined leukocyte telomere length (LTL) in patients with depression, but have shown inconsistent results.

Methods: We conducted meta-analyses by pooling relevant results strictly from all eligible case–control studies for cross-sectional comparison of LTL between depressive patients and control subjects (16 studies involving 7207 subjects). The effect sizes (shown as Hedges' g) of each individual study were synthesized by using a random effects model.

Results: Our analysis revealed telomere length is significantly shorter in subjects with depression in comparison to healthy controls (Hedges' $g = -0.42$, $p = 1 \times 10^{-5}$, corresponding to $r = -0.21$). Significant heterogeneity among studies examining LTL in subjects with depression was found ($Q = 116.07$, $df = 16$, $I^2 = 86.21\%$, $p < 1 \times 10^{-8}$), which can possibly be explained by methods used in measuring telomere length ($Q = 18.42$, $df = 2$, $p = 1 \times 10^{-4}$). There was no significant publication bias, nor moderating effect of age, female percentage, or illness duration of depression on synthesized results.

Conclusions: Our results support the hypothesis that depression is associated with accelerated cell aging. Future studies are required to clarify whether the association is mediated through environmental stress, and whether effective treatment can halt cell aging.

1. Introduction

Telomeres, complexes composed of both tandem repeated guanine-rich DNA and specified proteins, cap the ends of eukaryotic chromosomes. They protect DNA from damage and related consequences of genome instability when cells undergo repetitive mitotic divisions (Blackburn, 2001, 2005). The rate of telomere shortening can be decreased by the cellular enzyme telomerase, an RNA-dependent DNA polymerase (Blackburn, 2005). The function of telomerase is to maintain telomere length by synthesizing telomeric repeat sequences to the ends of chromosomal DNA during cell replication to maintain a healthy cell status (Epel et al., 2006; Kim et al., 2003), and telomerase activity is positively associated with telomere length (Lin et al., 2010; Wolkowitz et al., 2012). Normal human somatic cells are reported to have 5–15 kilobase pairs (kbp) in telomere length, which shortens on average 15–20 bp per year through cell division (Allsopp et al., 1992; Bekaert et al., 2005). Cells will be susceptible to senescence and apoptosis when telomeres length becomes critically short, between 0 and 2.8 kbp (Allsopp and Harley, 1995; Blackburn, 2005).

Telomere length is proposed to be a valuable biomarker of aging (Bekaert et al., 2005; O'Donovan et al., 2012), which is related to declining physiological integrity, the following functional impairment and susceptibility to death (Lopez-Otin et al., 2013). Aside from normal aging, mounting evidences suggest that telomere length is not only related to individual's age-related physical illnesses, such as cardiovascular disease (CVD) (Fitzpatrick et al., 2007; Haycock et al., 2014), cancer (Campisi, 2005; Ma et al., 2011), Alzheimer disease (Hochstrasser et al., 2012), cancer mortality or all-cause mortality (Cawthon et al., 2003; Rode et al., 2015; Weischer et al., 2013), but also associated with major depressive

* Corresponding author. Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, 123, Dapi Road, Niaosong District, Kaohsiung City 833, Taiwan.
E-mail addresses: paoyenilin@gmail.com, py1029@adm.cgmh.org.tw (P.-Y. Lin), ychuang01@gmail.com (Y.-C. Huang), chifa.hung@gmail.com (C.-F. Hung).
[1] Drs. Pao-Yen Lin and Yu-Chi Huang contributed equally as the first authors.

http://dx.doi.org/10.1016/j.jpsychires.2016.01.015
0022-3956/

disorder (MDD) (Hartmann et al., 2010).

MDD has been recognized as a serious public health problem causing detrimental impact and excess medical costs (Ferrari et al., 2013). MDD has worldwide high point and lifetime prevalence of 4.4% and nearly 16.2% respectively (Ferrari et al., 2013; Kessler et al., 2007). The patients with MDD not only suffer from psychological impact, but also endure excess risks for age-related physical diseases, including CVD, stroke, diabetes, metabolic syndrome, dementia, and related mortality (Brown et al., 2004; Irwin and Miller, 2007; McCusker et al., 2007; Musselman et al., 1998). Among them, the risk of cardiac death was increased by 68% in those with depression (Gasse et al., 2014). The association among depression and accelerated age-related physical and functional decline supports the concept of premature telomere length shortening over time in patients with MDD.

In the past decade, clinical investigations have shown shortened telomere length in leukocytes in patients with depression (Cai et al., 2015; Hartmann et al., 2010; Simon et al., 2006; Wikgren et al., 2012). It was estimated that telomere length shortening may represent 4–10 years of accelerated aging in subjects with MDD (Simon et al., 2006; Verhoeven et al., 2014). But some conflicting results were also discovered (Ladwig et al., 2013; Teyssier et al., 2012). The discrepancy in their results may be related to differences in study design, including sample population, diagnosis assessment of psychiatric disorders, and methods in measuring telomere length. In addition, individual studies with small sample sizes may have insufficient statistical power to detect small but significant effects. Recently, two meta-analytic studies have examined the relationship between depression and telomere length (Ridout et al., 2015; Schutte and Malouff, 2015). The study by Schutte and Malouff (2015), including 25 studies with 21,040 participants, found that depression was associated with shorter leukocyte telomere length (LTL). The latest meta-analysis by Ridout et al. (2015), expanding the subjects to 38 studies with 34,347 participants and including samples from saliva and brain tissues, confirmed the association between depression and shorter telomere length. However, the significance of these studies was undermined by their inclusion of many studies examining the correlation between LTL and the degree of depressive symptoms in the general population, rather than direct comparison between clinically-diagnosed depression and control subjects. And high heterogeneity among studies may have resulted from pooling of correlation studies and case–control studies and including samples other than leukocytes. In addition, various self-report assessments of depression may have contributed to the publication bias in estimating the magnitude of the effect size.

In this study, we aimed to conduct a meta-analysis to pool relevant results strictly from all eligible case–control studies to analyze LTL in patients with depression, and examine the overall difference in LTL between patients with depression and healthy controls and determine possible moderating effects to account for the difference.

2. Methods

2.1. Literature search

To identify eligible studies, two independent reviewers (P.-Y. Lin and Y.-C. Huang) searched for studies available by July 2015 in the electronic databases of PubMed at the National Library of Medicine, Scopus, and Google Scholar. The search was performed by using the search terms (telomere) AND (depression), without special limitation in language. The references of relevant articles and review articles in this area were searched for citations not indexed in above databases. The titles and abstracts of studies obtained by this search strategy were screened by the independent reviewers to determine if the studies were potentially eligible for inclusion in this meta-analysis, and to exclude studies that were apparently non-eligible, such as review articles, non-human studies, and studies not mentioning telomere. In case of disagreement in eligibility, we reached agreement through consensus.

2.2. Inclusion criteria of studies in the meta-analysis

The included manuscripts passing the initial screening were examined based on the inclusion criteria used in this meta-analysis, including studies that: (1) included patients with depression, (2) used samples from leukocyte DNA, (3) measured telomere length, (4) included case–control comparison between subjects with depression and control subjects, and (5) dataset that did not overlap with other studies. There is no limitation about the type of diagnostic criteria of depression, if it clearly described cases and non-cases in the manuscript. In addition, leukocytes are the predominant nuclear cells in peripheral blood, and the main leukocyte subtypes include neutrophils, monocytes, and lymphocytes. Hence, the telomere samples which were designated from “peripheral blood” or peripheral blood mononuclear cell (PBMC) was regarded as equivalent to being from leukocytes. When dataset from two studies overlapped, we included only the study with the larger sample size between them. The process of study selection was described in Fig. 1.

2.3. Meta-analytic methods

The first purpose was to compare LTL between patients with depression and controls. The diagnoses of depression were based on criteria provided in individual studies.

For each identified study, the effect sizes (ESs) expressing the difference in telomere length between patients and controls were described as standardized mean differences (SMDs) based on Hedges' adjusted *g*, where values greater than 0 indicated that the telomere was longer in patients. The means and standard deviations of telomere length of both patients and controls were used to derive the ES from each included study. When these data could not be available from these articles, we contacted the authors to acquire the data or derived the ES from other statistical parameters, such as *t* value or *p* value. The ESs of individual studies were synthesized by the random effects model (Shadish and Haddock, 1994). The significance of the pooled ES was determined by the z-test. Sensitivity analyses were performed in the analysis that resulted in significant difference to determine if any individual study was responsible for the significant result. Each study was individually removed and the significance was re-tested.

Heterogeneity was examined to determine whether the group of ESs came from a homogeneous source and assessed by Q statistics, their related *p*-value, and the I^2 statistic, which is the percentage of the variability in the estimate of effects that is due to heterogeneity rather than random error. A larger value of I^2 statistic indicates higher heterogeneity. A rejection of homogeneity suggests that there may be systemic differences existing among the included studies. In addition, we used Egger's regression to statistically test for evidence of publication bias (Egger et al., 1997). To examine whether mean age, gender distribution (percentage of females), or duration of illness of included subjects moderates the ES, we performed meta-regression by using the unrestricted maximum likelihood method. In addition, we examined the pooled effect in separate groups of studies based on the methods used for measuring telomere length (southern blot, polymerase chain reaction (PCR), or fluorescent in situ hybridization (FISH)).

Statistics in meta-analyses were performed by applying