Pain Is Associated With Short Leukocyte Telomere Length in Women With Fibromyalgia

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Abstract: Telomere length, considered a measure of biological aging, is linked to morbidity and mortality. Psychosocial factors associated with shortened telomeres are also common in chronic pain; yet, little is known about telomere length in pain populations. Leukocyte telomere length was evaluated in 66 women with fibromyalgia and 22 healthy female controls. Participants completed questionnaires and a subgroup of fibromyalgia patients underwent quantitative sensory testing (QST; n = 12) and neuroimaging (n = 12). Telomere length was measured using the quantitative polymerase chain reaction method. Although patients had shorter telomere length than controls, the difference was not statistically significant. However, higher levels of pain within fibromyalgia were associated with shorter telomere length (P = .039). When pain and depression were combined, patients categorized as high-pain/high-depression had an age-adjusted telomere length 265 base pairs shorter than those with low-pain/low-depression (P = .043), a difference consistent with approximately 6 years of chronological aging. In the subset tested, telomere length was also related to pain threshold and pain sensitivity, as well as gray matter volume, such that patients with shorter telomeres were more sensitive to evoked pain and had less gray matter in brain regions associated with pain processing (eg, primary somatosensory cortex). These preliminary data support a relationship between pain and telomere length.

Perspective: Our findings support a link between premature cellular aging and chronic pain. These preliminary data imply that chronic pain is a more serious condition than has typically been recognized in terms of bodily aging.

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Key words: Pain, fibromyalgia, telomere, premature aging, neuroimaging.

Telomeres are specialized DNA-protein structures that cap chromosomal ends and are essential for chromosome stability.4,5 During mitosis, the telomere is not fully replicated; thus, telomeres shorten with age.5 Telomere length can also be influenced by stressors independent of chronological age19,36,40,43,48,57,60,75 and is consequently thought to represent an individual's cumulative exposure to and ability to cope with stress.84 Supportive of this notion, several studies have linked aspects of hypothalamic-pituitary-adrenal axis dysfunction (thought to be reflective of chronic stress arousal) to telomere length.9,20,41,73,77 Overall, telomere length may more accurately reflect the biological age of an organism and has been shown to be predictive of the incidence of age-related diseases (eg, coronary heart disease, cancer, hypertension, rheumatoid arthritis),22,25,70,78,79 disease burden,67 and mortality.6,8,21,79

Chronic pain affects over 100 million Americans53 and is arguably one of the most protracted and debilitating forms of stress. The associations between chronic pain and stress, morbidity, and mortality have long been recognized44,49,51,52,81,83; however, we are just now exploring the association between persistent pain and telomere integrity. A recent study by Sibille et al88 assessing patients with osteoarthritis reported that having high levels of pain and stress together was associated with telomere shortening. Although this study was small
and its data preliminary, the findings suggest a potential link between chronic pain and premature aging.

Fibromyalgia is one form of chronic pain that has been linked to many of the same factors that are associated with shortened telomere length (eg, psychological stress, trauma, depression, obesity, hypothalamic-pituitary-adrenal axis dysfunction). To date there have been no studies evaluating telomere length in fibromyalgia or studies examining the influence of pain alone on telomere length. Beyond sharing factors associated with shortened telomeres, the possibility that fibromyalgia could be a condition associated with premature aging is supported by several lines of evidence. First, individuals with fibromyalgia report significant lifetime comorbidity with age-related diseases including cardiovascular disease, neurological disorders, endocrine disorders, and respiratory illness. Second, several but not all epidemiologic studies have shown that the presence of chronic widespread pain is associated with an increased risk of death. For example, a recent study found that having higher levels of pain conferred increased risk for mortality, and those who met American College of Rheumatology survey criteria for fibromyalgia had a greater risk of death than those who did not. Third, there is some evidence that the cognitive performance of young females with fibromyalgia is more like the performance of healthy women 20 years older. Finally, studies of brain morphology in fibromyalgia have found decreases in gray matter volume consistent with the notion of premature aging.

We propose a model in which the relationship between telomere length and chronic pain is bidirectional and additive, such that 1) genetic and various stress factors result in telomere shortening, which denotes vulnerability to chronic pain; and 2) once present, chronic pain contributes to the physiological and psychological load that accelerates telomere shortening (Fig 1). The present study was designed to take an incremental step in evaluating this model. Because depression is common in fibromyalgia and is associated with telomere shortening, we examined telomere length in female fibromyalgia patients both with and without depression. We also compared telomere length in patients to a small group of healthy female controls. We hypothesized that 1) individuals with fibromyalgia would have shorter telomeres compared to healthy controls; 2) clinical pain and sensitivity to experimentally induced pain would be related to telomere length; and 3) pain and depression would have both unique and additive effects related to telomere length. Lastly, because decreases in gray matter volume consistent with premature aging have been reported in fibromyalgia, we explored the relationship between telomere length and gray matter volume using voxel-based morphometry.

Methods

Subjects

This study consisted of a convenience sample of individuals who had given informed consent to have their questionnaire data and DNA used for pain research. As such, individuals in these analyses were taken from 2 different sources, the Fibromyalgia Registry at the Chronic Pain & Fatigue Research Center (CPFRC) at the University of Michigan (fibromyalgia: n = 17 and healthy controls: n = 22) and from a CPFRC study conducted in collaboration with the Avera Research Institute (fibromyalgia only: n = 49). Common assessment protocols permitted the aggregation of data across studies. This study was approved by the Institutional Review Board of the University of Michigan Medical School.

Every available whole blood sample from a female fibromyalgia patient or female healthy control subject was considered. Samples were omitted only if the storage tube was damaged or pertinent demographic data were missing. The samples from a total of 66 individuals with fibromyalgia and 22 healthy controls were considered for analysis. In addition, some participants had quantitative sensory testing (QST) data (fibromyalgia: n = 12) and structural neuroimaging scans (fibromyalgia: n = 12; controls: n = 5) available for analysis. Every individual with such additional data was included in the subsequent analyses.

Inclusion/Exclusion Criteria

Inclusion criteria consisted of the following: 1) meeting 1990 American College of Rheumatology criteria for fibromyalgia, 2) ≥18 years of age; and 3) under the standard medical care of a physician. Subjects were excluded from participation if they had any of the following: 1) severe physical impairment precluding meaningful participation; 2) comorbid medical illnesses capable of causing a worsening of functional status, such as Class III obesity (body mass index [BMI] ≥40), autoimmune diseases, cardiopulmonary disorders, uncontrolled endocrine disorders, malignancy within 2 years; 3) psychiatric disorders involving psychosis, current suicide risk or attempt within 2 years, or substance abuse within 2 years; and 4) pending status associated with disability or receipt of disability compensation within 2 years. Healthy controls fulfilled the above exclusion criteria but also did not meet criteria for fibromyalgia or depression.

Clinical Measures

Clinical pain was assessed using the 15-item Brief Pain Inventory-Short Form (BPI). The BPI has good reliability.
Quantitative Sensory Testing

Pressure pain sensitivity was evaluated in 12 females with fibromyalgia (mean ± SD age in years: 43.5 ± 12.1). Discrete pressure stimuli were delivered by a custom-built apparatus that eliminated direct patient contact by the examiner. This device employed a hydraulic system to apply pressure to the thumbnail bed via a 1-cm² hard rubber circular probe. The thumbnail was chosen because it represents a "neutral site" that is not associated with fibromyalgia tender points and has been shown to be highly representative of overall pressure sensitivity. The probe was positioned over the center of the patient's nondominant thumbnail by a hand-held plastic housing, and the hydraulic system was activated by placing calibrated weights on a moveable platform and adjusting valves to control stimulus timing. The probe was lowered to apply pressure consistent with the weight on the moveable platform. The combination of valves and calibrated weights produced controlled and repeatable stimulation. The testing sequence consisted of an ascending series of pressure stimuli of 5-second duration delivered at 20-second intervals, beginning at .25 kg/cm² and increasing in .25 to .50 kg/cm² increments, up to tolerance or to a maximum of 10 kg/cm². Patients rated each pressure sensation using a numerical descriptor scale of pain intensity. This scale lists the numbers 0 to 20 in descending order next to a set of words ranging from "no pain sensation" (0) to "extremely intense pain" (20). Custom software calculated the pressure pain threshold (defined as the first pressure rated greater than 0), as well as the amount of pressure required to evoke pain sensations rated between 1 and 2 ("slightly intense" pain) and 3 and 4 ("mild" pain) and 13 and 14 ("intense pain").

Voxel-Based Morphometry (VBM)

Twelve female fibromyalgia patients (mean ± SD age in years: 45.1 ± 11.3) and 5 healthy controls (age in years: 34.2 ± 11.4) had undergone magnetic resonance imaging at 3 Tesla (TR = 12.3 ms, TE = 3.4 ms, flip angle = 25°, field of view = 24 cm, yielding 106 sagittal slices with acquired voxel size of .94 × .94 × 1.5 mm and reconstructed to 1 × 1 × 1). Eleven of the 12 patients were also those with QST data as described above. No patients with available QST or VBM data were excluded. Anatomical scans were acquired using a high-resolution T1-weighted anatomical protocol. All data preprocessing was performed using Statistical Parametric Mapping 5 (SPM5; http://www.fil.ion.ucl.ac.uk/spm/software/) operating within Matlab (Natick, MA). Data preprocessing included rean-gulation (centering the images on the anterior commissure), spatial normalization, segmentation, modulation, and smoothing with a Gaussian kernel of 8 full width at half maximum. Classification of brain tissue into gray matter, white matter, and cerebral spinal fluid was performed by the SPM5 VBM toolbox. A whole brain regression analysis was performed using a general linear model with voxel gray matter volume as the dependent variable and with telomere length as a covariate. In this model, the relationship between telomere length and regional gray matter volume is compared across the entire brain. Age was also included as a nuisance variable. Statistical maps were generated separately for patients and controls. Clusters of 69 contiguous voxels, reaching a threshold of $P < .001$ were considered significant and survived multiple comparisons based on calculations performed by the Alphasim software toolbox. Regions of interest showing a significant relationship between gray matter volume and telomere length were extracted and analyzed using SPSS version 19 (SPSS Inc, Chicago, IL).
Statistical Analysis

Between-group comparisons of demographic and psychosocial variables were conducted using t-tests for continuous variables and Chi square tests for categorical variables. To explore the relationships between telomere length, clinical pain, and other factors previously shown to be associated with telomere length (ie, BMI, depressive symptoms, perceived stress, and state and trait anxiety), Pearson's correlations were calculated for the whole group (patients and controls), followed by separate partial correlations controlling for age (for patients only because most controls were not evaluated for the other variables). To evaluate differences in telomere length between patients and controls, a linear model was used with age as a covariate. To assess the effects of having higher and lower levels of pain on telomere length, analysis of covariance (ANCOVA) with age as a covariate was used to compare patients divided into 2 groups: higher levels of pain (BPI ≥5/10) and lower levels of pain (BPI <5/10). A second ANCOVA, also using age as a covariate, was conducted to compare patients with higher levels of depressive symptoms (CES-D scores ≥19) to those with lower levels (CES-D scores <19) in regard to telomere length. To assess the combined effects of pain and depression, a median split was used to categorize patients as having a) high or low pain; and b) high or low depression. Using a median split resulted in groups more equivalent in size when categorizing as 1) high-pain and high-depression; 2) high-pain and low-depression; 3) low-pain and high-depression; and 4) low-pain and low-depression. Analysis of variance of telomere length, using age as a covariate and followed by Tukey's HSD test, was used to evaluate differences among groups.

To expand our analyses beyond clinical pain, the relationships between experimental pain (QST) and telomere length were evaluated using partial Pearson's correlations controlling for age for 3 levels of pressure intensity (kg/cm²) corresponding to pain threshold, mild pain, and slightly intense pain ratings. We also considered VBM neuroimaging data to assess the associations between gray matter volume in pain processing areas of the brain and telomere length. For the VBM analysis, we examined the relationship between telomere length and gray matter volume separately for patients and controls. The VBM data analytic strategy is described in the related section above. All other data were analyzed using the R statistical programming environment. P values were not adjusted for multiple comparisons unless otherwise indicated.

Results

Telomere Length in Patients and Controls

Sample characteristics are described in Table 1. Overall, the fibromyalgia patients were older than the healthy controls (t = −3.15, P = .002) but similar in regard to BMI and ethnic/racial composition. Patients also had more depressive symptoms compared to healthy controls (t = −9.78, P < .001). As hypothesized, in an analysis using the full sample (patients and controls), older age was associated with shorter telomere length (r = −.595, P < .001), as was higher BMI (r = −.337, P = .001). Partial correlations revealed, however, that BMI was marginally associated with telomere length after controlling for age (r partial = −.247, P = .077). Because patients were older than controls, a linear model that included age was used to evaluate potential differences in telomere length. The difference in telomere length between patients (1.02 ± .16) and controls (1.11 ± .17) was not statistically significant (P = .183).

Associations Between Telomere Length and Pain and Psychosocial Factors

To assess the associations between telomere length and clinical pain, depression, perceived stress, and anxiety, partial correlations controlling for age were conducted for all fibromyalgia patients with data available. We found significant relationships between telomere length and both pain (r partial = −.267, P = .039) and depressive symptoms (r partial = −.247, P = .048). A similar analysis for perceived stress approached significance (r partial = −.209, P = .110), while no significant relationships were found for telomere length and measures of state (r partial = .105, P = .477) and trait anxiety (r partial = .005, P = .975). Other correlational analyses conducted revealed that duration of illness was not significantly associated with telomere length when controlling for age (P = .129). Also, pain severity and depressive symptoms were not related although the expected trend was observed (P = .075). Lastly, age was not associated with pain (P = .915) or depressive symptoms (P = .375).

Investigation of the Relationship Between Pain, Depression, and Telomere Length

Finding both pain and depressive symptoms to have important relationships with telomere length, we explored individual and combined effects of these variables. In a comparison of patients categorized as having higher levels of pain (BPI ≥5/10; n = 30) and lower levels of pain (BPI <5/10; n = 31), those with higher levels of pain were more likely to have shorter telomere length than those with low levels of pain despite chronological age (F = 5.39, P = .024) (Fig 2). Fig 3 depicts telomere lengths by age for low- and high-pain groups. The difference in telomere length between higher pain and lower pain groups was estimated at 193 base pairs (age adjusted). In a similar comparison of telomere length between those with likely depression (CES-D scores ≥19; n = 24) and those likely without depression (CES-D scores <19; n = 42), no significant group differences were detected (P = .175). However, the combined effects of depressive symptoms and pain severity revealed a significant relationship with telomere length. Analysis of the effects of the 4 pain/depression subgroups (allocated based on a median split), controlling for age, showed a significant difference between the low-pain/low-depression and the high-pain/high-depression groups.
The difference in telomere length between low-pain/low-depression and high-pain/high-depression groups was approximately 265 base pairs (age adjusted).

**Quantitative Sensory Testing**

Similar to the clinical pain data above, significant relationships between telomere length and evoked pain sensitivity were found in fibromyalgia patients, even when controlling for age. Short telomere length was associated with having a lower pressure pain threshold ($r_{\text{partial}} = .728, P = .017$) and greater sensitivity to both mild ($r_{\text{partial}} = .642, P = .045$) and slightly intense ($r_{\text{partial}} = .706, P = .023$) pressure intensities.

**Voxel-Based Morphometry**

Additional evidence supportive of telomere shortening in chronic pain came from a subset of patients with fibromyalgia with whom we had also collected structural brain imaging data. Controlling for age, we found telomere length to be positively correlated with gray matter volume across patients. Fibromyalgia patients showed significant positive correlations ($P < .05$, corrected for multiple comparisons) between telomere length and gray matter volume within the right primary somatosensory cortex ($r = .725$), the left middle frontal gyrus ($r = .858$), and the left precuneus ($r = .661$) (Fig 4). Gray matter volumes from these same regions were extracted from the healthy control participants and none of these regions displayed a significant correlation with telomere length.

**Discussion**

To our knowledge, this is the first study to examine the unique relationships between leukocyte telomere length and clinical pain in fibromyalgia and pain sensitivity in any chronic pain condition. We found that having higher levels of pain was associated with shorter telomere length despite one’s age. For example, when patients with higher levels of clinical pain were compared to those with lower levels of pain, we found an age-adjusted difference in telomere length of 193 base pairs. Given that the rate of loss of base pairs has been estimated to be $\sim 42$ per year, the higher pain group demonstrated an additional loss of telomere length comparable to 4 to 5 years of chronological aging. A similar significant difference in telomere length did not exist between depression groups.

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**Table 1. Characteristics of the Samples**

<table>
<thead>
<tr>
<th></th>
<th>Fibromyalgia Patients ($n = 66$)</th>
<th>Healthy Controls ($n = 22$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>44.6 (12.1)</td>
<td>33.5 (11.2)</td>
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<td>Race/ethnicity, white non-Hispanic, % (n)</td>
<td>92.4 (61)</td>
<td>88.5 (20)</td>
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<td>BMI, mean (SD)</td>
<td>27.8 (4.9)</td>
<td>26.2 (5.9)</td>
<td>.176</td>
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<td>Duration of fibromyalgia, years, mean (SD)</td>
<td>8.8 (6.1)</td>
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<td>-</td>
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<td>CES-D depressive symptoms, mean (SD)*</td>
<td>17.1 (11.6)</td>
<td>2.4 (1.8)</td>
<td>&lt; .001</td>
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<td>BPI pain severity score, mean (SD)</td>
<td>4.8 (1.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PSS perceived stress, mean (SD)</td>
<td>16.1 (6.4)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Telomere length (T/S ratio)</td>
<td>1.02 (1.16)</td>
<td>1.11 (1.17)</td>
<td>.017</td>
</tr>
</tbody>
</table>

*CES-D data for all patients and 17 controls.

**Figure 2.** Dot plot depicting telomere length in fibromyalgia patients with higher levels of pain versus those with lower levels of pain. Individuals with higher levels of pain had significantly shorter telomeres than did those with lower levels of pain while controlling for age ($P = .024$). Telomere length shown has been standardized to the median patient age of 47.

**Figure 3.** Telomere lengths by age for low- and high-pain groups (patients only). Curves indicate Loess smooths; gray represents the 95% confidence bands.
While telomere length did not differ among dichotomous depression groups, level of depressive symptoms was related to telomere length, and high levels of depressive symptoms seemed to compound the effect that pain had on telomere shortening. Individuals with fibromyalgia in the high-pain/high-depression group had a mean adjusted telomere length that was 265 base pairs shorter than those in the low-pain/low-depression group. This difference between groups translates to over 6 years of chronological aging. Finding an association between depressive symptoms and telomere length in our study was anticipated. A lifetime history of depression is estimated to occur in over half of individuals with fibromyalgia in the high-pain/high-depression group had a mean adjusted telomere length that was 265 base pairs shorter than those in the low-pain/low-depression group. This difference between groups translates to over 6 years of chronological aging. Finding an association between depressive symptoms and telomere length in our study was anticipated. A lifetime history of depression is estimated to occur in over half of individuals with fibromyalgia in the high-pain/high-depression group had a mean adjusted telomere length that was 265 base pairs shorter than those in the low-pain/low-depression group.

What is unique about this study was that pain was explored in addition to depressive symptoms, and we found that pain appears to have a distinctive and potentially stronger relationship with telomere length than depression—at least in fibromyalgia. We also observed that there was a trend for patients with fibromyalgia to have shorter telomere length than controls; however, the limited number of patients and even smaller number of controls (n = 22) evaluated herein do not enable us to draw firm conclusions from these early data. Further, several other initial studies evaluating now well-appreciated risk factors for telomere shortening (eg, perceived stress, depression, trauma) failed to find group differences in early investigations—mostly due to relying on small samples. 

This also appears to be true for the only other published clinical study comparing patients with and without chronic pain. Nonetheless, in that same study, differences were found among the patients when both pain and stress were considered. Studies are needed that possess sufficient sample sizes and the rigorous measurement of the many comorbidities known to be associated with decreased telomere length that were not captured in our preliminary convenience sample. The lack of such comorbidities data is a significant limitation of this study.

In a subset of fibromyalgia patients, we observed relationships between telomere length and evoked pain sensitivity where patients with shorter telomeres tended to be more sensitive to pressure pain. These findings support those from our assessment of clinical pain and telomere length. In regard to QST findings, both pressure pain threshold and suprathreshold pressures (pressures that evoked pain sensations rated as “mild” and “slightly intense”) were related significantly to telomere length. This is the first demonstration of a relationship between QST findings and telomere length. Although replication in a larger cohort with additional pain modalities is warranted, these data from a small subset of patients suggest a potential link between sensory processing in chronic pain and telomere length.

Our exploratory VBM analysis provided preliminary evidence supporting a relationship between gray matter volume and telomere length in several regions of the brain associated with pain processing (ie, primary somatosensory cortex, left middle frontal gyrus, and left precuneus). Additionally, the middle frontal gyrus and precuneus have been implicated in working memory, a process that differentiates individuals with fibromyalgia from healthy controls. There is precedent for demonstrating a relationship between the brain and circulating leukocyte telomere length. For example, both hippocampal brain volume and cerebellar telomere length have been associated with leukocyte telomere length. However, the factors accounting for the indirect relationship between leukocyte telomere length and brain volumetric measures are unknown, but it could be due to a common biochemical environment. It may be that the experience of chronic pain, including the physiological response to pain over time, contributes to gray matter loss in sensory/pain processing areas (somatosensory cortex), as well as areas involved in attention and cognition (ie, middle frontal gyrus, precuneus). This gray matter loss could be due to a number of factors including excitotoxicity of neurons resulting from elevated glutamatergic neurotransmission leading to changes in synaptic plasticity and/or neuronal cell death. Any of these processes could decrease relative gray matter within a given area.

Overall, the mechanisms by which chronic pain is associated with telomere shortening are unclear, although persistent stress and related biochemical factors (eg, cortisol, oxidative stress, glutamate-induced excitotoxicity, proinflammatory cytokines) are presumed to play an important role in telomere shortening. Although the data are generally mixed, there are a number of recent studies, reviews, and meta-analyses supporting an association between fibromyalgia and hypocortisolism, high levels of oxidative stress, high levels of glutamate, and elevations of proinflammatory cytokines, especially IL-6 and IL-8. Further, obesity is common in fibromyalgia, and increased fat mass, especially abdominal obesity and alterations in adipocytokines, has been related to telomere length. A limitation of this current study was that such biochemical factors were not assessed. Future studies of pain and telomere length should include the assessment of these factors to begin to elucidate underlying mechanisms.
At the center of our model are the bidirectional and additive effects of physiological stress arousal: stress factors, high perceived stress, and/or depression result in telomere shortening, rendering the organism vulnerable to chronic pain; once chronic pain is manifested, it contributes to the physiological and psychological load and accelerates telomere shortening (Fig 1). Yet, we did not find a significant association between perceived stress and telomere shortening among fibromyalgia subjects. Upon re-examination of our data we observed that the perceived stress scores of the fibromyalgia patients in this study were uniformly higher than norms for female

Figure 4. Statistical parametric maps indicating brain regions showing a significant positive correlation between gray matter volume and telomere length overlaid on a standard SPM5 template. (A) Right primary somatosensory cortex; (B) Left middle frontal gyrus; (C) Left precuneus.
patients in this age group. \cite{13,54} It is possible that uniform high levels of perceived stress across the fibromyalgia sample could have attenuated the relationship between perceived stress and telomere length in our study.

As for the clinical implications of our research, it is not likely that short telomeres will serve as a biomarker specific for fibromyalgia since telomere shortening seems to represent a more universal vulnerability of the organism. However, telomere length could potentially predict who with fibromyalgia might experience increased pain, depression, age-related disease, and mortality, thus directing the management plan. It is also possible that short telomere length in individuals without pain could be predictive of the later development of chronic pain, perhaps postsurgery or after an injury. Lastly, there is some preliminary evidence that interventions such as exercise and meditation significantly increase telomerase activity, which can help stabilize telomere length. \cite{15,58} These studies raise the possibility that telomere length and telomerase activity could be used as potential biomarkers for treatment response.

This study is limited by a number of factors including a cross-sectional design, relying on a convenience sample that included a small number of healthy controls who were generally overweight, the absence of assessment data for all participants on all instruments, and a focus on fibromyalgia. Also, we relied on self-report measures that tend to focus more on state than on trait characteristics. This is particularly salient for depression since it has been shown that the duration of depression may have the greatest impact on telomere shortening. \cite{85} Of particular importance, the limited number of healthy controls and the fact that variables associated with telomere shortening were not exclusionary (eg, smoking, Class I or II obesity, high levels of perceived stress, sedentary lifestyle) precludes drawing firm conclusions about potential differences between groups. Another limitation is that although 3 key confounds in the assessment of telomere length—age, sex, and BMI—were considered, other potential confounds and mediators may account for some of the results. Further, the assessment of biological stress markers was absent from this study. A larger prospective study of well-phenotyped participants could address these limitations. Also, although the data are intriguing, the number of patients who took part in QST and neuroimaging was also small and thus the results should be interpreted with care. Lastly, it is not known if these results are specific to fibromyalgia or generalizable to other chronic pain populations, although a recent study by Sibille et al \cite{68} examining telomere length in osteoarthritis suggests that such research could be informative.

In summary, we have shown that, in fibromyalgia, pain is associated with shortened telomere length independent of chronological age; moreover, the relationship between pain and telomere length was present in clinical, QST, and neuroimaging data. We also observed that when severe pain and depression are comorbid, telomere shortening may be particularly pronounced. Although these results are preliminary, they suggest that chronic pain may have unique contributions to cellular aging that require further study.

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