



Accelerated aging in adults with knee osteoarthritis pain: consideration for frequency, intensity, time, and total pain sites

Kimberly T. Sibille^{a,b,*}, Huaihou Chen^c, Emily J. Bartley^b, Joseph Riley III^b, Toni L. Glover^d, Christopher D. King^e, Hang Zhang^c, Yenisel Cruz-Almeida^{a,b}, Burel R. Goodin^f, Adriana Sotolongo^g, Megan E. Petrov^h, Matthew Herbertⁱ, Hailey W. Bulls^f, Jeffrey C. Edberg^g, Roland Staud^j, David Redden^k, Laurence A. Bradley^g, Roger B. Fillingim^b

Abstract

Introduction: Individuals with osteoarthritis (OA) show increased morbidity and mortality. Telomere length, a measure of cellular aging, predicts increased morbidity and mortality. Telomeres shorten with persisting biological and psychosocial stress. Living with chronic OA pain is stressful. Previous research exploring telomere length in people with OA has produced inconsistent results. Considering pain severity may clarify the relationship between OA and telomeres.

Objectives: We hypothesized that individuals with high OA chronic pain severity would have shorter telomeres than those with no or low chronic pain severity.

Methods: One hundred thirty-six adults, ages 45 to 85 years old, with and without symptomatic knee OA were included in the analysis. Peripheral blood leukocyte telomere length was measured, and demographic, clinical, and functional data were collected. Participants were categorized into 5 pain severity groups based on an additive index of frequency, intensity, time or duration, and total number of pain sites (FITT). Covariates included age, sex, race or ethnicity, study site, and knee pain status.

Results: The no or low chronic pain severity group had significantly longer telomeres compared with the high pain severity group, $P = 0.025$. A significant chronic pain severity dose response emerged for telomere length, $P = 0.034$. The FITT chronic pain severity index was highly correlated with the clinical and functional OA pain measures. However, individual clinical and functional measures were not associated with telomere length.

Conclusion: Results demonstrate accelerated cellular aging with high knee OA chronic pain severity and provide evidence for the potential utility of the FITT chronic pain severity index in capturing the biological burden of chronic pain.

Keywords: Cellular aging, Osteoarthritis, Telomere length, Pain severity, Stress

1. Introduction

Approximately 22.7% of adults in the United States are diagnosed with osteoarthritis (OA).^{4,32,44} Osteoarthritis is not only a leading cause of disability, it is also associated with increased morbidity and mortality^{11,23,47,56,57}; OA may also

contribute toward a biological footprint. Telomere length is a marker of cellular aging. Telomeres are the DNA repeats that provide the protective covers at the ends of chromosomes, which attrite with cell divisions, a natural process of aging.⁷ Leukocyte telomere length (LTL) is negatively associated with biological and

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^a Department of Aging and Geriatric Research, University of Florida, Gainesville, FL, USA, ^b Pain Research and Intervention Center of Excellence, University of Florida, Gainesville, FL, USA, ^c Department of Biostatistics, University of Florida, Gainesville, FL, USA, ^d Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, FL, USA, ^e Department of Anesthesia, Cincinnati Children's Hospital, Cincinnati, OH, USA, ^f Department of Psychology, University of Alabama at Birmingham, Birmingham, AL, USA, ^g Department of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA, ^h College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, USA, ⁱ Center of Excellence for Stress and Mental Health (CESAMH), VA San Diego Healthcare System and University of California, San Diego, CA, USA, ^j Department of Medicine, University of Florida, Gainesville, FL, USA, ^k Biostatistics Department, School of Public Health University of Alabama at Birmingham, Birmingham, AL, USA

*Corresponding author. Address: Department of Aging and Geriatric Research, University of Florida, P.O. Box 112610, Gainesville, FL 32610-3628. Tel.: 352-294-5846; fax: 352-273-5920. E-mail address: ksibille@ufl.edu (K. T. Sibille).

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psychosocial stress^{13,41} and is predictive of morbidity and mortality.^{7,16,51}

The relationship between LTL and OA is unclear.^{55,60} In a population-based study of women, LTL was shorter in individuals with hand OA than those without the condition and negatively associated with radiographic disease severity.⁶⁰ By contrast, a second study found no differences in LTL between individuals diagnosed with OA and healthy controls.⁵⁵ Sample size, type, and extent of OA are a few factors likely contributing to these discrepancies. In addition, based on LTL studies across differing health conditions, clinical factors such as the severity and persistence are important to consider.

Leukocyte telomere length is indicated as a “downstream” marker of cumulative, persistent, biological, or psychosocial stress.⁴¹ Qualities of the “stressor” such as frequency, intensity, and duration seem to be particularly relevant in driving the biological burden of various life experiences.^{12,15,25,37,51,59} Pain is stressful. Over time, OA pain extends to other body regions and is associated with hyperalgesia, allodynia, and decreased efficiency of endogenous inhibitory mechanisms.^{19,23,29,36,43,50} Decreased physical activity and a decline in functioning are key features in OA, both of which are primarily attributable to pain.^{23,42}

A few publications have explored the possible relevance of LTL in chronic pain conditions.^{22,52,54} With an improved understanding of stress-related qualities that contribute to a cumulative biological burden (frequency, intensity, duration, and type or extent of stress)²⁸ and the limitation of current pain measures in capturing duration beyond 3 to 6 months, we recently investigated a new measure of chronic pain severity.⁵³ The chronic pain severity index is an additive index comprising 4 pain characteristics (FITT): (1) frequency of pain (intermittent or persistent); (2) intensity of pain; (3) time (duration) of chronic pain; and (4) total number of pain sites. In a large population study of individuals endorsing chronic pain, the chronic pain severity index was positively associated with biological burden, and the combined index appears to be a better predictor compared with individual pain domains.⁵³

The purpose of this study was to investigate the relationship between chronic pain severity and LTL in individuals with and without symptomatic knee OA. We hypothesized that (1) individuals with high chronic knee pain severity would have shorter telomeres compared with individuals with no or low chronic knee pain severity, (2) the individual FITT domains would not be associated with LTL, (3) the FITT index would be associated with OA pain and functioning measures, and (4) OA pain and functioning measures would not be associated with LTL.

2. Methods

2.1. Study design

Participants were recruited for a cross-sectional study from the communities surrounding the University of Florida (UF) and the University of Alabama at Birmingham (UAB) from 2010 to 2013. Participants involved in the current investigation are from a larger study titled *Understanding Pain and Limitations in Osteoarthritic Disease* (UPLOAD), which involved a biopsychosocial investigation of ethnically diverse individuals with and without symptomatic knee OA, see **Table 1** for inclusion and exclusion criteria. Participants with available baseline telomere length measures and complete data on the FITT chronic pain severity questions (described below) were considered in the current investigation. All procedures described were reviewed and approved by the University of Florida and University of Alabama at Birmingham institutional review boards.

Table 1

Inclusion and exclusion criteria.

Exclusion Criteria

Prosthetic knee replacement or nonarthroscopic surgery to the symptomatic knee
 Serious medical conditions (eg, uncontrolled hypertension \geq 150/95, heart failure, history of acute myocardial infarction)
 Peripheral neuropathy
 Systemic rheumatologic disorders (eg, rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia)
 Daily opioid use
 Mini-Mental Status Examination (MMSE) score \leq 22
 Excessive anxiety regarding protocol procedures (eg, intravenous catheter insertion, experimental pain procedures)
 Psychiatric hospitalization within the preceding year

General inclusion criteria

Between the ages of 45 and 85
 Self-identified as either African American or non-Hispanic white

Knee osteoarthritis screening questions⁴⁶

During the last 4 wk, have you had knee pain on most days?
 During the last 4 wk, have you had knee pain while climbing down stairs or walking down slopes?
 During the last 4 wk, have you had swelling in one or both knees?
 Do you have knee osteoarthritis? (If you do, was the diagnosis made by a rheumatologist or a general practitioner?)

2.2. Participants

With an initial sample size of 229, 138 individuals had complete FITT data and were eligible for inclusion in the current analysis. Two individuals had conflicting phenotyping data and were excluded resulting in a sample size of 136 adults aged 45 to 85 with and without symptomatic knee OA pain. The measures and procedures described are limited to those included in the current investigation. Inclusion and exclusion criteria are listed in **Table 1**. After a phone screening,⁴⁹ participants were seen for 2 appointments. All measures were typically collected within a 2- to 3-week period. A health assessment and physical examination were completed, knee radiographs taken, and Kellgren Lawrence scores were determined.¹ Demographics and health history information were collected. Additional measures are described below.

2.3. Clinical pain and functioning measures

Participants completed self-report measures of clinical pain and functional limitations. The Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) is a 24-item scale assessing knee OA symptoms in the last 48 hours. A 5-point Likert scale was used with items ranging from 0 to 4 (higher scores reflect greater symptom severity). Three subscales comprise the WOMAC, including pain during activities (5 items), daytime stiffness (2 items), and impairments in physical function (17 items).⁶ The Graded Chronic Pain Scale (GCPS) consists of 7 items (rated on a 0-10 scale) and examines pain severity and disability over the last 6 months. Participants rate the intensity of their current knee pain and their worst and average knee pain during the previous 6 months (characteristic pain intensity score). A disability score is also obtained by having participants rate the degree to which their knee pain interfered with daily activities during the last 6 months. Items are averaged and multiplied by 10 to generate index scores for characteristic pain intensity and disability, with higher scores indicating greater symptoms. Disability points are computed by adding points for disability days over the last 6 months with the disability score. The overall pain grade is determined by characteristic pain intensity and disability points and range

from 0 to 4.⁵⁸ Physical function was assessed with the Short Physical Performance Battery (SPPB), which includes tasks measuring standing balance, 4-m gait speed, and chair rising. Ranging from 0 to 12, a single summary performance score is calculated with lower scores indicating greater functional limitation.^{20,21}

2.4. Chronic pain severity

Pain domains of frequency of knee pain, intensity of knee pain, duration of knee pain on most days (time), and total number of pain sites were assessed. Knee pain frequency is a categorical variable (knee pain on most days, no or yes). Median splits were computed for the other 3 variables. Computation of the median splits for characteristic knee pain intensity and knee pain time (duration) were limited to those reporting knee pain in the overall sample ($n = 169$) and based on available data for each variable. Of note, the cut points incorporated in the study align for average pain intensity in adults with knee and hip OA reported by Kapstad and colleagues: 1 to 4 = mild pain, >4 to 6 = moderate pain, and >6 to 10 = severe pain.²⁴ Thus, the cut point in our article falls between the “no to mild pain” and “moderate to severe pain.” In addition, the cut point is similar to the average pain intensity cut point incorporated in the FITT index in the previously reported population-based study.⁵³

A median split for total number of pain sites was computed for the overall sample of those with and without knee pain ($n = 229$, median of 3) and for the knee pain group only (median of 4). Noteworthy, Lacey and colleagues reported that the median number of pain sites lasting 1 day or more in the previous 4 weeks in a community-based group of adults in the United Kingdom ≥ 50 years of age was 4.³¹ Similarly, the cut point for the total number of pain sites incorporated in the FITT index in the previously reported population-based study was 3 or less and 4 or greater.⁵³ In this study, the total number of pain sites with pain more days than not over the last 3 months was defined as 0 to 3 and 4 or greater. Once median splits were computed, an additive index was compiled as previously described,⁵³ see **Table 2**.

2.5. Telomere length analysis

A blood sample was collected during the second study session and placed on ice. It was centrifuged at 4°C for 10 minutes at 3000 rpm. Once a sample was received, the blood was mixed with 1 × phosphate-buffered saline (PBS), layered onto a volume of Lymphoprep solution that was contained in a centrifuge tube. After centrifugation, the lymphocyte band was separated, washed, and centrifuged to form a pellet. The pellet was resuspended in 1 × PBS, and the sample was stored at -80°C. The DNA isolation was achieved using the Qiagen FlexiGene kit. Lysis buffer was added to the sample before being mixed and centrifuged. The resulting pellet was resuspended in denaturation buffer containing protease and incubated. DNA was then precipitated, washed, centrifuged, and resuspended in hydration buffer. Telomere length was analyzed by the Blackburn Lab, University of California San Francisco.³⁴

The telomere length assay is adapted from the published original method by Cawthon.^{10,34} The telomere thermal cycling profile consists of the following—Cycling for T (telomic) polymerase chain reaction (PCR): 96°C for 1 minute; denature at 96°C for 1 second, anneal or extend at 54°C for 60 seconds, with fluorescence data collection, 30 cycles. Cycling for S (single-copy gene) PCR: PCR: 96°C for 1 minute; denature at 95°C for 15

Table 2

Chronic pain severity pain domains and FITT groups.

Pain domains	Question	Median and score
Frequency	Do you currently experience knee pain on most days?	0 = no 1 = yes
Intensity	GCPS characteristic pain intensity (current + worst + average pain over last 6 mo/3 × 10)	0 = 0–47 1 = 48–100
Time or duration	How long have you experienced knee pain on most days (in months)?	0 = 0–23 mo 1 = 24–360 mo
Total number of pain sites	Number of body regions with pain more days than not over the last 3 months	0 = 0–3 1 = 4–18
FITT Groups	Classification	Domain total
1	No or low pain	0
2	Mild pain	1
3	Moderate pain	2
4	Moderate to high pain	3
5	High pain	4

GCPS, Graded Chronic Pain Scale.

seconds, anneal at 58°C for 1 second, extend at 72°C for 20 seconds, 8 cycles; followed by denature at 96°C for 1 second, anneal at 58°C for 1 second, extend at 72°C for 20 seconds, hold at 83°C for 5 seconds with data collection, 35 cycles. The primers for the telomere PCR are tel1b [5'-CGGTTT(GTTTGG)₅GTT-3'], used at a final concentration of 100 nM, and tel2b [5'-GGCTTG(CCTTAC)₅CCT-3'], used at a final concentration of 900 nM. The primers for the single-copy gene (human beta globin) PCR are hbg1 [5' GCTTCTGACACAACCTGTGTTCACTAGC-3'], used at a final concentration of 300 nM, and hbg2 [5'-CACCAACTT-CATCCACGTTCCACC-3'], used at a final concentration of 700 nM. The final reaction mix contains 20 mM Tris-HCl, pH 8.4; 50 mM KCl; 200 mM each dNTP; 1% DMSO; 0.4x Syber Green I; 22 ng E. coli DNA per reaction; 0.4 Units of Platinum Taq DNA polymerase (Invitrogen Inc, Waltham, MA) per 11 mL reaction; 6 ng of genomic DNA. Tubes containing 26, 8.75, 2.9, 0.97, 0.324, and 0.108 ng of a reference DNA (pooled samples of leukocyte genomic DNA from 100 female donors) are included in each PCR run so that the quantity of targeted templates in each research sample can be determined relative to the reference DNA sample by the standard curve method. The same reference DNA was used for all PCR runs.

To control for interassay variability, 8 control DNA samples are included in each run. In each batch, the telomere to single-copy gene (T/S) ratio of each control DNA is divided by the average T/S for the same DNA from 10 runs to obtain a normalizing factor. This is performed for all 8 samples, and the average normalizing factor for all 8 samples is used to correct the participant DNA samples to obtain the final T/S ratio. The T/S ratio for each sample was measured twice. When the duplicate T/S value and the initial value vary by more than 7%, the sample was run the third time and the 2 closest values were reported. The average coefficient of variation for this study is 1.9%. The laboratory personnel who performed the assays received deidentified blood samples and were blind to demographic and clinical data.

To determine the conversion factor for the calculation of approximate base pair telomere length from T/S ratio, the above method was used to determine the T/S ratios, relative to the same reference DNA, for a set of genomic DNA samples from

the human fibroblast primary cell line IMR90 at different population doublings, as well as with the telomerase protein subunit gene (hTERT) transfected into a lentiviral construct. The mean terminal restriction fragment (TRF) length from these DNA samples was determined using Southern blot analysis, and the slope of the plot of mean TRF length vs T/S for these samples served as the conversion factor for calculation of telomere length in base pairs from the T/S ratio. The equation for conversion from T/S ratio to base pairs for this study was base pairs = 3274 + 2413 × (T/S).

2.6. Data analysis

Descriptive analyses for the categorical and continuous variables were completed. Differences by chronic pain severity (FITT) groups were tested using either analysis of variance F-test or χ^2 test. Pearson and Spearman correlational analyses were calculated between telomere length and the following variables: age, race or ethnicity (African American, non-Hispanic whites), sex, waist-hip ratio (WHR), employment (8 categories), exercise (≥ 1 time a week or ≤ 1 time a week), smoking status (nonsmoker or current smoker), comorbidities (cumulative total past and cumulative total current), education (\leq high school or \geq some college), annual income (1–10 categorical), and Kellgren Lawrence knee OA radiograph score (0–4). An analysis of

covariance was conducted to compare the no or low chronic pain severity group (FITT 1) with the high chronic pain severity group (FITT 5) adjusting for primary covariates which included age, race or ethnicity, sex, study site, and knee pain status. Secondary analyses for additional covariates were completed, which were selected based on variables associated with telomere length after controlling for age which was limited to WHR. Linear regression models were used to conduct model-based tests for analyses of FITT domains and FITT as an interval variable predicting telomere length and for clinical and functional pain measures predicting FITT and telomere length adjusting for primary and secondary covariates. The data analysis was conducted using SAS 9.4.

3. Results

3.1. Demographics and clinical and functional descriptors by FITT

Tables 2 and 3 provide a descriptive overview across demographic, biobehavioral, and clinical pain and functional measures by the FITT chronic pain severity groups. Telomere length was correlated with age ($r = -0.398$, $P < 0.0005$); race or ethnicity ($r = -0.229$, $P = 0.007$); WHR ($r = -0.222$, $P = 0.009$); past comorbidities ($\rho = -0.191$, $P = 0.026$), and employment status ($\rho = -0.219$, $P = 0.01$). Telomere length was not

Table 3
FITT groups by demographics, bio-behavioral measures, and FITT domains.

	FITT					P
	1 (n = 21)	2 (n = 17)	3 (n = 22)	4 (n = 41)	5 (n = 35)	
Demographics						
Age, mean (SD), y	60.43 (7.74)	56.88 (8.92)	57.14 (8.03)	57.66 (7.79)	54.11 (8.27)	0.081
Race/Ethnicity, %						0.008
African Americans	33.33	58.82	54.55	41.46	77.14	
Non-Hispanic Whites	66.67	41.18	45.45	58.54	22.86	
Gender, %						0.789
Female	76.19	70.59	68.18	65.85	60.00	
Male	23.81	29.41	31.82	34.15	40.00	
Site, %						<.0001
UF	90.48	76.47	54.55	29.27	40.00	
UAB	9.52	23.53	45.45	70.73	60.00	
Employment, %						0.896
Employed	47.62	52.94	54.55	60.98	54.29	
Not employed	52.38	47.06	45.45	39.02	45.71	
Marital Status, %						0.638
Married	33.33	35.29	45.45	46.34	31.43	
Not married	66.67	64.71	54.55	53.66	68.57	
Bio-behavioral						
BMI, mean (SD), kg/m ²	25.85 (6.01)	30.41 (6.72)	31.03 (8.03)	31.15 (6.38)	34.94 (10.51)	0.002
Smoking, %						0.643
Non-smoker	55.00	47.06	50.00	53.66	40.00	
Former smoker	25.00	29.41	36.36	19.51	22.86	
Current smoker	20.00	23.53	13.64	26.83	37.14	
Exercise frequency, %						0.511
<1 time/wk	20.00	52.94	27.27	26.83	40.00	
1–3 times/wk	60.00	29.41	45.45	51.22	40.00	
≥ 4 times/wk	20.00	17.65	27.27	21.95	20.00	
KL scores, mean (SD)	0.43 (0.75)	0.93 (1.22)	1.35 (1.42)	1.38 (1.48)	1.68 (1.59)	0.004*
FITT Domains						
Frequency, %						
Yes	0	41.18	86.36	100	100	<0.0001
No	100	58.52	13.64	0	0	
GCPS CPI	13.33	33.33	46.67	50	73.33	<0.0001
Time/Duration	0	0	12	36	50	<0.0001
Total Pain Sites	1	3	3	5	7	<0.0001

GCPS CPI, Graded Chronic Pain Scale Characteristic Pain Intensity; KL, Kellgren Lawrence score.

* Spearman's rho.

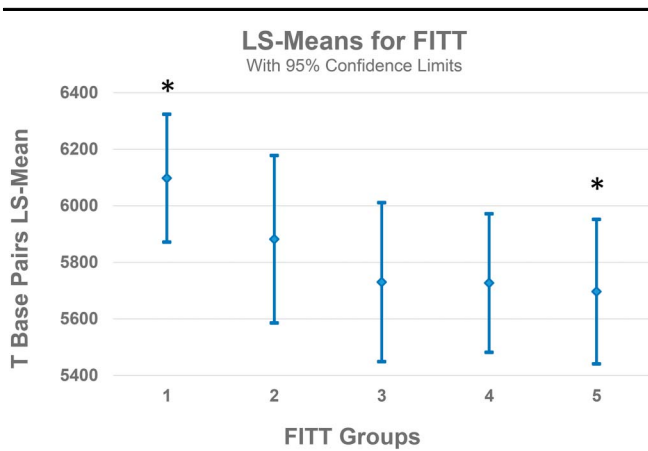


Figure 1. Telomere length by FITT groups—groups defined by combined scores for frequency, intensity, and time or duration of knee pain on most days, and total number of pain site. Covariates in the model: age, race or ethnicity, sex, site, and knee pain status. *Significant difference for FITT 1 and FITT 5, $P = 0.025$.

associated with Kellgren Lawrence knee OA radiograph scores on the most affected knee ($\rho = -0.094$, $P = 0.311$).

3.2. FITT groups and telomere length

The no or low FITT group had significantly longer telomeres compared with the high chronic pain severity FITT group ($P = 0.025$), see **Figure 1**. These findings persisted with a secondary analysis with WHR added in the model ($P = 0.036$).

3.3. FITT domains, FITT, and telomere length

Linear regression analyses were conducted with the individual FITT components and primary covariates (age, race or ethnicity, sex, study site, and knee pain status) as predictor variables. These analyses showed that individual FITT domains were not predictive of telomere length (all $P > 0.05$). An additional linear regression analysis was completed with FITT index as a numerical predictor with primary covariates in the model. This analysis showed that FITT significantly predicted telomere length ($P = 0.034$), and this relationship persisted with the addition of WHR in the model ($P = 0.048$).

3.4. FITT groups and clinical and functional measures

FITT was significantly associated with all WOMAC and GCPS measures (all $P < 0.0001$) and with performance on the SPPB Chair Stand ($P = 0.02$), but not with other SPPB subscales and total, **Table 4**. These findings, with the exception of the SPPB Chair Stand, persisted after controlling for WHR and incorporating Bonferroni correction adjustments.

3.5. Clinical or functional knee osteoarthritis measures and telomere length

The WOMAC, SPPB, and GCPS and associated subscales were not associated with telomere length (all $P > 0.07$), **Table 5**.

4. Discussion

There are a number of key findings from our investigation. First, as hypothesized, individuals with high knee OA chronic pain severity based on an FITT index had shorter telomeres compared with individuals with no/low knee OA chronic pain severity. Second, as anticipated, the individual FITT domains were not associated with telomere length. However, the combined FITT index captures a cumulative contribution from each domain that has an additive predictive value as demonstrated in a significant dose–response relationship. Third, the FITT index was highly associated with recognized and frequently used measures of OA pain and functioning. However, recognized and frequently used measures of OA pain and functioning were not associated with telomere length. Our findings suggest that the FITT chronic pain severity index seems to capture the biological interface of knee OA chronic pain severity more effectively than commonly used clinical and functional measures of OA which assess symptom severity over a shorter duration (48 hours to 6 months) and do not include measures of frequency or extent of body sites with pain.

4.1. FITT groups and telomere length

A number of studies have indicated group differences in telomere length when phenotypic extremes with persisting duration are compared.^{12,37,59} Similarly, our findings demonstrate that telomere length differed in individuals with chronic pain–related phenotypic extremes: no/low chronic knee pain severity

Table 4
FITT groups by clinical and functional measures: unadjusted mean and SD with adjusted group comparisons.

Clinical measures	FITT					P
	1 (n = 21)	2 (n = 17)	3 (n = 22)	4 (n = 41)	5 (n = 35)	
WOMAC						
Pain	1.67 (2.39)	4.76 (2.41)	6.14 (3.36)	7.56 (3.47)	10.26 (3.73)	<0.0001
Stiffness	0.90 (1.45)	2.18 (1.13)	2.86 (1.52)	4.27 (1.63)	5.31 (1.81)	<0.0001
Physical function	6.00 (7.54)	16.59 (9.09)	17.86 (9.77)	26.34 (12.31)	35.66 (13.4)	<0.0001
Total	8.57 (10.26)	23.53 (11.87)	26.86 (12.8)	38.17 (16.54)	51.23 (17.88)	<0.0001
GCPS						
CPI	11.75 (10.63)	35.29 (18.49)	48.48 (17.17)	53.17 (15.11)	72.57 (14.14)	<0.0001
Disability	0 (0)	0.94 (1.53)	2.00 (1.9)	2.02 (1.75)	3.60 (1.91)	<0.0001
Pain grade	0.71 (0.46)	1.38 (0.96)	2.10 (1.14)	2.15 (0.99)	3.06 (0.87)	<0.0001
SPPB						
Chair stand	3.00 (0.84)	2.59 (1.33)	2.73 (1.39)	2.66 (1.32)	2.17 (1.44)	0.02
Gait	3.71 (0.72)	3.82 (0.39)	3.41 (1.01)	3.59 (0.84)	3.34 (1)	0.47
Balance	3.86 (0.36)	3.82 (0.39)	3.73 (0.94)	3.9 (0.3)	3.74 (0.85)	0.77
Total	10.57 (1.03)	10.24 (1.48)	9.86 (2.53)	10.15 (1.84)	9.26 (2.25)	0.12

CPI, Characteristic Pain Intensity; GCPS, Graded Chronic Pain Scale; SPPB, Short Physical Performance Battery; WOMAC, Western Ontario and McMaster Universities Index of Osteoarthritis. P-value reflects adjusted comparison controlling for age, race, sex, site, and knee pain status.

Table 5
Relationship between clinical measures and telomere length.

Measures	F Value	P
WOMAC		
Pain	1.32	0.25
Stiffness	1.60	0.21
Physical function	3.30	0.07
Total	2.93	0.09
SPPB		
Chair stand	0.01	0.94
Gait	1.96	0.16
Balance	2.59	0.11
Total	0.02	0.90
GCPS		
Characteristic pain intensity	0.96	0.33
Total disability points	0.05	0.82
Pain grade	0.12	0.73

Covariates: age, race or ethnicity, sex, site, and knee pain status. SPPB, Short Physical Performance Battery; GCPS, Graded Chronic Pain Scale; WOMAC, Western Ontario and McMaster Universities Index of Osteoarthritis.

compared with those with high chronic knee pain severity. This association persisted with secondary covariates in the model. Importantly, the observed difference in telomere length reflects an increase of approximately 16 years of accelerated aging between the no or low and moderate or high and high severity groups. Importantly, in this study, telomere length was appropriately associated with age, race, and WHR. As joint changes in the knee can occur without indications of pain and functional limitations,^{9,17} the lack of association between Kellgren Lawrence scores and telomere length is not surprising.

4.2. FITT domains and telomere length

A burgeoning body of evidence indicates the importance of considering frequency, intensity, duration, and extent or severity of stress in the evaluation of physiological dysregulation and pain-related biological and health-related changes.^{25,33,38} For example, pain intensity and pain duration contribute toward the functional limitations and disability in individuals with knee OA²³ and predict functional and structural changes in the brain.^{3,18,30} In addition, pain intensity and number of pain sites are predictive of mortality.^{40,56} Likewise, pain frequency contributes to the biological burden of pain. Leistad and colleagues demonstrated that after an acute stressor, individuals with chronic pain compared with those with episodic pain demonstrated dysregulated stress system responses.³³ Pain frequency has also been linked to pain-related changes in the brain. In individuals with chronic migraines for 3 years or more, individuals with low-frequency migraines had greater bilateral hippocampal volume compared with those with high-frequency migraines, who also demonstrated decreased functional connectivity between the hippocampus and pain processing regions.³⁸ Hence, it seems that episodic or intermittent pain does not produce the same biological consequences as persisting or high-frequency pain.

Accelerated cellular aging as measured by telomere length has been investigated across an extensive array of health conditions and behavioral and psychosocial factors, and these studies demonstrate similar findings regarding frequency, intensity or severity, and duration of the stressor as described above. Consistent with theoretical understanding of telomere biology, short-term chronic stress in the range of 3 months is anticipated to facilitate telomere lengthening.⁵ In addition, intermittent stress in the case of exercise is associated

with longer telomeres.^{37,46} Reduced telomere length has been repeatedly shown for a high “stressed” group compared with healthy controls when the high stress group comprises individuals who have experienced frequent, persisting duration, and moderate-to-high stress.^{12,15,59} Failure to adequately characterize various stressors (frequency, intensity, duration, and severity) may explain inconsistencies in previous clinical investigations of telomere length.^{39,48,55} Importantly, our findings indicate that the additive combination of factors rather than any individual dimension (frequency, intensity, time or duration, and total number of pain sites) is negatively associated with telomere length. Similar patterns have emerged in other lines of investigation.^{2,30,53}

4.3. Clinical and functional knee osteoarthritis measures, FITT, and telomere length

Although FITT was highly correlated with the OA clinical and functional measures, the clinical and functional measures were not associated with telomere length. The WOMAC is a frequently used measure that assesses lower extremity pain and function over a timeframe of 48 hours. It is designed to capture recent pain and, although correlated with a measure of chronic pain (GCPS), it will capture dynamic pain experiences and may poorly reflect other characteristics of chronic pain such as duration, frequency, and extent of body pain.

The SPPB is a functional screening measure and in our sample showed a limited score range. Although correlated with clinical measures of knee pain, it is a measure of current functional performance that does not capture features of clinical pain (frequency, intensity, duration, and body sites with pain). The GCPS is a well-recognized measure of chronic pain evaluating intensity of pain and pain-related disability over the last 6 months. However, it may not accurately reflect the overall duration of pain beyond 6 months and does not capture the frequency of pain experience or the extent of pain across other areas of the body. Thus, the findings that telomere length is not associated with the WOMAC, SPPB, or the GCPS are not surprising and are consistent with other telomere findings in which phenotypes were not characterized and differentiated by duration, severity, and persistence of stress.

4.4. Relevance of telomere length and FITT to osteoarthritis and pain research

Telomeres are dynamic and influenced by the biochemical environment (cortisol, inflammation, and oxidative stress). Essentially, they are molecular measures of life experience, altered by persisting biological and psychosocial stress, and to some degree reflect general health and disease susceptibility.^{8,27} As such, telomeres are not specific to OA or chronic pain but seem to provide a relative indication of whether a system is in balance vs overloaded. In addition, there is evidence that telomere shortening may be reduced or buffered by health promoting interventions^{14,26,45,46} which could reduce the biological burden of chronic pain and associated psychosocial stress on the individual.²⁸

4.5. Limitations and future directions

Although the findings reported are encouraging, the next phase of investigation requires prospective analysis. The relevance of telomere length and the FITT index in OA and chronic pain research will best be determined by the replication of findings and longitudinal investigations. Second, phenotyping with

comprehensive and detailed biopsychosocial and behavioral data will be essential to confirm the sensitivity of telomere length to changes in the OA pain severity experience. Longitudinal data and access to medical records that provide information regarding frequency, intensity, and duration of pain would greatly improve the phenotyping process. Third, confounding factors that contribute to the pathophysiological mechanisms may influence findings and warrant further investigation. Fourth, in this study, 3 domains of FITT were assessed specific to knee pain experiences. It is anticipated that an FITT index reflective of the cumulative pain experience in individuals with OA or other chronic pain conditions might be a more “effective” index than the typical assessment of a site-specific pain. Fifth, median splits were used to create the FITT chronic pain severity index. Although the cut points align with previous findings, investigations to determine the weighting of domains and actual clinical ranges would be helpful in better understanding the characteristics of pain that facilitate biological burden and accelerated aging. Sixth, little is known regarding the relationship between telomeres and pharmacological management of pain. Findings on psychotropics and telomeres can provide guidance to these important future investigations.³⁵ Finally, the biological burden equation is not unidirectional, as protective factors can reduce the load of biopsychosocial stress.^{28,45,46,53} A better understanding of this dynamic multidimensional relationship will help facilitate efforts to promote resilience and buffer the biological burden of chronic pain and associated psychosocial stress, thus promoting more optimal health outcomes and possibly improved quality of life.

5. Conclusions

Our findings demonstrate accelerated cellular aging with increasing severity of knee OA pain. Importantly, telomere length is predictive of morbidity and mortality; chronic pain and OA are related to increasing morbidity and mortality; and now, telomere length shortening is associated with knee OA chronic pain severity. In addition, we replicate a chronic pain severity dose-response pattern in telomere length that was previously demonstrated in a population-based study investigating an immune and metabolic risk factor composite.⁵³ Results suggest there may be a biological burden associated with chronic OA pain and clinical measures capturing the frequency, intensity, time or duration, and extent of body pain which may help elucidate those changes.

Disclosures

The authors report no conflicts of interest.

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