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Chronic Pain and Premature Aging – The Moderating Role of Physical Exercise

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Abstract: **Chronic pain induces a multitude of harmful effects; recently it has been suggested that chronic pain is also associated with premature aging, manifested in shortened telomere length (TL). However, evidence for this hypothesis is scarce and inconsistent. The aim was twofold: 1) Investigate whether chronic pain is associated with premature aging, and 2) Determine whether physical exercise (PE) moderates this association if it exists. Participants were 116 male subjects, with (n = 67) and without chronic pain (n = 49). Blood samples for TL analysis were collected and participants were interviewed and completed questionnaires. As a part of the cohort, we included people with physical disability; this variable was controlled in the analysis. The TL of individuals with chronic pain was significantly shorter than that of pain-free individuals. Regression analysis revealed a significant moderating effect of PE on chronic pain and TL, above and beyond the effects of disability, age, and weight. Whereas chronic pain was associated with shorter telomeres in participants who did not exercise, this association was nonsignificant among participants who did exercise. The results suggest that chronic pain is associated with premature ageing; however, PE may mitigate this association and may protect individuals against the harmful effects of chronic pain.**

Perspective: ***The study suggests that it is important to monitor signs of premature ageing among chronic pain patients as they are at risk. However, chronic pain patients may benefit from regular PE in this respect as it may moderate premature ageing.***

Keywords: *Chronic pain, premature ageing, telomere length, physical exercise.*

Chronic pain, estimated to occur among ~20% of individuals globally,[37,47,55] is a major global health concern with significant ramifications. These include restricted mobility and function,[14] limited vocational, social, and employment capacity,[20,58,76] reduced quality of life,[25] opioid dependence,[75] depression, anxiety, and emotional exhaustion.[26,40] As such, chronic pain is viewed as a persistent endogenous stressor that might wear down body systems and lead to deleterious health-related outcomes.[66]

Chronic pain, similar to chronic stress, has been associated with cardiac, cerebrovascular,[11,24] and pulmonary diseases.[6] In addition, high mortality rates among people with severe chronic pain, compared to mild or lack of pain, were reported.[2] Cognitive decline such as memory problems and loss of gray matter in the brain[5] have also been found to co-morbid with chronic pain.[3,19] Since these conditions are more frequent at a later age, chronic pain is possibly associated with accelerated or premature aging, a state that bears significant, clinical implications.

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One biomarker of aging that is increasingly gaining attention is telomere length (TL). Telomeres are nucleoprotein complexes that cap chromosomal ends and protect the stability and integrity of the chromosomes from insults suchlike oxidative damage and from being recognized as double strand breaks that otherwise require repair. Telomeres shorten with each DNA replication, serving as a mitotic clock that dictates the lifespan of cells and the organism itself. As such, they are considered as robust biomarkers of cellular senescence and predictors of mortality, both timely and premature.[12] Although short telomeres were associated with age-related conditions and diseases[63] and also with mortality,[50,60] little is known about TL's association with chronic pain.

Sibille et al[65] reported that TL was shorter in people with osteoarthritis knee pain than pain free controls, later confirmed in a larger cohort.[64] Conversely, Hassett et al[33] reported that TL of women with fibromyalgia was similar to that of pain free women however, TL correlated inversely with chronic pain intensity. Similarly, among community-dwelling adults (>20 years), the relationship between chronic pain and TL was nonsignificant.[67] Thus, the association of chronic pain and premature or accelerated aging remains unclear and requires investigation. Moreover, if patients suffering from chronic pain are in a state of accelerated ageing, potential moderators associated with chronic pain and TL should be explored.

One such potential moderator is physical exercise (PE). PE lowers the risk of various age-related diseases and conditions,[13,18,38,51,52,74] improves fitness,[18,39] and is associated with longer TL.[18,54] Since PE is frequently prescribed to chronic pain patients[18,27,69,73] and chronic pain may be a risk factor for cellular aging, we studied whether PE can interfere with this potential risk. Our study investigated TL among chronic pain patients and explored the role of PE and its association with chronic pain and TL. Only male subjects were included given the known gender effect on TL. We hypothesize that: 1) presence of chronic pain will be inversely associated with TL; 2) PE will be positively associated with TL; and 3) PE will moderate the association between chronic pain and TL.

Methods

Participants

The study consisted of a sample of 116 adult participants (mean age 54.25 years, range 35–70) of whom 86 had a physical disability due to Poliomyelitis or spinal cord injuries; and 30 were able-bodied. The sample included only males given the known differences in TL as well as in telomere attrition rate between genders.[29,71] Inclusion criteria for all the participants were as follows: 1) good health and lack of substantial medical conditions (or a history of such conditions) according to individual reports, which were randomly confirmed by cross checking medical records and 2) intact cognition and the ability to comprehend and complete questionnaires. Able-bodied individuals were recruited from the population of employees at Tel Aviv University and Sheba Medical Center. Participants who had a physical disability were recruited from the outpatient clinics of the Department of Neurological Rehabilitation, or from the rehabilitation center recreational groups at Sheba Medical Center, Tel Hashomer. Recruitment was done by ads and flyers that were available at the outpatient clinics and the rehabilitation center. People who agreed to participate in the study were contacted for further explanations and upon their agreement, they were invited for data collection. The present study was approved by the Helsinki Committee of Sheba Medical Center and the intuitional review board of Tel-Aviv University.

Procedures

The study was cross sectional. The sample size was calculated based on preliminary average and SD values of TL in a population sample, considering the probability of a type I error of 0.05, the probability of a type II error of 0.2, an enrolment ratio of 2:1 (for precaution), and a power of 80%. This calculation resulted in a total sample of 36 participants (24 and 12 participants in the chronic pain and pain-free groups, respectively). However, considering the confounder of physical disability, we took additional precaution measures and tripled the sample size.

Each participant was invited to a single testing session. Prior to data collection, each participant signed a consent form after receiving a full explanation of the study's goals and protocols. Afterwards, the participants were interviewed by the physicians and using a structured questionnaire and completed self-reported questionnaires. In addition, venous blood was sampled to analyze TL.

Measures

Chronic Pain

Participants who reported pain that lasted more than 6 months were defined as suffering from chronic pain. The presence of chronic pain was then confirmed during the interview by the physicians who were present during data collection (authors A.O. or G.Z.). Presence of chronic pain was also confirmed using the participants' medical records at the outpatient clinics from which they were recruited. Chronic pain characteristics were assessed via an interview. Participants with chronic pain were asked to report the duration of their pain and indicate on a body chart, the body regions in which they feel their pain. In order to calculate the number of painful body regions, the body was divided into 13 regions: foot, shin, thigh, buttocks, hand, forearm, arm, shoulder, abdomen, chest, lower back, upper back, and neck. Then the number of areas with chronic pain from the 13 regions was counted for each patient.[31]

The participants were asked to rate the average severity of their chronic pain during the past four weeks on a

visual analog scale (VAS). The VAS consisted of a 10 cm line with end points ranging between 0 and 10. The end points were set as "no pain sensation" (0) and "the most intense pain sensation imaginable" (10).

Pain interference, which refers to the degree to which pain limits or interferes with individuals' physical, mental, and social activities was evaluated using the Bodily Pain subscale of the Medical Outcomes Study SF-36 questionnaire.[46] The original item addresses pain interference at work. Since we were interested to investigate the general impact of pain, and given that not all the participants were employed, we asked how pain interferes with life as follows: "During the past 4 weeks, how much did pain interfere with your normal life?". Pain interference was scored on a 1 to 5 scale, with response options: "Not at all," "A little bit," "Moderately," "Quite a bit," and "Extremely."

Telomere Length

The blood draw for measuring TL in leukocytes was taken during the same visit of the interview. Terminal Restriction Fragment (TRF), representing TL, was measured by Southern blot with a DIG-labeled probe according to the manual provided in the TeloTAGGG Telomere Length Assay (Roche, Mannheim, Germany). First, genomic DNA was extracted using the ArchivePure 5′ DNA blood kit (Hilden Deutschland) and quantified by NanoDrop (Thermo, Waltham, MA). Next, 5 mg DNA were digested for 16 hours with RSAI and HINFI restriction enzymes. The digested DNA was separated by gel electrophoresis (0.8% Agarose), depurinated by 0.25 M HCl, denatured by alkaline denaturing solution (0.5 M NaOH; 1.5 M NaCl), and then neutralized in 0.5 M Tris HCl, 3 M NaCl. Then, the DNA was capillary transferred onto a positively charged Whatman nylon membrane (Roche, Manheim, Germany) for 16 hour and then UV-cross-linked (120 mJ) to the membrane and incubated for 16 hour with a DIG-labeled TL probe $(CCCTAA)_4$. Subsequently, membranes underwent washes while being agitated: twice in stringent wash buffer I (2X SSC, 0.1% SDS) for 5 minutes at RT, twice in stringent wash buffer II (0.2X SSC, 0.1% SDS) for 15 minutes at 50°C, in 1X maleic acid buffer for 5 minutes, in blocking solution for 30 minutes at room temperature (RT), in anti-DIG solution for 30 minutes at RT, twice in washing buffer for 15 minutes at RT, and finally in detection solution for 5 minutes at RT. Then ~40 drops of CSPD substrate were applied to the membrane, which was exposed to a sensitive film for 1.5 hour. The film was developed and then scanned and quantified by Quantity One software (Versadoc; BioRad). To calculate TRF, each smear representing a heterogenic signal was segmented and its intensity was measured. TRF was calculated according to the following equation:

$$\frac{\sum(OD_i)}{\sum\left[\left(\frac{OD_i}{Li}\right)\right]}$$

where ODi is the chemiluminiscent signal and Li is the length of the TRF at position i.[69]

Physical Exercise and Additional Information

The participants completed a questionnaire including questions about age, years of education, employment, marital status, cohabiting with a partner, weight, and more. The participants were also asked if they perform PE on a regular basis (yes/no). Details regarding PE were obtained by using questions 1 to 4 of the International physical activity questionnaire short form[15] that query about days per week and duration per day. Note that while the International physical activity questionnaire short form quarries about physical activities in the past 7 day, which may not represent the individual's usual level of activity, we asked the participants to answer with respect to the past four weeks. In addition, participants were asked to state the type of the PE in which they engage.

The interview also included questions about the physical disability, including etiology (eg, disease, motor vehicle accident, and fall), duration (in years), functional level (requires assistance in activities of daily living, requires partial assistance in some activities, fully independent) and use of assistive devices such as cane, braces, crutches or a wheelchair (yes/no). Data on the diagnosis of disability, its etiology and the date it was performed were cross checked with the participants' medical records. In addition, the Functional Independence Measure (FIM) locomotion subscale was used as an indication of physical disability status.[53] To perform the FIM locomotion a 50-foot walking area was used. A score was assigned on a 7-point scale, depending on the assistance the participant used for ambulation: 1 = requires total assistance, 2 = maximum assistance with 1 person, 3 = moderate assistance, 4 = minimal assistance with hands on contact, 5 = supervision, 6 = modified independence (with equipment), and 7 = independent without equipment.[32] The advantage of this subscale as opposed to other ambulation tests is that it has 2 distinct subscales (for walking and for wheelchair) which allows individuals with widely varying ability to participate.

Data Analysis

Data were analyzed using IBM SPSS Statistics 25 and PROCESS computational macro. Continuous variables are presented as means and standard deviations and categorical variables as medians and interquartile range. Dichotomous variables are presented as percentages.

F-test or X^2 test was conducted to explore the differences in demographics, physical disability, and PE data between individuals with and without chronic pain. Two 1-way Analyses of Covariance (ANCOVAs) were conducted, to assess the effects of both PE and chronic pain on TL. Given the dependence of TL on chronological age, the age parameter was added as a covariate in these analyses. Furthermore, in order to explore the relations between chronic pain and TL while neutralizing the potential effects of physical disability, we explored the effects of chronic pain on age-adjusted TL

only among participants with physical disability via an additional ANCOVA. Physical disability, PE and chronic pain were dummy variables: absence was coded 0 and presence was coded as 1.

In order to assess the moderating role of PE, in the association between chronic pain and TL, a regression analysis was conducted. The analysis consisted of chronic pain, which was treated as an independent variable; PE, which was treated as a moderator; and the interaction between chronic pain and PE. Additionally, since chronological age,[49] physical disability,[48] and weight[71] are associated with TL, these variables were also included in the model as covariates. All the study variables were entered into the model in 1 step. All the variable scores were standardized. In order to understand the nature of the interaction, we used the PROCESS (model 1) computational macro with tests of Simple Slopes.[34] These analyses indicated the effects of the chronic pain (independent variable) on TL among the 2 categories of the PE (moderators), namely among people who exercise versus among people who do not exercise.

Results

Data on Chronic Pain, Physical Exercise and Demographics

Chronic pain intensity was rated as relatively high (6.79 ± 2.04 VAS units) and ranged between 3 and 10 VAS units. The median pain interference score was 3, ranged between 1 and 4 units, and the interquartile range was 1. The average chronic pain duration was 14 years (14.42 ± 9.09, range 1−40 years). On average, participants with chronic pain had 2 painful body regions (2.28 ± 1.51, range 1−8 regions); regions with the highest frequency being the lower back region, the shins and arms.

Preliminary analyses exploring age-adjusted TL as a function of pain intensity ($\beta = .00$, $P = .98$), pain interference ($\beta = .14$, $P = .40$), pain duration ($\beta = -0.16$, $P = .23$), and number of painful body regions ($\beta = .01$, $P = .92$) all revealed non-significant effects. Therefore, all individuals with chronic pain were combined into a single group for further analyses, and these pain variables were not included thereafter.

Table 1 presents the characteristics of individuals with and without chronic pain. The groups did not differ in demographic data except of a higher prevalence of physical disability among participants who suffered from chronic pain. However, within the disability sample, participants with chronic pain did not differ from participants without chronic pain in the duration of physical disability (27.56 ± 11.5 and 26.00 ± 12.3 years, respectively, for people with and without chronic pain, F = .15, $P = .70$); cause of disability (38.7% illness, 38.7% motor vehicle accident, 11.3% gunshot wounds, 11.3% fall of height vs 52.4%, 23.8%, 18.9%, and 4.9%, respectively, Z = −.61, $P = .54$); use of assistive devices (95.5% and 97.5%, respectively, Z = −.03, $P = .96$), functional status (39.1% require assistance, 54.7% require some assistance, 6.3% fully independent vs 43.5%, 56.5%, and 0%, respectively, Z = −.64, $P = .52$) and FIM locomotion (median of 3 and 2, respectively, Z = −.99, $P = .32$).

Of the 116 participants (entire sample), 57 (49.1%) reported that they regularly perform PE. The types of PE included swimming (n = 13, 22.8%), participating in ball games (n = 12, 21.1%) exercising in the gym (n = 11, 19.3%), cycling (n = 10, 17.5%), and others (n = 9, 15.5%). The average number of times per week in which PE was performed was 1.38 ± 1.39; each session lasted 1.60 ± 0.60 hours, on average. As can be seen on Table 1, participants with chronic pain did not differ from pain free participants in the prevalence of PE (about a third in each group). In addition, the 2 groups did not differ in the frequency of performing PE per week and in the duration of PE each time.

Telomere Length as a Function of Chronic Pain

For the entire sample, TL varied between 3.20 and 10.1 kilo base pairs (kb), with a mean of 6.25 ± 1.67 kb. TL was in the recommended acceptable range for skewness (0.40) and kurtosis (−0.70), with no outliers.

The ANCOVA test, which explored the effects of chronic pain on age-adjusted TL, was statistically significant ($F(1, 113) = 32.29$, $P < .001$; Fig 1). Participants with chronic pain had a significantly shorter TL compared with those who were pain free, after controlling for age (5.51 ± 1.40 vs 7.21 ± 1.54 kb). Similar results were

Table 1. Characteristics of the Study Groups

	Participants with chronic pain (n = 67)	Participants without chronic pain (n = 49)	F or X^2
Age (M,SD)	55.36 (7.00)	52.73 (8.87)	3.16
Weight (M,SD)	81.12 (12.36)	81.20 (16.37)	.00
Years of education (M,SD)	13.65 (3.13)	13.60 (3.23)	.01
Marital status (married: N,%)	51(76.1)	40 (81.6)	1.59
Cohabiting with partner (yes: N,%)	52 (77.6)	40 (81.6)	1.95
Physical disability (yes: N,%)	64 (95.5)	22 (44.9)	37.83***
Physical exercise (yes: N,%)	33 (49.3)	24 (49.0)	.00
Exercise frequency (sessions/week: M,SD)	1.35 (1.36)	1.42 (1.44)	.05
Exercise duration (per session: M, SD)	1.68 (0.59)	1.48 (0.62)	1.42

Abbreviations: M, mean; SD, standard deviation; N, number.
***$P < .001$.

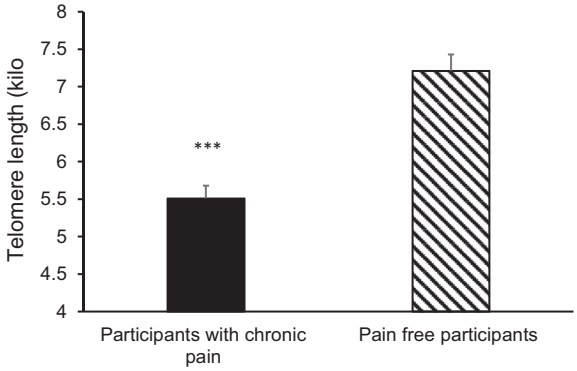

Figure 1. The age-adjusted TL of participants with chronic pain was significantly shorter than that of pain-free participants (***$P < .001$). Values are means and standard errors.

found after controlling for physical disability ($F(1, 112) = 4.75$, $P < .05$), and in the analysis that specifically explored the effects of chronic pain on age-adjusted TL only among participants with physical disability ($F(1,83) = 4.12$, $P < .05$); participants with physical disability and chronic pain had a significantly shorter TL than those with physical disability who were pain free.

Telomere Length as a Function of Physical Exercise

ANCOVA, which investigated the effects of PE on age-adjusted TL, indicated a nonsignificant effect for PE ($F(1, 113) = .00$, $P = .968$). There was no difference in TL between participants who reported regular exercise (6.12 ± 1.40 kb) versus those who did not (6.38 ± 1.89 kb) after controlling for age.

Effect of Physical Exercise

The results of the linear regression are presented in Table 2. The regression model explained 48.6% of the variance of TL ($F(6,109) = 17.21$, $P < .001$). The results indicated that physical disability and chronological age had a significant effect in explaining TL; thus, participants with physical disability as well as older participants had shorter telomeres. Weight was nonsignificantly associated with TL.

Table 2. Regression Beta Standardized Coefficients Predicting Telomere Length

	β	SE
Age	−.25*	.12
Physical disability	−.62**	.11
Weight	−.02	.08
Chronic Pain	−.18	.10
Physical exercise	.08	.08
Interaction between chronic pain and physical exercise	.19*	.08

Abbreviation: SE, standard error.
Note: All study variables were standardized.
*$P < .05$.
**$P < .001$.

Table 3. The Effects of Chronic Pain as a Function of Physical Exercise

	β	SE	T
Exercise	.05	.11	.42
Do not exercise	−.34*	.13	−2.56*

Abbreviation: SE, standard error.
Note: All study variables were standardized.
*$P < .05$.

Furthermore, the results of the linear regression indicated that although chronic pain and PE had nonsignificant main effects, the interaction between them was significant above and beyond the effects of physical disability, age, and weight. Simple slope analyses by PROCESS indicated that the effect of chronic pain on TL was influenced by PE. The effect of chronic pain on TL as a function of PE is presented in Table 3; the means and standard error of TL for the four groups of participants (participants with/without chronic pain, participants who are active/not active) are presented in Fig 2. As can be seen, chronic pain had a significant effect on TL only among participants who do not regularly exercise, since TL was shorter among participants with chronic pain compared with those without chronic pain. The effect of chronic pain on TL was nonsignificant among participants who regularly exercise, namely, participants with and without chronic pain in this subgroup had a similar TL. These effects were found after controlling for physical disability, age, and weight.

Discussion

The results indicated that people suffering from chronic pain had a shorter TL than did pain-free peers. Nevertheless, PE moderated the association between chronic pain and TL; chronic pain was associated with short TL only among participants who did not regularly exercise.

TL in chronic pain

Participants who suffer from chronic pain had significantly shorter telomeres than those who were pain free, adjusting for age. Given that short telomeres are associated with age-related conditions and diseases[59,63] and predict early mortality,[23] and given that TL serves as a biomarker of aging, the present findings suggest that chronic pain might be associated with premature aging.

In order to substantiate this conclusion, we searched for large population studies in which leukocytes TL was measured as a function of age and health status. These studies report a significant and linear decline in TL from the mid-50s (as in the present sample) to the mid-70s age groups, by ~8% or ~0.75 kb (eg, [7,10,29]). The TL difference herein, between participants with and without chronic pain; 1.4 kb which is about 20% decline, thus seems substantial. Interestingly, the effect of various comorbidities (eg, diabetes, hypertension, and depression) lost significance after adjusting for age, suggesting that age was the single most significant factor associated

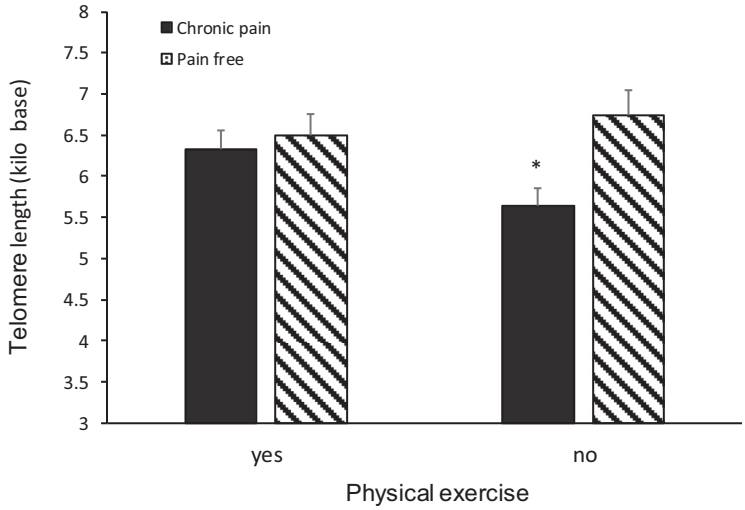

Figure 2. The moderating effect of physical exercise and its association with chronic pain and TL after controlling for physical disability, age, and weight. TL was significantly shorter (*$P < .05$) among participants with chronic pain compared with those without chronic pain among participants who did not regularly engaged in physical exercise.

with TL.[29] In the present study, chronic pain significantly affected TL even after adjusting for age, demonstrating its important contribution to telomere shortening. An additional step in substantiating our conclusion was to compare the values of TL obtained herein, to those of 46 healthy elderly individuals (mean age 77.5 years) whose TL was analyzed by members of our group in a previous study.[72] Our participants with chronic pain herein had similar TL as that of these elderly individuals (5.75 ± 1.48 kb).

Current evidence of aging processes among individuals with chronic pain is scarce. Our conclusion corresponds with Sibille et al in which 35 patients with high intensity osteoarthritis knee pain (ages 45–85 years) had shorter TL than did 21 people with low intensity pain or lack of it.[64] Our results also corroborate with those of Cruz-Almeida et al who reported an "older" epigenetic age, estimated by Horvath's epigenetic DNA methylation status, among 20 individuals (65–80 years) with unspecified chronic pain compared with nine pain-free individuals.[16] Advantages of our study are the larger sample size and the ability to compare TL of the participants to that of elderly people analyzed in the same laboratory. Another advantage is our investigation of chronic pain characteristics; severity, duration, interference and widespread, which showed no distinct effect on TL above that of pain presence. Thus, the impact of chronic pain presence upon the body, manifested in TL seems far more remarkable than the individual's perception of its severity or inference.

However, in a nationally representative study of 7,816 adults by Steward et al, TL of people with widespread pain, ages between 20 years to older than 80 years, did not differ from pain-free controls.[67] This wide age range may have contributed to the inconsistency between studies, and so could the differences in chronic pain definition; ≥3 months as opposed to ≥6 months herein. Taken together this difference, the long chronic pain duration (average of 14 years) and the relatively high chronic pain ratings (7/10) herein, suggest a stronger impact of chronic pain in the present study manifested in TL. In Hasset et al,[33] although TL of woman with Fibromyalgia did not differ from pain free controls, those with more severe chronic pain had shorter TL than those with low levels of chronic pain. Thus, although additional research comparing various types of chronic pain is recommended, individuals with chronic pain, especially of severe magnitude, seem to experience signs of cellular senescence and may therefore be at risk of increased morbidity and mortality rates.

The mechanisms underlying the link between chronic pain and short TL are presently unknown; however, a potential mechanism may be allostatic overload due to chronic stress.[66] Acute stressors activate adaptive, survival-promoting responses of the stress, metabolic, and immune systems termed "allostasis," which subsides when the stressor terminates.[60] Chronic or repeated exposure to stressors may however, lead to excessive, dysregulated activation of these systems, ie, to "allostatic overload," which wears and tears and subsequently alters body and brain function.[17,45] Indeed, shorter TL than normal has been found among people exposed to significant stressors including childhood adversities,[22] combat,[8,80] and intimate partner violence.[35] Moreover, individuals who suffered from both chronic pain and high perceived stress had shorter TL than did pain-free individuals with low levels of stress.[65] Furthermore, depression, which is often co-morbid with chronic pain,[36] is also associated with accelerated aging.[79] Given that chronic pain may act as a persistent stressor, it may induce allostatic overload, leading to cumulative damage hence accelerated aging, manifested in short TL.

Our sample included people with physical disability, more frequently in the chronic pain group, which by itself may be associated with shorter telomeres.[57] Consequently, it could be argued that the link

between chronic pain and TL resulted from the negative effects of physical disability on cellular aging. Although this possibility is viable, the statistical analysis reveals otherwise. First, physical disability-related variables did not differ between those with and without chronic pain within the disability subsample. Second, within the disability sample, TL was shorter among people with chronic pain versus those without. Third, the regression model indicated that chronic pain was associated with short TL among inactive individuals above and beyond the effects of physical disability.

Mitigating Role of Physical Exercise

Although chronic pain may produce enduring stress, not all individuals with chronic pain are equally vulnerable to premature aging. Our study revealed, for the first time, the moderating effect of PE; chronic pain was associated with short telomeres, ie, with premature aging, only among participants who did not exercise regularly, whereas this association did not exist among physically active participants. The moderating effect of PE was significant after controlling for age, physical disability, and weight. Thus, PE may be a protective mechanism against the harmful effects of chronic pain on the body.

PE is often recommended for chronic pain patients,[1,18,68] particularly considering the Center for Disease Control and Prevention's new opioid-prescribing guidelines, which promotes nonopioid and nonpharmacological treatments.[21] Although PE is recommended for everyone, it is particularly important for people with physical disability considering the potential barriers, and the increased risk of chronic pain, they may face.[56] PE is thought to reduce chronic pain[1,18,30,66] in both the short and long term[61,77] even though inconsistencies exist across interventions and follow–up periods.[27] Our findings indicate yet another important benefit of PE; mitigation the negative effects of chronic pain on cellular senescence.

PE might induce its mitigating effect on premature aging and on chronic pain by directly affecting the pain system. PE has been known to increase the production and release of endocannabinoids[78] and endogenous opioids,[43] which mediate endogenous pain inhibition. The enhanced pain modulation capacity of athletes may support this notion.[28] PE is also implicated in shifting the cytokine balance to more anti-inflammatory than inflammatory cytokines, thereby reducing activity in, and sensitization of nociceptors.[9,42] PE may further contribute to chronic pain reduction indirectly, by strengthening muscles and improving tissue flexibility, thereby preventing secondary adverse effects.[27] On the cellular level, PE might lead to an overall diminished burden of oxidative stress and inflammation, which are associated with leukocyte telomere attrition,[4,13',19] thus promoting tissue conditioning as well as that of the organism as a whole.

PE may also mitigate the negative effects of chronic pain by improving general well-being[18,62] and reducing depression, anxiety[26,40,41] and pain catastrophizing,[2] conditions that increase pain-related disability and suffering. PE has been found to moderate the association of stress and TL; although stress was linked to shorter TL in physically inactive participants, this association was nonsignificant among physically active participants.[54] The additive effect of stress on chronic pain has also been linked to short TL.[65] These findings together, and the reports of longer TL among people engaging in PE compared with sedentary people[44,70] propose that the participants herein may have benefitted from both the physical and emotional effects of PE on chronic pain.

Limitations and Implications

The results should be considered in light of several limitations. First, although the associations between TL, chronic pain, and PE were significant beyond the effect of physical disability, future studies should investigate this association in chronic pain patients without physical disability for the purpose of generalizability. Second, the male-only sample limits the generalizability to females, who represent the greatest proportion of chronic pain sufferers. Third, this study is cross-sectional and cannot determine the causality or directionality of the associations, that may be affected by residual confounding.

Notwithstanding, the study's proposal that individuals who suffer from chronic pain might experience premature ageing has important theoretical and clinical implications. Thus, chronic pain patients should be monitored for age-related diseases and pathological conditions already in adulthood as part of their clinical management. At the same time, however, this study indicates that PE may buffer the potential pathological consequences of premature aging in chronic pain patients. Implementation of PE interventions for chronic pain seems to be essential not only to achieve pain relief and improve the associated symptoms, but also as a way to impede the aging process.

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