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Brief Report

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The Effects of Exercise on Telomere Length in Persons With Heart Failure

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Background: Telomere length is reduced in persons with heart failure (HF). Inflammation is a putative mechanism contributing to telomere shortening. Although physical activity is known to increase telomere length, its effects in HF are unknown. **Objective:** The aim of this study was to examine the effects of exercise on telomere length and its relationship with interleukin (IL)-1β in persons with HF. **Methods:** This secondary analysis of a 3-month home-based aerobic exercise intervention measured total telomere length and IL-1β levels in persons with HF (69% with reduced ejection fraction). **Results:** Total telomere length increased and plasma IL-1β levels decreased in the exercise group from baseline to 3 months. Total telomere length was negatively associated with IL-1β at baseline ($r = -0.441$ $P = .001$). **Conclusions:** The association between telomere length and IL-1β suggests a relationship between inflammation and cellular aging. Moderate-intensity exercise may help maintain cellular functions. Further research is needed to examine the effects on outcomes in persons with HF.

KEY WORDS: exercise, heart failure, inflammation, interleukin-1, telomere shortening

Telomeres are DNA sequences at the end of chromosomes in eukaryotes that preserve genome information.[1] Telomere length may mark an individual's biological age as opposed to his/her calendar age, acting as a *mitotic clock* indicative of cellular aging. Thus, telomere shortening is a hallmark sign of cellular aging.[2] Heart failure (HF) is considered a disorder of premature cellular aging, and telomere length is reduced in persons with HF with reduced ejection fraction and preserved ejection fraction.[3,4]

There is compelling evidence demonstrating an association between inflammation and HF, especially in relation to cardiac remodeling.[5,6] However, the relationship between the effects of inflammation and telomere dynamics is less distinct. It is possible that the correlation between telomere attrition and disease is confounded by underlying chronic inflammation.[7] In addition, systemic oxidative stress and inflammation related to cardiovascular risk factors may accelerate telomere attrition.[8]

Chronic inflammation in persons with HF is associated with increased morbidity and mortality related to adverse cardiac remodeling such as hypertrophy and fibrosis.[9] Interleukin (IL)-1β is a proinflammatory cytokine associated with innate immunity, and secretion is

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dictated by the strength of inflammatory stimuli.[10] Under conditions of extreme inflammatory distress, such as chronic illness, activation of IL-1β may contribute to cell damage or death.[10]

Although inflammation is a putative mechanism contributing to telomere shortening, this relationship is yet to be explored in persons with HF. Increased levels of IL-1β in persons with HF are linked to myocardial dysfunction and exacerbation of the disease in both severity and mortality.[5] Interleukin-1β induces nitric oxide production, which contributes to ventricular remodeling in individuals with HF.[5] An overabundance of nitric oxide, in combination with other reactive oxygen species, increases oxidative stress and inflammation, and accelerates telomere shortening in individuals with chronic illnesses.[11]

Although studies have found that exercise interventions are associated with increased telomere length or decelerated telomere shortening, the exact mechanisms are not yet fully understood.[12] However, the relationship between physical activity and telomere length may be related to the anti-inflammatory and antioxidant effects of exercise, reducing inflammation and oxidative stress that contribute to telomere attrition.[12] The effects of physical activity and exercise interventions on telomere length in persons with HF are unknown.

Although HF is a clinical syndrome, defined by signs and/or symptoms caused by a structural and/or functional cardiac abnormality and associated with distinct and varied clinical disease states,[13] shared pathophysiologic mechanisms, such as inflammation, oxidative stress, and mitochondrial dysfunction, contribute to premature cellular aging and cellular senescence, driving the myocardial remodeling and cardiac dysfunction characteristic of HF (Figure).[3] As cellular senescence is linked to telomere attrition,[14] routine physical activity may manage or regress age-related chronic diseases that negatively impact telomere length.[15] In this study, we examined the effects of exercise on telomere length and the relationship with IL-1β in persons with HF.

Methods

Study Design

This study was a secondary analysis using previously collected data and stored samples from persons with HF who participated in a 3-month home-based aerobic exercise intervention (n = 17) or received attention control (n = 15), as previously described.[16,17] A subset of participants with available genomic data were included in this study. In brief, participants were randomized to receive an exercise intervention or attention control for 3 months. The exercise group received the exercise prescription using a progressive, moderate-intensity, and dose-specific exercise protocol based on the maximum heart rate obtained during the symptom-limited, modified Balke treadmill test at baseline. Participants in the exercise group walked for 30 minutes 3 times per week at 60% maximum heart rate for the first 2 weeks, 45 minutes 3 times per week at 60% maximum heart rate for weeks 3 and 4, and 45 minutes 3 times per week at 70% maximum heart rate for the remaining 8 weeks. The attention control group received HF education materials and instructions on flexibility and stretching movements to control for the possible confounding variable of receiving attention from a healthcare professional. Data collection occurred from December 2014 to October 2016.

All studies were performed under research protocols approved by the institutional review board of Emory University. Each subject was informed of testing protocols and potential risks and benefits of participation. All participants provided written informed consent before participation and provided consent to participate in a substudy using stored samples for genetic analyses.

Measurements

Interleukin-1β levels were measured in triplicate using enzyme-linked immunosorbent assay (eBioscience, Waltham, Massachusetts) as part of the original study.[16,18] Plates were read on a BioTek microplate reader and analyzed using Gen5 software (Applied Biosystems, Waltham, Massachusetts). Curve fitting was selected among linear, quadratic, and 4-point based on the best regression coefficient.

DNA was extracted from previously stored buffy coat stored at −80°C until analysis. Total extracted DNA was quantified (Qubit dsDNA HS Assay Kit, Invitrogen, Waltham, Massachusetts). Total absolute telomere length was measured in triplicate via quantitative polymerase chain reaction (Absolute Human Telomere Length Quantification qPCR Assay Kit, ScienCell, Carlsbad, California), per manufacturer's instructions. Briefly, quantitative polymerase chain reaction was performed using a telomere primer and a single-copy reference primer; a reference genomic DNA sample with known telomere length served as a reference for calculating the absolute telomere length of target samples.

Data Analysis

Descriptive statistics were analyzed for the study variables, and the data were reviewed for normality assumptions and outliers. Descriptive statistics were reported as mean (SD) for continuous variables, and frequency and percentage for categorical variables. Analysis of covariance was used to examine between-group differences at 3 months, controlling for baseline. Paired *t* tests were used to examine within-group differences over time. Pearson correlations were used to examine the relationship between telomere length and cytokines. Effect sizes

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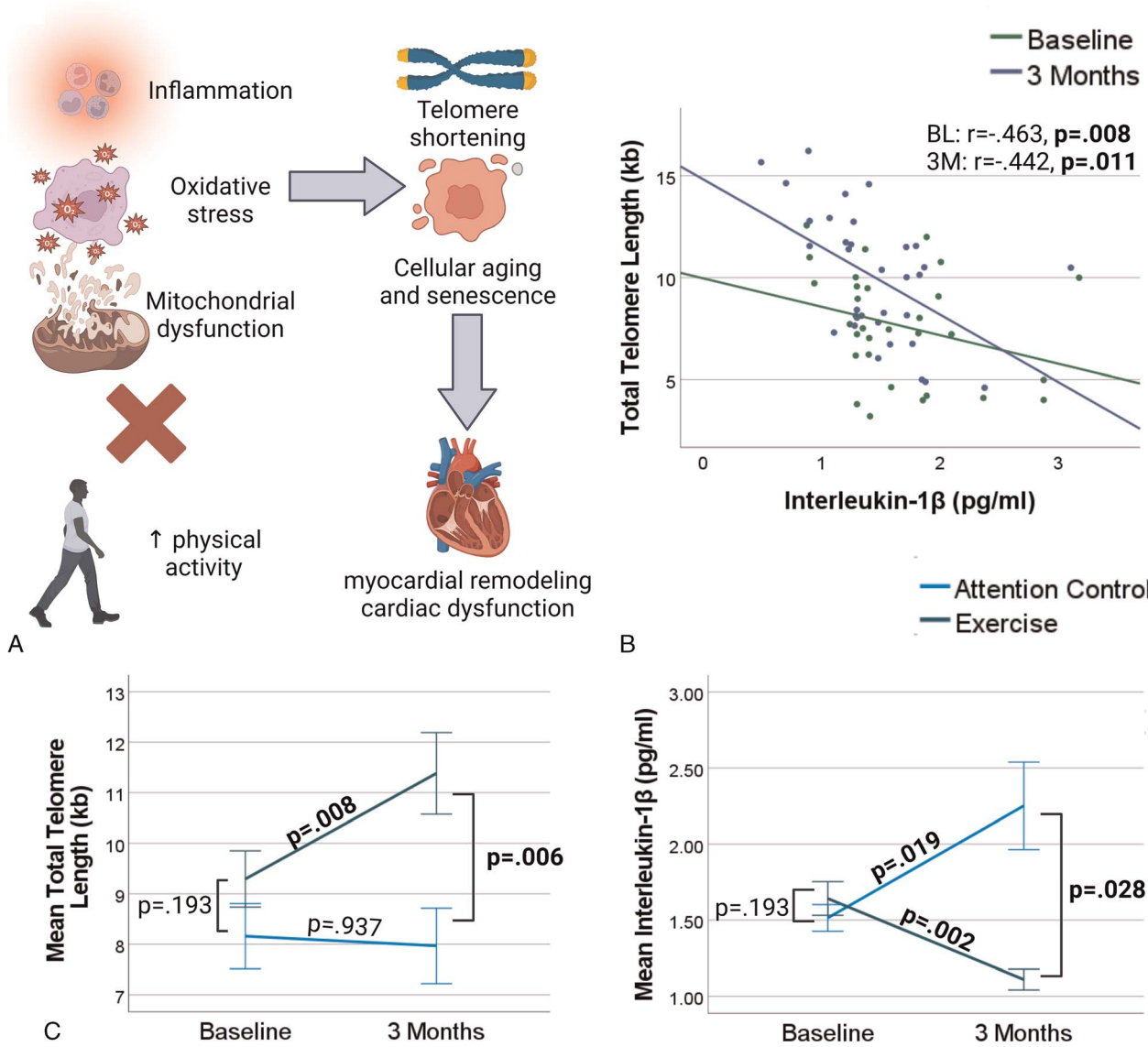

FIGURE. *Total telomere length is associated with interleukin-1β and was increased after a short-term exercise intervention in persons with heart failure. A, Increases in inflammation, oxidative stress, and mitochondrial dysfunction are associated with decreased telomere length and cellular aging and senescence, leading to myocardial remodeling and cardiac dysfunction. Exercise may slow this process by decreasing these pathophysiologic processes associated with cellular aging. B, Total telomere length was negatively associated with interleukin-1β at baseline (BL) and 3 months (3M). C, Although there were no differences at baseline, total telomere length was higher and interleukin-1β was lower in the exercise group as compared with the attention control group at 6 months.*

were calculated using Hedges' *g* for paired *t* tests and η^2 for analysis of covariance models. All data were analyzed using SAS version 9.4 with an α set at .05.

Results

The mean (SD) age of participants (N = 32) was 60 (10) years, 48% were female, and 55% identified as Black or African American. The mean (SD) body mass index was 30.64 (6.2) kg/m^2, and mean (SD) left ventricular ejection fraction (LVEF) was 34.25% (13.6%), with 69% (n = 22) of participants categorized as having HF with reduced ejection fraction (LVEF < 40%). A higher proportion of participants in the exercise group had a history of dyslipidemia as compared with the attention control group (71% vs 27%; $P = .032$). No other clinical or demographic differences were observed between the groups (Table). Total telomere length was not associated with age, sex, race, LVEF, or comorbidities. Total telomere length was higher among exercise group participants compared with attention control group participant at 3 months (10.38 [1.2] vs 7.96 [2.6] kb/chromosome end; $P = .006$), with a medium effect size ($\eta^2 = 0.410$) (Figure). There were no differences in the effects between participants with HF with reduced ejection fraction and those with HF with preserved ejection fraction in either

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TABLE Demographic and Clinical Characteristics

Characteristic (N = 32)	Control (n = 15) Mean (SD) or n (%)	Exercise (n = 17) Mean (SD) or n (%)	*P*
Demographic characteristics			
Age, y	57 (12)	62 (8)	.225
Female	7 (47%)	6 (35%)	.720
Black/African American	11 (73%)	7 (41%)	.087
Clinical characteristics			
BMI, kg/m^2	30.55 (6.0)	30.72 (6.6)	.939
LVEF, %	35 (13)	34 (15)	.904
HFrEF	11 (73%)	11 (65%)	.712
Hypertension	10 (67%)	10 (59)	.265
Dyslipidemia	4 (27%)	12 (71%)	.032
Arthritis	8 (53%)	6 (35%)	.476
Diabetes	6 (40%)	6 (35%)	.536
Myocardial infarction	3 (20%)	7 (41%)	.265

Abbreviations: BMI, body mass index; HFrEF, heart failure with reduced ejection fraction (LVEF < 40%); LVEF, left ventricular ejection fraction.

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group. Plasma IL-1β was lower among exercise group participants compared with attention control group participants at 3 months (1.31 [0.6] vs 1.75 [0.4] pg/mL; $P = .028$), with a medium effect size ($\eta^2 = 0.367$). Total telomere length increased in exercise group participants from baseline to 3 months (9.29 [1.2] vs 10.38 [1.2] kb/chromosome end; $P = .008$), with a medium effect size (Hedges' $g = 0.76$). Plasma IL-1β decreased in exercise group participants from baseline to 3 months (1.51 [0.3] vs 1.31 [0.6] pg/mL; $P = .002$), with a small effect size (Hedges' $g = 0.41$). No significant changes over time were observed in the attention control group. Total telomere length was negatively associated with IL-1β levels at baseline ($r = -0.463$ $P = .008$) and 3 months ($r = -0.442$, $P = .011$).

Discussion

In this study, we report that total telomere length increased after a 3-month exercise program in persons with HF. Furthermore, total telomere length was negatively associated with IL-1β, suggesting a potential role for inflammation in cellular aging in persons with HF. We previously demonstrated that a 3-month at-home walking intervention was related to epigenetic changes with resultant changes in gene expression associated with decreased inflammasome activation.[16] Here, we add further evidence suggesting aerobic exercise may lead to DNA changes associated with cellular aging.

The progression of aging diseases, including HF, seems to be related to telomere attrition, because it may correlate with disease severity and outcomes.[15,19] It is important to note that telomere length shortens with each mitotic division, because of incomplete duplication of the telomeric ends on the lagging-strand during DNA synthesis.[7] In humans, telomere length is thought to decrease at a rate of 24.8 to 27.7 base pairs per year.[20,21] When telomeres become critically short, they can trigger cellular senescence or apoptosis, mechanisms that prevent damaged or dysfunctional cells from proliferating. Although an absolute critical telomere length has yet to be defined, telomere attrition beyond a minimum critical size triggers cell apoptosis, and shorter-than-average telomere length for biological age is associated with an increased incidence of diseases associated with aging and/or decreased life span.[22–24] As such, there is an intrinsic need to balance the factors that erode telomeres and those that extend them to maintain functional telomere length across an individual's life span.[22]

Both innate and adaptive immune mechanisms are implicated in the pathophysiology of HF[25] and are associated with adverse clinical outcomes related to acute and chronic HF.[26] Disease etiology is associated with secretion of inflammatory cytokines, particularly IL-1β, leading to myocardial injury that allows the heart to adapt to increased physiologic stress.[25] In addition, chronic systemic inflammatory processes trigger a cascade whereby increased white blood cell turnover causes an uptick in telomere attrition rates.[27] Elevated white blood cell turnover increases cellular replication, which in turn leads to telomere shortening.[27] Many diseases associated with chronic inflammation are associated with shortened telomere length, and higher inflammation is associated with decreased telomere length.[22]

Other factors that affect telomere length include diet, stress, and physiological state, which are also known to be related to HF progression and exacerbation. Several studies have indicated a relationship between diet and telomere length. Specifically, the consumption of alcohol, red meats, and processed meats is associated with telomere attrition, whereas increased consumption of legumes, fruits, coffee, and dairy products is associated with telomere length preservation.[28] Moreover, higher 24-hour total fruit and vegetable intake was associated with longer telomere length.[29] Other study authors suggest the Mediterranean diet and omega-3 fatty acid intake have positive effects on telomere length.[30,31]

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Higher antioxidant balance, as measured by the oxidative balance score (dietary and lifestyle prooxidants and antioxidants), was associated with longer telomere length.[32]

Chronic stress affects the lives of many individuals and is thought to be implicated in various chronic disease states. Notably, higher levels of psychosocial stress and stress-related cortisol activity are associated with decreased telomere length.[33–35] Furthermore, psychosocial stress seems to have intergenerational effects, because higher cortisol during pregnancy predicts shorter telomere length in offspring.[22] A study in Finland found that multiple (≥3) childhood adversities were associated with shorter telomere length in adulthood.[36] The authors of this study suggest that telomere length may be one mechanism whereby chronic psychosocial stress mediates chronic disease progression. Authors of future studies should measure the protective effects of physical activity on chronic stress via alterations in telomerase activity.

Routine physical activity may attenuate the progression of age-related chronic diseases associated with telomere shortening given the protective properties of exercise in relation to telomere dynamics. Exploring the mechanistic effects of physical exercise as a therapeutic tool is especially advantageous for those at risk for chronic diseases associated with increased oxidative stress and systemic inflammation, because telomeres are vulnerable to oxidative damage.[15,22,27] Potential mechanisms that demonstrate a parallel relationship between physical activity and telomere length include telomerase activity, oxidative stress, and inflammation.[25] Understanding the mechanisms by which the effects of physical activity are involved in telomere reserves, the elongated telomeres that allow for fidelity in DNA replication, can provide therapeutic implications that target the progression of biological aging and reduce the risk of chronic disease states (ie, cardiovascular disease).

Telomerase is an enzymatic protein responsible for maintaining telomere length at the 3′ end of chromosomes, reversing the loss of DNA with each subsequent replication, and has been shown to be exploited in tumor cells lines as evidenced by their infinite proliferative capabilities.[37] Authors of studies in mice models suggest that certain factors can upregulate telomerase activity, providing a basis for longevity without enhancing cancer risk.[38,39] Ethical considerations limit the ability to replicate genetic manipulation experiments with animal models involving human subjects; however, investigation of modifiable external factors, such as physical activity, and their role in longevity may provide an indirect, noninvasive target aimed at slowing biological aging and chronic disease progression.[27] Studies in adult athletes found upregulation of telomeric repeat-binding factor 2, a protein with protective functions against telomere attrition, and Ku, a protein involved in DNA repair, as compared with sedentary controls.[40] These findings emphasize the long-term effects of physical exercise in modulating gene expression via epigenetic mechanisms, thereby preventing telomere degradation, cellular senescence, and age-related disease processes. Future studies should capture time sensitivity in relation to the onset of physical activity (ie, early or later in life) and the degree to which these benefits can significantly mitigate aging/disease processes.

Mechanisms that drive telomerase activity consequently alter telomere reserves. Depleted reserves stimulate cellular senescence, which can contribute to genomic instability in precancerous cell lines, attenuating biological aging and age-related disease processes, including cardiovascular disease. Another putative mechanism associated with telomere attrition and subsequent pathogenesis of degenerative diseases is oxidative stress and inflammation. The primary source of reactive oxygen species production seems to coincide with chronic activation of innate inflammatory pathways, because reactive oxygen species are produced by immune cells used to target invading pathogens, thus establishing the connection between inflammation, reactive oxygen species, and chronic disease.[40] Inflammatory diseases characterized by oxidative stress markers are also associated with marked telomere degeneration.[41] Oxidative stress markers secondary to chronic inflammation may serve as targets of novel interventions against the progression of telomere degradation and subsequent age-related disease processes.

Considering the known role of inflammation and oxidative stress in persons with HF,[5,42] more work is needed to better understand the role of cellular aging in the context of the HF inflammatory milieu. Telomerase dysfunction and shorter leukocyte telomere length are associated with increased cardiovascular risk and mortality[43] and should be considered as part of the pathophysiological changes that lead to cardiovascular disease risk and development. As exercise can stimulate telomerase enzyme activity and therefore preserve telomere length, further work is needed to identify the duration and intensity of physical activity that are effective in stimulating telomerase activity in persons with HF.[8,12,43]

Healthy lifestyle choices, including physical activity or exercise, as well as sustaining healthy body weight, may contribute to adequate telomere length and protection from the harmful effects of inflammation and oxidative stress.[27] However, individuals with chronic diseases, such as HF, may be more prone to sedentary lifestyles, functional limitations, and disabilities.[27]

Disease management programs that include tailored patient education may be the first line in promoting regular physical activity as part of HF self-care. A meta-analysis of HF care management interventions found that patients receiving such education reported significantly better HF-related quality of life, significantly lower hospital readmission rates, and lower mortality rates.[44] In addition, nurse-led education programs seem to produce

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What's New and Important

- A 3-month walking program was associated with increased telomere length in persons with HF.
- Total telomere length was negatively associated with IL-1β.
- Moderate-intensity exercise may help to maintain cellular function in persons with HF.

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the greatest improvement in patients' HF self-care with evidence that a standard set of program components endorsed by professional associations, such as the American Heart Association, could lead to further adoption of such practices by clinicans.[44,45]

Cardiac rehabilitation programs are essential components of HF patient management and are strongly recommended in HF guidelines.[46] Cardiac rehabilitation programs are specifically designed to help patients with HF improve their physical fitness, reduce symptoms, and improve their overall health outcomes. They can also potentially help reduce telomere shortening in patients with HF. Studies have shown that regular physical activity can help to reduce the rate of telomere shortening. In addition, exercise reduces oxidative stress, inflammation, and other factors that contribute to telomere shortening. Overall, integrating physical activity and cardiac rehabilitation into HF patient management may reduce telomere shortening and improve overall health outcomes. However, further research is needed to fully understand the relationship between exercise, cardiac rehabilitation, and telomere length in patients with HF.

Limitations

This study was a secondary analysis of a randomized controlled trial and thus was not powered or designed for telomere analyses. Owing to the small sample size, this study is not generalizable to the population of persons living with HF. Furthermore, most participants (69%) had an LVEF ≤ 40%, which is higher than the approximately 50% of the population with HF living with HF with reduced ejection fraction. However, it provides evidence warranting further testing of the effects of aerobic exercise on telomere length, telomerase activity, and assessment of cellular senescence. In addition, we were unable to examine telomerase activity in stored samples. It is important to consider that, in this study, we examined peripheral white blood cells, so the interpretation of the effects of exercise on telomere length does not extend to other cell types. There is a correlation between telomere lengths in different cell types, and white blood cells provide insight into the link between inflammation and HF. Immune cells are ideal for telomere research for several reasons: they are easy to obtain from the blood and readily available, and because they circulate throughout the body, immune cells are exposed to both internal (from cells) and external (from diet and exposure) factors that affect telomere maintenance. Because this was an analysis of stored samples and previously collected data, we did not have measures of psychosocial stress and other related measures in the sample. In this study, we used an absolute telomere length assay using a genomic sample of known telomere length to calculate absolute telomere length. Authors of other studies in HF and healthy aging have used different approaches to calculating telomere length, making absolute comparisons difficult.

Conclusion

We demonstrated that exercise intervention in persons with HF is associated with increased telomere length. Critically short telomeres are associated with aging and age-related diseases. Therefore, preserving telomere length and preventing telomere shortening may be important strategies for health promotion in persons with HF. Moderate-intensity exercise may help maintain cellular function, thus improving the outcomes in persons with HF. Further research examining the contribution of inflammation and oxidative stress and the effects of exercise on cellular health in persons with HF is needed. Nurses can play a key role in the promotion of risk factor modification through physical activity in persons with persistent HF.

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