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Original Research Article

Lack of association between PBMC telomere length and endurance exercise

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ABSTRACT

Telomeres are repetitive DNA located at the ends of chromosomes that preserve genomic stability. Excessive leukocyte telomere shortening is associated with cardio-metabolic disease and increased mortality risk. Although most studies indicate exercise training could attenuate leukocyte telomere attrition, data is somewhat equivocal. The inconsistencies could be partly explained by the different populations of leukocytes isolated for telomere length assessment. Accordingly, average peripheral blood mononuclear cell (PBMC) and whole blood leukocyte telomere length were assessed in 44 endurance athletes and 40 healthy controls using quantitative PCR. While whole blood leukocyte telomeres were, on average, 6.1% longer in endurance athletes compared to controls, PBMC telomere length was similar between the two cohorts in age and sex-adjusted analyses (athletes vs controls, mean T/S ratio ± SE: 3.25 ± 0.05 vs 3.23 ± 0.05, $p = 0.72$). Other than a weak inverse correlation with sitting ($r = -0.25$, $p = 0.03$), no statistically significant correlations were found between PBMC telomere length and exercise parameters. Unlike whole blood leukocytes, PBMC telomere length is not associated with endurance exercise and exercise parameters. These findings suggest the need for future work to quantify short and long telomeres of sorted immune cell populations and to measure them in context with cell counts and exercise traits.

Introduction

Telomeres are a genetically conserved repetitive DNA located at the ends of chromosomes that are crucial for preserving genomic stability (Hande et al., 1999). Telomeres shorten due to the end replication problem and thus telomere length reflects biological age (Levy et al., 1992; Lopez-Otin et al., 2013). Excessive telomere shortening is often observed in leukocytes of patients with age-related chronic disease, including type 2 diabetes (Sampson et al., 2006), atherosclerosis (Codd et al., 2013; Samani et al., 2001) and some cancers (Ma et al., 2011). Telomere length is commonly assessed in leukocytes or peripheral blood mononuclear cells (PBMC) because they correlate with other somatic cells and are easily obtainable (Daniali et al., 2013). Although shortened telomeres are associated with cardio-metabolic disease (D'mello et al., 2015) and psychological stress (Schutte and Malouff, 2014), regular exercise training may attenuate telomere attrition to prevent age-related chronic diseases and premature biological ageing (Denham et al., 2016a).

The evidence indicating a role for exercise training or physical activity in telomere maintenance is mounting. Whilst the optimum amount of exercise that maintains telomere length is unclear, most data indicate exercise is associated with long average leukocyte telomere length (Denham et al., 2016a). For instance, individuals who regularly engage in intense, endurance exercise training possess longer telomeres in whole blood leukocytes (Denham et al., 2013, 2016b; Sassenroth et al., 2015), skeletal muscle (Osthus et al., 2012) and buccal cells (Borghini et al., 2015). Others have, however, found no association between exercise parameters and leukocyte telomeres (Mathur et al., 2013; Song et al., 2010; Woo et al., 2008). There are numerous explanations for the inconsistencies throughout the literature, such as genetic diversity of participants, DNA isolation and telomere length quantitation methods (Denham et al., 2014, 2016a). The cell type assessed in telomere assays is an alternative that could account for some of the equivocal findings.

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The aim of the present study was to measure PBMC telomere length in context with endurance exercise and cardiorespiratory fitness parameters in a subset of the participants from a previous investigation (Denham et al., 2016b). Considering the previous leukocyte telomere length data (Denham et al., 2013, 2016b), it was hypothesised that endurance athletes would possess longer PBMC telomeres compared to healthy controls and that PBMC telomere length would positively correlate to exercise parameters (resting heart rate and maximum oxygen uptake [$\dot{V}O_{2max}$]).

Materials and methods

Participants and testing procedures

A subset of Caucasian participants (n = 84) from a previous investigation (Denham et al., 2016b) was involved in the present study. In short, the average telomere length of 44 endurance athletes, who self-reported training at least thrice weekly for a minimum of one year, were compared to 40 recreationally active individuals who were not engaged in any structured exercise training. All participants attended a morning (7–10 a.m.) testing session, completed physical assessments (height, weight and blood pressure), self-administered questionnaires (International Physical Activity Questionnaire [IPAQ] Long Form and Perceived Stress Scale) and a maximum oxygen uptake test as detailed previously (Denham et al., 2016b). Data was processed according to the IPAQ guidelines and average weekly sitting duration was calculated (Denham et al., 2016b). All participants gave written informed consent and this study was approved by Federation University Australia's Human Research Ethics Committee.

Telomere length assessment

Participants donated a preprandial, resting blood sample after an overnight fast. Approximately 20 ml of peripheral blood was drawn from the antecubital vein into EDTA tubes using standard phlebotomy procedures and was temporarily stored on ice before further processing. PBMCs were isolated by Histopaque (1077, Sigma-Aldrich, Australia) after density gradient centrifugation, according to the manufacturer's guidelines. Specifically, 3 ml of whole blood was layered over 1 vol of Histopaque-1077 reagent and spun at 400 G for 30 min. PBMCs were washed twice with phosphate buffered saline (PBS) (Thermofisher Scientific, Australia) and spun at 250 G for 10 min. PBMCs were resuspended in PBS before DNA isolation. Genomic DNA was extracted from whole blood and isolated PBMCs obtained from a single blood donation using the Purelink Genomic DNA Mini Kit (Thermofisher Scientific, Australia) according to the recommended guidelines. DNA yield and purity was assessed using a Nanodrop 2000 Spectrophotometer (Thermofisher Scientific, Australia) and stored at −20 °C. DNA quality was acceptable as the average 260/280 and 260/230 ratios for both whole blood and PBMC DNA samples were 1.84 ± 0.07 and 1.77 ± 0.50, respectively. Average telomere length was assessed using an established quantitative PCR method outlined previously (Denham et al., 2013, 2016b; Mainous et al., 2010). Briefly, 10 μl reactions were comprised of 2 × SensiFast SYBR Lo-ROX master mix (Bioline, Australia), primer-sets (Bioneer Pacific, Australia) and 10 ng of DNA. Samples were run in triplicate on a 384-well plate with positive and a no template control on the ViiA7 Real Time PCR System (Thermofisher Scientific, Australia). Details of the primer-sets and thermo cycling conditions can be found elsewhere (Mainous et al., 2010). For each sample, the telomere (T) repeat copy number was compared to the single (S) copy gene and was expressed in arbitrary units as a T/S ratio.

Statistical analysis

From previous data (Denham et al., 2013, 2016b), it was calculated that a minimum of 80 participants (40 in each group) were required to reach >80% power to detect a difference ($d > 0.65$) in PBMC telomere length between athletes and controls. Two-tailed independent samples *t*-tests were used to determine differences in physical attributes, exercise parameters and PBMC telomere length between athletes and controls. Pearson's correlations were used to determine linear relationships between telomere length and exercise parameters. ANCOVA was used to establish differences in PBMC telomere length whilst controlling for covariates. Statistical significance was set at $p < 0.05$.

Results

Physical characteristics

The characteristics of participants involved in this study are outlined in Table 1. The athletes were taller, spent less time sitting, exhibited a lower body weight, BMI and resting heart rate, and higher $\dot{V}O_{2max}$ and maximum running speed compared to controls (all $p < 0.05$, Table 1).

PBMC telomere length and endurance exercise

The intra-assay coefficient for the PBMC telomere assays was 1.97%, 0.90% and 4.23% for the telomere primer sets, 36B4 primer sets and T/S ratios, respectively. The athletes exhibited a comparable PBMC telomere length to that of their less fit peers in crude (Table 1), age and sex-adjusted analyses (athlete vs controls, mean T/S ratio ± SE: 3.25 ± 0.05 vs 3.23 ± 0.05, $p = 0.72$, Fig. 1) and after further adjustment for BMI, systolic BP, psychological stress, resting heart rate, sitting duration and relative $\dot{V}O_{2max}$ (3.23 ± 0.09 vs 3.24 ± 0.07, $p = 0.96$). In the cohort analysed in the present study, however, endurance athletes possessed 6.1% longer whole blood leukocyte telomeres compared to the controls (3.63 ± 0.06 vs 3.41 ± 0.06, $p = 0.01$, Supplementary Fig. 1).

Telomere length, cardiorespiratory fitness and sitting

Weak, positive correlations were observed between average PBMC and whole blood leukocyte telomere lengths in all subjects

Table 1
Characteristics of endurance athletes and healthy controls.

Variable	Athletes (n = 44)	Controls (n = 40)	*p*-value
Men/women (n)	34/10	29/11	
Age (y)	32.1 ± 9.85	29.7 ± 9.9	0.26
Height (cm)	177.2 ± 8.6	172.9 ± 9.1	0.03
Weight (kg)	71.6 ± 9.6	78.8 ± 11.0	0.002
BMI (weight/height^2)	22.8 ± 2.1	26.3 ± 2.7	<0.001
Systolic BP (mmHg)	123.1 ± 9.4	124.9 ± 11.1	0.41
Diastolic BP (mmHg)	72.8 ± 6.8	75.6 ± 9.0	0.11
Resting heart rate (beats min^{-1})	53 ± 8	69 ± 11	<0.001
$\dot{V}O_{2max}$ (ml kg^{-1} min^{-1})	57.6 ± 7.1	42.7 ± 7.3	<0.001
Maximum treadmill speed (km h^{-1})	17.1 ± 2.0	13.0 ± 2.0	<0.001
Maximum wattage (W)	362 ± 68	–	–
PSS	11.5 ± 4.6	11.1 ± 6.1	0.71
Sitting (min week^{-1})	2125.2 ± 950.7	4676.8 ± 3971.1	<0.001
PBMC telomere length (T/S ratio)	3.25 ± 0.30	3.23 ± 0.36	0.82

Data is expressed as mean ± SD from two-tailed paired *t*-tests.

Legend: BMI, body mass index; BP, blood pressure; $\dot{V}O_{2max}$, maximum oxygen uptake; PSS, perceived stress scale; PBMC, peripheral blood mononuclear cell; T/S, telomere to single copy gene.

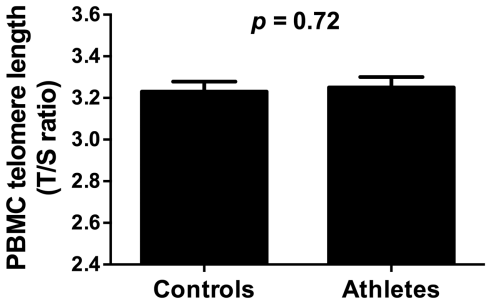

Fig. 1. Comparable average PBMC telomere lengths between athletes and controls. PBMC telomere length (T/S ratio): athlete; n = 44, 3.25 ± 0.05 vs controls; n = 40, 3.23 ± 0.05, $p = 0.72$. Data is from age and sex-adjusted two-tailed ANCOVA and is expressed as mean ± SE. Legend: PBMC, peripheral blood mononuclear cell; T/S, telomere to single copy gene.

and when the analysis was performed when athletes and controls were separated (Supplementary Fig. 2A–C). Regardless, no statistically significant correlations were observed between PBMC telomere length and $\dot{V}O_{2max}$, resting heart rate or maximum treadmill speed (all $p > 0.05$, Fig. 2). There was, however, a weak, statistically significant inverse correlation between PBMC telomere length and self-reported, weekly sitting duration ($r = -0.25$, $p = 0.03$, Fig. 2).

Discussion

The purpose of this study was to analyse PBMC telomere length in context with endurance exercise and exercise parameters. Despite having longer whole blood leukocyte telomeres, which is consistent with previous data (Denham et al., 2013, 2016b), the endurance athletes in the present study possessed an average PBMC telomere length comparable to their non-athletic peers. Furthermore, there were no statistically significant linear relationship between PBMC telomere length and exercise parameters (resting heart rate and $\dot{V}O_{2max}$ or maximum treadmill speed).

The evidence indicating a role for exercise training in telomere maintenance is mounting (Denham et al., 2016a). Although most studies indicate positive associations between exercise and immune cell telomere length, findings are equivocal (Denham et al., 2016a). For example, some found middle-aged endurance athletes had longer leukocyte telomeres compared to their less-active controls (Denham et al., 2013, 2016b; Larocca et al., 2010; Sassenroth et al., 2015), whilst others revealed no association between endurance athlete status and telomere length (Laine et al., 2015; Mathur et al., 2013). There are numerous potential explanations for the discordant findings, including DNA extraction procedure (Denham et al., 2014), participant genetic diversity, method of telomere quantification and particularly relevant to the present study, the cell type included for telomere length assessment.

Accordingly, an analysis of whole blood leukocyte and PBMC telomere length was performed in this study, using a subset of participants from a previous investigation (Denham et al., 2016b). While the whole blood leukocyte telomeres were longer in the athletes, PBMC telomere length was similar between athletes and controls. This finding was unexpected, considering somatic cell telomeres seem to shorten at equivalent rates (Daniali et al., 2013) and the synchrony of telomere lengths amongst hematopoietic

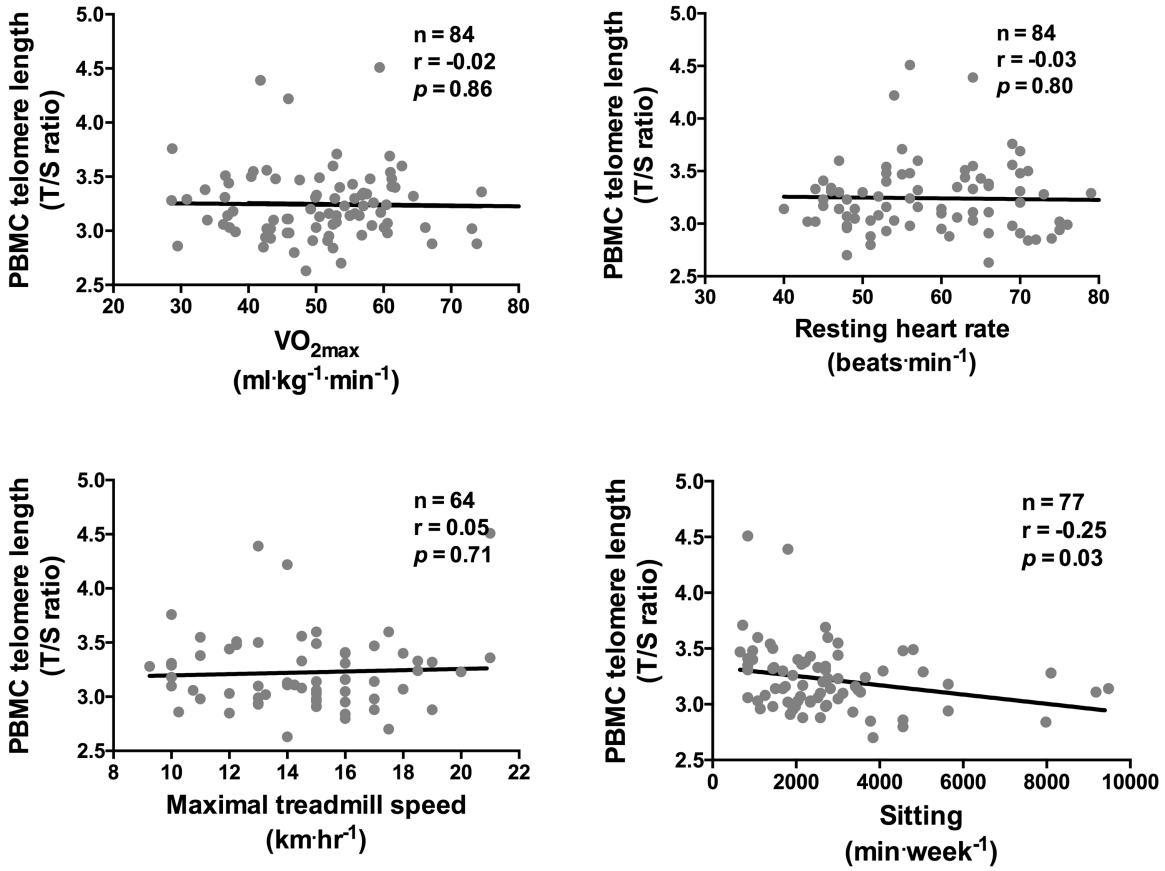

Fig. 2. Linear correlations between PBMC telomere length and exercise parameters. Data is from two-tailed Pearson's correlation. Legend: PBMC, peripheral blood mononuclear cell; T/S, telomere to single copy gene; $\dot{V}O_{2max}$, maximum oxygen uptake ($ml\,kg^{-1}\,min^{-1}$).

cells (Kimura et al., 2010). Conversely, there is a marked difference in the telomere shortening of lymphocytes compared to granulocytes, and telomere heterogeneity increases in myeloid cells with ageing (Hoffmann et al., 2009). Thus, exercise training might preferentially maintain telomeres of specific leukocyte subsets. This would suggest a role for exercise in maintaining neutrophil telomeres, as these are present at a higher frequency in whole blood samples, relative to eosinophil and basophils, which are removed during density gradient centrifugation. Acute strenuous exercise shortens telomeres (Borghini et al., 2015) and is associated with increased reactive oxygen species (ROS) (Mastaloudis et al., 2001). Given that telomeres are vulnerable to oxidative stress (Von Zglinicki, 2002), the anti-oxidant capacity of different immune cells could lead to differential telomere length in athletes. This notion is supported by previous findings that indicate the protective effects of exercise on age-related telomere attrition are cell-specific (Ludlow et al., 2012). Although a relatively weak positive correlation was observed between whole blood leukocyte telomeres and PBMC telomere length in the entire cohort, the correlation just reached statistically significance in athletes and was not statistically significant in the control cohort. Poor statistical power or technical error could account for the lack of association between whole blood and PBMC telomere length and exercise parameters, yet a well-established qPCR method was used (Denham et al., 2013, 2016b; Mainous et al., 2010). The intra-coefficient of variation between experimental replicate samples was also acceptable ($<$2%). The strong correlations previously observed between telomere lengths of different haematopoietic subsets were performed using southern blot (Kimura et al., 2010), implicating methodological differences were accountable for the weaker correlations observed in the present study. Alternatively, altered leukocyte populations in athletes could account for their long leukocyte telomeres (Horn et al., 2010; Parisotto et al., 2003). Habitual exercise could also alter the distribution of long or short telomeres, which would be biologically significant given the shortest telomeres lead to chromosomal instability (Hemann et al., 2001). Notably, this study was not designed to explain the lack of association between endurance exercise training and PBMC telomere length. Nonetheless, this is an important finding and it is recommended that future work focus on determining the influence of endurance exercise on specific leukocyte populations measured in conjunction with leukocyte population frequencies.

Unlike the previous study where whole blood leukocyte telomeres were analysed (Denham et al., 2016b), the present study did not reveal any statistically significant correlations between exercise parameters (relative $\dot{V}O_{2max}$, resting heart rate, maximum treadmill speed) and average PBMC telomere length. Previous work has identified statistically significant positive correlations between maximal oxygen uptake and leukocyte telomere length (Denham et al., 2016b; Larocca et al., 2010; Mason et al., 2013), but not granulocyte telomere length (Mathur et al., 2013). There was, however, a weak inverse correlation between sitting duration and PBMC telomere, suggesting that sedentary activity could accelerate telomere shortening. This finding corroborates previous studies (Denham et al., 2016b; Sjogren et al., 2014) and provides additional evidence supporting the premise that excessive sitting could encourage telomere shortening. There is considerable epidemiological data associating prolonged sitting with disease incidence and mortality risk, independent of physical activity levels (Biswas et al., 2015; Katzmarzyk et al., 2009; Patel et al., 2010). It is plausible that prolonged sitting could lead to an increased risk of disease and mortality risk through a process involving excessive telomere shortening. Prolonged sitting is hypothesised to increase the risk of disease through skeletal muscle deconditioning and promoting a pro-inflammatory and oxidative environment, which facilitates telomere shortening (Von Zglinicki, 2002). Interrupting prolonged sitting with short bouts of light to moderate exercise leads gene expression changes in anti-inflammatory and anti-oxidant genes (Latouche et al., 2013). Although speculative, sedentary behaviour could accelerate telomere shortening of mononuclear cells that rely heavily on aerobic metabolism (Pearce and Pearce, 2013), by augmenting reactive oxygen species. Granulocytes, however, predominantly utilise glycolysis for metabolism (Pearce and Pearce, 2013) and as such, intense exercise training may be more important for granulocyte telomere maintenance, especially considering the exercise-associated increases in blood lactate is linked to telomere protection through NRF1- and AMPK-mediated increased expression of the telomere transcript, TERRA (Diman et al., 2016).

A limitation of the present study is that it involved a cross-sectional analysis and causation cannot be inferred. Furthermore, particular diets may also impact telomere maintenance and dietary information was not analysed in this study. Larger, randomised controlled trials will be required to verify whether sedentary behaviour and endurance exercise accelerates and attenuates biological ageing, respectively.

Conclusions

Unlike whole blood leukocyte telomeres, average PBMC telomere length is not associated with endurance exercise training or other exercise parameters. Future work should establish the association between exercise and telomere length amongst sorted leukocyte populations and determine the frequency of short and long telomeres to identify whether exercise prevents immunosenescence and biological ageing.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jab.2016.09.004.

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