Published in final edited form as:

Mech Ageing Dev. 2010 February ; 131(2): 165–167. doi:10.1016/j.mad.2009.12.009.

Leukocyte Telomere Length is Preserved with Aging in Endurance Exercise-Trained Adults and Related to Maximal Aerobic Capacity

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Abstract

Telomere length (TL), a measure of replicative senescence, decreases with aging, but the factors involved are incompletely understood. To determine if age-associated reductions in TL are related to habitual endurance exercise and maximal aerobic exercise capacity (maximal oxygen consumption, VO_2max), we studied groups of young (18 – 32 years; $n = 15$, 7m) and older (55 – 72 years; $n = 15$, 9m) sedentary and young ($n = 10$, 7m) and older endurance exercise-trained ($n = 17$, 11m) healthy adults. Leukocyte TL (LTL) was shorter in the older (7059 ± 141 bp) vs. young (8407 ± 218) sedentary adults ($P < 0.01$). LTL of the older endurance-trained adults (7992 ± 169 bp) was ~900 bp greater than their sedentary peers ($P < 0.01$) and was not significantly different ($P=0.12$) from young exercise-trained adults (8579 ± 413). LTL was positively related to VO_2max due to a significant association in older adults ($r = 0.44$, $P < 0.01$). Stepwise multiple regression analysis revealed that VO_2max independently explained ~60% of the variance in LTL. Our results indicate that LTL is preserved in healthy older adults who perform vigorous aerobic exercise and is positively related to maximal aerobic exercise capacity. This may represent a novel molecular mechanism underlying the "anti-aging" effects of maintaining high aerobic fitness.

Telomere length (TL) is a measure of replicative senescence (Aubert & Lansdorp, 2008) and a proposed marker of biological aging (Bekaert *et al.*, 2007). TL decreases progressively with aging (Gilley *et al.*, 2008) and is associated with numerous pathologies (Brouillette *et al.*, 2007; Demissie *et al.*, 2006; Fitzpatrick *et al.*, 2007) and all-cause mortality (Cawthon *et al.*, 2003; Farzaneh-Far *et al.*, 2008). Moreover, cellular senescence induced by telomere shortening is a potential mechanism underlying reductions in physiological function with aging (Muller, 2009; Fuster & Andrés, 2006).

At any age, TL is determined by the combination of the TL at birth and the rate of age-related decline (Aubert & Lansdorp, 2008). Despite its biological and biomedical importance, the factors that influence the age-associated decrease in TL are incompletely understood, particularly with regard to factors that may act to preserve TL. In this context, habitual aerobic exercise and high aerobic exercise capacity generally are associated with better maintenance of cellular function with aging compared with a sedentary lifestyle. However, associations between TL and habitual physical activity are inconsistent (Cherkas *et al.*, 2008; Woo *et al.*, 2008; Ludlow *et al.*, 2008; Shin *et al.*, 2008) and there is no information on TL and objective measures of aerobic capacity.

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Accordingly, we tested the hypothesis that TL is at least partially preserved with aging in humans who perform regular vigorous aerobic exercise, and is positively related to maximal aerobic exercise capacity. We studied 57 men and women: 15 young (18 – 32 years, 7 male) and 15 older (55 – 72 years) sedentary (9 male), and 10 young (7 male) and 17 older habitually exercising (11 male). Subjects were non-obese, non-smokers and healthy as assessed by medical history, physical examination, blood chemistries and exercise ECG (older subjects only). Sedentary subjects performed no regular aerobic exercise (< 2 days/week, < 30 min/day), whereas exercising subjects had performed regular vigorous aerobic exercise (≥ 5 days/week, > 45 min/day) for ≥ 5 years.

Leukocyte TL (LTL), the most commonly used human telomere sample and a proposed marker of systemic biological aging (Bekaert *et al.*, 2007; Aviv, 2002; Cherkas *et al.*, 2008), was measured in genomic DNA extracted from isolated leukocytes using a modification of the Southern blot analysis described previously (Middleman *et al.*, 2006). Maximal oxygen consumption (VO_2max) was assessed during treadmill exercise and used as a measure of maximal aerobic exercise capacity as described earlier (DeSouza *et al.*, 2000). Subject characteristics were assessed using standard techniques described elsewhere (Pierce *et al.*, 2008). All measurements were performed after a 12-h fast and 24-h abstention from alcohol and physical activity. Group differences were determined by analysis of variance. Bivariate Pearson correlation analyses were used to assess relations of interest. Stepwise linear regression analysis was performed to identify independent predictors of LTL.

Several subject characteristics differed among the groups in the expected directions (Table 1). Diet composition and nutrient intake, adjusted for total calories, were similar among the groups (data not shown). LTL was shorter in the older (7059 ± 141 bp) vs. young (8407 ± 218) sedentary adults ($P < 0.01$, Figure 1). LTL of the older endurance-trained adults (7992 ± 169 bp) was ~ 900 bp greater than their sedentary peers ($P < 0.01$) and was not significantly different ($P = 0.12$) from young exercise-trained adults (8579 ± 413).

LTL was positively related to VO_2max in the overall sample ($r = 0.44$, $P < 0.01$, Figure 1) due to a positive correlation among the older adults ($r = 0.44$, $P < 0.01$), as there was no relation among young adults ($r = -0.02$, $P = 0.92$). Stepwise multiple regression analysis revealed that in the overall sample VO_2max was the only variable that entered and independently explained 62% of the variance in LTL ($R^2 = 0.62$, $b = 0.51$, $P < 0.01$), whereas in the older subjects alone VO_2max explained 60% of the variance ($R^2 = 0.60$, $b = 0.077$, $P < 0.01$) with age explaining an additional 28% ($R^2 = 0.88$, $b = -0.051$, $P < 0.01$). The relation between LTL and VO_2max in the overall and older groups was not affected by other subject characteristics. LTL did not correlate with leisure-time physical activity in any group ($r = 0.15 - 0.28$, $P = 0.11 - 0.52$). LTL was not influenced by the sex of the subjects ($P = 0.21$).

The results of the present study provide evidence that LTL is related to regular vigorous aerobic exercise and maximal aerobic exercise capacity with aging in healthy humans. LTL is not influenced by aerobic exercise status among young subjects, presumably because TL is intact (i.e., already normal) in sedentary healthy young adults. However, as LTL shortens with aging it appears that maintenance of aerobic fitness, produced by chronic strenuous exercise and reflected by higher VO_2max , acts to preserve LTL.

The exact nature of these relations and the underlying mechanisms are not clear. Risk factors for cardiovascular disease may influence LTL (Chen *et al.*, 2009; Fitzpatrick *et al.*, 2007), but did not explain the relations with VO_2max in the present study. Habitual aerobic exercise modulates VO_2max , but as much as $\sim 50\%$ of the latter is determined primarily by genetic factors (Bouchard *et al.*, 1998 & 1999). Shorter-term exercise training has no effect on LTL in humans or mice (Shin *et al.*, 2008; Werner *et al.*, 2008), but does modulate telomere-

regulating proteins (Werner *et al.*, 2008). This may suggest that longer-term or more strenuous exercise is required to influence LTL. It also is possible that habitual exercise behavior, higher VO₂max and longer LTL all are part of the same phenotype expressed in some older adults. Although previous findings are inconsistent (Cherkas *et al.*, 2008; Ludlow *et al.*, 2008; Woo *et al.*, 2008), the fact that leisure-time physical activity was unrelated to LTL in our study suggests a more direct association with maximal aerobic exercise capacity.

In conclusion, LTL is preserved with age in endurance exercise-trained humans and is related to maximal aerobic exercise capacity among healthy older adults. This may represent a novel molecular mechanism linking vigorous habitual exercise/aerobic fitness to reduced cellular senescence and preserved physiological function with aging.

Acknowledgments

We thank John Anderson for his efforts in DNA isolations and Arthur Zaug for his assistance with Southern blot procedures.

Sources of funding

Supported by National Institutes of Health awards AG013038, AG006537, AG022241, AG015897, AG031141, AG000279 and RR00051.

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Figure 1.

(A) Compared with sedentary (Sed) and exercising (Ex) young adults, mean LTL was shorter in sedentary, but not exercising older adults (* $P < 0.01$ vs. young groups and older exercising group). (B) Mean LTL is positively related to maximal aerobic exercise capacity.

Table 1**Subject Characteristics**

	Young Sedentary	Young Exercising	Older Sedentary	Older Exercising
n	15	10	15	17
Sex	7M,8F	7M, 3F	9M,6F	11M,6F
Age	23 ± 1	21 ± 1	65 ± 1 [*]	62 ± 2 [#]
VO ₂ max, ml/kg/min	43.7 ± 2.0	55.8 ± 1.4 [*]	25.9 ± 1.8 [*]	40.5 ± 1.7 ^{#†}
Leisure time physical activity, (MET hrs/wk)	32 ± 6	137 ± 22 [*]	12 ± 3 [*]	75 ± 11 ^{#†}
Body mass index, kg/m ²	22.1 ± 0.7	22.3 ± 0.4	25.5 ± 1 [*]	23.2 ± 0.9
% Body Fat	24.6 ± 2.6	13.4 ± 2.5 [*]	33.7 ± 2.7 [*]	21.4 ± 2.0 ^{#†}
Waist:hip ratio	0.76 ± 0.02	0.71 ± 0.03	0.87 ± 0.03 [*]	0.85 ± 0.02 [#]
Systolic blood pressure, mm Hg	104 ± 9	102 ± 10	125 ± 4 [*]	120 ± 4 [#]
Diastolic blood pressure, mm Hg	57 ± 2	54 ± 5	75 ± 2 [*]	75 ± 3 [#]
Total cholesterol, mg/dL	150 ± 11	144 ± 19	186 ± 7 [*]	190 ± 11 ^{#†}
LDL cholesterol, mg/dL	82 ± 9	88 ± 11	110 ± 7 [*]	109 ± 10
HDL cholesterol, mg/dL	53 ± 3	50 ± 4	56 ± 4	63 ± 3 [#]
Triglycerides, mg/dL	76 ± 7	77 ± 7	99 ± 11 [*]	110 ± 15 [#]
Glucose, mg/dL	84 ± 3	87 ± 3	88 ± 1	89 ± 2
C-reactive Protein, mg/L	0.5 ± 0.2	0.6 ± 0.2	1.3 ± 0.5	1.2 ± 0.4

Values are means ± SEs. MET, metabolic equivalent; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance;

^{*} P < 0.01 vs. Young Sedentary;

[#] P < 0.01 Older Exercising vs. Younger Exercising;

[†] P < 0.01 Older Exercising vs. Older Sedentary.