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Telomere length is associated with decline in grip strength in older persons aged 65 years and over

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Abstract Telomere length (TL) attrition is associated with chronic diseases characterized by chronic inflammatory states. Inflammatory cytokines may play a role in sarcopenia. This study examines the association between TL and the diagnosis of sarcopenia based on appendicular skeletal mass index (ASMI), grip strength, walking speed, and chair stand in a prospective study over 5 years of 976 men and 1,030 women aged 65 years and over living in the community. TL in leukocytes was measured using the quantitative PCR method. TL was divided into quartiles, and analysis of covariance (ANCOVA) was adopted to examine its association with components of sarcopenia, adjusting for age, education, body mass index, smoking, physical activity, and probable dementia. In both men and women, the percentage decline in grip strength over the 5-year period of follow-up was slower in those in the highest quartile of TL than those in the lower quartiles (multivariate-adjusted $p<0.05$). No association between TL and the diagnosis of sarcopenia, ASMI, walking speed, or chair stand was observed. In conclusion, longer TL was associated with slower decline in grip strength in Chinese older persons.

Keywords Telomere length · Sarcopenia · Grip strength · Inflammatory cytokines

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Introduction

Leukocyte telomere length (TL) attrition is associated with chronic diseases (Kong et al. 2013) as well as geriatric syndromes such as cognitive impairment (Ma et al. 2013). There are few studies examining the relationship between TL and sarcopenia, the physical component of frailty. Inflammatory cytokines contribute to muscle wasting and/or dysfunction (Cesari et al. 2012), and TL attrition occurs with chronic diseases associated with chronic inflammatory states (Woo et al. 2010). Grip strength, a component in the definition of sarcopenia (Cruz Jentoft 2014), has been shown to be associated with oxidative stress genes (Starr et al. 2008). Therefore, grip strength and sarcopenia may be associated with shortened TL.

To date, clinical studies have been conflicting. One study reports no association between TL and age-sensitive indicators of physical function in mid and later life (Mather et al. 2010). However, another study in

community-dwelling elderly reported shorter TL among those with sarcopenia (Lorenzi et al. 2014).

In a community-dwelling cohort of 976 men and 1,030 women followed prospectively, we examined the relationship between TL and the diagnosis of sarcopenia as well as the individual factors used in the diagnosis: appendicular skeletal mass index (ASMI), grip strength, and physical performance measures, examining the cross-sectional and prospective data over 5 years.

Subjects and methods

Four thousand community-dwelling Chinese men and women aged 65 years and older were invited to attend a health check carried out in the School of Public Health of the Chinese University of Hong Kong between August 2001 and February 2003. Recruitment was done by placing recruitment notices in community centers for older adults and housing estates. Several talks were also given at these centers explaining the purpose, procedures, and investigations to be carried out. Subjects were volunteers, and the aim was to recruit a stratified sample so that approximately 33 % would each be aged 65–69, 70–74, and 75 years and older. All subjects gave written consent, and the study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. The present study includes data from 976 men and 1,030 women (50.2 % all subjects) for whom TL was available.

At baseline, questionnaire containing information regarding demographics, educational level, smoking habit, physical activity level, and cognitive function was administered to subjects. Physical activity level was assessed using the Physical Activity Scale of Elderly (PASE) (Washburn et al. 1993). Cognitive function was assessed using the cognitive score of the Chinese version of the Community Screening Instrument of Dementia (CSI-D), the validity of which had been examined elsewhere. A CSI-D value of <28.4 has been used as a cutoff value to indicate the presence of probable dementia (Prince et al. 2003; Chan et al. 2003).

Body weight was measured using Physician Balance Beam Scale (Health-O-Meter, Arlington Heights, IL, USA) with the subject in light clothing. Height was measured using Holtain Harpenden stadiometer (Holtain, Crosswell, UK). Body mass index (BMI) was documented. DXA was used to measure whole and regional body composition. Appendicular skeletal muscle mass (ASM) was calculated as the sum of appendicular lean mass minus bone mineral content of both arms and legs, with the operator adjusting the cut lines of the limbs according to specific anatomical landmarks as described by Heymsfield et al. (1990). Grip strength was measured using a dynamometer (JAMAR Hand Dynamometer 5030JO; Sammons Preston, Bolingbrook, IL). Two readings were taken from each side, and the maximum value of the right/left was used for analysis. Walking speed was measured using the best time in seconds to complete a walk along a straight line 6 m long in distance. A warm up period of less than 5 min was followed by two walks and the best time was recorded. Subjects were also asked to stand up with folded arms from a chair five times, and the time required was recorded. After 4 years of follow-up, 1,562 subjects returned, and assessment was repeated. The mean age at follow-up was 75.6±4.9 years.

Diagnosis of sarcopenia

Sarcopenia was diagnosed according to the Asian Working Group for Sarcopenia (AWGS) algorithm (Chen et al. 2014) in which a person who has low muscle mass, low muscle strength, and/or low physical performance was categorized as having sarcopenia. As suggested by AWGS, low muscle mass was defined as ASMI (ASM/height^2) <7.0 kg/m^2 for men and <5.4 kg/m^2 for women; low muscle strength was defined as grip strength <26 kg for men and <18 kg for women and low physical performance as walking speed <0.8 m/s.

Laboratory measurements

The quantitative PCR method was used to determine telomere length and has been reported previously (Woo et al. 2008b). In brief, the genomic DNA was extracted from the peripheral blood by standard phenol–chloroform extraction method using commercial kits (General Electric, USA). Afterwards, purified DNA samples are stored at over 100 ng/μl in Milli-Q water on the 96-well plates and stored at −20 °C until use.

Measurement of telomere length of DNA samples follows the method published by Cawthon (2002) with modification (Gil and Coetzer 2004). The principle of this technique is to measure the factor of the ratio between the telomere repeat copy number and a single

copy gene copy number in our sample with respect to a reference DNA sample (known as T/S ratio). Real-time quantitative polymerase chain reaction (RTQPCR) was performed on Roche LightCycler 480 (Roche, Mannheim, Germany). The threshold cycle numbers (C_t) of the DNA samples were recorded. This number is inversely proportional to log (amount of DNA templates) (Higuchi et al. 1993).

The reference DNA and additional quality control samples were used to estimate efficiency and quality assurance. These reactions were carried out in duplicates. A standard curve of C_t versus concentration was plotted to get the efficiency for each PCR reaction. This efficiency (E) can be obtained by the formula $10^{-(1/\text{slope})}$, with an acceptable range 1.5–2.2. The relative *T/S* ratio (second derivative of *T/S* ratio or ΔΔCt) was obtained by the formula.

$$\left\{E_{(\text{tel})}{}^{\wedge\left[C_{t(\text{reference tel})}-C_{t(\text{sample tel})}\right]\wedge}\right\}\Big/\left\{E_{(36B4)}{}^{\wedge\left[C_{t(\text{reference 36B4})}-C_{t(\text{sample 36B4})}\right]\wedge}\right\}.$$

The *T/S* ratio or ΔΔCt was then plotted against a standard calibration curve using samples with pre-determined telomere length to obtain the telomere length in unit of kilobps (kb). The average coefficient of variation % (CV%) of the C_t readings were 3.6 and 1.8 % for telomere and 36B4 primers reactions, respectively. The overall average precision of ΔΔCt and telomere length was 11.1 %. Two control samples were analyzed in duplicates in each batch of assays; one sample was collected from a volunteer in his/her 20s representing a long telomere control (long QC, telomere length=11.3 kb) and another from an elderly subject representing a short telomere control (short QC, telomere length=8.2 kb). Within-batch and between-batch analytical imprecision were determined from over 20 batches of assays using these two samples. The within-batch and between-batch CV percentage of ΔΔCt were 11.9 and 11.2 for the long QC sample. For the short QC sample, they were 8.1 and 14.2 % respectively.

A calibration curve of telomere length versus ΔΔCt was plotted using four additional reference samples with pre-determined telomere length that has been previously measured by terminal restriction fragment length polymorphism (TRFLP) and Southern blot. Thus, by comparing the raw sample ΔΔCt to this calibration curve, the telomere length can also be estimated for each sample. The average coefficient of correlation between the two parameters was r^2=0.63 which is not different from that reported in the original paper by Cawthon (r^2=0.68) (2002). The coefficients of variation (CV) of the telomere and reference gene assay (36B4) were 1.93 and 1.27 %, respectively. These values were comparable to the values from two other studies using comparable methods: 0.9 and 2.4 % (Wang et al. 2008) and 2.46 and 2.26 % (McGrath et al. 2007). Within-batch and between-batch analytical imprecision were determined using two control samples with known telomere length by TRFLP (long QC [quality control], telomere length= 11.3 kbp; short QC, telomere length=8.2 kbp) using results obtained from over 20 batches of assays. The within-batch and between-batch CV percentage of calibrated telomere length was 8.5 and 7.5 % for the long QC sample. For the short QC sample, they were 6.3 and 6.1 %, respectively.

Statistical analysis

The association between TL and sarcopenia and its individual factors was analyzed separately for men and women because women have longer telomeres. Independent two-sample *t* test was used to test between two groups for continuous variables, while chi-square test was used for categorical variables. Logistic regression was used to evaluate the association between TL and the diagnosis of sarcopenia at baseline and incident sarcopenia. Subsequently, TL was divided into quartiles. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to examine differences in mean ASMI, grip strength, walking speed, and chair stand test and their follow-up values and percentage change by telomere quartiles. Both linear and quadratic trends were examined. Percentage change was calculated as the baseline value minus the value at the fifth year follow-up divided by the baseline value multiplied by 100. The analysis was repeated after adjustment for possible confounders including age, education level, BMI, smoking, physical activity, and probable dementia. All analyses were carried out using Windows-based Statistical Package for the Social Science version 21.0 software (SPSS, Chicago, IL, USA). p values <0.05 were considered to be statistically significant.

Results

There were 2,006 subjects (976 men and 1,030 women) at baseline. After 4 years, 444 were lost to follow-up, and 1,562 were re-interviewed. Subjects lost to follow-

Table 1 Characteristics of study population

	Men	Women	Both gender	*p* value[a]
Age (years)				
All (baseline)	72.8±5.0	72.0±5.2	72.4±5.1	0.001
Remained in follow-up	72.1±4.6	71.7±5.0	71.9±4.8	0.092
Loss to follow-up	74.8±5.7*	73.4±5.7*	74.2±5.7*	0.011
All (fifth year FU)[b]	75.8±4.6	75.4±5.0	75.6±4.9	0.129
Education level (secondary school or above)				
All (baseline)	374 (38.3)	189 (18.3)	563 (28.1)	<0.001
Remained in follow-up	295 (40.1)	159 (19.2)	454 (29.1)	<0.001
Loss to follow-up	79 (32.8)*	30 (14.8)	109 (24.5)	<0.001
BMI (kg/m^2)				
All (baseline)	23.4±3.1	23.9±3.5	23.6±3.3	0.004
Remained in follow-up	23.6±3.0	23.9±3.5	23.8±3.3	0.024
Loss to follow-up	23.0±3.3*	23.6±3.7	23.3±3.5*	0.109
All (fifth year FU)[b]	23.4±3.0	23.8±3.6	23.6±3.3	0.008
Current smoker				
All (baseline)	121 (12.4)	23 (2.2)	144 (7.2)	<0.001
Remained in follow-up	84 (11.4)	15 (1.8)	99 (6.3)	<0.001
Loss to follow-up	37 (15.3)	8 (3.9)	45 (10.1)*	<0.001
Physical activity (PASE total score)				
All (baseline)	94.8±49.3	89.7±35.0	92.2±42.6	0.008
Remained in follow-up	99.4±49.9	90.5±35.1	94.7±42.9	<0.001
Loss to follow-up	80.9±44.7*	86.3±34.4	83.4±40.4*	0.149
All (fifth year FU)[b]	99.8±46.8	100.5±39.3	100.2±43.0	0.735
Cognitive function (probable dementia, CSI-D score <28.4)				
All (baseline)	54 (5.5)	222 (21.6)	276 (13.8)	<0.001
Remained in follow-up	22 (3.0)	166 (20.1)	188 (12.0)	<0.001
Loss to follow-up	32 (13.3)*	56 (27.6)*	88 (19.8)*	<0.001
Telomere length (kb)				
All (baseline)	8.8±1.6	9.3±2.3	9.1±2.0	<0.001
Remained in follow-up	8.8±1.6	9.4±2.3	9.1±2.0	<0.001
Loss to follow-up	8.8±1.6	9.3±2.3	9.0±2.0	0.007
Grip strength (kg)				
All (baseline)	34.04±6.8	22.3±4.56	28.0±8.2	<0.001
Remained in follow-up	34.9±6.6	22.4±4.5	28.3±8.3	<0.001
Loss to follow-up	31.4±6.7*	21.5±4.8*	26.9±7.7*	<0.001
All (fifth year FU)[b]	31.7±6.4	20.5±4.5	25.8±7.9	<0.001

Data are presented as mean±SD or number (percentage). Percentages may not add up to 100 % due to rounding

BMI body mass index, *CSI-D* Community Screening Instrument of Dementia, *FU* follow-up, *PASE* Physical Activity Scale of the Elderly

**p* value <0.05 of *t* test for continuous variables or chi-square for categorical variables comparing subjects remained in (n=1,562) and loss to follow-up (n=444)

[a] *p* value of *t* test for continuous variables or chi-square for categorical variables comparing men and women

[b] Data are based on valid case (n) observed at fifth year FU, for age (years) (n=1,562), BMI (kg/m^2) (n=1,560), PASE score (n=1,561), and grip strength (kg) (n=1,562)

up were older, had lower mean values in their BMI, PASE score, and grip strength, were less likely to be current smokers, and had lower prevalence of probable dementia. There were no significant differences in the distribution of education level and TL. The characteristics of the subjects remained in follow-up and those lost to follow-up are shown by gender (Table 1).

There was no association between TL and the diagnosis of sarcopenia at baseline nor incident sarcopenia. Similarly, there was no association between TL and ASMI, walking speed, and chair stand, either cross-sectionally or changes in values on follow-up.

However, men with longer TL tended to show lower grip strength at baseline, but the difference in grip strength across quartiles of TL did not reach statistical significance (p=0.169). After 4 years, the percentage decline in grip strength was slower in those in the highest quartile of TL than those in the lower quartiles (Q_{IV} compared with $Q_{I–II}$, multivariate-adjusted $p<0.05$; p for linear trend <0.01; Table 2). The p value for quadratic trend in TL was not significant (p=0.605, data not shown).

Women with longer TL tended to show higher grip strength at follow-up (Q_{IV} compared with Q_{III}, $p<0.05$; p for quadratic trend <0.05). The percentage decline in grip strength was slower in those in the highest quartile of TL than those in the lower quartiles (Q_{IV} compared with Q_{I-III}, multivariate-adjusted $p<0.05$; p for quadratic trend <0.05; Table 3). However, the p value for linear trend in TL was only marginally significant (p=0.059, data not shown).

Discussion

To our knowledge, this is the first large scale study examining the relationship between TL and sarcopenia in community-dwelling older persons using both cross-sectional as well as prospective data. Using the current definitions of sarcopenia, we did not demonstrate any relationship with TL. This finding is compatible with the

Table 2 Baseline mean (SE) grip strength (kg) and its percentage change over follow-up by different level of telomere length in men

	Quartiles of telomere length (kb)[a], estimated mean (SE)				p difference[c]	p linear[c]
	I	II	III	IV		
Grip strength (baseline)[b]	34.06 (0.42)	34.18 (0.42)	34.64 (0.45)	33.29[§] (0.44)	0.169	0.339
Grip strength (fifth year FU)[b]	31.45 (0.44)	31.41 (0.50)	32.27 (0.51)	31.71 (0.46)	0.569	0.442
Grip strength % change (fifth year FU)	9.49 (1.30)	10.10 (1.34)	7.01 (1.32)	5.65[†‡] (1.28)	0.053	0.012
Grip strength % change (fifth year FU), age-adjusted[d]	9.66 (1.30)	10.07 (1.34)	6.87 (1.32)	5.65[†‡] (1.28)	0.044	0.009
Grip strength% change (fifth year FU), multivariate-adjusted[e]	9.72 (1.31)	10.02 (1.34)	6.82 (1.33)	5.69[†‡] (1.29)	0.047	0.009
Grip strength % change (fifth year FU), multivariate-adjusted[f]	9.75 (1.31)	10.01 (1.34)	6.79 (1.33)	5.69[†‡] (1.29)	0.046	0.008

Percentage change=(baseline−fifth year)/baseline×100 %

BMI body mass index, *FU* follow-up, *PASE* Physical Activity Scale of the Elderly

[†] $p<0.05$ (comparing II, III, and IV with I); [‡] $p<0.05$ (comparing III and IV with II); [§] $p<0.05$ (comparing IV with III)

[a] Values for telomere length quartiles: I, <7.63; II, 7.63–8.62; III, 8.63–9.81; and IV, ≥9.82 kb

[b] Data are based on valid case (n) observed at baseline (n=976) and fifth year FU (n=735)

[c] p value of analysis of variance (ANOVA)/analysis of covariance (ANCOVA)

[d] Adjusted for age

[e] Adjusted for age, education, BMI, smoking, and PASE

[f] Adjusted for age, education, BMI, smoking, PASE, and probable dementia

Table 3 Baseline mean (SE) grip strength (kg) and its percentage change over follow-up by different level of telomere length in women

	Quartiles of telomere length (kb)[a], estimated mean (SE)				*p* difference[c]	*p* quadratic[c]
	I	II	III	IV		
Grip strength (baseline)[b]	22.56 (0.28)	22.11 (0.27)	22.15 (0.29)	22.23 (0.30)	0.678	0.361
Grip strength (fifth year FU)[b]	20.54 (0.31)	20.30 (0.32)	20.01 (0.33)	21.11[§] (0.30)	0.084	0.033
Grip strength % change (fifth year FU)	8.95 (1.17)	7.88 (1.16)	9.27 (1.16)	4.42[†‡§] (1.15)	0.012	0.104
Grip strength % change (fifth year FU), age-adjusted[d]	8.86 (1.17)	7.96 (1.15)	9.22 (1.16)	4.48[†‡§] (1.15)	0.015	0.097
Grip strength% change (fifth year FU), multivariate-adjusted[e]	8.38 (1.17)	8.01 (1.15)	9.53 (1.15)	4.61[†‡§] (1.14)	0.017	0.049
Grip strength % change (fifth year FU), multivariate-adjusted[f]	8.35 (1.17)	8.02 (1.15)	9.58 (1.15)	4.57[†‡§] (1.15)	0.015	0.043

Percentage change=(baseline−fifth year)/baseline×100 %

BMI body mass index, *FU* follow-up, *PASE* Physical Activity Scale of the Elderly

[†] $p<0.05$ (comparing II, III, and IV with I); [‡] $p<0.05$ (comparing III and IV with II); [§] $p<0.05$ (comparing IV with III)

[a] Values for telomere length quartiles: I, <7.78; II, 7.78–9.02; III, 9.03–10.80; and IV, ≥10.81 kb

[b] Data are based on valid case (n) observed at baseline (n=1,030) and fifth year FU (n=827)

[c] p value of analysis of variance (ANOVA)/analysis of covariance (ANCOVA)

[d] Adjusted for age

[e] Adjusted for age, education, BMI, smoking, and PASE

[f] Adjusted for age, education, BMI, smoking, PASE, and probable dementia

findings from a cross-sectional study in Australia (Mather et al. 2010), but contrasts with the cross-sectional study in an Italian community-dwelling population of 107 older persons aged 65 years and over (Lorenzi et al. 2014).

The lack of association may be related to the greater role played by inflammatory cytokines in muscle wasting and in cachexia as opposed to sarcopenia (Evans et al. 2008). Cachexia accompanies many chronic diseases where associations with TL have been noted and where a chronic inflammatory state exists (Woo et al. 2010). By contrast, protein synthesis and protein undernutrition may play a more prominent role in the pathogenesis of sarcopenia. Nevertheless, a clear association with decline in grip strength was observed, and it is possible that changes in grip strength represent a more sensitive indicator of muscle function.

Grip strength indirectly reflects physical activity/exercise training. Many cross-sectional studies have described different associations with TL in immune cells: a positive or U-shaped association and no association (Puterman et al. 2010; Du et al. 2012; Ludlow et al. 2008; Mathur et al. 2013; Woo et al. 2008a). Both the sedentary state and extremes of activity are associated with shorter TL. Currently, the overall consensus is that moderate levels of physical activity are associated with longer TL in immune cells.

However, the relationship between exercise and skeletal muscle TL may be different from that of immune cell TL since the former is linked to proliferative demand exercise places on the muscle. Muscle-specific TL may be shortened by damage to muscle induced by demanding exercise together with the increased generation of reactive oxygen species (Ludlow et al. 2013). We did not examine muscle-specific TL in this study.

Furthermore, it has been pointed out that longitudinal changes in TL are needed throughout the life course taking into account confounding factors to address the question of whether TL can be used as a biomarker of diseases or as an indicator of biological age (Zhang et al. 2014). Different methods in measuring TL and examination of TL in different tissues may also yield different results (Sanders and Newman 2013; Hoffmann and Spyridopoulos 2011).

There are limitations in this study. Our cohort was more educated and more physically active than the general elderly population in Hong Kong, and we did not include those residing in long-term care institutions; therefore, findings should not be generalized to those who are institutionalized or with lower educational levels. The follow-up data may be subject to attrition bias towards younger age and those with better health status since these subjects were more likely to return to follow-up. Moreover, subjects lost to follow-up had lower mean values of grip strength, which might have underestimated the association between TL and grip strength. Furthermore, TL in peripheral blood leukocyte may not correlate well with that in myocytes, which are the cell lines involved in sarcopenia. Finally, we did not have information regarding the longitudinal changes in TL. The strength of the study lies in the sufficiently large sample size for both men and women, which allows observations relating to gender differences to be made. The PCR method used in this study has the advantages of ease of use and high throughput, which are prerequisites for large-scale epidemiological studies.

In conclusion, the association between TL and sarcopenia is not strong, the only positive association being noted with decline in grip strength. This association has clinical implications because of the potential predictive value of TL. Follow-up studies with changes in TL are needed to disentangle the impact of TL attrition on aging.

Conflict of interest The authors have no conflict of interest to declare.

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