Leukocyte telomere length is related to appendicular lean mass: cross-sectional data from the Berlin Aging Study II (BASE-II)[1,2]

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ABSTRACT

Background: Age-related progressive loss of muscle mass is an increasing problem in our aging society, affecting physical ability, risk of falls, and need for health care. Telomere length has been recognized as a marker of biological age on the population level. The relation between muscle mass in advanced age and telomere length, however, has rarely been examined.

Objective: We evaluated the relation between appendicular lean mass (ALM) and relative leukocyte telomere length (rLTL) in 1398 participants of the Berlin Aging Study II (mean ± SD age: 68.2 ± 3.7 y; 49.6% men).

Design: rLTL was determined by real-time polymerase chain reaction. Lean mass was estimated by dual X-ray absorptiometry and examined as leg lean mass (LLM), ALM, and the ratio of ALM to body mass index (ALM_{BMI}).

Results: Weak, but highly significant ($P < 0.001$), correlations of rLTL with ALM ($r = 0.248$), ALM_{BMI} ($r = 0.254$), and LLM ($r = 0.263$) were found. In the fully adjusted model that included age, BMI, low-grade inflammation, lifestyle factors, and morbidities as potential confounders, rLTL was associated with ALM ($\beta = 1.11$, SEM = 0.46, $P = 0.017$), LLM ($\beta = 1.20$, SEM = 0.36, $P = 0.001$), and ALM_{BMI} ($\beta = 0.04$, SEM = 0.02, $P = 0.013$) in men and with LLM in women ($\beta = 0.78$, SEM = 0.35, $P = 0.026$).

Conclusions: Our results suggest that short telomeres may be a risk factor for lower ALM, particularly for low LLM. To confirm the association between telomere attrition and loss of LLM and ALM_{BMI}, which are highly relevant for physical ability, further research in a longitudinal context is needed. The medical portion of this trial was registered in the German Clinical Trials Registry (http://drks-neu.uniklinik-freiburg.de/drks_web/navigate.do?navigationId=start) as DRKS00009277. *Am J Clin Nutr* 2016;103:178–83.

Keywords: appendicular lean mass, BASE-II, leukocytes, muscle mass, sarcopenia, telomere length

INTRODUCTION

The gradual decrease in muscle mass with aging has been associated with a decline in physical strength and mobility and with an increased risk of falls and disability (1, 2). Thus, maintaining skeletal muscle mass is highly relevant to independence and quality of life in advanced ages (3).

Telomeres, the terminal repetitive sequences of human chromosomes, shorten with each round of DNA replication, which can result in cellular senescence and/or apoptosis when they reach a certain limit (4). The enzyme telomerase can counteract telomere attrition, but its activity is mostly restricted to germ line cells and has limited activity in somatic cells (5). Telomere length has been widely discussed as a biomarker of cellular aging (6). Results on associations between telomere length and mortality (6), and different diseases such as type 2 diabetes and cardiovascular diseases, have been conflicting (7, 8). The rationale of the few recent studies on the association between telomere length and skeletal muscle mass (9–12) or functional muscle parameters (12–16) is that critically shortened telomeres might limit the regenerative capacity of muscular cells (5) and thereby affect muscle mass. These studies have shown rather inconsistent results. Venturelli et al. (9) reported a strong positive correlation between muscle telomere length measured in muscle biopsies by quantitative polymerase chain reaction (PCR)[6] and leg lean mass (LLM). Thériault et al. (11) showed significant correlations between midthigh muscle cross-sectional area and minimal muscle telomere length determined by Southern blot. Larger studies determined relative leukocyte telomere length (rLTL) by using quantitative PCR and appendicular lean mass (ALM) standardized for height squared. Woo et al. (12) have found no associations between rLTL and lean mass in a large study in Chinese people aged ≥65 y. In contrary, Marzetti and colleagues (10) have shown significant associations between rLTL and lean mass. Recently, the Foundation for the National Institutes of Health (FNIH) sarcopenia project suggested using the ratio of ALM to BMI (ALM_{BMI}) and showed significantly lower grip

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[2] Supplemental Table 1 and Supplemental Figures 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[6] Abbreviations used: ALM, appendicular lean mass; ALM_{BMI}, ratio of appendicular lean mass to BMI; BASE-II, Berlin Aging Study II; CRP, C-reactive protein; FNIH, Foundation for the National Institutes of Health; LLM, leg lean mass; PCR, polymerase chain reaction; rLTL, relative leukocyte telomere length.

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strength and gait speed in subjects with low ALM_{BMI} (17). The standardization of ALM for BMI accounts for the effect of fat mass on overall muscle mass. We recently showed that using ALM_{BMI} instead of ALM standardized for height only predicted self-reported physical limitations far better in participants in the Berlin Aging Study II (BASE-II) (18).

Here, we analyzed the relation between rLTL and ALM_{BMI} in the large BASE-II cohort of community-dwelling elderly. The use of comprehensive BASE-II baseline data allowed us to take known and potential confounders, such as markers of inflammation, lifestyle factors, and diseases, into account. To the best of our knowledge, this was the first large cohort study to examine this relation considering ALM_{BMI} as the measure of muscle mass, as suggested by McLean et al. (17).

METHODS

Study population and design

BASE-II is a multidisciplinary project, with the current study being part of a series of planned analyses investigating medical, physical, cognitive, and social conditions related to "healthy" and "unhealthy" aging. The study population consisted of 2172 (~75% aged 60–80 y and ~25% aged 20–35 y at baseline recruitment) community-dwelling people from the greater metropolitan area of Berlin, Germany. Recruitment details were described by Bertram et al. (19). All participants gave written informed consent. The study was approved by the Ethics Committee of the Charité–Universitätsmedizin Berlin (approval number EA2/029/09).

Telomere length determination

Genomic DNA was extracted from EDTA-containing blood by using the LGC Plus XL manual kit (LGC Genomics GmbH) from 1519 participants aged ≥60 y. DNA extracts of 18 samples did not contain a sufficient amount of genomic DNA for further analysis (**Supplemental Figure 1**). Mean rLTL was examined by quantitative real-time PCR following a modified version of the protocol originally described by Cawthon (20). For further details, see Meyer et al. (21). The average CV from all reference samples, measured at least as triplicates, was 0.4% for the telomere assay and 0.5% for single-copy gene (36B4) assay with a PCR efficiency ranging from 75% to 101% (telomere PCR; mean ± SD efficiency: 87% ± 7%) and 84% to 102% (single-copy PCR; mean ± SD efficiency: 95% ± 4%). All 1501 participants' samples were measured at least in triplicate, and their mean was used for further analysis. The average interplate CV for all participants' samples ranged from 0.01% to 5.9% (telomere PCR; mean CV: 0.5%) and 0.00% to 3.7% (single-copy gene PCR; mean CV: 0.4%). The mean intraplate CV was <0.8% (telomere PCR) and 0.5% (single-copy gene PCR). Only data from participants with a CV ≤2% in both PCRs (comprising telomere PCR and single-copy gene PCR) were included in the statistical analysis, a quality criterion met by 1460 samples measured in older BASE-II participants. The rLTL was subsequently calculated according to Pfaffl et al. (22).

Parameters of body composition

Lean mass, fat mass, and bone mineral content were estimated by dual-energy X-ray absorptiometry (Hologic Discovery Wi and APEX software version 3.0.1). Dual-energy X-ray absorptiometry scans were performed by a trained technician. ALM was calculated by adding the lean mass of each limb without bone mineral content. LLM was defined as the summed lean mass of the lower limbs without bones. For the statistical evaluations, LLM, ALM, and ALM_{BMI}, as suggested by the FNIH sarcopenia project (17), were used. In addition, we classified all subjects into 2 groups (low ALM_{BMI} and normal ALM_{BMI}), following the FNIH suggestion for cutoff values: low ALM_{BMI} was defined as ALM <0.789 for men and <0.512 for women. We also identified the participants as being frail, prefrail, or nonfrail following the classification as previously described by Spira et al. (18). Because only one participant in our study population was classified as frail, we were not able to perform the calculation for being frail compared with nonfrail. However, we compared the prefrail with the nonfrail participants. Weight (in kg) and height (in cm) were measured, by using an electronic weighing and measuring station (SECA 764), while the patients were wearing light clothes.

Covariates

Alcohol consumption was assessed as part of the validated, self-administered, 146-item food-frequency questionnaire from the European Prospective Investigation into Cancer and Nutrition (23). The evaluated food-frequency questionnaire (24) was used to calculate average daily intake of ethanol (in g/d), based on the German food item database Bundeslebensmittelschlüssel 3.01 (25).

Self-reported smoking status was used as categories (current and former smokers and nonsmokers); pack-years was also used. Because of a skewed distribution, pack-years and average alcohol intake were $\log_{10}$ transformed.

The activity levels of the participants were examined by using the 7 items of the Rapid Assessment of Physical Activity questionnaire, as described by Topolski and colleagues, and were classified into 7 groups based on self-reported activity intensity levels, which ranged from light to vigorous activity performed rarely to 20 min or longer on ≥3 d/wk (26).

Serum C-reactive protein (CRP) concentrations were measured by using an immunoturbidimetric assay (CRPL3; Roche Diagnostica). In models 3 and 4, participants with CRP values >4 mg/dL were excluded to avoid acute inflammation bias. CRP values of the remaining participants were split in 2 groups: level 1 (low CRP concentration, defined as <1 mg/dL) and level 2 (low-grade inflammation, defined as CRP concentrations of 1–4 mg/dL), as earlier described by Myers et al. (27).

The morbidity index was based on the following domains of the Charlson Index (28): myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, ulcer disease, dementia, chronic pulmonary disease, connective tissue disease, mild liver disease, diabetes, diabetes with end-organ damage, renal disease, hemiplegia, lymphoma, leukemia, any tumor, and moderate to severe liver disease. The covariates were selected based on the literature addressing similar research questions in the context of muscle mass and telomere length and were included stepwise to make their effects visible.

Statistical analysis

The statistical analysis was carried out by using the software package SPSS Statistics 22, IBM. The graphics (**Supplemental**

Figures 2 and **3**) were designed with Excel 2010. Statistical significance was established a priori at $P < 0.05$. The overlap of telomere length data matching a CV ≤2% and available data for lean mass led to a sample of 1398 remaining participants from the BASE-II population for further examination.

To analyze differences in participant characteristics, ANOVA was used for parametric data and a Mann-Whitney *U* test for skewed variables. Continuous variables with normal distribution are reported as means ± SDs, and variables with skewed distribution are reported as medians (IQRs). Variances in categorical variables, expressed as a percentage of the total, were conducted by using chi-square tests. After $\log_{10}$ transformation of nonparametric data (alcohol intake and pack-years), Pearson correlations and general linear models were used for continuous variables. The association between low ALM_{BMI} and rLTL was assessed by means of binary logistic regression models. Analysis with sex as a confounder showed highly significant associations. Therefore, and because of sex differences in telomere lengths, all regression models were analyzed independently for men and women. Risk factors were stepwise included in regression models. First adjustments accounted for age and BMI (model 1). In addition, physical activity level and consumption of alcohol and cigarettes were included in model 2. Model 3 was conducted after extending model 2 with CRP concentrations (low/medium). Addition of the morbidity index to model 4, to all previous covariates, led to the fully adjusted model in this examination.

RESULTS

Baseline characteristics

For this study, cross-sectional data for rLTL and lean mass were available from a total of 1398 older subjects, 694 men and 704 women. Sample characteristics are summarized in **Table 1**. The examined study population included 9.3% current smokers, 42.6% former smokers, and 48.1% never-smokers. Men, on average, were 0.7 y older than women. Not surprisingly, ALM with or without adjustment for BMI, use of alcohol and cigarettes, and BMI was significantly greater in men. About 50% of all participants reported being "active" according to the definition of the Rapid Assessment of Physical Activity score (26). Interestingly, rLTL was significantly longer in men. The frequency of prefrail participants was 31%, equally distributed in men and women ($P = 0.86$).

rLTL correlates with muscle mass

The rLTL correlated positively with ALM ($r = 0.248$, $P < 0.001$) and ALM_{BMI} ($r = 0.254$, $P < 0.001$). The strongest correlation was found between rLTL and LLM ($r = 0.263$, $P = 0.001$). After adjustment for sex, correlations remained significant

TABLE 1
Participant characteristics in the current sample of BASE-II[1]

	Total (n = 1398)	Men (n = 694)	Women (n = 704)	P value[2]
ALM, kg	20.0 ± 4.7[3]	23.9 ± 2.9	16.1 ± 2.3	<0.001
ALM/height^2, kg/m^2	6.9 ± 1.1	7.7 ± 0.8	6.1 ± 0.8	<0.001
ALM_{BMI}[4]	0.8 ± 0.2	0.9 ± 0.1	0.6 ± 0.1	<0.001
LLM, kg	15.1 ± 3.4	17.8 ± 2.2	12.4 ± 1.9	<0.001
rLTL	1.1 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	<0.001
Low ALM_{BMI}, %	16.3	19.6	13.1	0.001
Covariates				
Age, y	68.2 ± 3.7	68.5 ± 3.8	67.8 ± 3.5	<0.001
BMI, kg/m^2	26.8 ± 4.2	27.2 ± 3.6	26.5 ± 4.7	0.001
Current smoker,[5] %	9.3	10.6	8.1	<0.001
Alcohol intake,[6] g/d	8.5 (2.9–19.5)[7]	12.7 (5.4–26.1)	5.4 (2.1–12.9)	<0.001[8]
Sedentary lifestyle,[9] %	1.5	1.9	1.1	0.139
CRP concentration,[10] %				0.010
Low (<1 mg/dL)	42.4	42.9	41.8	
Medium (1–4 mg/dL)	46.8	48.8	44.8	
High (>4 mg/dL)	10.8	8.3	13.3	
Morbidity index >1,[11] %	30.3	33.0	27.9	0.039

[1]ALM, appendicular lean mass; ALM_{BMI}, ratio of appendicular lean mass to BMI; BASE-II, Berlin Aging Study II; CRP, C-reactive protein; LLM, leg lean mass; rLTL, relative leukocyte telomere length.
[2]Effects were analyzed by using paired-sample tests for parametric data, chi-square tests for categorical variables, and Mann-Whitney *U* test for nonparametric data.
[3]Mean ± SD (all such values).
[4]Low ALM_{BMI} is defined as <0.789 for men and <0.512 for women.
[5]n = 1384.
[6]n = 1375.
[7]Median; IQR in parentheses (all such values).
[8]Skewed distribution.
[9]n = 1381.
[10]n = 1374.
[11]n = 1272.

for ALM_{BMI} ($P < 0.023$) and LLM ($P = 0.008$). ALM_{BMI} showed weak inverse correlations with age ($r = -0.115$, $P < 0.001$), CRP ($r = -0.074$, $P = 0.006$) when adjusted for sex and pack-years of smoking ($r = -0.039$, $P = 0.001$). When analyzed independently for both sexes, correlations were significant only in men for LLM and rLTL ($r = 0.099$, $P = 0.009$) (Supplemental Figures 2 and 3).

Relation between muscle parameters and telomere length

To examine rLTL as a potential risk factor for low lean mass, we adjusted stepwise for covariates known to affect muscle mass in linear regression models (**Table 2**). After adjustment for age and BMI (model 1), highly significant associations were found between LLM and rLTL in men. Associations between rLTL and ALM, ALM_{BMI}, and low ALM_{BMI} in men failed to reach the a priori defined level of statistical significance of $P < 0.05$. In women, no association was found between muscle parameters and rLTL.

In model 2, potentially relevant lifestyle factors (activity level, alcohol consumption, and smoking) were included, which led to similar results: the relation between rLTL and ALM_{BMI} as a continuous and categorical variable became significant in men, whereas the significance of rLTL with LLM remained. Low-grade inflammation based on 2 categories of CRP concentrations (>1 and 1–4 mg/L) was included in model 3, whereas participants with acute inflammation—indicated by CRP values >4 mg/L—were excluded. Addition of the morbidity index as a covariate led to the previously defined fully adjusted model 4, as shown in Table 2. The rLTL was significantly associated in men with all muscle parameters analyzed after full adjustment (model 4): longer telomeres were associated with higher ALM, LLM, and ALM_{BMI} and with normal ALM_{BMI}. The strongest association was found for LLM.

Higher age, sedentary lifestyle, elevated CRP concentrations, and a lower BMI were associated with lower lean mass in men. No statistically significant associations were found between the morbidity index, cigarette and alcohol consumption, and LLM. Significant associations between rLTL and muscle parameters in women were found only for LLM in models 3 and 4 (Table 2). However, even the fully adjusted model explained only 35% of the LLM variance in women and 23% in men. The rLTL was not associated with frailty status (prefrail group compared with nonfrail group) in our analysis, which was performed separately for men and women (**Supplemental Table 1**).

DISCUSSION

This was the first large cohort study to examine the relation of rLTL with ALM, with the use of ALM standardized for BMI, which takes the potentially disproportionate relation between lean mass and fat mass into account. We found that shorter rLTL was weakly associated with low ALM_{BMI} in men and with LLM

TABLE 2
Association of relative leukocyte telomere length and muscle mass parameters[1]

	Men			Women		
	β Coefficient ± SEM	P value	R^2	β Coefficient ± SEM	P value	R^2
ALM (without bone)						
Model 1[2]	0.717 ± 0.403	0.075	0.207	0.191 ± 0.384	0.620	0.280
Model 2[3]	0.815 ± 0.423	0.055	0.211	0.195 ± 0.395	0.621	0.309
Model 3[4]	0.779 ± 0.448	0.083	0.250	0.667 ± 0.421	0.114	0.279
Model 4[5]	1.111 ± 0.464	0.017	0.250	0.569 ± 0.442	0.198	0.306
ALM_{BMI}						
Model 1[2]	0.028 ± 0.015	0.061	0.340	0.011 ± 0.015	0.469	0.354
Model 2[3]	0.032 ± 0.016	0.046	0.0334	0.012 ± 0.015	0.432	0.366
Model 3[4]	0.032 ± 0.017	0.061	0.335	0.030 ± 0.017	0.067	0.358
Model 4[5]	0.044 ± 0.018	0.013	0.337	0.025 ± 0.017	0.151	0.358
LLM						
Model 1[2]	0.947 ± 0.311	0.002	0.186	0.482 ± 0.300	0.109	0.316
Model 2[3]	0.989 ± 0.327	0.003	0.190	0.464 ± 0.309	0.134	0.339
Model 3[4]	0.934 ± 0.347	0.007	0.231	0.824 ± 0.328	0.012	0.320
Model 4[5]	1.197 ± 0.360	0.001	0.227	0.775 ± 0.346	0.026	0.348
Low ALM_{BMI}[6]						
Model 1[2]	0.800 ± 0.447	0.074	0.249	−0.067 ± 2.685	0.918	0.290
Model 2[3]	1.023 ± 0.473	0.031	0.239	−0.171 ± 0.678	0.801	0.338
Model 3[4]	1.105 ± 0.510	0.030	0.234	1.140 ± 0.793	0.151	0.384
Model 4[5]	1.345 ± 0.553	0.015	0.279	0.684 ± 0.924	0.548	0.428

[1]Statistical analysis consisted of linear regression for continuous variables and binary logistic regression for the categorical variable. Statistical significance was established a priori at $P < 0.05$. ALM, appendicular lean mass; ALM_{BMI}, ratio of appendicular lean mass to BMI; CRP, C-reactive protein; LLM, leg lean mass; RAPA, Rapid Assessment of Physical Activity.

[2]$n = 1398$. Adjusted for age and BMI.

[3]$n = 1274$. Adjusted as for model 1 plus pack-years ($\log_{10}$), alcohol (g/d) ($\log_{10}$), and RAPA score.

[4]$n = 1110$. Adjusted as for model 1 plus CRP levels 1 and 2 (CRP >4 mg/dL excluded).

[5]$n = 1014$. Adjusted as for model 1 plus morbidity index.

[6]Defined as <0.789 for men and <0.512 for women.

in men and women. Next to rLTL, advanced age, low BMI, and elevated CRP were associated with low ALM_{BMI} in men.

Interestingly, the highest associations were obtained for LLM and rLTL which were also observed in women. Maintaining LLM, and thus retaining mobility, is mandatory for maintaining a certain level of quality of life and independence in advanced age.

Telomere length has been suggested as a risk factor for age-associated loss of muscle mass in previous in vitro investigations, which indicates that satellite cells—the stem cells of muscle tissue—also underlie telomere attrition with each cycle of DNA replication, eventually leading to apoptosis or cellular senescence (29). With advancing age, the telomere length of satellite cells shortens and the number and replicative capacity of satellite cells decline (30–32), which may result in a decrease in skeletal muscle mass and eventually in muscle function. The studies by Venturelli et al. (9), who compared 3 groups of young, old-mobile, and old-immobile subjects, and the study by Thériault et al. (11) investigated the telomere length of muscle cells from biopsies and found significant correlations between telomere length and leg muscle mass or midthigh muscle area. Because of the invasiveness of this method, these studies have a relatively small sample size. Determining rLTL from blood samples by quantitative PCR allows larger sample sizes, and earlier investigations have reported close correlations of telomere length between leukocytes and muscle cells (33, 34).

Older participants in the BASE-II cohort showed significantly shorter rLTL when compared with the young reference group [data shown previously in the study by Meyer et al. (21)], which is in line with the literature (35). Men in our study population had significantly longer leukocyte telomeres than did women. Reports on sex differences in telomere lengths are contradictory and may depend, at least in part, on the method of analysis used, as reviewed by Gardner et al. (36) and previously discussed in detail elsewhere (21).

Measurements of rLTL determined by quantitative PCR were used in 2 recent studies on muscle parameters, which had different results. Marzetti et al. (10) examined the association of rLTL, with lean mass determined by bioelectrical impedance analysis, using ALM/height^2 and showed highly significant correlations with rLTL. Significant associations were also seen when 2 categories for lean mass (low and normal) were used. In comparison, Woo and colleagues (12) did not find this association when analyzing quartiles of rLTL and ALM/height^2 in their study population from Hong Kong, China. However, both studies used ALM solely corrected for height, which limited the comparability with our results. We corrected ALM for BMI as recently proposed by McLean et al. (17), because body weight has a significant effect on muscle mass and muscle quality (37, 38). We also previously showed that ALM_{BMI} predicts self-reported physical limitations and low grip strength in BASE-II more precisely than does ALM/height^2 (18).

Loss of skeletal muscle mass has been suggested to be associated with various lifestyle factors such as cigarette smoking (39), physical inactivity, various diseases, and dietary patterns [reviewed by Buford et al. (40)]. Alcohol consumption can also lead to a decrease in protein synthesis (41) and thus contributes to the reduction in muscle mass. Hence, control for these confounders is necessary. Moreover, because several studies have shown a negative influence of oxidative stress (42) and inflammation on lean mass (43, 44) and on telomere attrition (45), we included CRP as a confounder in our analysis. As expected, younger age, a higher BMI, and a low CRP concentration contributed to higher ALM and LLM in our study population and to a higher ALM_{BMI}. We could, however, not confirm an influence of morbidities, smoking, and alcohol consumption on lean mass in our study population. The population-based study BASE-II consists of comparably healthy individuals (19), which may explain that morbidities are not significantly associated with lean mass in our study. Smoking and alcohol consumption were also generally low, although significantly higher in men than in women. Accordingly, the association of rLTL and lean mass was consistent, despite the inclusion of nonsignificant covariates in the statistical models.

In conclusion, although our results need to be confirmed in a longitudinal context to evaluate the prospective association of telomere attrition and loss of muscle mass in old age, short leukocyte telomere length may be a risk factor for low lean mass.

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The authors' responsibilities were as follows—AM: conducted the research, analyzed and interpreted the data, performed the statistical analysis, and wrote the manuscript; BS: conducted the research; DS and ES-T: provided the data; KN and ID: provided the data, designed the research, interpreted the data, and wrote the manuscript; AM, KN, and ID: had primary responsibility for the final content; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. J Appl Physiol (1985) 2000;88:1321–6.
2. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, Corsi AM, Rantanen T, Guralnik JM, Ferrucci L. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol (1985) 2003;95:1851–60.
3. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889–96.
4. Harley CB. Telomere loss: mitotic clock or genetic time bomb? Mutat Res 1991;256:271–82.
5. Di Donna S, Renault V, Forestier C, Piron-Hamelin G, Thiesson D, Cooper RN, Ponsot E, Decary S, Amouri R, Hentati F, et al. Regenerative capacity of human satellite cells: the mitotic clock in cell transplantation. Neurol Sci 2000;21(Suppl 5):S943–51.
6. Sanders JL, Newman AB. telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither? Epidemiol Rev 2013;35:112–31.
7. Willeit P, Raschenberger J, Heydon EE, Tsimikas S, Haun M, Mayr A, Weger S, Witztum JL, Butterworth AS, Willeit J, et al. Leucocyte telomere length and risk of type 2 diabetes mellitus: new prospective cohort study and literature-based meta-analysis. PLoS One 2014;9:e112483.
8. D'Mello MJ, Ross SA, Briel M, Anand SS, Gerstein H, Pare G. Association between shortened leukocyte telomere length and cardiometabolic outcomes: systematic review and meta-analysis. Circ Cardiovasc Genet 2015;8:82–90.
9. Venturelli M, Morgan GR, Donato AJ, Reese V, Bottura R, Tarperi C, Milanese C, Schena F, Reggiani C, Naro F, et al. Cellular aging of skeletal muscle: telomeric and free radical evidence that physical inactivity is responsible and not age. Clin Sci 2014;127:415–21.
10. Marzetti E, Lorenzi M, Antocicco M, Bonassi S, Celi M, Mastropaolo S, Settanni S, Valdiglesias V, Landi F, Bernabei R, et al. Shorter telomeres in peripheral blood mononuclear cells from older persons with sarcopenia: results from an exploratory study. Front Aging Neurosci 2014;6:233.
11. Thériault ME, Pare ME, Maltais F, Debigare R. Satellite cells senescence in limb muscle of severe patients with COPD. PLoS One 2012;7:e39124.

12. Woo J, Yu R, Tang N, Leung J. Telomere length is associated with decline in grip strength in older persons aged 65 years and over. Age (Dordr) 2014;36:9711.
13. Baylis D, Ntani G, Edwards MH, Syddall HE, Bartlett DB, Dennison EM, Martin-Ruiz C, von Zglinicki T, Kuh D, Lord JM, et al. Inflammation, telomere length, and grip strength: a 10-year longitudinal study. Calcif Tissue Int 2014;95:54–63.
14. Gardner MP, Martin-Ruiz C, Cooper R, Hardy R, Sayer AA, Cooper C, Deary IJ, Gallacher J, Harris SE, Shiels PG, et al. Telomere length and physical performance at older ages: an individual participant meta-analysis. PLoS One 2013;8:e69526.
15. Mather KA, Jorm AF, Milburn PJ, Tan X, Easteal S, Christensen H. No associations between telomere length and age-sensitive indicators of physical function in mid and later life. J Gerontol A Biol Sci Med Sci 2010;65:792–9.
16. Goldeck D, Pawelec G, Norman K, Steinhagen-Thiessen E, Oettinger L, Haehnel K, Demuth I. No strong correlations between serum cytokine levels, CMV serostatus and hand-grip strength in older subjects in the Berlin BASE-II cohort. Biogerontology 2015 Apr 24 (Epub ahead of print; DOI 10.1007/s10522-015-9577-9).
17. McLean RR, Shardell MD, Alley DE, Cawthon PM, Fragala MS, Harris TB, Kenny AM, Peters KW, Ferrucci L, Guralnik JM, et al. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the foundation for the National Institutes of Health (FNIH) sarcopenia project. J Gerontol A Biol Sci Med Sci 2014;69:576–83.
18. Spira D, Buchmann N, Nikolov J, Demuth I, Steinhagen-Thiessen E, Eckardt R, Norman K. Association of low lean mass with frailty and physical performance: a comparison between two operational definitions of sarcopenia-data from the Berlin Aging Study II (BASE-II). J Gerontol A Biol Sci Med Sci 2015;70:779–84.
19. Bertram L, Bockenhoff A, Demuth I, Duzel S, Eckardt R, Li SC, Lindenberger U, Pawelec G, Siedler T, Wagner GG, et al. Cohort profile: the Berlin Aging Study II (BASE-II). Int J Epidemiol 2014;43:703–12.
20. Cawthon RM. Telomere measurement by quantitative PCR. Nucleic Acids Res 2002;30:e47.
21. Meyer A, Salewsky B, Buchmann N, Steinhagen-Thiessen E, Demuth I. Relative leukocyte telomere length, hematological parameters and anemia - data from the Berlin Aging Study II (BASE-II). Gerontology. In press.
22. Pfaffl MW. A new mathematical model for relative quantification in real-time RT-PCR. Nucleic Acids Res 2001;29:e45.
23. Nöthlings U, Hoffmann K, Bergmann MM, Boeing H. Fitting portion sizes in a self-administered food frequency questionnaire. J Nutr 2007; 137:2781–6.
24. Kroke A, Klipstein-Grobusch K, Voss S, Moseneder J, Thielecke F, Noack R, Boeing H. Validation of a self-administered food-frequency questionnaire administered in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: comparison of energy, protein, and macronutrient intakes estimated with the doubly labeled water, urinary nitrogen, and repeated 24-h dietary recall methods. Am J Clin Nutr 1999;70:439–47.
25. Hartmann B, Vásquez-Caicedo A, Bell S, Krems C, Brombach C. The German nutrient database: basis for analysis of the nutritional status of the German population. J Food Comp Anal 2008;21(suppl):115–8.
26. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The Rapid Assessment of Physical Activity (RAPA) among older adults. Prev Chronic Dis 2006;3:A118.
27. Myers GL, Rifai N, Tracy RP, Roberts WL, Alexander RW, Biasucci LM, Catravas JD, Cole TG, Cooper GR, Khan BV, et al. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: report from the laboratory science discussion group. Circulation 2004;110:e545–9.
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
29. Kadi F, Ponsot E. The biology of satellite cells and telomeres in human skeletal muscle: effects of aging and physical activity. Scand J Med Sci Sports 2010;20:39–48.
30. Decary S, Mouly V, Hamida CB, Sautet A, Barbet JP, Butler-Browne GS. Replicative potential and telomere length in human skeletal muscle: implications for satellite cell-mediated gene therapy. Hum Gene Ther 1997;8:1429–38.
31. Barberi L, Scicchitano BM, De Rossi M, Bigot A, Duguez S, Wielgosik A, Stewart C, McPhee J, Conte M, Narici M, et al. Age-dependent alteration in muscle regeneration: the critical role of tissue niche. Biogerontology 2013;14:273–92.
32. Renault V, Piron-Hamelin G, Forestier C, DiDonna S, Decary S, Hentati F, Saillant G, Butler-Browne GS, Mouly V. Skeletal muscle regeneration and the mitotic clock. Exp Gerontol 2000;35:711–9.
33. Daniali L, Benetos A, Susser E, Kark JD, Labat C, Kimura M, Desai K, Granick M, Aviv A. Telomeres shorten at equivalent rates in somatic tissues of adults. Nat Commun 2013;4:1597.
34. Dlouha D, Maluskova J, Kralova Lesna I, Lanska V, Hubacek JA. Comparison of the relative telomere length measured in leukocytes and eleven different human tissues. Physiol Res 2014;63(Suppl 3):S343–50.
35. Müezzinler A, Zaineddin AK, Brenner H. A systematic review of leukocyte telomere length and age in adults. Ageing Res Rev 2013;12: 509–19.
36. Gardner M, Bann D, Wiley L, Cooper R, Hardy R, Nitsch D, Martin-Ruiz C, Shiels P, Sayer AA, Barbieri M, et al. Gender and telomere length: systematic review and meta-analysis. Exp Gerontol 2014;51: 15–27.
37. Brady AO, Straight CR, Schmidt MD, Evans EM. Impact of body mass index on the relationship between muscle quality and physical function in older women. J Nutr Health Aging 2014;18:378–82.
38. McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. Longev Healthspan 2014;3:9.
39. Steffl M, Bohannon RW, Petr M, Kohlikova E, Holmerova I. Relation between cigarette smoking and sarcopenia: meta analysis. Physiol Res 2015;64:419–26.
40. Buford TW, Anton SD, Judge AR, Marzetti E, Wohlgemuth SE, Carter CS, Leeuwenburgh C, Pahor M, Manini TM. Models of accelerated sarcopenia: critical pieces for solving the puzzle of age-related muscle atrophy. Ageing Res Rev 2010;9:369–83.
41. Reilly ME, Mantle D, Richardson PJ, Salisbury J, Jones J, Peters TJ, Preedy VR. Studies on the time-course of ethanol's acute effects on skeletal muscle protein synthesis: comparison with acute changes in proteolytic activity. Alcohol Clin Exp Res 1997;21:792–8.
42. Ludlow AT, Spangenburg EE, Chin ER, Cheng WH, Roth SM. Telomeres shorten in response to oxidative stress in mouse skeletal muscle fibers. J Gerontol A Biol Sci Med Sci 2014;69:821–30.
43. Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med 2006;119: 526.e917.
44. Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, Woo J, Baumgartner R, Pillard F, Boirie Y, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging 2008;12:433–50.
45. Wong JY, De Vivo I, Lin X, Fang SC, Christiani DC. The relationship between inflammatory biomarkers and telomere length in an occupational prospective cohort study. PLoS One 2014;9:e87348.