Biogerontology (2018) 19:209–221
https://doi.org/10.1007/s10522-018-9749-5

REVIEW ARTICLE

A review of telomere length in sarcopenia and frailty

Maria Lorenzi · Stefano Bonassi · Teresa Lorenzi · Silvia Giovannini · Roberto Bernabei · Graziano Onder

Received: 19 October 2017 / Accepted: 23 February 2018 / Published online: 16 March 2018

Abstract Sarcopenia and frailty are associated with several important health-related adverse events, including disability, loss of independence, institutionalization and mortality. Sarcopenia can be considered a biological substrate of frailty, and the prevalence of both these conditions progressively increases with age. Telomeres are nucleoprotein structures located at the end of linear chromosomes and implicated in cellular ageing, shorten with age, and are associated with various age-related diseases. In addition, telomere length (TL) is widely considered a molecular/cellular hallmark of the ageing process. This narrative review summarizes the knowledge about telomeres and analyzes for the first time a possible association of TL with sarcopenia and frailty. The overview provided by the present review suggests that leukocyte TL as single measurement, calculated by quantitative real-time polymerase chain reaction (qRT-PCR), cannot be considered a meaningful biological marker for complex, multidimensional age-related conditions, such as sarcopenia and frailty. Panels of biomarkers, including TL, may provide more accurate assessment and prediction of outcomes in these geriatric syndromes in elderly people.

Keywords Telomere length · Oxidative stress · Inflammation · Sarcopenia · Frailty · Ageing · Age-related diseases

M. Lorenzi (✉) · S. Giovannini
Laboratory of Biogerontology, Department of Geriatrics, Neurosciences and Orthopedics, A. Gemelli Foundation, Catholic University of the Sacred Heart, School of Medicine, L.go F. Vito 1, 00168 Rome, Italy
e-mail: mlorenziusa@yahoo.it; labgeriatria.cemi@gmail.com

S. Bonassi
Unit of Clinical and Molecular Epidemiology, IRCCS San Raffaele Pisana, Via di Val Cannuta 247, 00166 Rome, Italy

T. Lorenzi
Department of Experimental and Clinical Medicine, Section of Neuroscience and Cell Biology, School of Medicine, Università Politecnica delle Marche, Via Tronto 10/A, 60020 Ancona, Italy

R. Bernabei · G. Onder
Department of Geriatrics, Neurosciences and Orthopedics, A. Gemelli Foundation, Catholic University of the Sacred Heart, School of Medicine, L.go F. Vito 1, 00168 Rome, Italy

Introduction

Sarcopenia is a geriatric syndrome characterized by progressive age-related decline in skeletal muscle mass, function, and quality (Fielding et al. 2011). Sarcopenia might represent one key determinant of frailty, which is defined as a decreased reserve, vulnerability to stressors, and increased risk of adverse health outcomes such as mortality, morbidity, disability, hospitalization and institutionalization

(Rodriguez-Manas et al. 2013). The physical frailty (PF) phenotype, proposed by Fried et al. (2001), is the most widely used model to identify frailty, and it explores the physical domain of the frailty syndrome. An alternative approach to the assessment of frailty in elderly has been proposed by Rockwood et al. (2005), which is based on the count of a number of health "deficits" that an individual has, leading to the calculation of a frailty index (FI). PF is strongly linked to muscle mass and function, and therefore the occurrence of this condition can be mediated by sarcopenia (Cesari et al. 2014). Indeed, sarcopenia is often considered to be a biological substrate of physical frailty (Landi et al. 2015), and impaired physical function is the core feature shared by the two syndromes (Marzetti et al. 2012). To date, several imaging, functional, and biological parameters have been proposed as biomarkers for sarcopenia and frailty. Most of the available tissue or circulating biological markers are typically associated with skeletal muscle mass, strength, and function (Fougère et al. 2015) and oxidative stress, genomic instability and DNA damage and repair biomarkers have also been proposed to be linked to frailty (Sánchez-Flores et al. 2017). The identification of a panel of complementary biomarkers, belonging to different classes, through multivariate analysis (Calvani et al. 2015, 2017) will allow the characterization and follow-up of elderly people with sarcopenia and frailty, also in response to interventions.

Considerable research effort has been devoted to finding clinical and biological markers that reflect biological ageing and can be better indicators of individual's functional and health status than chronological age (Sprott 2010). Telomeres are implicated in cellular ageing, shorten with age, and are associated with various age-related diseases; as such telomere length (TL) is widely considered a senescence biomarker (Fossel 2012). The present review is unique because it differs from the previous ones above mentioned for its particular study of the available literature describing the possible role of leukocyte TL as a biological marker for sarcopenia and frailty. To accomplish this aim, an overview of telomere biology and the available techniques used to measure TL will be also evaluated and thoroughly discussed, as well as the role of lifestyle factors, which are known to influence the onset of sarcopenia and frailty, on determining TL. A section reviewing the literature examining skeletal muscle specific TL will also be included.

Telomeres and senescence

Telomeres are gene-poor chromosomal regions located at the end of linear chromosomes (Varela and Blasco 2009). They are nucleoprotein structures made of a repetitive DNA sequence of six nucleotides—TTAGGG—which in human extends at birth around 10–15 kilobases (Blackburn 2001). Leukocyte TL is mostly heritable (Broer et al. 2013) and associated with ethnic group (Hunt et al. 2008) and gender (Aviv et al. 2005). Telomeres end in a 150–200 nucleotide long single-stranded overhang of the G-rich strand (Blasco 2005). The G-strand overhang can fold back and anneal with the double-stranded region of the TTAGGG repeats to form a large telomeric loop known as the T loop (Nikitina and Woodcock 2004). The closed three-dimensional (3D) structure of the T-loop protects telomere ends to be recognized as DNA-double-strand breaks (Blasco 2007), thus preventing the activation of the DNA damage response cascade that induces apoptosis and/or cellular senescence (Campisi 2013). In in vitro somatic cell cultures, telomeres shorten by 50–100 base pair at every cell division since the replication machinery does not copy fully to the ends, a phenomena referred to as the end-replication problem (Proctor and Kirkwood 2002). Therefore, telomeres act as a mitotic clock that "records" the number of divisions a cell has undergone. After a defined number of doublings, a critically short TL is reached, leading to telomere dysfunction, loss of telomere end-protection and chromosomal instability, causing cells to enter cellular senescence or apoptosis (Kong et al. 2013). Telomere erosion, due to a progressive loss of TTAGGG repeats, explains the Hayflick limit or replicative senescence, which is the maximum number of population doublings an in vitro culture of somatic cells may undergo (Hayflick and Moorhead 1961).

The number of telomere-driven senescent cells in tissues increases with age, resulting in an aged phenotype with impaired function (de Magalhães 2004). Telomere attrition and dysfunction are also associated with many age related diseases, including cancer, type2 diabetes mellitus, cardiovascular disease, osteoarthritis, dementia, and immunosenescence, where the rate of

shortening seems to accelerate, playing a synergistic role with ageing (Xi et al. 2013). Some studies have also reported an association between TL and mortality in people between 60 and 75 years (Cawthon et al. 2003) but not in persons aged over 80 years (Martin-Ruiz et al. 2005). Therefore, TL is widely considered an ageing biomarker, although the question of whether shortening is the cause or consequence of physiological ageing and age-related diseases is still open. Therefore, it might be hypothesized that TL represents a biomarker of age-related phenomena such as sarcopenia and frailty.

Telomerase and shelterin: suite of proteins involved in telomere maintenance

In contrast to that of somatic cells, telomerase helps to maintain TL homeostasis, overcoming the end-replication problem (Bodnar et al. 1998), in cells with high mitotic activity such as in human reproductive cells, stem cells (Wright et al. 1996), and tumor cells (Kim et al. 1994; Shay and Bacchetti 1997). Telomerase is a ribonucleotide complex, which synthesizes and adds new telomere repeats to the chromosome ends, following DNA replication (Shay et al. 2001). It is a reverse transcriptase encoded by the *tert* (telomerase reverse transcriptase) gene which elongates the 3′-OH group of the overhang using an RNA molecule encoded by the *terc* (telomerase RNA component) gene (Collins et al. 1995) as a template. Telomerase knockout mice (knockout for *tert* and *terc*) have been used as models for age-related diseases, like cardiovascular diseases (Wong et al. 2009). Reactivation of *tert* in aged *tert*-deficient mice, mitigates the ageing process underlying the crucial role of telomere system in ageing and in age-associated diseases (Jaskelioff et al. 2011).

Telomerase activity is influenced by the proteins of the telomere binding protein complex called shelterin. Shelterin binds telomere DNA in a tightly regulated stoichiometry and functions to monitor TL by controlling the access of telomerase to telomeres (Nandakumar and Cech 2013) and protecting DNA telomere ends from being recognized by DNA damage sensing proteins and nucleases (Palm and de Lange 2008). Shelterin folds the G-strand overhang back into the three-dimensional structure of the T-loop, probably representing a mechanism for chromosome end-protection and restricting the access of telomerase to telomeres (Griffith et al. 1999). Shelterin consists of six proteins. Three molecules interact directly with telomere DNA: telomere-repeat binding factors 1 and 2 (TRF1 and TRF2) (Smogorzewska et al. 2000) and protection of telomeres 1 (POT1) (Nandakumar and Cech 2013); the other three proteins interact with the three telomere DNA-binding proteins (de Lange 2005). Studies of gain and loss of function have shown the importance of these proteins in the regulation of TL (de Lange 2010; Smogorzewska et al. 2000).

Methods for measuring TL

Multiple methods have been developed for the study of telomeres and the two commonly used techniques include quantification of TL by terminal restriction fragmentation (TRF) and quantitative real-time polymerase chain reaction (qRT-PCR).

TRF was the earliest tool proposed for TL assessment (Moyzis et al. 1988; Allshire et al. 1989) and, hence, is often described as the "gold standard" method. It is still a widely used technique to measure TL by southern blotting or in-gel hybridization and it provides mean length measure of the whole cell population in kilobases, but not recognition of individual short telomeres or ends lacking a telomere. The limitation of the technique is that it requires large amount of DNA, is labour- intensive, and subtelomeric polymorphisms can impact data. The TRF method is not suitable for assessing TL in epidemiological studies (Aubert et al. 2012).

Cawthon's (2002, 2009) qRT-PCR technique is the most frequently used method by investigators. TL was quantified by comparing the amount of the telomere amplification product (T) to that of a single-copy gene (S). The T/S ratio was calculated to obtain a value that correlates with the average TL without providing absolute kilobase length estimate. The PCR-based method is less labor intensive, requires smaller amounts of DNA, is relatively low cost, and is well suited for large epidemiological studies. However, it provides mean TL measure of the 92 telomeres of the specimen to be evaluated and not allow recognition of individual short telomeres or ends lacking a telomere.

Single Telomere Length Analysis (STELA) (Baird et al. 2003; Bendix et al. 2010) is a qPCR-based

method to provide single TL analysis for a subset of chromosomes. STELA analysis identifies critically short telomeres and needs only a small sample, making it suitable for very rare specimens rather than for screening patients. A limitation of this method is that it is labor intensive, technically challenging (Aubert et al. 2012), and sensitive to the amount of template DNA added (Bendix et al. 2010).

Fluorescence In situ Hybridization (FISH) methods are based on their ability to measure TL in cell suspensions or histological sections using digital fluorescence microscopy (Q-FISH) (Poon and Lansdorp 2001) and flow cytometry (Flow-FISH) (Baerlocher et al. 2006). An advantage of the Q-FISH approach is that it allows the estimation of sizes for each of the individual 92 telomeres in humans and is not limited to an average or small telomeres. Moreover, this method allows the recognition of "telomere free" ends. Q-FISH is suitable for measuring TL in rare specimens but it needs cells to be mitotically active with a low proliferative rate. The technique is labor intensive, costly, and it is not well suited for epidemiological studies. The flow-FISH approach allows sorting cells into subpopulations and is suited for determining mean TL in hematopoietic cell subtypes. It can be used as a clinical diagnostic tool, primarily for use with fresh blood samples (Aubert et al. 2012), but provides a mean telomere value.

Lifestyle factors affecting TL

Telomere shortening and dysfunction are a record of the replicative history of a cell and may also be due to the chronic exposure to DNA damaging agents such as inflammation and oxidative stress (von Zglinicki 2000; Houben et al. 2008; Wolkowitz et al. 2011), which are important contributors of several age-related diseases. Indeed, studies have shown that telomere attrition is associated with greater risk of various chronic diseases, including hypertension, diabetes, cardiovascular diseases, and cancer (Samani et al. 2001; van der Harst et al. 2007; Demissie et al. 2006; Reuter et al. 2010; Zhang et al. 2014; Zhao et al. 2013; Fyhrquist and Saijonmaa 2012).

TL may be affected by lifestyle factors that influence oxidative and inflammatory responses. Dietary intake of components with antioxidative and anti-inflammatory effects, like omega-3 fatty acids, vitamin E and C, and beta-carotene is associated with reduced rate of telomere shortening, whereas a lack of these constituents correlates with increased telomere attrition rates (Farzaneh-Far et al. 2010; Shen et al. 2009). Some studies have demonstrated a positive association between serum 25-hydroxyvitamin D and leukocyte TL (Richards et al. 2007; Liu et al. 2013) and show that vitamin D supplementation contributes to preserve TL (Zhu et al. 2012; Borras et al. 2012). A diet rich in fruit, vegetables, fiber, and whole grains, which are dietary factors with antioxidant and anti-inflammatory effects, may be associated with longer leucocyte TL, while a diet high in polyunsatured fatty acids and processed meat, inducing inflammatory and oxidative stress, would be associated with shorter leucocyte TL (Cassidy et al. 2010). Exercise also seems to be associated with reduced oxidative stress, elevated expression of telomerase activity, and reduced telomere shortening (Ludlow et al. 2008; Cherkas et al. 2008; Werner et al. 2009). Even smoking and obesity are associated with increased oxidative stress, which can accelerate telomere shortening and ageing (McGrath et al. 2007; Valdes et al. 2005). All the above mentioned factors (diseases, diet, and exercise) might play a role in the onset of sarcopenia and frailty, providing a need to investigate the association of TL with these conditions.

Skeletal muscle TL dynamics

As already mentioned, the clinical framing of frailty, as PF, is likely to overlap with sarcopenia, and both ageing conditions are related to muscle atrophy (Cesari et al. 2014). Among the mechanisms that may contribute to muscle wasting in ageing, such as apoptosis (Dupont-Versteegden 2006) and protein degradation pathways (Bechet et al. 2005; Du et al. 2004; Bodine et al. 2001), reduced satellite cell function plays a critical role (Barberi et al. 2013). Skeletal muscle is considered postmitotic, with only the satellite cells actively dividing in response to stimuli of growth, remodeling, and muscle injury (Morgan and Partridge 2003) and incorporating new myonuclei into skeletal muscle fibers with shorter telomeres over time. Satellite cell activation and proliferation are enhanced in trained muscles and can be associated with changes in TL. This is consistent with the findings that TL is shorter in

skeletal muscle from long-term exercise-trained animals compared with young and age-matched sedentary animals (Ludlow et al. 2012). Besides, when satellite cells are heavily recruited for regenerative events as in the skeletal muscle of athletes, TL has been found to be either dramatically shortened or maintained and even longer than in non-trained individuals (Kadi and Ponsot 2010). This suggests the existence of mechanisms allowing the maintenance of TL even in muscles with a high turnover. About that, telomerase activity has been reported in many normal tissues such as skeletal muscle (Radak et al. 2001). Contrary to most tissues, TL of skeletal muscle is stable with ageing, due to the lower regenerative potential of its satellite cells (Garcia-Prat et al. 2013; Jang et al. 2011; Chakkalakal and Brack 2012). Indeed the literature, despite mixed results (Wernig et al. 2005; Decary et al. 1997), reports a lack of association between TL of skeletal muscle in vivo and ageing (Gardner et al. 2007; Ponsot et al. 2008). However, it is worth considering that skeletal muscle is exposed to reactive oxygen species (ROS) during ageing, which could induce oxidative DNA damage and telomere shortening (Ludlow et al. 2014).

Telomeres and sarcopenia

As shown in Table 1, only three studies have assessed the association of TL with sarcopenia and muscle related measures (i.e. muscle strength and mass).

Marzetti et al. (2014) examined the cross-sectional association between TL and sarcopenia in 142 community dwelling persons aged 65 years and over referred to a geriatric outpatient clinic. Presence of sarcopenia was determined according to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria (Cruz-Jentoft et al. 2010). TL was evaluated in PBMCs using qRT-PCR and calculated by T/S method (Cawthon 2002). PBMC TL resulted significantly shorter in sarcopenic individuals when compared to non-sarcopenic persons, and it was significantly associated with skeletal mass index (SMI) but not with measures of muscle performance (handgrip strength and gait speed). The authors concluded that age-related telomere erosion and muscle atrophy were affected by common age-related pathological conditions; indeed, long-term exposure to oxidative stress and chronic inflammation, occurring during ageing, are the cause of both telomere shortening (Richter and von Zglinicki 2007; O'Donovan et al. 2011) and muscle atrophy (Marzetti et al. 2009; Visser et al. 2002). Ludlow et al. (2014) were the first to demonstrate that oxidative stress exposure results in telomere shortening in isolated adult skeletal muscle fibers of mice. Also the absence of an association between TL with measures of muscle performance has been explained, taking into account that muscle mass and function decline occur during ageing at different speeds (Delmonico et al. 2009). Indeed, the single PBMC TL might be a reliable marker of muscle mass, but not an adequate marker of more complex and multi-organ phenomena such as those underlying the muscle performance (Finkel et al. 1995).

In another study, the association between TL and sarcopenia was examined in a five-year prospective study of 2006 older community-dwelling Chinese persons (976 men and 1030 women) aged 65 years and over (Woo et al. 2014). Diagnosis of sarcopenia was made according to the Asian Working Group for Sarcopenia (AWGS) algorithm (Chen et al. 2014) and dual-energy X-ray absorptiometry was used to measure body composition. TL was measured in leukocytes by qRT-PCR according to T/S method proposed by Cawthon (2002). Longer TL was associated only with slower decline in grip strength, but no significant association was observed with sarcopenia, muscle mass, or other measures of physical performance, including walking speed and the chair stand test. Batsis et al. (2017) evaluated the association of TL with sarcopenia in 2672 subjects from the 1999–2002 NHANES aged 60 years and over. Sarcopenia was defined using the two Foundation for the National Institute of Health definitions: reduced appendicular lean mass (ALM) or ALM divided by body mass index (BMI). TL was assessed in peripheral blood mononuclear cells (PBMCs) by qRT-PCR according to T/S method (Cawthon 2002). No adjusted differences were observed in TL in those with/without sarcopenia.

Telomeres and frailty

Few studies have evaluated the association between TL and frailty (Table 1).

Woo et al. (2008) assessed the association between frailty, measured by FI (Mitnitski et al. 2001), and TL

Table 1 Association studies of telomere length (TL) with sarcopenia and frailty

Reference	Study design	Measures examined	Sample size	Age	DNA source	Method of TL measurement	Main findings
Sarcopenia							
Marzetti et al. (2014)	Cross-sectional	Sarcopenia (EWGSOP[a] criteria), SMI[b], grip strength and gait speed	142	≥ 65	PBMCs[c]	qRT-PCR[d]	TL is associated with sarcopenia and SMI but not with grip strength and gait speed
Woo et al. (2014)	Prospective study (5 years FU[e])	Sarcopenia (AWGS[f] criteria), gait speed, grip strength, chair stand test	2,006	≥ 65	PBMCs	qRT-PCR	TL is associated with slower decline in grip strength, but not with sarcopenia and other measures of physical performance
Batsis et al. (2017)	Cross-sectional	Sarcopenia (Foundation for the National Institute of Health), ALM[g] and ALM:BMI[h]	2672	≥ 60	PBMCs	qRT-PCR	TL is not associated with sarcopenia
Frailty							
Woo et al. (2008)	Prospective study (5 years FU)	FI[i]	2,006	≥ 65	PBMCs	qRT-PCR	TL is not associated with frailty
Collerton et al. (2012)	Cross-sectional	PF[j] and FI	845	≥ 85	PBMCs	qRT-PCR	TL is not associated with frailty
Marzetti et al. (2014)	Cross-sectional	PF and FI	142	≥ 65	PBMCs	qRT-PCR	TL is not associated with frailty
Saum et al. (2014)	Cross-sectional	FI	3,537	50–75	Whole blood	qRT-PCR	TL is not associated with frailty
Yu et al. (2015)	Prospective study (5 years FU)	PF	2,006	≥ 65	PBMCs	qRT-PCR	TL is not associated with frailty
Breitling et al. (2016)	Cross-sectional	DNA methylation age and FI	1,820	50–75	Whole blood	qRT-PCR	DNA methylation age is associated with frailty but not with TL

[a]European working group on sarcopenia in older people

[b]Skeletal Mass Index

[c]Peripheral blood mononuclear cell

[d]Quantitative real-time polymerase chain reaction

[e]Follow up

[f]Asian Working Group for Sarcopenia

[g]Appendicular lean mass

[h]Appendicular lean mass: Body Mass Index

[i]Frailty Index

[j]Physical frailty

evaluated in 2006 older community-dwelling Chinese persons (976 men and 1030 women) aged 65 years and over. TL was measured in PBMCs by qRT-PCR according to T/S method (Cawthon 2002). In men, TL was inversely related to age, but no association with frailty was observed in either men or women. The lack of association between FI and TL, and the different distribution curve of values for the two measures in either sex, suggested that TL and frailty represent distinct processes. The authors interpreted these findings assuming that TL is a specific measure and biomarker of cellular senescence, while frailty is multicomponent, due to the cumulative effect of many deficits occurring in the whole lifespan. The authors underline that no single biological marker would be able to track the multitude of environmental factors responsible for frailty. In this study, women were more often frail than men, in accordance with previous studies (Goggins et al. 2005), despite having longer TL (Aviv et al. 2005; Cherif et al. 2003). These observations again support the lack of association between telomeres and frailty. Woo et al. found positive regulators of telomerase activity in estrogens (Bayne and Liu 2005), which may be a possible explanation of the gender difference in TL and of the absence in women of a negative association between TL and age. They also suggested that women were more frail than men because of exposure to different environmental factors associated with frailty (Markle-Reid and Browne 2003). In the same population Yu et al. (2015) assessed the association of TL with frailty, measured by PF rather than FI, confirming a lack of association between these two measures.

Using cross-sectional data from the Newcastle 85+ Study, a population-based study of a large cohort (n = 845) of persons aged 85 years and older (Collerton et al. 2007), Collerton et al. (2012) examined the association of frailty, measured by both PF (Fried et al. 2001) and FI (Searle et al. 2008), with a range of biomarkers of inflammation, immunosenescence, and cellular ageing. The study confirmed the importance of inflammatory markers in very old frail individuals, which previously had only been established in the younger old across different frailty models (Hubbard et al. 2008, 2009). There was limited evidence concerning the role of immunosenescence in frailty, and no association was found between the two measures of frailty with PBMC TL, determined by qRT-PCR according to T/S method (Cawthon 2002). Marzetti et al. (2014) assessed the association between PBMC TL and frailty status in a sample of 142 persons aged 65 years and over. Frailty was determined both by the Fried's criteria (PF) (Fried et al. 2001) and a modified Rockwood's FI (Searle et al. 2008). PBMC TL was unrelated to either PF or FI.

The association between TL and frailty has also been assessed in a cross-sectional analysis of 3537 community-dwelling older adults aged 50–75 years from the ESTHER cohort study (Saum et al. 2014). The authors measured frailty by FI (Mitnitski et al. 2001), and TL was assessed by qRT-PCR using whole blood DNA and calculated by T/S method (Cawthon 2002). TL was inversely related to age but not associated with frailty, neither overall nor in different subgroups defined by sex and age. In addition, women had longer telomeres than men in line with what has been previously described (Cherif et al. 2003). The authors proposed that the reduced rate of telomere shortening with age in women compared to men was possibly due to a positive influence of endogenous hormones on telomerase (Bayne and Liu 2005), and by the protective role of estrogens from oxidative stress, already related to telomere shortening (Aviv 2002). In line with the study by Woo et al. (2008) previously described, women were more frequently frail than men despite having longer TL, corroborating the hypothesis that TL cannot be considered a biomarker for frailty.

Breitling et al. (2016) investigated the correlation of the epigenetic age acceleration or epigenetic clock, quantified by the difference between the predicted methylation age (DNAm age) (Horvath 2013) and chronological age, with TL and frailty. Indeed, it has been suggested that the epigenetic clock correlates with clinically relevant ageing-related phenotypes, and TL and frailty can be considered major correlates of age on the genomic and clinical level. This cross-sectional study included 1820 community-dwelling older adults aged 50–75 years from the ESTHER cohort in Germany. Frailty was measured by FI while TL was determined in whole blood by qRT-PCR according to T/S method (Cawthon 2002). The results of the study pointed out an association of the epigenetic age acceleration with frailty but not with TL, suggesting that methylation age acceleration does not reflect mitotic age (cellular senescence), which is the major determinant of age-dependent telomere shortening. Furthermore they hypothesized that the

lack of correlation was responsible for the inconclusive prior reports about an association of TL with frailty.

Discussion

Leukocyte TL is widely considered a biomarker of ageing because it is implicated in cellular ageing and its attrition is found to be important in determining variations in biological ageing and age-related diseases. Telomeres shortening is the result of the combined effect of repeated cell replication, oxidative stress, and inflammation, which are major risk factors and the common underlying pathogenic mechanisms of several age-related diseases. Indeed, telomere attrition is associated with greater risk of various chronic diseases such as hypertension, diabetes, cardiovascular diseases, and cancer. To date, only one paper indicates that PBMC TL is shorter in older outpatients with sarcopenia when compared with age-matched controls. This relationship is most likely driven by muscle mass reduction, given the lack of correlation between TL and measures of muscle performance. In another study, an association of TL with decline in grip strength was described. Moreover, population-based cross-sectional and longitudinal analyses have not found any association between TL and frailty. This result is consistent regardless of the definition used to identify frailty (FI or PF), and the characteristics of the study population. In summary, existing evidence suggests that TL, as single measurement, cannot be considered as a unique biomarker for describing the life-course multiplicity of the pathogenic underlying mechanisms of sarcopenia and frailty where, in addition to inflammation and oxidative stress, other pathophysiologic processes play a role (Marzetti et al. 2013; Meng and Yu 2010; Walston 2012; Inglés et al. 2014; Fried et al. 2009). Besides, even considering all the circulating biomarkers currently available, there is no single biomarker that can be effectively used to identify the two conditions, to monitor their progression over time, or their response to interventions. Indeed, even the most sensitive biomarkers are specific for single pathogenic processes and inconclusive for investigating the clinical outcomes of the two syndromes (Calvani et al. 2015). It is noteworthy that Mitnitski et al. (2015) proposed the development of a frailty index based on the combination of different biomarker measures associated with frailty (Biomarker-based Frailty Index), which collectively can predict adverse outcomes and mortality better than the individual biomarkers or the Fried frailty phenotype. Likewise, because of the intrinsic multi-causal and multi-system nature of the ageing process, the MARK-AGE study, which is a recent Large-Scale Integrating Project, proposed to perform a wide population study aiming to identify a combination of biomarkers of human ageing across a range of physiological systems which can measure biological ageing better than a single biomarker (Bürkle et al. 2015). Thus, future directions will develop panels of biomarkers by multivariate analysis with varied individual sensitivity and specificity, which may provide a more accurate assessment and prediction of outcomes, also in response to interventions such as physical exercise and nutrition in frail and sarcopenic elderly people.

Further, all the papers reviewed examined average TL by qRT-PCR. Given that it has been suggested that a single or small number of critically short telomeres serve as signals leading to cellular senescence/apoptosis (Abdallah et al. 2009; Hemann et al. 2001), measuring only mean TL may not provide the complete story regarding whether what is occurring in cells is related to sarcopenia/frailty. Thus further study is needed using assays that can detect the length of specific, individual telomeres and the proportion of the telomeres which are short, before concluding if TL is associated more or less with the two syndromes.

Moreover, in all the papers of the review, TL was usually measured in the DNA extracted from PBMCs. Blood samples are more accessible tissues for large population studies and leukocyte TL has been proposed as evaluation of the relative TL of all tissues (Friedrich et al. 2000). TL in peripheral blood may not represent the case of telomere biology in skeletal muscle, the organ most effected by sarcopenia and likely to lead to frailty. Indeed, there is a very low correlation between the TL within most tissues and the TL in blood leukocytes (Dlouha et al. 2014). It also seems questionable that leukocyte TL, which is positively correlated with lifespan and is an expression of the tremendous turnover in peripheral blood cells, could be used for the age estimation of skeletal muscle which is a postmitotic tissue. Hence, future perspectives should study mechanisms underlying telomere shortening in skeletal muscle, which is still largely

unknown, to confirm or disprove that TL is or is not related to sarcopenia/frailty. However, TL in skeletal myofibers cannot be useful as a biomarker in clinical practice because obtaining muscle biopsies from sarcopenic/frail patients has practical obstacles. Indeed, because of the invasiveness of the method, TL can be measured in a relatively small sample size, making difficult a longitudinal context.

Acknowledgements We thank "Centro Studi Achille e Linda Lorenzon" for supporting ML. We are grateful to Katie Palmer for the English language revision.

Funding The work of ML has been supported by the "Centro Studi Achille e Linda Lorenzon".

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abdallah P, Luciano P, Runge KW, Lisby M, Géli V, Gilson E, Teixeira MT (2009) A two-step model for senescence triggered by a single critically short telomere. Nat Cell Biol 11:988–993. https://doi.org/10.1038/ncb1911

Allshire RC, Dempster M, Hastie ND (1989) Human telomeres contain at least three types of G-rich repeat distributed non-randomly. Nucleic Acids Res 17:4611–4627

Aubert G, Hills M, Lansdorp PM (2012) Telomere length measurement-caveats and a critical assessment of the available technologies and tools. Mutat Res 730:59–67. https://doi.org/10.1016/j.mrfmmm.2011.04.003

Aviv A (2002) Telomeres, sex, reactive oxygen species, and human cardiovascular aging. J Mol Med (Berl) 80:689–695

Aviv A, Shay J, Christensen K, Wright W (2005) The longevity gender gap: are telomeres the explanation? Sci Aging Knowl Environ 2005:pe16 (review)

Baerlocher GM, Vulto I, de Jong G, Lansdorp PM (2006) Flow cytometry and FISH to measure the average length of telomeres (flow FISH). Nat Protoc 1:2365–2376

Baird DM, Rowson J, Wynford-Thomas D, Kipling D (2003) Extensive allelic variation and ultrashort telomeres in senescent human cells. Nat Genet 33:203–207

Barberi L, Scicchitano BM, De Rossi M, Bigot A, Duguez S, Wielgosik A, Stewart C, McPhee J, Conte M, Narici M, Franceschi C, Mouly V, Butler-Browne G, Musarò A (2013) Age-dependent alteration in muscle regeneration: the critical role of tissue niche. Biogerontology 14:273–292. https://doi.org/10.1007/s10522-013-9429-4

Batsis JA, Mackenzie TA, Emeny RT, Rippberger P, Lopez-Jimenez F, Bartels S (2017) Sarcopenia, telomere length and mortality: NHANES 1999-2002. Innov Aging 1(1):204

Bayne S, Liu JP (2005) Hormones and growth factors regulate telomerase activity in ageing and cancer. Mol Cell Endocrinol 240:11–22

Bechet D, Tassa A, Taillandier D, Combaret L, Attaix D (2005) Lysosomal proteolysis in skeletal muscle. Int J Biochem Cell Biol 37:2098–2114

Bendix L, Horn PB, Jensen UB, Rubelj I, Kolvraa S (2010) The load of short telomeres, estimated by a new method, Universal STELA, correlates with number of senescent cells. Aging Cell 9:383–397

Blackburn EH (2001) Switching and signaling at the telomere. Cell 106:661–673

Blasco MA (2005) Telomeres and human disease: ageing, cancer and beyond. Nat Rev Genet 6:611–622

Blasco MA (2007) TL, stem cells and aging. Nat Chem Biol 3:640–649

Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, Poueymirou WT, Panaro FJ, Na E, Dharmarajan K, Pan ZQ, Valenzuela DM, DeChiara TM, Stitt TN, Yancopoulos GD, Glass DJ (2001) Identification of ubiquitin ligases required for skeletal muscle atrophy. Science 294:1704–1708

Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, Harley CB, Shay JW, Lichtsteiner S, Wright WE (1998) Extension of life-span by introduction of telomerase into normal human cells. Science 279:349–352

Borras M, Panizo S, Sarró F, Valdivielso JM, Fernandez E (2012) Assessment of the potential role of active vitamin D treatment in TL: a case-control study in hemodialysis patients. Clin Ther 34:849–856

Breitling LP, Saum KU, Perna L, Schöttker B, Holleczek B, Brenner H (2016) Frailty is associated with the epigenetic clock but not with TL in a German cohort. Clin Epigenetics 8:21. https://doi.org/10.1186/s13148-016-0186-5

Broer L, Codd V, Nyholt DR, Deelen J, Mangino M, Willemsen G, Albrecht E, Amin N, Beekman M, de Geus EJ, Henders A, Nelson CP, Steves CJ, Wright MJ, de Craen AJ, Isaacs A, Matthews M, Moayyeri A, Montgomery GW, Oostra BA, Vink JM, Spector TD, Slagboom PE, Martin NG, Samani NJ, van Duijn CM, Boomsma DI (2013) Meta-analysis of TL in 19,713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect. Eur J Hum Genet 21:1163–1168

Bürkle A, Moreno-Villanueva M, Bernhard J, Blasco M, Zondag G, Hoeijmakers JH, Toussaint O, Grubeck-Loebenstein B, Mocchegiani E, Collino S, Gonos ES, Sikora E, Gradinaru D, Dollé M, Salmon M, Kristensen P, Griffiths HR, Libert C, Grune T, Breusing N, Simm A, Franceschi C, Capri M, Talbot D, Caiafa P, Friguet B, Slagboom PE, Hervonen A, Hurme M, Aspinall R (2015) MARK-AGE biomarkers of ageing. Mech Ageing Dev 151:2–12. https://doi.org/10.1016/j.mad.2015.03.006

Calvani R, Marini F, Cesari M, Tosato M, Anker SD, von Haehling S, Miller RR, Bernabei R, Landi F, Marzetti E, the SPRINTT consortium (2015) Biomarkers for physical frailty and sarcopenia: state of the science and future developments. J Cachexia Sarcopenia Muscle 6:278–286

Calvani R, Marini F, Cesari M, Tosato M, Picca A, Anker SD, von Haehling S, Miller RR, Bernabei R, Landi F, Marzetti E, the SPRINTT consortium (2017) Biomarkers for

physical frailty and sarcopenia. Aging Clin Exp Res 29(1):29–34. https://doi.org/10.1007/s40520-016-0708-1
Campisi J (2013) Aging, cellular senescence, and cancer. Annu Rev Physiol 75:685–705
Cassidy A, De Vivo I, Liu Y, Han J, Prescott J, Hunter DJ, Rimm EB (2010) Associations between diet, lifestyle factors, and TL in women. Am J Clin Nutr 91:1273–1280
Cawthon RM (2002) Telomere measurement by quantitative PCR. Nucleic Acids Res 30:e47
Cawthon RM (2009) Telomere length measurement by a novel monochrome multiplex quantitative PCR method. Nucleic Acids Res 37:e21
Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA (2003) Association between TL in blood and mortality in people aged 60 years or older. Lancet 361:393–395
Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E (2014) Sarcopenia and physical frailty: two sides of the same coin. Front Aging Neurosci 6:192. https://doi.org/10.3389/fnagi.2014.00192
Chakkalakal J, Brack A (2012) Extrinsic regulation of satellite cell function and muscle regeneration capacity during aging. J Stem Cell Res Ther Suppl 11:001
Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JS, Lee WJ, Lee Y, Liang CK, LimpawattanaP LC, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H (2014) Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 15:95–101
Cherif H, Tarry JL, Ozanne SE, Hales CN (2003) Ageing and telomeres: a study into organ- and gender-specific telomere shortening. Nucleic Acids Res 31:1576–1583
Cherkas LF, Hunkin JL, Kato BS, Richards JB, Gardner JP, Surdulescu GL, Kimura M, Lu X, Spector TD, Aviv A (2008) The association between physical activity in leisure time and leukocyte telomere length. Arch Intern Med 168:154–158. https://doi.org/10.1001/archinternmed.2007.39
Collerton J, Barrass K, Bond J, Eccles M, Jagger C, James O, Martin-Ruiz C, Robinson L, von Zglinicki T, Kirkwood T (2007) The Newcastle 85 + study: biological, clinical and psychosocial factors associated with healthy ageing: study protocol. BMC Geriatr 7:14
Collerton J, Martin-Ruiz C, Davies K, Hilkens CM, Isaacs J, Kolenda C, Parker C, Dunn M, Catt M, Jagger C, von Zglinicki T, Kirkwood TB (2012) Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85 + Study. Mech Ageing Dev 133:456–466
Collins K, Kobayashi R, Greider CW (1995) Purification of Tetrahymena telomerase and cloning of genes encoding the two protein components of the enzyme. Cell 81:677–686
Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People (2010) Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 39:412–423
de Lange T (2005) Shelterin: the protein complex that shapes and safeguards human telomeres. Genes Dev 19:2100–2110
de Lange T (2010) How shelterin solves the telomere end-protection problem. Cold Spring Harb Symp Quant Biol 75:167–177
de Magalhães JP (2004) From cells to ageing: a review of models and mechanisms of cellular senescence and their impact on human ageing. Exp Cell Res 300:1–10
Decary S, Mouly V, Hamida CB, Sautet A, Barbet JP, Butler-Browne GS (1997) Replicative potential and telomere length in human skeletal muscle: implications for satellite cell-mediated gene therapy. Hum Gene Ther 8:1429–1438
Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, Boudreau R, Manini TM, Nevitt M, Newman AB, Goodpaster BH, Health, Aging, and Body (2009) Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J ClinNutr 90:1579–1585
Demissie S, Levy D, Benjamin EJ, Cupples LA, Gardner JP, Herbert A, Kimura M, Larson MG, Meigs JB, Keaney JF, Aviv A (2006) Insulin resistance, oxidative stress, hypertension, and leukocyte TL in men from the Framingham Heart Study. Aging Cell 5:325–330
Dlouha D, Maluskova J, Kralova Lesna I, Lanska V, Hubacek JA (2014) Comparison of the relative telomere length measured in leukocytes and eleven different human tissues. Physiol Res 63(Suppl 3):S343–S350
Du J, Wang X, Miereles C, Bailey JL, Debigare R, Zheng B, Price SR, Mitch WE (2004) Activation of caspase-3 is an initial step triggering accelerated muscle proteolysis in catabolic conditions. J Clin Invest 113:115–123
Dupont-Versteegden EE (2006) Apoptosis in skeletal muscle and its relevance to atrophy. World J Gastroenterol 12:7463–7466
Farzaneh-Far R, Lin J, Epel ES, Harris WS, Blackburn EH, Whooley MA (2010) Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. JAMA 303:250–257
Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M (2011) Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 12:249–256
Finkel D, Whitfield K, McGue M (1995) Genetic and environmental influences on functional age: a twin study. J Gerontol B 50:P104–P113
Fossel M (2012) Use of TL as a biomarker for aging and age-related disease. Curr Transl Geriatr Exp Gerontol Rep 1:121–127
Fougère B, Vellas B, van Kan GA, Cesari M (2015) Identification of biological markers for better characterization of older subjects with physical frailty and sarcopenia. Transl Neurosci 6:103–110
Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative

Research Group (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A 56:M146–M156
Fried LP, Xue QL, Cappola AR, Ferrucci L, Chaves P, Varadhan R, Guralnik JM, Leng SX, Semba RD, Walston JD, Blaum CS, Bandeen-Roche K (2009) Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J Gerontol A 64:1049–1057. https://doi.org/10.1093/gerona/glp076
Friedrich U, Griese E, Schwab M, Fritz P, Thon K, Klotz U (2000) Telomere length in different tissues of elderly patients. Mech Ageing Dev 119(3):89–99
Fyhrquist F, Saijonmaa O (2012) TL and cardiovascular aging. Ann Med 44:S138–S142
García-Prat L, Sousa-Victor P, Muñoz-Cánoves P (2013) Functional dysregulation of stem cells during ageing: a focus on skeletal muscle stem cells. FEBS J 280(17):4051–4062. https://doi.org/10.1111/febs.12221
Gardner JP, Kimura M, Chai W, Durrani JF, Tchakmakjian L, Cao X, Lu X, Li G, Peppas AP, Skurnick J, Wright WE, Shay JW, Aviv A (2007) Telomere dynamics in macaques and humans. J Gerontol A 62(4):367–374
Goggins WB, Woo J, Sham A, Ho SC (2005) Frailty index as a measure of biological age in a Chinese population. J Gerontol A 60:1046–1051
Griffith JD, Comeau L, Rosenfield S, Stansel RM, Bianchi A, Moss H, de Lange T (1999) Mammalian telomeres end in a large duplex loop. Cell 97:503–514
Hayflick L, Moorhead PS (1961) The serial cultivation of human diploid cell strains. Exp Cell Res 25:585–621
Hemann MT, Strong MA, Hao LY, Greider CW (2001) The shortest telomere, not average telomere length, is critical for cell viability and chromosome stability. Cell 107(1):67–77
Horvath S (2013) DNA methylation age of human tissues and cell types. Genome Biol 14(10):R115
Houben JM, Moonen HJ, van Schooten FJ, Hageman GJ (2008) TL assessment: biomarker of chronic oxidative stress? Free Radic Biol Med 44:235–246
Hubbard RE, O'Mahony MS, Calver BL, Woodhouse KW (2008) Nutrition, inflammation, and leptin levels in aging and frailty. J Am Geriatr Soc 56:279–284
Hubbard RE, O'Mahony MS, Savva GM, Calver BL, Woodhouse KW (2009) Inflammation and frailty measures in older people. J Cell Mol Med 13:3103–3109
Hunt SC, Chen W, Gardner JP, Kimura M, Srinivasan SR, Eckfeldt JH, Berenson GS, Aviv A (2008) Leukocyte telomeres are longer in African Americans than in whites: the National Heart, Lung, and Blood Institute Family Heart Study and the Bogalusa Heart Study. Aging Cell 7:451–458
Inglés M, Gambini J, Carnicero JA, García-García FJ, Rodríguez-Mañas L, Olaso-González G, Dromant M, Borrás C, Viña J (2014) Oxidative stress is related to frailty, not to age or sex, in a geriatric population: lipid and protein oxidation as biomarkers of frailty. J Am Geriatr Soc 62(7):1324–1328. https://doi.org/10.1111/jgs.12876
Jang YC, Sinha M, Cerletti M, Dall'Osso C, Wagers AJ (2011) Skeletal muscle stem cells: effects of ageing and metabolism on muscle regenerative function. Cold Spring Harb Symp Q Biol 76:101–111. https://doi.org/10.1101/sqb.2011.76.010652
Jaskelioff M, Muller FL, Paik JH, Thomas E, Jiang S, Adams AC, Sahin E, Kost-Alimova M, Protopopov A, Cadiñanos J, Horner JW, Maratos-Flier E, Depinho RA (2011) Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. Nature 469:102–106
Kadi F, Ponsot E (2010) The biology of satellite cells and telomeres in human skeletal muscle: effects of ageing and physical activity. Scand J Med Sci Sports 20(1):39–48. https://doi.org/10.1111/j.1600-0838.2009.00966.x
Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PL, Coviello GM, Wright WE, Weinrich SL, Shay JW (1994) Specific association of human telomerase activity with immortal cells and cancer. Science 266:2011–2015
Kong CM, Lee XW, Wang X (2013) Telomere shortening in human diseases. FEBS J 280:3180–3193
Landi F, Calvani R, Cesari M, Tosato M, Martone AM, Bernabei R, Onder G, Marzetti E (2015) Sarcopenia as the Biological Substrate of Physical Frailty. Clin Geriatr Med 31:367–374
Liu JJ, Prescott J, Giovannucci E, Hankinson SE, Rosner B, Han J, De Vivo I (2013) Plasma vitamin D biomarkers and leukocyte TL. Am J Epidemiol 177:1411–1417
Ludlow AT, Zimmerman JB, Witkowski S, Hearn JW, Hatfield BD, Roth SM (2008) Relationship between physical activity level, telomere length, and telomerase activity. Med Sci Sports Exerc 40(10):1764–1771. https://doi.org/10.1249/MSS.0b013e31817c92aa
Ludlow AT, Witkowski S, Marshall MR, Wang J, Lima LC, Guth LM, Spangenburg EE, Roth SM (2012) Chronic exercise modifies age-related telomere dynamics in a tissue-specific fashion. J Gerontol A 67(9):911–926. https://doi.org/10.1093/gerona/gls002
Ludlow AT, Spangenburg EE, Chin ER, Cheng WH, Roth SM (2014) Telomeres shorten in response to oxidative stress in mouse skeletal muscle fibers. J Gerontol A 69(7):821–830. https://doi.org/10.1093/gerona/glt211
Markle-Reid M, Browne G (2003) Conceptualizations of frailty in relation to older adults. J Adv Nur 44:58–68
Martin-Ruiz CM, Gussekloo J, van Heemst D, von Zglinicki T, Westendorp RG (2005) TL in white blood cells is not associated with morbidity or mortality in the oldest old: a population-based study. Aging Cell 4:287–290
Marzetti E, Lees HA, Wohlgemuth SE, Leeuwenburgh C (2009) Sarcopenia of aging: underlying cellular mechanisms and protection by calorie restriction. BioFactors 35:28–35
Marzetti E, Calvani R, Bernabei R, Leeuwenburgh C (2012) Apoptosis in skeletal myocytes: a potential target for interventions against sarcopenia and physical frailty—a mini-review. Gerontology 58:99–106
Marzetti E, Calvani R, Cesari M, Buford TW, Lorenzi M, Behnke BJ, Leeuwenburgh C (2013) Mitochondrial dysfunction and sarcopenia of ageing: from signaling pathways to clinical trials. Int J Biochem Cell Biol 45(10):2288–2301. https://doi.org/10.1016/j.biocel.2013.06.024
Marzetti E, Lorenzi M, Antocicco M, Bonassi S, Celi M, Mastropaolo S, Settanni S, Valdiglesias V, Landi F, Bernabei R, Onder G (2014) Shorter telomeres in peripheral blood mononuclear cells from older persons with sarcopenia: results from an exploratory study. Front Aging Neurosci 6:233

McGrath M, Wong JY, Michaud D, Hunter DJ, De Vivo I (2007) TL, cigarette smoking, and bladder cancer risk in men and women. Cancer Epidemiol Biomark Prev 16:815–819

Meng S-J, Yu L-J (2010) Oxidative stress, molecular inflammation and sarcopenia. Int J Mol Sci 11(4):1509–1526. https://doi.org/10.3390/ijms11041509

Mitnitski AB, Mogilner AJ, Rockwood K (2001) Accumulation of deficits as a proxy measure of ageing. Sci World J 1:323–336

Mitnitski A, Collerton J, Martin-Ruiz C, Jagger C, von Zglinicki T, Rockwood K, Kirkwood TB (2015) Age-related frailty and its association with biological markers of ageing. BMC Med 13:161. https://doi.org/10.1186/s12916-015-0400-x

Morgan JE, Partridge TA (2003) Muscle satellite cells. Int J Biochem Cell Biol 35(8):1151–1156

Moyzis RK, Buckingham JM, Cram LS, Dani M, Deaven LL, Jones MD, Meyne J, Ratliff RL, Wu JR (1988) A highly conserved repetitive DNA sequence, (TTAGGG)n, present at the telomeres of human chromosomes. Proc Natl Acad Sci USA 85(18):6622–6626

Nandakumar J, Cech TR (2013) Finding the end: recruitment of telomerase to telomeres. Nat Rev Mol Cell Biol 14:69–82

Nikitina T, Woodcock CL (2004) Closed chromatin loops at the ends of chromosomes. J Cell Biol 166:161–165

O'Donovan A, Pantell MS, Puterman E, Dhabhar FS, Blackburn EH, Yaffe K, Cawthon RM, Opresko PL, Hsueh WC, Satterfield S, Newman AB, Ayonayon HN, Rubin SM, Harris TB, Epel ES (2011) Health Aging and Body Composition Study. Cumulative inflammatory load is associated with short leukocyte TL in the Health, Aging and Body Composition Study. PLoS ONE 6:e19687

Palm W, de Lange T (2008) How shelterin protects mammalian telomeres. Annu Rev Genet 42:301–334

Ponsot E, Lexell J, Kadi F (2008) Skeletal muscle telomere length is not impaired in healthy physically active old women and men. Muscle Nerve 37(4):467–472. https://doi.org/10.1002/mus.20964

Poon SS, Lansdorp PM (2001) Measurements of telomere length on individual chromosomes by image cytometry. Methods Cell Biol 64:69–96

Proctor CJ, Kirkwood TB (2002) Modelling telomere shortening and the role of oxidative stress. Mech Ageing Dev 123:351–363

Radak Z, Taylor AW, Sasvari M, Ohno H, Horkay B, Furesz J, Gaal D, Kanel T (2001) Telomerase activity is not altered by regular strenuous exercise in skeletal muscle or by sarcoma in liver of rats. Redox Rep 6(2):99–103

Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB (2010) Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 49:1603–1616

Richards JB, Valdes AM, Gardner JP, Paximadas D, Kimura M, Nessa A, Lu X, Surdulescu GL, Swaminathan R, Spector TD, Aviv A (2007) Higher serum vitamin D concentrations are associated with longer leukocyte TL in women. Am J Clin Nutr 86:1420–1425

Richter T, von Zglinicki T (2007) A continuous correlation between oxidative stress and telomere shortening in fibroblasts. Exp Gerontol 42:1039–1042

Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A (2005) A global clinical measure of fitness and frailty in elderly people. CMAJ 173:489–495

Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, Gonzalez-ColaçoHarmand M, Bergman H, Carcaillon L, Nicholson C, Scuteri A, Sinclair A, Pelaez M, Van der Cammen T, Beland F, Bickenbach J, Delamarche P, Ferrucci L, Fried LP, Gutiérrez-Robledo LM, Rockwood K, Rodríguez Artalejo F, Serviddio G, Vega E (2013) Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A 68:62–67

Samani NJ, Boultby R, Butler R, Thompson JR, Goodall AH (2001) Telomere shortening in atherosclerosis. Lancet 358:472–473

Sánchez-Flores M, Marcos-Pérez D, Costa S, Teixeira JP, Bonassi S, Pásaro E, Laffon B, Valdiglesias V (2017) Oxidative stress, genomic features and DNA repair in frail elderly: a systematic review. Ageing Res Rev 37:1–15. https://doi.org/10.1016/j.arr.2017.05.001

Saum KU, Dieffenbach AK, Müezzinler A, Müller H, Holleczek B, Stegmaier C, Butterbach K, Schick M, Canzian F, Stammer H, Boukamp P, Hauer K, Brenner H (2014) Frailty and TL: cross-sectional analysis in 3537 older adults from the ESTHER cohort. Exp Gerontol 58:250–255

Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K (2008) A standard procedure for creating a frailty index. BMC Geriatr 8:24

Shay JW, Bacchetti S (1997) A survey of telomerase activity in human cancer. Eur J Cancer 33:787–791

Shay JW, Zou Y, Hiyama E, Wright WE (2001) Telomerase and cancer. Hum Mol Genet 10:677–685

Shen J, Gammon MD, Terry MB, Wang Q, Bradshaw P, Teitelbaum SL, Neugut AI, Santella RM (2009) TL, oxidative damage, antioxidants and breast cancer risk. Int J Cancer 124:1637–1643

Smogorzewska A, van Steensel B, Bianchi A, Oelmann S, Schaefer MR, Schnapp G, de Lange T (2000) Control of human TL by TRF1 and TRF2. Mol Cell Biol 20:1659–1668

Sprott RL (2010) Biomarkers of aging and disease: introduction and definitions. Exp Gerontol 45:2–4

Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, Aviv A, Spector TD (2005) Obesity, cigarette smoking, and TL in women. Lancet 366:662–664

van der Harst P, van der Steege G, de Boer RA, Voors AA, Hall AS, Mulder MJ, van Gilst WH, van Veldhuisen DJ, MERIT-HF Study Group (2007) TL of circulating leukocytes is decreased in patients with chronic heart failure. J Am Coll Cardiol 49:1459–1464

Varela E, Blasco MA (2010) 2009 nobel prize in physiology or medicine: telomeres and telomerase. Oncogene 29:1561–1565

Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, Nevitt M, Harris TB (2002) Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. J Gerontol A 57:M326–M332

von Zglinicki T (2000) Role of oxidative stress in TL regulation and replicative senescence. Ann N Y Acad Sci 908:99–110

Walston JD (2012) Sarcopenia in older adults. Curr Opin Rheumatol 24(6):623–627

Werner C, Fürster T, Widmann T, Pöss J, Roggia C, Hanhoun M, Scharhag J, Büchner N, Meyer T, Kindermann W, Haendeler J, Böhm M, Laufs U (2009) Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. Circulation 120:2438–2447

Wernig A, Schäfer R, Knauf U, Mundegar RR, Zweyer M, Högemeier O, Martens UM, Zimmermann S (2005) On the regenerative capacity of human skeletal muscle. Artif Organs 29(3):192–198

Wolkowitz OM, Mellon SH, Epel ES, Lin J, Dhabhar FS, Su Y, Reus VI, Rosser R, Burke HM, Kupferman E, Compagnone M, Nelson JC, Blackburn EH (2011) Leukocyte TL in major depression: correlations with chronicity, inflammation and oxidative stress–preliminary findings. PLoS ONE 6:e17837

Wong LS, Oeseburg H, de Boer RA, van Gilst WH, van Veldhuisen DJ, van der Harst P (2009) Telomere biology in cardiovascular disease: the TERC-/- mouse as a model for heart failure and ageing. Cardiovasc Res 81:244–252

Woo J, Tang NL, Suen E, Leung JC, Leung PC (2008) Telomeres and frailty. Mech Ageing Dev 129:642–648

Woo J, Yu R, Tang N, Leung J (2014) TL is associated with decline in grip strength in older persons aged 65 years and over. Age (Dordr) 36:9711

Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW (1996) Telomerase activity in human germline and embryonic tissues and cells. Dev Genet 18:173–179

Xi H, Li C, Ren F, Zhang H, Zhang L (2013) Telomere, aging and age-related diseases. Aging Clin Exp Res 25:139–146

Yu R, Tang N, Leung J, Woo J (2015) TL is not associated with frailty in older Chinese elderly: cross-sectional and longitudinal analysis. Mech Ageing Dev 152:74–79

Zhang L, Hu XZ, Li X, Li H, Smerin S, Russell D, Ursano RJ (2014) TL—a cellular aging marker for depression and post-traumatic stress disorder. Med Hypotheses 83:182–185

Zhao J, Miao K, Wang H, Ding H, Wang DW (2013) Association between TL and type 2 diabetes mellitus: a meta-analysis. PLoS ONE 8:e79993

Zhu H, Guo D, Li K, Pedersen-White J, Stallmann-Jorgensen IS, Huang Y, Parikh S, Liu K, Dong Y (2012) Increased telomerase activity and vitamin D supplementation in overweight African Americans. Int J Obes (Lond) 36:805–809