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Telomere Length and Aging

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1. Introduction

Telomeres, the TTAGGG tandem repeats at the ends of chromosomes, become progressively shortened with each replication of cultured human somatic cells (reviewed in Wong and Collins (Wong & Collins 2003)) until a critical length is achieved, at which point the cell enters replicative senescence. This situation can be reversed by the enzyme named telomerase that is responsible for Telomere Length maintenance. Activation of the telomerase will result in telomere elongation and regulation of its activity can save the cell from senescence (Zvereva et al., 2010). Though increased activity of telomerase has been noted in cancer cell lines, telomere length could be in steady state suggesting alternative pathways for telomere length maintenance (Ouellette et al. 1999). The length of the telomere is longest at birth and decreases with increasing age. It has been demonstrated in cross-sectional analyses that age affects attrition of Telomere Length in white blood cells (Slagboom et al., 1994; Benetos et al., 2001; Nawrot et al., 2004). The rate of attrition is different between individuals and tissues and is influenced by multiple factors including oxidative stress and activity of telomerase enzyme. Telomere Length reflects the cumulative burden of oxidative stress and repeated cell replication (Serra et al., 2003), and such oxidative stress may represent the link between telomeres and aging-related disease in humans. Telomere shortening has been implicated as a mechanism explaining variations in life expectancy and aging-related diseases.

In this chapter we will review the alterations in Telomere Length with aging and its association with multiple age-related diseases. We will discuss the mechanism of telomere shortening and how it is affected by the aging process. Finally we will review the various genetic components that play a part in either telomere attrition or maintenance with aging.

2. Telomere Length and aging

It is well established that telomere shortens with age (figure 1). Cross-sectional studies have demonstrated that adult telomeres become shorter with age at a relatively constant rate. As demonstrated in figure 1, there is an individual variation of Telomere Length change with age but the cumulative trend is that telomeres shorten with age. It should be pointed out that many of the studies evaluating the association of Telomere Length with age contain relatively few subjects with exceptional longevity (Frenck et al., 1998; Rufer et al., 1999;

Cawthon et al., 2003). Age associated attrition in telomere is linked to many age related diseases and their complications. This raises an important question if the link between Telomere Length and age related diseases are associative or causative. In the subsequent sections, we will review the changes associated with Telomere Length in various age related diseases and their progression.

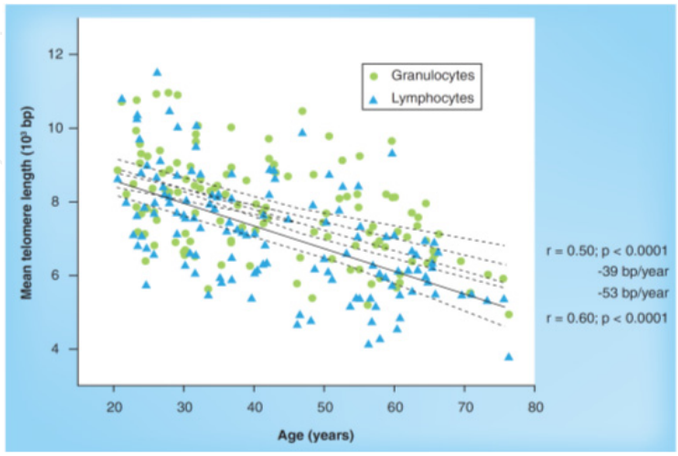

Fig. 1. Age-related telomere shortening in granulocytes and lymphocytes. (Hoffmann & Spyridopoulos 2011)

2.1 Telomere and age associated disease

"Chronological Aging" is a risk factor for multiple age-associated diseases (figure 2). However, the long and vivacious debate whether aging is a cause or effect is not settled. The supporters for chronological aging as a "cause" for age-related diseases put force the notion that age associated physiological deterioration, systems decline and immunological weakening resulting from the lost of natural shields, allows "chronological aging" to be an optimal situation for disease penetration. The opponents claim that the "physiological aging phenomenon" is a result of age-associated diseases. This hypothesis can be backed by the early onset of most of the claimed age associated diseases (i.e. Hypertension (HT), Diabetes, Cancer etc.) in the current western world. Can telomere pattern solve this debate?

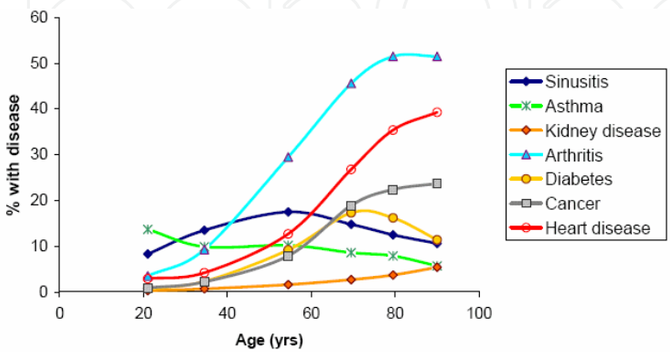

Fig. 2. Prevalence of selected chronic conditions, expressed in percentages, as a function of age for the US population (2002-2003 dataset). All forms of cancer and heart disease are featured. Source: National Center for Health Statistics, Data Warehouse on Trends in Health and Aging.

Telomere attrition with aging has been demonstrated in numerous studies, independent of the presence of any age related diseases. This supports the notion that shortened Telomere Length, seen in chronologic aging may serve as a biomarker of age independent of age-related diseases. In addition, occurrence of age-related diseases can accelerate the rate of telomere attrition. In fact older adults with one or more age associated diseases demonstrated higher attrition rate compare to healthy cohorts. Thus, aging and concurrent age-related diseases may play independent roles on Telomere Length; presence of both is synergistic in their effects on Telomere Length.

2.1.1 Telomere and hypertension

Hypertension is one of the most prevalent medical conditions among elderly. Almost 50% of the western world's 50 years old subjects suffer from high blood pressure. The prevalence increases with age to about 70% in the 80 years old. Multiple factors including environmental and genetic background and Telomere Length have been tied to this increased incidence. Though HT is more prevalent among elderly, a relationship between HT and Telomere Length has also been reported in the young; Jeanclos and colleagues (Jeanclos et al., 2000) had show that Telomere Length is shorter among younger patients with hypertension compared to healthy subjects at the same age. No studies have demonstrated a direct effect or established the mechanism by which Telomere Length affects blood pressure.

2.1.2 Telomere and Cardiovascular diseases

In addition to hypertension, age-associated Cardio Vascular Diseases (CVDs) include atherosclerosis, coronary artery disease, Myocardial infarction (MI), and heart failure. Telomere Length has been proposed as a marker for biological aging of the cardiovascular system.

Telomere attrition and vascular aging

Studies (Benetos et al., 2004; Brouilette et al., 2007; Fitzpatrick et al., 2007) have shown that high rate of telomere attrition is associated with elevated CVD risk. Welleit et al. (Willeit et al., 2010) demonstrated higher rate of telomere shortening among people with CVD compared to people without CVD. In addition, Telomere Length has been established as independent risk predictor for myocardial infarction and stroke (figure 3). As presented in figure 3, while subjects among the higher tertile of Telomere Length have significantly lower hazard risk to develop MI, CVD, stroke and vascular death over 10 years of follow up, subjects in the middle or lower tertile are substantially at greater risk. Furthermore, in a 5 years longitudinal study, those individuals with shorter telomeres were at a higher risk of developing coronary artery disease (CAD). Risk factors for CVD such as smoking were associated with telomere shortening as well (Parks et al., 2011).

Mainous et al. (Mainous & Diaz 2010) studied the relationship between Telomere Length and atherosclerosis on the background of aging. He concluded that Telomere Length is inversely associated with arterial calcification and is highly correlated to arterial age rather than chronological age, supporting the notion of telomere being a yardstick for biological aging. Endothelial cells at the atherosclerotic plaque have been shown to have shorter telomeres compared to endothelial cells from subjects without CAD (Ogami et al., 2004).

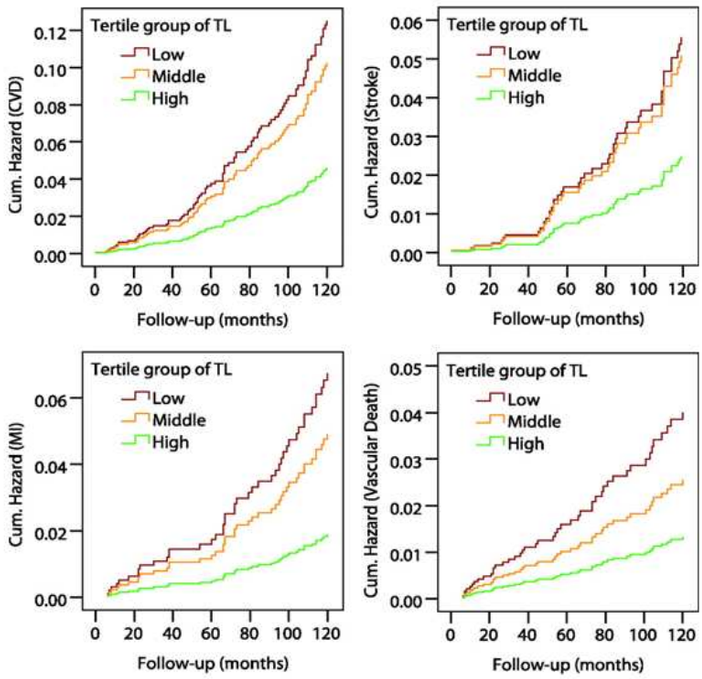

Fig. 3. Cumulative hazard curves for CVD, vascular death, myocardinal infraction, and stroke manifesting between 1995 and 2005. (Willeit et al. 2010)

In the first clinical observation, Samani et al. showed that severe coronary heart disease (CHD) is associated with shorter Telomere Length (Samani et al., 2001). Since then, many studies have shown that shortened Telomere Length is linked to severity of CVD (Table 1), (Hoffmann & Spyridopoulos 2011); however no causal role for shortened telomere in etiology of CVD or its progression has been established.

Accumulated evidence places oxidative stress as an accelerator of telomere attrition during cell replication (von Zglinicki 2002). Studies (Libby 2002; Stocker & Keaney 2004) denote inflammation and oxidative stress as the major contributors to pathophysiology of aging and age-related cardiovascular disease. In the Cardiovascular Health Study (CHS), in the face of subclinical and clinical cardiovascular disease and Telomere Length, the authors demonstrated negative correlation of IL-6 and C-reactive proteins with Telomere Length, highlighting the role of inflammation in Telomere Length regulation (Fitzpatrick et al., 2007). O'Donovan et al. reported of increased systemic inflammation with shorter Leukocyte Telomere Length in the Health, Aging and Body Composition Study (Health ABC) cohort (O'Donovan et al., 2011). Multiple studies have shown a relationship between oxidative stress and short telomeres. In the West of Scotland Coronary Prevention Study (WOSCOP) trial by Brouilette et al. (Brouilette et al., 2007), pravastatin treatment attenuated the risk of coronary heart disease even though the shorter telomeres persisted, illustrating that the short telomere is not causatively linked to coronary artery disease.

The review of literature unequivocally highlights the fact that the short Telomere Length is associated with CVD, risk factors for CVD such as hypertension and smoking and may be a prognostic indicator; however, no causative link between Telomere Length and CVD has been established.

Author (year)	Association with shorter Telomere Length
Leukocyte TL	
(Cawthon et al., 2003)	Cardiovascular mortality (+)
(Brouilette et al., 2003)	Premature myocardial infarction (+)
(Benetos et al., 2004)	Carotid atherosclerosis in hypertension (+)
(Valdes et al., 2005)	Smoking (+), obesity (+) in women
(Fitzpatrick et al., 2007)	Risk of myocardial infarction (+), diabetes (+)
(Kurz et al., 2006)	Degenerative aortic valve stenosis (+)
(Brouilette et al., 2007)	Occurrence of coronary heart disease (+)
(Collerton et al., 2007)	Left ventricular function in healthy 85 year olds (-)
(van der Harst et al., 2007)	Congestive heart failure (+)
(Farzaneh-Far et al., 2008)	Mortality in patients with stable coronary heart disease (+)
(Cherkas et al., 2008)	Physical activity (-)
(De Meyer et al., 2009)	Carotid plaque/intima media ratio (#)
(Vasan et al., 2009)	LV mass (-)
(Kuznetsova et al., 2010)	LV mass (-)
(Panayiotou et al., 2010)	Carotid intima-media thickness (+)
(Atturu et al., 2010)	Aortic abdominal aneurysm (+)
(Huzen et al., 2011)	CHD (-), carotid plaques (#)
Telomere Length in other cells	
(Wilson et al., 2008)	Patients with aortic abdominal aneurysm: aortic tissue (+)
(Spyridopoulos et al., 2008)	Patients with CHD: bone marrow cells (+)
(Spyridopoulos et al., 2009)	Patients with CHD: CD34+ progenitor cells (+), granulocytes (+), monocytes (+), T-cells (+), B-cells (+)

Table 1. **Selected cardiovascular studies measuring Telomere Length. (**adopted from Hoffmann & Spyridopoulos 2011), positive (+) or negative (-) association with shorter Telomere Length

2.1.3 Telomere and diabetes

Type 2 diabetes mellitus (T2DM) is estimated to affect 438 million people globally by 2030, and is recognized as an epidemic in most developed countries. T2DM is a chronic metabolic disease resulting from a combination of genetic susceptibility, environment, behavior, and as yet unexplained risk factors (Saxena et al., 2007). Considerable increased prevalence and earlier age of onset (Ness et al., 1999; Robbins et al., 2000) have been observed in older people (Dewan & Wilding 2003; Selvin et al., 2006), suggesting that genetic factors may influence both timing and prevalence with advance age. Earlier onset of diabetes could also be related to the global epidemic of obesity, leading to the coining of the relatively new term "Diabesity" (diabetes due to obesity). Today obesity is considered a pandemic as it affects 1.5 billion people across the world. This is a major economic and health care burden. However, obesity is just the beginning of cascade of physiologic events that results in a variety of age-associated diseases including diabetes. The relevant issues are how Leukocyte Telomere Length is associated with diabesity, how Telomere Length is regulated, and if Leukocyte Telomere Length is a coincidence, a biomarker or part of the mechanism.

Gardner et al. (Gardner et al., 2005) reported of shorter telomeres among diabesity patients. In addition, they show that earlier obesity increases the risk to develop diabesity, and these subjects had shorter telomeres. Thus, they put force the idea that telomere is a biomarker and showed negative correlation of Leukocyte Telomere Length with development of diabesity. Shorter Telomere Length has been observed in patients with insulin resistance, type 1 and type 2 diabetes mellitus. Al-Attas et al. determined the associations of Leukocyte Telomere Length to insulin resistance in middle-aged adult male and female Arabs with and without T2DM and show that Telomere Length is inversely associated with fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR). In this study, analysis revealed that HOMA-IR was the most significant predictor for Telomere Length in males. (Al-Attas et al., 2010).

Multiple variables related to glycemic control including glucose, HbA1C reveal negative correlation with Leukocyte Telomere Length (Olivieri et al., 2009). In subjects with diabetes, Telomere Length is linked to the duration of diabetes; patients with more than 10 years of diabetes had a shorter Telomere Length compared to patients with shorter duration of diabetes. Moreover, Telomere Length has been established as a marker for patients' overall condition; shorter leukocyte Telomere Length has been demonstrated in patients with diabetes complications compared to healthy control subjects. There is a positive correlation between telomere attrition and increased number of diabetes complications. (Fuller et al., 1990). Using multivariate analysis including diabetes, van der Harst et al. demonstrate that shorter Telomere Length is associated with a higher risk for death and thus can serve as a predictor for death or hospitalization in patients with heart problems. (van der Harst et al., 2010). In addition, short telomeres have been suggested by Fyhrquist et al. to be an independent predictor of progression of diabetic nephropathy in type 1 diabetes patients (Fyhrquist et al., 2010). Olivieri et al. showed that Leukocyte Telomere Length were shorter in elderly patients with both T2DM and MI compared to elders with just one of them. Similarly, Tentolouris showed that patients with both T2DM and microalbuminuria (MA) have shorter telomere compared to patients with MA only, this could partly be due to the observation that T2DM patients have increased arterial stiffness (Tentolouris et al., 2007). Indeed, significant telomere shortening among T2DM patients with atherosclerotic plaques

has been reported compared to those without plaques (Adaikalakoteswari et al., 2007). Such trend between multiple risks and shorter telomere was reported in the central part of Italy (figure 4) (Testa et al., 2011). However, while in the study conducted by Fyhrquist et al., Telomere Length could serve as predictor of diabetic type 1 nephropathy progression (Fyhrquist et al., 2010), in a study reported by Astrup et al., Telomere Length did not differ between type 1 diabetic patients with or without nephropathy (Astrup et al., 2010).

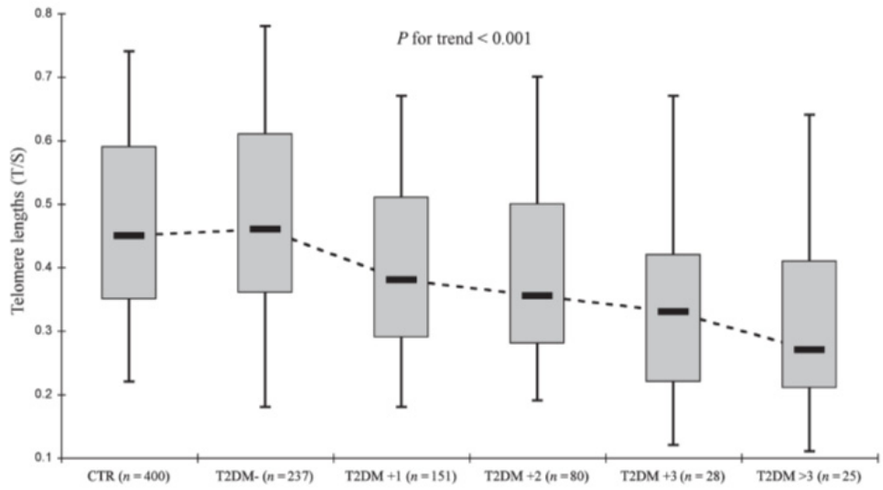

Fig. 4. Box plot of leukocyte Telomere Length (T/S) according to the number of diabetic complications. CTR -control, T2DM(–)- Diabetes only ,TSDM+N- for diabetes with complication. (Testa et al., 2011)

From a mechanistic standpoint, Verzola et al. demonstrated that telomere gets shorter when cultivated cells were introduced to high glucose level, leading them to propose that telomere shortening is due to replicative senescence. Indeed, investigation of kidney with T2DM nephropathy displays similar effects (accelerated senescence in various renal cell types under high glucose levels), suggesting diabetes may boost common pathways involving kidney cell senescence (Verzola et al., 2008). As indicated in the section on CVD, shorter Leukocyte Telomere Length could also be attributed to the high oxidative stress observed in patients with T2D (Salpea et al., 2010).

2.1.3.1 Telomere and diabetes: genetic perspective

Telomere Length, like most of the quantitative traits follows a polygenic mode of inheritance (Falconer & Mackay 1996). The most pronounced enzyme associated with telomere is Telomerase (which will be discussed further on sub chapter 3) including both a protein and an RNA subunit encoded by TERT and TERC. Telomerase activity contributes to telomere elongation, while other factors including exonucleases and end replication problem contribute to telomere shortening. The net Telomere Length depends on both telomere elongation and shortening factors. However, the attempt to explore the entire cascade of genetic elements that affecting Telomere Length are far from completion. Here we review this search on the background of diabetes. In the Women's Genome Health Study, genetic variation within the telomere-pathway gene loci has been associated with T2DM risk (Zee et al., 2011). Salpea et al. reported association of Leukocyte Telomere Length with functional

variant in the promoter area of uncoupling proteins 2 (UCP2) among T2DM patients suggesting a link between mitochondrial production of reactive oxygen species and Leukocyte Telomere Length (Salpea et al., 2010). Whole-genome screening with a copy number variation by Kudo et al. in T2DM patients revealed that loss of copy number within the 1.3-Mb of chromosome 4p16.3 sub-telomeric region (contains 34 putative genes)was associated with early-onset T2DM. (Kudo et al., 2011).

In summary, there is mixed evidence for an association between short Telomere Length and diabetes, risk factors for diabetes, and complications of diabetes. Presence of more than one risk factor for diabetes does have a correlation with Telomere Length suggesting that it (Telomere Length) could be a cause rather than an effect; however, more studies are necessary before definitively drawing this conclusion.

2.1.4 Telomere and Alzheimer's disease

Alzheimer's is a neurodegenerative disease associated with aging (Rolyan et al., 2011). Currently, more than 35 million people around the world are effected, and this number is predicted to dramaticaly increase as life expectency is prolonged.

Memory deterioration and other cognitive domains decline are the main features of Alzheimer Disease (AD) which may lead to death in 3–9 years after diagnosis. Early signs of dementia, family history and potentially modifiable risk factors as well as biological factors such as Telomere Length and telomerase dysfunction can serve as early disease markers. (Lukens et al., 2009; Saeed et al., 2011).

Paul presented a different view of the role of Telomere Length in age-related diseases and suggested that the telomere dysfunction can be linked to certain diseases including Alzheimer's. In addition, he proposed that nutrients as well as epigenetic changes accompanied the disease progression, and can affect the telomerase activity and thus Telomere Length. (Paul 2011). Thomas et al. demonstrated significant differences of Telomere Length between Alzheimer patients and control subjects not only in the leukocytes but also in buccal and hippocampus cells. Interestingly enough, while the leukocyte and buccal cells telomere were shorter among the Alzheimer patients, in the hippocampus cells telomeres were longer, suggesting deferential telomere maintenance to protect the brain of Alzheimer's patients. (Thomas et al., 2008). Panossian et al. reported the immune system involvement in telomere maintenance among Alzheimer patients. However only T cell and B cell Telomere Length were correlated with Alzheimer's disease progression (Panossian et al., 2003).

A support for the notion that Telomere Length modulates disease progression came from a study done by Rolyan et al. Using aged telomerase knockout mice (G3Terc-/-), they show loss of neuron and impaired short-term memory in carriers of short telomere. Conversely, opposite effects were demonstrated in mouse model for Alzheimer's disease, both for memory decline as well as restoration of amyloid plaque, suggesting beneficial effects of telomere shortening with Alzheimer (Rolyan et al., 2011).

In contrast, Lukens et al. did not find any association between Alzheimer progression and cerebellum Telomere Length (figure 5) (Lukens et al., 2009). Similar results have been reported by Zekry at al. in a longitudinal study among large oldest old cohorts. After two

years of follow-up, Alzheimer patients did not present significant shorter telomere compared to either demented or normal cognition groups (Zekry et al., 2010). Lof-Ohlin et al. compared Vascular demented patients versus Alzheimer patients and did not find any Telomere Length differences between the groups in such a way that it can serve as a predictor for either form of dementia (Lof-Ohlin et al., 2008). Though the exact association between Telomere Length and neurodegenerative diseases is inconclusive, there is evidence to suggest that "local" Telomere Length could be more relevant and a better index than Leukocyte Telomere Length.

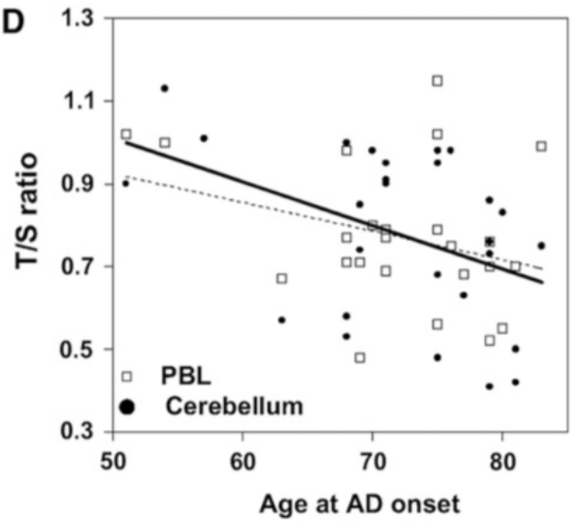

Fig. 5. Relationships between age of AD onset and cerebellar T/S ratio (n = 30, solid circles and solid line; *P* = 0.027) and peripheral blood leukocyte (PBL) T/S ratio (n = 29, open squares and dotted line; *P* = 0.108). (Lukens et al., 2009)

2.1.5 Telomere Length and cognition

Advances in technology and medical treatment increase the life expectancy substantially across the world, thus more people are living to their old age. One consequence of such trend is that number of people with dementia that are not much prevalent at young age is increasing (Matthews et al., 2009).

Cellular aging (senescence) is associated with telomere shortening but little is known about how it can affect dementia among the elderly. Harris et al. tested the hypothesis that telomere attrition with age can affect cognition changes, among the Lothian Birth Cohort 1921. Follow adjustment for multiple covariates including childhood IQ, they reported of an insignificance association (Harris et al., 2006). Harris et al. also checked whether Telomere Length can serve as a biomarker for cognitive function in 1000 elderly Scots from the Lothian Birth Cohort of 1936 and found significant evidence only with higher general cognitive ability scores (Harris et al., 2010). In the Leiden 85 plus study, Martin-Ruiz et al. reported the lack for association between Leukocyte Telomere Length and mini–mental state examination (MMSE) , and they demoted this observation to telomere instability in this highly frail population (Martin-Ruiz et al., 2005). Similar results have been obtained in the

Nurses' Health Study (NHS) of 2000 elderly subjects (Devore et al., 2011) as well as study preformed in two narrow age-range cohort of the Canberra-Queanbeyan region of Australia (Mather et al., 2010), suggesting that Telomere Length could not serve as predictor for memory decline.

In contrast, Valdes et al. reported association between sub sets of cognitive measurements and Leukocyte Telomere Length in the UK twin cohort study, suggesting Leukocyte Telomere Length as a potential biomarker of cognitive dysfunction with age (Valdes et al., 2010). Supporting such observation, Yaffe et al. have demonstrated that subject with better baseline Digit Symbol Substitution Test (DSST) scored have longer telomere in the Health ABC study (Yaffe et al., 2011). Canela et al. have used FISH to assess Telomere Length and found a significant correlation between telomere attrition and cognitive decline but only in subjects 60–69 years of age (Canela et al., 2007). Although brain aging research has progressed in the last decade, it is still poorly understood. The majority of the cognitive deficits are still attributable to either age associated senescence or AD (Gress 2001) and not Telomere Length.

2.2 Telomere and frailty

The prevalence of severe disability among older Americans is estimated to be as much as 37 percent (http://www.aoa.gov/PROF/Statistics/profile/2007/16.aspx.). This number is predicted to grow given the increased life expectancy and rise in conditions such as obesity (Manton 2008). Seniors with mobility disability experience worse quality of life than those without activity limitations with more falls, and more days of pain (CDC 1998; Ganz et al., 2005). They are more likely to be isolated from the community, suffer more morbidity and have higher incidence of mortality (Hirvensalo et al., 2000; Simonsick et al., 2001; Newman et al., 2003; Newman et al., 2006).

Frailty at a clinical level encompasses various chronic diseases associated with aging and therefore has been suggested to serve as a measure for biological ageing. Accumulated reports propose Telomere Length as an ageing biomarker. To test the theory that Telomere Length can serve as a biological marker for frailty, Woo et al. longitudinally studied healthy population using "frailty index" (figure 6) (Woo et al., 2008), and found no significant association between frailty index and telomere attrition either in whole group or after dichotomization for sex (Woo et al., 2008).

Various explanations have been proposed for the relationship between frailty and Telomere Length, Waltson suggested in his review that underlying molecular changes such as telomere shortening and reduced telomerase activity make the older humans more susceptible to frailty (Walston 2004). Sharpless and DePinho associated the lack of rejuvenate stem cells due to telomere shortening an unwanted consequence which may induce aging phenotype such as frailty (Sharpless & DePinho 2007). Kirkwood suggested "Evolutionary theory" supported by empirical evidence that accumulation of cell and tissue damage with age will result in frailty. Cell damage could be part of processes such as DNA damage or oxidative stress and the cures lie in system maintenance or natural biological processes that either fix the damage or substantially slow it down. Such examples to support this theory for better maintenance can be seen in some of the observed differences between long and short live species (Kirkwood 2002).

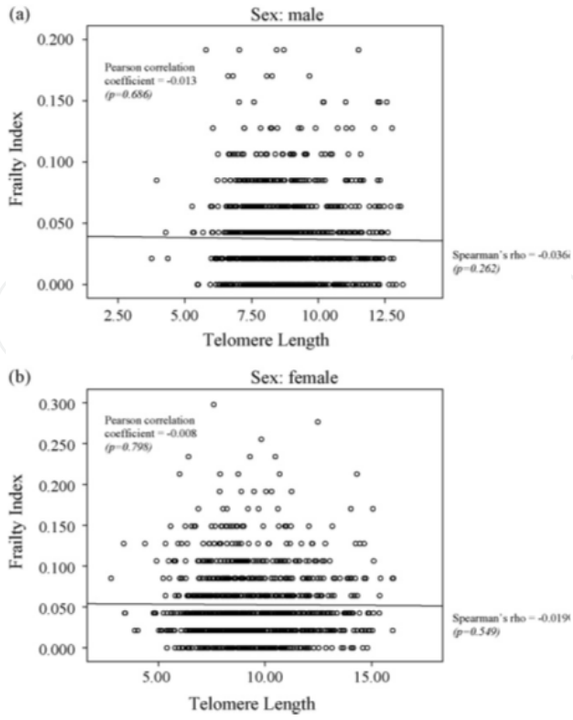

Fig. 6. Frailty index and Telomere Length (a) male and (b) female (Woo et al., 2008).

2.3 Telomere and bone structure

Aging accelerates osteoporosis and other bone diseases. More so, since the bone loses its flexibility with age, they become less sensitive to any treatment (Kepler et al., 2011). However, there are conflicting reports in the literature regarding the exact association of telomere shortening and age-related bone loss, pobably due to the different phenotypes that have been assessed. Sanders and collgue reported a lack of association between Telomere Length and Bone Mineral Density (BMD), osteoporosis, or fracture in older cohort in the Health ABC study (Sanders et al., 2009). In elder Chinese, similar observation has been seen with baseline BMD or bone loss over a 4-year period and Telomere Length (Table 2) (Tang et al., 2010).

Age (M/F)	TL1 vs. TL3 (OR (95% CI))	TL2 vs. TL3 (OR (95% CI))	p-Value	
			(TL1 vs. TL3)	(TL2 vs. TL3)
65-69 (963/904)	0.3 (0.06–1.52)/0.8 (0.36–1.81)	0.1 (0.01–1.29)/0.6 (0.26–1.44)	0.15/0.60	0.08/0.26
70-74 (963/904)	2.6 (0.47–14.21)/1.1 (0.51–2.58)	1.1 (0.17–7.32)/1.3 (0.54–2.92)	0.27/0.74	0.91/0.59
≥75 (963/904)	0.9 (0.33–2.33)/0.9 (0.42–1.89)	0.9 (0.33–2.30)/0.9 (0.43–1.99)	0.79/0.75	0.77/0.84

Table 2. Logistic regressions for association between (Bone Mineral Density)BMD and tertiled Telomere Length (TL) (Tang et al., 2010)

In contrast Valdes et al. (Valdes et al., 2007) reported that follow adjustments for multiple variants, BMD was correlated with Telomere Length. In addition, women with osteoporosis have shorter Telomere Lengths. Following their observation of negative correlation between Telomere Length and age and the association with bone loss, Bekaert et al. concluded that Telomere Length can serve as a predictor for bone loss (Bekaert et al., 2005). Kveiborg et al. took this comparison a step further and showed increased telomere attrition with age in cultured aging osteoblasts cells. However, this pattern was not observed in a groups of osteoporotic women and age matched elderly cohort, dismissing the notion that cell senescense occur much earlier in osteoporotic patients (Kveiborg et al., 1999).

Terc(-/-) mice (abolished telomerase activity) have been used to explore the mechanism behind telomere shortening in vivo and its association with bone loss. One of the phenotypes of this strain of mice is that they demonstrate accelerated rate of bone loss with age (Saeed et al., 2011). In cultured bone cells isolated from these mice, impaired osteogenic differentiation and reduced proliferation as well as accelerate senescence and DNA damage have been observed (Saeed et al., 2011). In addition, overexpression of proinflammatory genes involved in osteoclast differentiation was demonstrated by microarray screening. Thus, two mechanisms associate with bone deterioration with age have been demonstrated in telomerase deficient mice, suggesting presence of such a mechanism with aging: A) Bone cells damage and, B) Over expression of proinflammatory genes (Saeed et al., 2011). Similar observation of low bone mass phenotype and age-related osteoporosis has been reported in double knockout mice (the telomerase deficient and Wrn helicase which caused premature aging). In addition, mesenchymal stem cells (MSCs) from the double knockout mice have a short lifespan and impaired osteogenic *in vitro* (Pignolo et al., 2008).

2.4 Telomere and epigenetic

Chronological aging is a risk for numerous chronic diseases such as cardiovascular disease and type 2 diabetes mellitus (Resnick et al., 2000; Najjar et al., 2005) that affect the quality of life and lifespan. Epigenetics (acquired or heritable changes in gene function or phenotypes without changes in DNA sequence), has emerged as an important factor in gene expression and disease risk. Epigenetics refer to several mechanisms by which gene expression, DNA replication, DNA damage repair, and DNA recombination are modulated. In this section, we will review the advances in the research of epigenetics of aging and its relevance to Telomere Length.

Response of fetus to environmental stressors such as poor nutrition resulted in the early occurrence of age-associated diseases later in life (Barker Hypothesis). Such hypothesis was supported by animal models of IUGR (intra uterine growth restriction): these animals develop age-associated diseases significantly earlier than their normal birth cohorts. This observation was supported by growing evidence for the involvement of DNA methylation and histone modifications in gene expression during gestation, an effect leading to permanent cell damage and shorter Telomere Length (Barnes & Ozanne 2011).

A relationship between folate (precursors for nucleotide synthesis modulated by DNA methylation) and Telomere Length was proposed by Paul et al. Among a middle age and elderly cohort, subjects with higher folate plasma concentration had longer telomeres (Paul et al., 2009). Kim et al. proposed that artificial increase of folate in the diet can increase Telomere Length and telomerase activity, thus promoting healthy aging (Kim et al., 2009).

From a more mechanistic view, Gonzalez-Suarez & Gonzalo suggested that since aging is associated with increased chromatin defects as a result of alteration in processes associated with nuclear organization, an involvement of epigenetics in telomeric and subtelomeric region is crucial to decelerating cell senescence and therefore healthy aging. (Gonzalez-Suarez & Gonzalo 2008). Blasco report subtelomeric regions that are affected by histone modification of methyltransferases and DNA methyltransferases providing evidence for epigenetic regulation of telomere-length (Blasco 2007).

Another interestingly popular view was presented by Zeng, who hypothesized that the differentiation of undifferentiated Human Embryonic Stem Cells (hESCs) into somatic cell transforms them from immortal to mortal cells. Since the Telomere Length was maintained by active telomerase in the hESCs, transition to mortal cells results in loss of this maintenance and over time, will lead to cell death. Such a transition, the author argues, is modulated by epigenetic changes as the aging environment is changed. Controlling this environment by understanding the genomic and epigenetic of the immortal hESC can lead to successful control of somatic cell senescence and thus could offer a better treatment for age associated diseases (Zeng 2007). Tam et al. elaborated on this strategy and suggested reprogramming those cells by various techniques such as cell fusion, somatic cell nuclear transfer and more. Employing gene expression alteration or changing chromatin epigenetic state reverses the cellular ageing by controlling both Telomere Length and telomerase activity (Tam et al., 2007). Fraga et al. indicated a global perspective on hypomethylation and CpG island hypermethylation changes during aging to have their impact on cell senescence through the effect on telomere attrition and telomerase activity (Fraga et al., 2007). Thus, epigenetic regulation of Telomere Length is an extremely complex but potentially interesting avenue that could lead to modifications of disease risk and healthy aging.

2.5 Telomere and longevity

Extremely long life span or in its more common term “Longevity” is a result of multiple variables including genetic, epigenetic and environmental factors. Longevity, the right tail of life expectancy (increases steadily by quarter of a year every year (Oeppen & Vaupel 2002)) is more prevalent now due to improvements in not only medical treatment and knowledge, but also access to better nutrition, food availability, healthy environment, and overall self secure. Human longevity can be reached in many ways such as having a favourable genetic background (Schumacher et al., 2009), a low degree of disability (Terry et al., 2008), robust maintenance of physiological functions (Barzilai et al., 2010), diet (Hausman et al., 2011), front of the line healthcare (Michaud et al., 2011), environment (de Magalhaes et al., 2012), and cellular and DNA maintenance (Schumacher et al., 2009; Barzilai 2010). Can long Telomere Length be considered as one?

Telomere Length may play a role in the genetics of human longevity (Guan et al., 2007). The question is how and where? Guan et al. investigate this question among a wide range of aged people. They report decreased mean Telomere Length with age; a trend that was less steep among women (Guan et al., 2007). Friedrich et al. expanded their study to more advanced ages with three different sources of telomeres from the same donor. Interestingly, leukocytes demonstrated significantly shorter telomere compared to skin and synovial tissues within donors. In addition, the leucocyte and skin sources exhibit significant attrition with age, suggesting leukocytes as a surrogate indicator for Telomere Length for other

tissues (Friedrich et al., 2000). Stindl reported similar results for both negative correlation between mean Telomere Length and longevity and shorter telomeres among men. Stindl attributes these sex differences to different body size and propose that increased height differences are the main reason why women outlive men in the western countries (Stindl 2004). Manestar-Blazic took a step backwards and suggests that Telomere Length and longevity depend on the telomere state in the germ line of the parents at conception. Telomere Length in the gametes of the parents is a yin-yang situation; the longer they are, the faster they attrite, the best composition between the two opposing mechanism will define the starting point for the offspring Telomere Length and thus their longevity (Manestar-Blazic 2004). This is supported by Njajou et al., who studied a large cohort of the Amish. Telomere Length was negatively associated with aging, was not different between genders and positively correlated with paternal lifespan when offspring and their parents were tested, suggesting a positive influence of Telomere Length and cross generation lifespan (Njajou et al., 2007). In a different view, Bakaysa et al. established Telomere Length as a biomarker for survival on Swedish twins excluding environmental and familial effects. In their study, subjects with shorter telomeres have shorter survival compared to his/her twin sibling with longer telomeres (Bakaysa et al., 2007). Kimura et al. demonstrated the same in the oldest old; a decline of overall mean Telomere Length with age and difference between genders with females having longer mean Telomere Length compared to men. Interestingly enough, the average shorter telomere observed in the oldest old could be due to a higher percentage of short telomere fragments compared to young age subjects (Kimura et al., 2007). Further support for this phenomenon has been observed in gray and white matter autopsy samples from 72 subjects aged 0-100 YO. The authors reported of a decline in mean Telomere Length until the age of 79 followed by an increase in Telomere Length with age in the higher age group (Nakamura et al., 2007).

On the other hand multiple studies have reported a lack of association between Telomere Length and longevity. Njajou et al., using leukocyte from peripheral blood from a large cohort of mixed ethnicity, found no association for either survival or early death from major age associated disease. However, Telomere Length was linked to healthy aging suggesting that Telomere Length may be an indirect biomarker for longevity (Njajou et al., 2009). Graakjaer et al. used different technology to measure Telomere Length by fluorescent in situ hybridization (FISH) and report unique length distribution within individuals (on the cell level) and between individuals. Interestingly enough, this unique Telomere Length distribution doesn't change much through life and is partially inherited, suggesting a lesser involvement of Telomere Length with longevity and more as an accompanied trait (Graakjaer et al., 2006).

Searching for the secret of long-lived life of extremely old individuals, Terry et al. studied centenarians. Telomere Length was significantly longer in the healthy group compared to the unwell centenarians, suggesting health as a major component of telomere maintenance and not necessarily longevity mechanism. Terry et al. concluded that survival to old age is not a factor of Telomere Length rather than a signature for healthy performance (Terry et al., 2008). Taking extended centenarian cohort, we found that centenarian and their offspring exhibit longer telomeres compared to controls. Since this phenomenon was across the board including healthy and non healthy centenarians, we suggested Telomere Length as a longevity associated trait especially since the offspring of centenarians (inherited at least half of the genetic background of their extremely performed parents) demonstrate the same

trend. We attributed this observation to slow attrition rate, suggesting higher telomere maintenance among families with longevity (figure 7) (Atzmon et al., 2010). Same observation was reported by Ishikawa et al.. Cross sectional (0 and 100 years) measurement of Telomere Length in normal pituitary glands revealed decline in Telomere Length with age until certain point where the trend of Telomere Length attrition reversed and show longer telomere among the oldest old (Ishikawa et al., 2011). Such observation points to the fact that different mechanism of telomere maintenance exists in the extremely old people. This also suggests that observation of longer Telomere Length compared to age-matched controls in a cross-sectional assessment early in life could be a surrogate indicator for longevity.

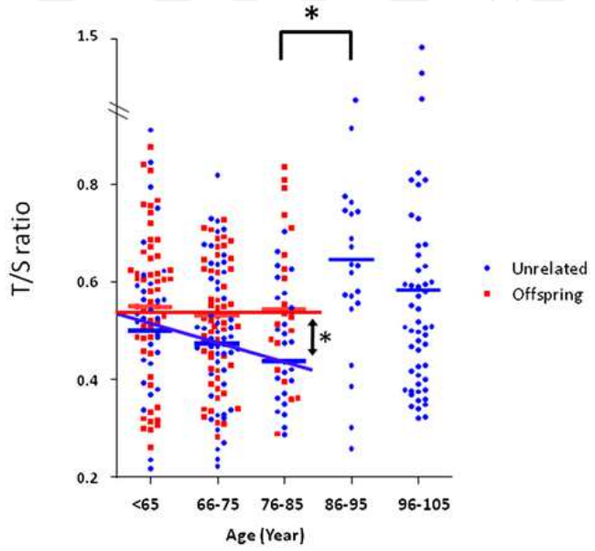

Fig. 7. Comparison of Telomere Length among Ashkenazi Jewish centenarians (n = 86), their offspring (n = 175), and controls (n = 93). Values are adjusted for age at recruitment and gender in the offspring and control groups and for gender alone in the centenarian group *P < 0.05. (Atzmon et al., 2010)

3. Telomere maintenance mechanisms

One of the critical mechanisms by which telomere is maintained, is through the enzyme telomerase reverse transcriptase (TERT) activity. Telomerase is the enzyme that is responsible for the elongation of the telomere, an action that reverses the telomere attrition. Higher telomerase activity would increase Telomere Length and extend cell proliferation potential, while lower activity would result in shorter telomere (Nicholls et al., 2011).

Using telomerase-deficient mice, Jaskelioff et al. demonstrated the crucial role of Telomere Length in cell senescence. Under conditional mutation, the mice that lack telomerase activity developed age associated phenotypes including shorter telomeres and increased DNA damage. Reactivation of the telomerase activity reversed the aging phenotypes and restored Telomere Length that in turn led to less DNA damage. This elegant study reemphasized the importance of Telomere Length and its maintenance by the telomerase activity for cell proliferation and longevity, supporting the notion of telomerase as longevity precursor (Jaskelioff et al., 2011)

The importance of telomerase activity in telomere maintenance and cell senescence was demonstrated by introducing an alternative strategy for telomere maintenance (ALT) (Wu et al.). This strategy is executed in telomerase deficient cells in order to preserve cell growth and maintain the balance between cell senescence and tumorigenesis. However, this introduced substantial Telomere Length variability, and therefore more complexity (Wu et al., 2009). Royle et al. expanded the ALT mechanism by including processes that are activated in the absence of telomerase activity such as telomere chromatid exchange elevation, blocking t-loops and activation of recombination-based processes that restore replication capability (Royle et al., 2009). Cell proliferation has been crafted through evolution to the point that each system is in harmony with its environment; hence any changes in this balance (although there are alternatives) will have deleterious impact. Pessos et al. suggested telomere attrition as the cause for cellular senescence, a mechanism that is similar to tumor suppressing. However, evidence exists for involvement of multiple processes in cell senescence such as mitochondrial function, ROS, chromatin, and functional and biochemical complexes (Passos et al., 2009). An alternative view of the impact of stress on Telomere Length was reviewed by Epel et al. They proposed a model of two opposing systems to demonstrate the effect of psychological function on Telomere Length; a. stress condition which increases cortisol, insulin and oxidative stress, all of which shorten telomere and lower telomerase activity; and b. positive cognition which increases androgen, GH axis activity and vagal tone and therefore telomere maintenance (figure 8) (Epel et al., 2009). Involvement of sex hormones in telomere maintenance and telomerase activity were further elucidated by Li et al.. Reviewing the role of estrogen in cell proliferation, Li et al. suggested mechanisms by which estrogen regulates the telomerase activity and therefore Telomere Length (Li et al., 2010). Since estrogen declines with age, its role as telomere homeostasis regulator are limited, thus other mechanisms are introduced to compensate for its absence (Li et al., 2010). On the protein level, The RecQ helicases (mainly WRN and BLM) were introduced by Bohr, as a protein family that is responsible for telomere maintenance, and defects in these proteins are associated with poor telomere maintenance and early aging. Interaction of the main proteins (i.e. WRN and BLM) with the telomere region exposes DNA damage and activates damage responses. The various mechanisms by which

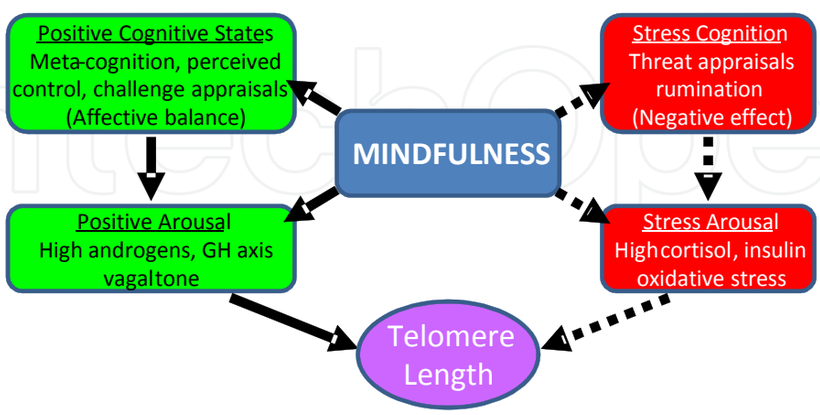

Fig. 8. Effects of Mindfulness Meditation on Telomere Length through Positive and Stressful Cognitive States. The dotted arrows represent inverse relationships specifically, we propose that positive arousal promotes and stress arousal prevents telomere maintenance (Epel et al., 2009)

RecQ helicases offer genome and specifically telomere maintenance can provide us with a clue towards successful aging (Bohr 2008). Stem cell research offers another interesting point of view. This source for cell renewal functionality declines with age; the same process was observed in telomerase deficient mice (Song et al., 2009). This connection has been further strengthened by demonstration of over expression of 4 genome maintenance proteins in plasma during aging in humans. Furthermore, this has been demonstrated in older people with age associated diseases suggesting that provocation of the DNA damage machinery interacts closely with telomere dysfunction status (Jiang et al., 2008).

4. Telomere Length in the genomic era

Candidate gene approach has been a major source in the revelation of the underline genetic mechanisms involved in telomerase activity and telomere maintenance. However, these discoveries were loci dependent, providing explanation very specifically on the immediate genetic components affecting telomerase activity and Telomere Length. Recent advances in genomic tools provide us with a more global view as well as network interaction on the genetic basis of telomerase activity and Telomere Length. From this perspective, Codd et al. conducted GWAS with mean leukocyte Telomere Length and demonstrate an area near the TERC locus that is significantly associated with mean Leukocyte Telomere Length (Codd et al., 2010). Similar analysis has been performed in a consortium of four Caucasian cohorts. In this study, the strength of the unbiased screening revealed new genes associated with Leukocyte Telomere Length such as OBFC1 and the cytokine CXCR4 as well as the TERC, demonstrating multi-component genetic effects on Telomere Length that could only have been discovered through unbiased genomic screening (Levy et al., 2010). Gu et al. conducted a multistage GWAS and found a locus next to a gene that involves in cytokine production PELI2 that is significantly associated with Leukocyte Telomere Length, thus increasing the palette of possible genes associated with Leukocyte Telomere Length (Gu et al., 2011). Prescott et al. replicated previously identified GWAS loci TERC in the Nurses' Health Study but failed to replicate other locus or identify any new loci significant associated with Telomere Length (Prescott et al., 2011). Shen et al., not surprisingly detected the TERC locus to have significant effect on Leukocyte Telomere Length in Chinese population through unbiased genome screening (Shen et al., 2011); the same two SNPs were found to be associated with Telomere Length as well as longevity in the oldest-old Danes (Soerensen et al., 2011).

Although there is evidence for association with Telomere Length in multiple facets of aging and age-related diseases, neither a conclusive causative link nor a predictable association has been established. Thus, the main question whether Telomere Length drives the aging process or is influenced by aging or age-associated diseases remains unresolved. Advance in technologies in genomics, more studies using animal models and human cells as well as improved understanding of telomere maintenance will help us answer this question unequivocally leading to the use of Telomere Length as a biomarker and ultimately personalized medicine.

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