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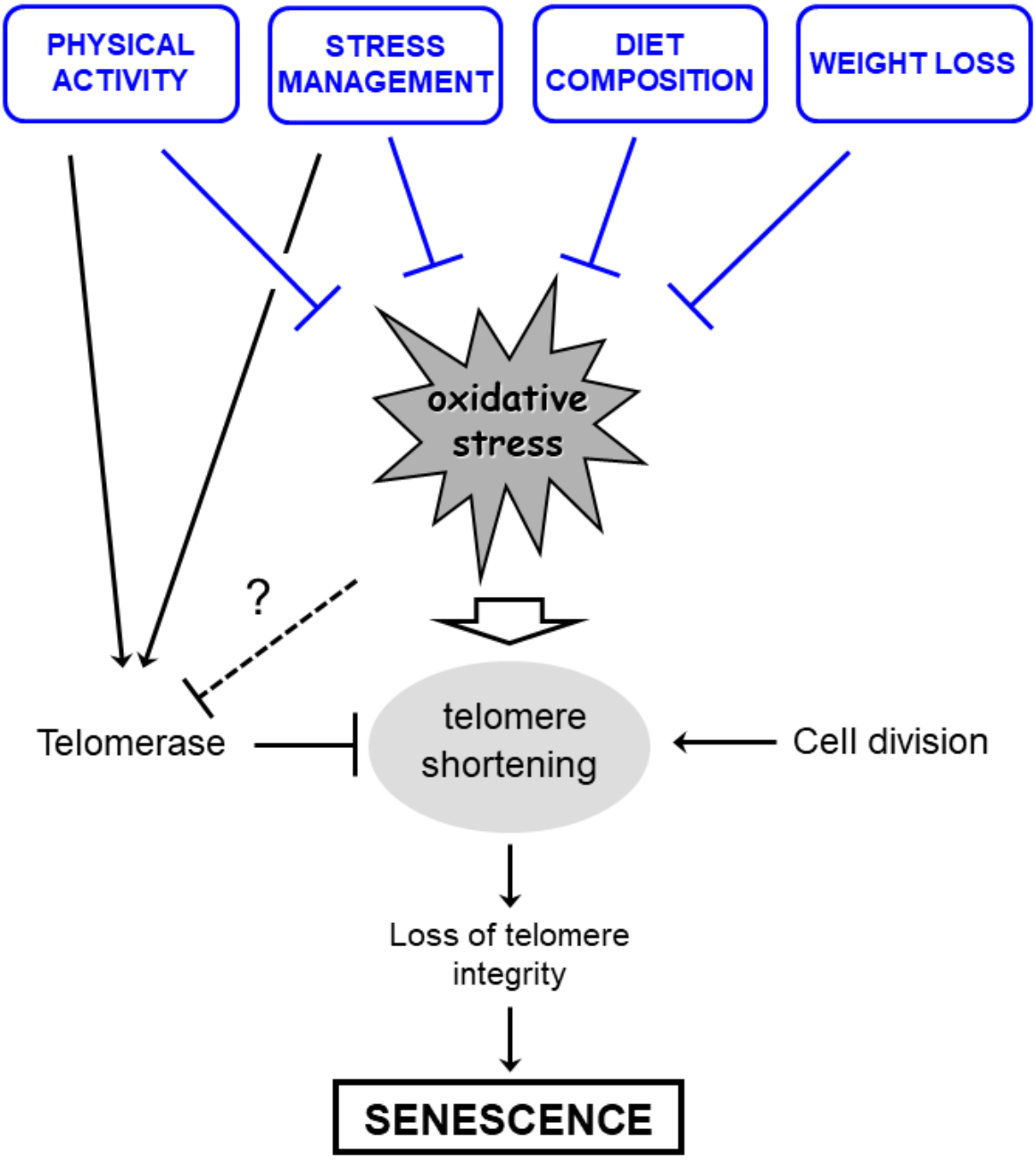
Graphical abstract



Oxidative stress, telomeres and cellular senescence: What non-drug interventions might break the link?

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Abstract

Telomeres are higher order structures that cap and protect chromosome ends. Telomeric DNA naturally shortens during somatic cell division and as a result of oxidative stress. Excessive shortening disrupts the integrity of the telomere, causing cellular senescence, one of the hallmarks of organismal ageing. The accumulation of senescent cells with ageing contributes to the loss of tissue homeostasis and the development of age-related pathologies. Hence, counteracting telomere shortening may be one relevant approach to develop strategies for healthier ageing. In this review I present the case for the existence of a link between oxidative stress, accelerated telomere shortening and cellular senescence. I also examine findings from human observational studies exploring associations between telomere length and oxidative stress-related parameters. Finally, I discuss results from randomised control trials testing the impact of non-pharmacological lifestyle interventions on the maintenance of telomere length, considering the potential mechanisms that might be involved.

Keywords

Ageing, diet, lifestyle, oxidative stress, physical activity, psychological stress, senescence, telomere, weight loss

Introduction

Telomeres are higher-order structures made of a tandemly repeated guanine-rich DNA sequence (TTAGGG in vertebrates) and a specialized protein complex called shelterin, that cap and stabilize the physical ends of chromosomes, protecting them from degradation and end-to-end fusions [1, 2]. Synthesis and maintenance of telomeric DNA requires in addition to DNA polymerase, a specialized reverse transcriptase called telomerase [3, 4]. In humans telomerase is tightly regulated by differentiation and proliferation signals. It is expressed at high levels in embryonic tissues and adult stem cell compartments, but is hardly detectable, in most other human adult somatic cell types [5, 6]. In addition, telomerase activity may be upregulated in some cells under stimulatory conditions, e.g. in endothelial cells by growth factors [6, 7] or in lymphocytes by activation signals [8].

Due to the inability of conventional DNA polymerases to replicate the 5'-end of the lagging strand, when telomerase is repressed DNA synthesis during cell division results in a gradual loss of telomeric DNA [9]. In addition, because of its high guanine content, telomeric DNA is intrinsically susceptible to oxidative modifications and single strand break formation [10]. Furthermore, since at the telomere oxidative lesions are less efficiently removed, at the time of replication persistent lesions may also lead to the truncation of the telomeric DNA backbone (reviewed in [11]). Accordingly, work with cultured cells has shown that oxidative stress accelerates telomere shortening [12, 13].

Erosion of telomeric DNA eventually compromises the functional integrity of the whole telomere structure, triggering a DNA damage response, which in turn may result in the onset of cellular senescence [14]. Cellular senescence is a distinctive stress-response phenomenon that enforces an essentially irreversible cell-cycle arrest. In addition, it gives rise to a secretory phenotype endowed with pro-inflammatory, growth promoting and tissue remodelling properties [15]. This response may be beneficial in early life and adulthood, for example as an anti-neoplastic mechanism [16], or to promote wound healing [17]. In contrast, in later life, due to the age-related impairment of clearance systems, an accumulation of senescent cells equipped with a pro-inflammatory baggage is thought to contribute to the loss of tissue homeostasis and the development of age-related pathologies (reviewed in [18].

In human cells telomeric DNA is heterogeneous in length, measuring between ~4 to ~15 kb. A decrease in leukocyte telomere length (LTL), which generally correlates with telomere length in other body tissues [19, 20], is a feature of normal ageing [21]. In addition, greater telomere shortening in leukocytes or peripheral blood mononuclear cells (PBMC) is associated with an increased risk of age-related diseases [4, 22, 23] and mortality [4, 24, 25]. Hence, counteracting telomere shortening may be relevant to reduce the accumulation of senescent cells and their pathological consequences.

Telomere length is influenced by biological [26-29], environmental [30], psychosocial [31-35] and life-style factors [36-40]. These include, gene variants of telomerase and telomere protective proteins, epigenetic signatures, sex, paternal age at birth, ethnicity, body size, biological stress responsivity, levels of inflammation, tobacco smoking, physical activity, diet and nutrition, as well as psychosocial stress, education and pollution levels. Some of these factors are also known to affect the oxidative burden of the organism, raising the possibility that they influence telomere shortening in this way. In this review I summarize evidence linking oxidative stress to telomere shortening *in vivo* and highlight areas of controversy. Furthermore, given that the harmful biological impacts of some of the above factors could be mitigated by changing life style behaviours, I also discuss non-drug interventions that may have the potential to reduce telomere shortening via oxidative stress-suppressing mechanisms.

The relationships between oxidative stress and telomere length in humans

Heightened levels of reactive oxygen species (ROS) can cause macromolecular damage and thus contribute to the development of ageing phenotypes [41-43]. This notion, together with early research in cultured cells showing that biological mediators of disease which induce oxidative stress, also shorten telomeres and lead to premature senescence (reviewed in [7]), prompted a search for associations *in vivo* between telomere length and markers of oxidative damage or antioxidant defences. One of the first indications that linked oxidative stress with shorter telomeres in humans came from a small study investigating the relationship of these parameters with perceived psychological stress in healthy pre-menopausal women [31]. An inverse correlation between LTL and urine levels of the isoprostane 8-epi-$PGF_{2\alpha}$, a marker of lipid peroxidation, was subsequently described in a larger sample

of Caucasian men [44]. However, further studies carried out in different population settings revealed a mixed picture (Table 1). Thus, associations between telomere length and selected markers of oxidative damage or antioxidant defences were found in type II diabetes or Parkinson's disease but not in healthy individuals [45-47]. Associations with plasma antioxidant micronutrients [48] and with oxidative stress-related gene polymorphisms [49] have also been documented. On the other hand, a handful of studies reported no associations. Thus, research investigating risks for breast cancer found no significant correlations between telomere length and urinary levels of 8-hydroxy-2-deoxyguanosine (8-OHdG) or 15-F_2-isoprostanes, either in the patient group or in the healthy controls [50]. Similarly, no correlations between LTL and diverse oxidative stress-related blood markers were found in Spanish patients with cardiovascular disease [51] or in mostly healthy Chinese individuals [52], except for a positive association with superoxide dismutase in the latter.

Importantly, in a recent study which examined interactions between redox state markers and telomere length in blood versus vascular tissue of patients with coronary artery disease, tissue-specific inverse associations between superoxide production and telomere length were described [53]. Furthermore, these relationships were influenced by the additive effects of two functional single nucleotide polymorphisms in the CYBA gene, which encodes one of the NADPH oxidase subunits, thus, suggesting causality. In addition, the study showed no associations between telomere length of blood cells and either plasma superoxide dismutase activity or total plasma anti-oxidant capacity, or between vascular telomere length and vascular superoxide dismutase activity, suggesting that antioxidant defences played no role in the regulation of telomere length.

Thus, taken together the available evidence only lends partial support to the concept that oxidative stress contributes to telomere shortening *in vivo*. Several factors could contribute to the discrepancies found between studies, including the ethnical and clinical characteristics of the populations studied, the type of tissue sampled and the markers of oxidative stress tested. Of note however, in those studies that reported associations with telomere length, only a minority showed these to be with antioxidant defences.

Non-pharmacological interventions

A substantial number of observational studies have described associations between telomere length and potentially modifiable lifestyle behaviours, although conflicting results have also been reported (reviewed in [54-60]). These observations led the way for interventional studies aimed at ascertaining whether non-pharmacological approaches focusing on life-style changes could influence telomere length. The first clear indication that such interventions might have an effect came from a five-year follow-up study carried out in men at low risk of prostate cancer [61]. At the end of the study the group that engaged in a comprehensive life-style change programme, which included diet, physical activity, stress management and social support, showed a significant increase in PBMC telomere length compared to a decrease in the control group [61]. Using a randomised control trial (RCT) design, other studies have evaluated mainly four distinct intervention modalities, namely diet composition, physical activity, weight loss and psychological stress management. Table 2 summarizes examples of such RCTs lasting for at least eight weeks. The studies were generally small and heterogeneous with respect to the age and health characteristics of the participants, as well as the duration of the interventions. The majority lasted for less than a year [62-72], while four trials were conducted for a year or more [73-77]. In all of them telomere length was determined in either leukocytes or PBMC before and after the intervention. However, although the type of interventions described are known to impinge on oxidative-stress responses [78-82], only a few related telomere length measurements to changes in oxidative stress-related parameters [62, 64, 65]. A brief description of these studies is summarized below.

Dietary interventions

Some of the health benefits of fish-rich diets have been attributed to a high content of long chain omega-3 (n-3) polyunsaturated fatty acids (PUFAs) and the capacity of these compounds to decrease oxidative stress [83, 84]. In this respect, small trials have attempted to ascertain whether n-3 PUFA supplementation also affected telomere length. In one trial where participants received two different doses of n-3 PUFAs or a placebo for four months, changes in plasma F_2-isoprostanes were also recorded. In this study increases in telomere length in the PUFA supplementation groups were observed, compared to a decrease in the placebo group, although the

differences between groups were not significant [62]. However, a secondary analysis revealed that the increases in telomere length were associated with decreasing plasma n-6:n-3 PUFA ratios. n-3 PUFA supplementation was also shown to significantly reduce F_2-isoprostanes, but an attempt to correlate this measure with telomere length was apparently not carried out in this case [62]. A second trial with participants suffering from mild cognitive impairment evaluated a six month intervention with supplements rich in the n-3 PUFAs eicosapentanoic acid (EPA) or docosahexanoic acid (DHA) against the n-6 PUFA linolenic acid (LA) as the control [63]. In this case, telomere length decreased more in the LA group than in the DHA or EPA groups, but the differences were not statistically significant. Nevertheless, it was found that in the DHA group an increase in red blood cell DHA levels correlated with reduced telomere shortening [63]. Thus, while the above two studies do not seem to have sufficient statistical power to reach to a firm conclusion, taken together they suggest that telomere shortening may be attenuated by n-3 PUFA supplementation. Consistent with these findings, in an opportunistic two year trial conducted in cognitively healthy elders, a diet rich in walnuts, which is a source of n-3 PUFAs, showed a trend to preserve telomere length when compared to a control diet [73].

The Mediterranean diet (MD) is rich in sources of bioactive compounds that are thought to play a role in protecting the organism against inflammation and other sources of oxidative stress [60]. This protective function may be achieved in part by activating detoxifying stress responses, which *in vitro* are known to ameliorate telomere shortening and senescence [85]. *In vivo*, the effect of the MD on telomere length has been examined in a relatively large RCT, which had been originally designed to investigate the effects of this diet on the primary prevention of cardiovascular disease. In this study participants who were given the MD supplemented with olive oil showed no differences in telomere erosion over a five year period when compared to a control group given a low fat diet; unexpectedly, accelerated telomere shortening was observed in participants on the MD supplemented with nuts [75]. Importantly however, the study found that greater adherence to the MD reduced telomere shortening in individuals carrying the Ala variant of the PPARγ2 gene, but not in those carrying the Pro variant [74]. Thus, although the study concluded that overall there was no beneficial effect of the MD

intervention on slowing telomere shortening in comparison to a low fat diet, it also highlighted the potential relevance of genetic factors when considering the effects of diets on telomere length. Unfortunately, although the MD is known to increase antioxidant defences [86] and reduce oxidative damage [87] in this high cardiovascular risk population, no comparisons between changes in oxidative stress markers and changes in telomere length were reported in this case.

Exercise and physical activity

Physical exercise increases ROS generation acutely. This in turn triggers an anti-oxidant defence response, which with regular exercise practice becomes protective [88]. This protection against oxidative stress is one mechanism by which physical activity might reduce telomere attrition. To test this concept, the effect of exercise training or increase in physical activity on telomere length was investigated in small RCTs carried out in a variety of settings (Table 2). Some of the studies also examined the effect of the intervention on enzymes involved in redox homeostasis [64, 65] or on telomerase activity [67, 89]. One intervention carried out in obese middle age women showed that although six month of aerobic exercise training resulted in an increase in glutathione peroxidase activity, it did not cause significant changes in telomere length [64]. In another study which evaluated the effect of a twelve week low frequency explosive-type resistance training in elderly people, telomere length increased in the intervention group and decreased in the control group, the difference in telomere length between trained and untrained participants being significant [65]. In this study, significant reductions of mitochondrial superoxide dismutase 2 and thioredoxin reductase 1 in PBMC, as well as in serum myeloperoxidase, were detected in the intervention group but not in controls [65]. In a third study in which overweight older adults received physical activity of low/moderate intensity on prescription for six months there were no significant differences in telomere length between the control and the intervention group. However, in the exercise group a reduction in the sitting time was strongly correlated with telomere lengthening, whereas no such correlation was observed in the control group [66]. More recently, in one RCT conducted with family caregivers, aerobic exercise training was shown to increase telomere length after six months, without causing changes in telomerase activity [67]. In contrast, in another RCT carried out

with healthy sedentary postmenopausal women, twelve month of aerobic exercise showed no effect on telomere length [76]. Finally, a recent RCT in healthy sedentary participants compared the effects of three exercise training modalities on telomerase activity and telomere length in PBMCs [89]. Notably, this study found that aerobic endurance training or high intensity interval training for six month increased both telomerase activity and telomere length; in contrast, no such changes were induced by resistance training. Thus, this study suggest that in otherwise sedentary healthy people, specific training protocols may have differential effects on telomere length.

Weight loss

Calorie restriction causing weight loss without malnutrition has been shown to improve telomere length maintenance [90, 91] as well as to reduce oxidative stress and senescence [90] in lean mice. Conversely, mice made obese by feeding a high fat diet show increased levels of oxidative DNA damage and a reduction in telomere length, compared to lean animals fed a normal chow [92]. In agreement with findings in mice, obesity is one of the factors more consistently associated with telomere shortness in human observational studies [29, 56]. However, whether low calorie diets aimed at reducing weight, ameliorate telomere attrition also in humans, remains to be demonstrated. Indeed, in a RCT that examined the effects of calorie restriction on predictors of longevity and disease risk factors in healthy non-obese individuals, telomere length was not measured [93]. Furthermore, in obese or overweight participants, low calorie diets on their own or in combination with physical activity have not reduced telomere shortening significantly [69, 77]. Thus, in a relatively large study in older women carried out over a twelve-month period, there were no significant changes in LTL in any intervention group, whether weight loss had been achieved by dietary restriction, aerobic exercise or a combination of both, compared to controls. In this study, no association between the magnitude of weight loss and telomere length was found either [77]. Similarly, in another smaller trial carried out in breast cancer survivors, which combined exercise with diet, while an increase in telomere length was detected in the intervention group at six months compared to a decrease in the control group, the difference between groups was not significant [69].

Stress management

A variety of studies has reported associations between telomere length, telomerase activity and psychosocial stress (reviewed in [94]) but the mechanisms underlying these relationships remain to be fully elucidated. Chronic psychological stress has been linked to higher levels of oxidative DNA damage and decrease in anti-oxidant defences [54], possibly triggered in part by higher levels of the stress-related hormone cortisol [95]. In support of this possibility, a longitudinal study in healthy late middle age people has recently suggested that heightened cortisol responsivity may mediate the relationship between psychological stress and telomere shortening [28]. It should be noted however, that the effect of cortisol on telomere length could be mediated also by an inhibition of telomerase activity [96] and not necessarily only by oxidative stress. In addition, other pathways could be involved in this relationship, including a psychological stress-induced increase in pro-inflammatory cytokines [97, 98], which are also known be associated to greater telomere attrition [62].

Attenuating the physiological components of the stress response is a reasonable strategy to reduce the effects of psychological stress on telomere length and cellular ageing. In this context, a growing interest in the relationship between telomere length and psychological stress management has emerged over the last few years [99]. Yoga and meditation are two modalities that might reduce levels of systemic inflammation, stress-hormones and oxidative stress. These practices have also been linked with increases in telomerase activity and/or the amelioration of telomere maintenance in some observational and interventional studies [82, 99]. Two studies in particular examined the effect of yoga on telomere-related parameters and redox markers [100, 101]. The first one was a case-control study, which found that experienced yoga practitioners had significantly longer leukocyte telomeres, a higher total anti-oxidant status, and lower levels of malondialdehyde and homocysteine in serum, compared to healthy controls. In addition, in this study a strong correlation between telomere length and each of the redox markers was reported, suggesting that habitual yoga practice ameliorates telomere shortening by reducing systemic oxidative stress levels [100]. The second study was a prospective single arm exploratory trial lasting for three months in which 94 healthy participants were subjected to a yoga and meditation-based lifestyle intervention [101]. In this study, levels of 8-OHdG and ROS were significantly lower after the intervention compared to baseline, while the total anti-oxidant capacity and telomerase activity were

significantly higher. In contrast, although telomere length was shown to increase, the difference was not significant [101]. Notably, and consistent with this finding a handful of small RCTs lasting between two and nine months has shown no effect of meditation practices on telomere length (Table 2). Taken together, these studies suggest that stress management techniques on their own are unlikely to demonstrate significant effects on telomere length if applied for relatively short periods of time (e.g. for less than two years).

Conclusions, challenges and future perspectives

Mounting evidence indicates that life-style changes aimed at promoting health and wellbeing do so by reducing the pro-inflammatory and oxidative burden of the organism. In line with this notion, as described in this review, over the last 10 years an increasing number of RCT have tested whether non-drug interventions known for their oxidative stress-reducing potential, could also help to maintain telomere length over time. However, although mechanistically plausible, the picture that emerges from those studies is at present equivocal (Figure 1). Aside from limitations in the precision and heterogeneity of methods to measure telomere length and oxidative stress, including in some cases, the shortcoming inherent to the use of a single biomarker to measure the latter, inconsistencies between findings may be due to a variety of additional factors. These include the demographic, genetic and health characteristics of the groups studied, as well as the duration and intensity of the interventions. Furthermore, some studies could have been statistically underpowered to detect significant changes in telomere length. Finally, concerning the duration of the interventions, it should be emphasised that the majority lasted for less than a year and it is unclear whether telomere length can indeed change with interventions of such length [102, 103].

In considering the biological mechanisms that are recruited by non-pharmacological treatments, one should contemplate the role of telomerase (Figure 1). The weight of evidence suggests that meditation can reactivate telomerase in leukocytes with relatively short interventions [99]. Similarly, mouse and human studies indicate that exercise can also induce an increase in telomerase activity [68, 104]. Notably, in one prospective human study the exercise-induced increase in telomerase activity was shown to precede an increase in telomere length [104]. However, telomerase activity

and telomere length do not show always a positive correlation [61, 99, 105]; thus, whether such re-activation can affect telomere shortening in different scenarios is unclear. Telomerase activity is under multiple controls, some of which are also influenced by redox mechanisms [106]. Furthermore, oxidative stress supresses telomerase activity *in vitro* [13], although it is not known whether this is relevant *in vivo*. Thus, in evaluating the link between oxidative stress and telomere length *in vivo*, cross-talk between telomerase activity and the redox status of the organism and/or the relevant cell type should also be considered.

For practical reasons in human studies telomere length has been mostly measured in leukocytes or PBMC. In this respect, it should be considered that the expansion of leukocyte subsets that occurs during inflammation and immunological responses may also cause accelerated telomere shortening, irrespective of the levels of oxidative stress to which these cells are subjected. In fact, measurement of telomere length in blood should be regarded as a measure of the senescent status of circulating immune cells. Thus, to take account of these potential confounding effects future interventional studies should also look at tissues other than blood, for example the buccal epithelium.

Taken together the current evidence suggest that longer, larger (adequately powered) and better-designed RCT are required in order to confirm whether lifestyle changes are effective in reducing telomere-related cellular senescence. Larger interventions would also allow for stratification according to genetic variants and thus establish if genetic factors modulate the effectiveness of some of these interventions. These studies should consider where possible, taking samples from tissues other than blood, and include several reliable measures of oxidative stress, which are relevant to the cells and tissues from which telomere length measurements are taken. Finally, we should not neglect the notion that social and public health measures, aimed at increasing the educational attainment of the population or reduce pollution levels, are *bona fide* non-pharmacological interventions with a much wider remit, which might also contribute to extend health span by reducing telomere-related cellular senescence.

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Figure Legend

Figure 1: Targeting telomere shortening and senescence by life-style interventions that activate telomerase and/or reduce oxidative stress. The dashed line indicates a possible connection

Table 1: Human observational studies exploring the association between telomere length and oxidative stress-related parameters

Tissue	Population or disease	Sample size	Age*	Association with oxidative stress-related parameters **	Reference
WBC vs urine/serum	Healthy women caregivers vs controls	19 control 39 carers	38 (20-50)	Negative w/ F_2-isoprostane/VitE index (F(1,40)=3.49;*P*=0.035)	[31]
WBC vs urine	Framingham Heart Study Caucasian men	327	62.2 (40-89)	8-epi-$PGF_{2\alpha}$ (r=−0.16; *P*=0.005)	[44]
WBC	Caucasian men with T2D vs controls	28 control 21 T2D	61.5 (50-65)	8-oxoguanine (*r*=−0.55; *P*=0.018) in T2D only	[45]
WBC vs plasma	Caucasian T2D patients	561	68 (24–92)	TAC (r=0.12, *P*<0.01)	[46]
WBC vs plasma	Parkinson's disease (PD) vs controls	20 PD 15 control	>65	protein carbonyls (r=−0.544, *P*=0.04) in PD only NOT w/SOD or GSH in either control, PD or overall	[47]
WBC vs plasma	Austrian Stroke Prevention Study	786	66 (46-85)	Antioxidant micronutrients: Lutein-zeaxanthin (β= 0.120, *P*=0.006), Vitamin C β=0.146, *P*=0.004	[48]
WBC	1921 Lothian Birth Cohort and Newcastle Thousand Family Study	190 LBC 318 NTF	79 50	Oxidative stress-related gene polymorphisms *Methionine sulfoxide reductase A* and *NADH:Ubiquinone dehydrogenase A3* in both cohorts	[49]
WBC vs urine	Women from the Long Island Breast Cancer Study	1061 cases 1108 controls	(20-98)	NOT w/ 15-F_2 isoprostane or 8-OHdG	[50]
WBC vs plasma	Spanish CVD patients of CORDIOPREV study	290	(20-75)	NOT with lipid peroxides, GSH,GSSG, protein carbonyls, nitrotyrosine, NO or GPx activity	[51]
WBC vs serum	Chinese population	556	53.2 (11.7)	Positive w/ serum SOD (*P*=0.001) NOT w/ glutathione reductase or 8-OHdG	[52]
WBC, plasma saphenous vein (SV), mammary artery (IMA)	Stable CAD patients	128 WBC 32 IMA 24 SV	65.9 (9.6)	Tissue specific with $O_2^{\cdot -}$ production (IMA: r=−0.49, *P*=0.004; SV: r=−0.52, *P*=0.01). Weak w/ plasma MDA. NOT w/ plasma SOD or plasma TAC. Influence of *CYBA* gene ($p22^{phox}$) polymorphisms	[53]

*Age is indicated as median or mean and/or (range or SD)

** Where data are available the strength of associations are described by correlations coefficients (r), ANCOVA F-statistics or standardized regression cofficients (β)

CAD, coronary artery disease; GSH, Glutathione; GSSG, oxidized glutathione; GPx, Glutathione peroxidase; MDA: malondyaldehyde; NO, nitric oxide; SOD, superoxide dismutase; TAC: total antioxidant capacity; T2D, type 2 diabetes; WBC, white blood cells

Table 2: Randomised controlled trials of non-drug interventions to modulate telomere length

Intervention	Population	Age*	Study Design	Main findings	Reference
n-3 PUFA supplements	Healthy overweight U.S. subjects	40-85	1.25 g/d (n=40) or 2.5 g/d (n=35) n-3 PUFA vs placebo (n=31); 4m	15% ↓urinary F-2 isoprostanes in PUFA groups ↔ΔTL between groups; association between ↑TL and ↓plasma n-6:n-3 PUFA ratio (*P*=0.02)	[62]
n-3 PUFA supplements	Australian subjects w/ MCI	>65	EPA (n=12) or DHA (n=12) vs LA (n=9); 6m	↔ΔTL between groups; correlation of RBC ΔDHA with ΔTL in DHA group (r=-0.67, *P*=0.02)	[63]
Walnut-rich diet	Cognitively healthy Spanish elders	63-79	Walnut rich diet (n=80) vs habitual diet (n=69); 2y	↔ΔTL between groups but tendency to reduced attrition in walnut diet group	[73]
Mediterranean diet	PREDIMED-NAVARRA high CVD risk Spanish subjects	55-80	MD +olive oil (n=211) or MD+ nuts (n=170) vs control low fat diet (n=140); 5y	↑ΔTL by high adherence to MD in PPARγ2 gene Ala carriers but not in Pro/Pro carriers (*P*< 0.001); ↔ΔTL in MD + EV olive oil vs control, ↑-ΔTL in MD + nuts vs control (*P*=0.003)	[74, 75]
Aerobic exercise	Obese middle age women	47 (6)	supervised aerobic exercise (EX) (n=8) vs control (n=8); 6m	↔TL in control or EX group; ↔serum MDA or SOD, ↑ GPX (*P*<0.05) in EX group	[64]
Resistance training	Elderly people	70-75	explosive moderate intensity resistance training (EMRT) (n=10) vs control (n=10); 12 w	↑ TL in EMRT group vs control group (*P*<0.05); ↓MnSOD (*P*<0.01), ↓TrxR1 (*P*<0.01), ↓MPO (*P*<0.05) in EMRT group vs baseline	[65]
Physical activity on prescription	Sedentary overweight older adults	68	individualised low/moderate intensity physical activity (n=24) vs control (n=25), 6m	↔TL exercise vs control; correlation of ΔTL with reduced sitting time in exercise group (r=−0.68, *P*=0.02)	[66]
Aerobic exercise	Family caregivers with high stress	61 (6)	highly supervised aerobic exercise (n=34) vs control (n=34); 6 m	↔TA in either group; ↔ ΔTL in control group ↑ΔTL in exercise group (*P*=0.03)	[67]
Aerobic exercise	Healthy postmenopausal sedentary women	50-74	highly supervised aerobic exercise (n=99) vs usual inactivity (113); 1y	↔ ΔTL between groups	[76]
Various exercise modalities	Healthy sedentary men and women	30-60	aerobic endurance (AET) (n=26), interval (IT) (n=29) or resistance training (RT) (n=34) vs control (n=35);	↑ΔTA (*P*<0.01) and ↑ΔTL (*P*<0.05) in AET or IT ↔ΔTA and ↔ΔTL in RT or controls	[89]

			6m		
Weight loss	Overweight or obese U.S older women	50-75	dietary weight loss (n=118), aerobic exercise (n=117) or diet + exercise (n=117) vs control (n=87); 1y	↔ΔTL in any intervention vs control; no association between Δ weight loss and ΔTL	[77]
Weight loss	Overweight or obese breast cancer surviving women	58 (8)	diet + exercise (n=93) vs usual care control (n=58), 6m	↔ΔTL between groups	[69]
Mindfulness-based group therapy	Patients with depression, anxiety or stress and adjustment disorders	20-64	mindfulness based group therapy (n=88) vs treatment as usual control (n=89); 8w	↔ TL vs baseline or between groups	[70]
Mindfulness-based group therapy	Breast cancer survivors	55 (9)	8w of mindfulness-based cancer recovery (n=34), 12w of supportive expressive group therapy (n=36) vs control (n=18)	↔TL vs baseline ,but trend effect between combined intervention groups vs control group ($F_{(1,84)}=3.82$, $P=0.054$)	[71]
Contemplative mental training	Healthy adults	20-55	mental training (n=222) vs control (n=76); 9 m	↔ ΔTL between groups	[72]

*age is indicated as mean (SD) or range

Abbreviations: CVD, cardiovascular disease; DHA, docosahexanoic acid; EPA, eicosapentanoic acid; LA, linolenic acid; MDA, malondyaldehyde; MCI, mild cognitive impairment, PUFA, polyunsaturated fatty acids; SOD, superoxide dismutase; TL, telomere length; RBC, red blood cells;

↔, no significant difference between groups, ↑, increase; ↓, decrease

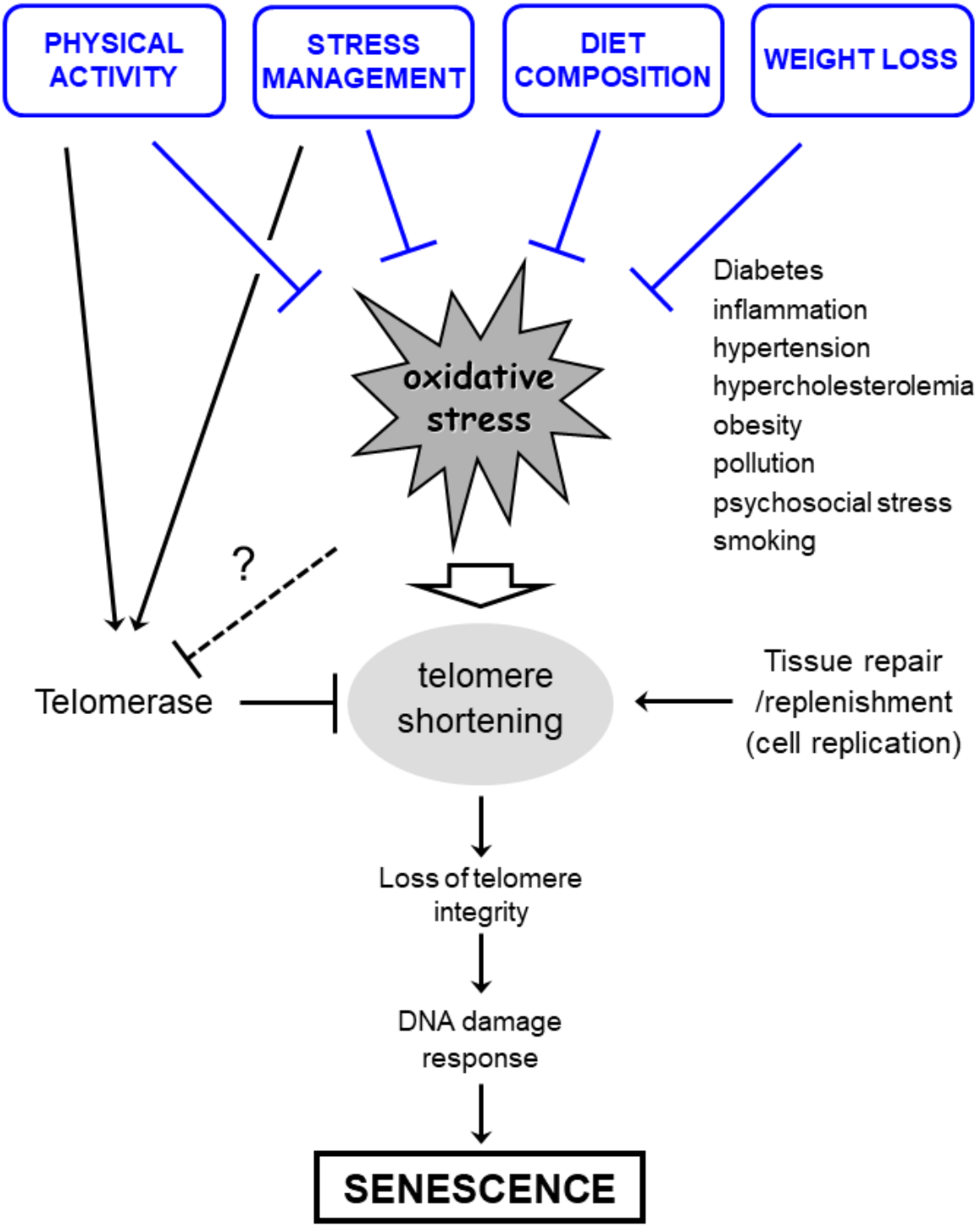
PHYSICAL ACTIVITY
STRESS MANAGEMENT
DIET COMPOSITION
WEIGHT LOSS
oxidative stress
Diabetes
inflammation
hypertension
hypercholesterolemia
obesity
pollution
psychosocial stress
smoking
?
Telomerase
telomere shortening
Tissue repair /replenishment (cell replication)
Loss of telomere integrity
DNA damage response
SENESCENCE

Figure 1

Highlights

- Oxidative stress accelerates telomere shortening resulting in cellular senescence
- There is evidence linking oxidative stress to telomere shortening in humans
- Non-drug interventions that curb oxidative stress may reduce telomere shortening