ISAGENIXSCIENCE

Factors of Telomere Length

How diet and lifestyle influence biomarkers of aging and longevity

HOW OXIDATIVE STRESS SHORTENS TELOMERES

Substantial evidence has led to findings that premature aging and its core cellular mechanisms are governed by the onset of chronic oxidative stress and resulting telomere attrition (1-5). The glutathione (GSH)-dependent antioxidant system is the cell's primary defense against oxidative stress, and plays a major role in detoxification and bolstering the body's immune system. Emerging data are elucidating the role of the GSH-redox cycle for preserving telomeres.

Structurally, telomeres are formed by non-coding DNA sequences along with specialized proteins that act as protective caps at the physical ends of chromosomes. Human telomeric DNA consists of repeated sequences of TTAGG and extends over several thousand base pairs. Because guanine-rich sequences are more sensitive and less capable of DNA repair, telomeres are more vulnerable to oxidation.

Telomeres fold back onto themselves in a loop to provide functional stability. The telomeric DNA is synthesized by the enzyme telomerase, the absence of which results in a progressive erosion.

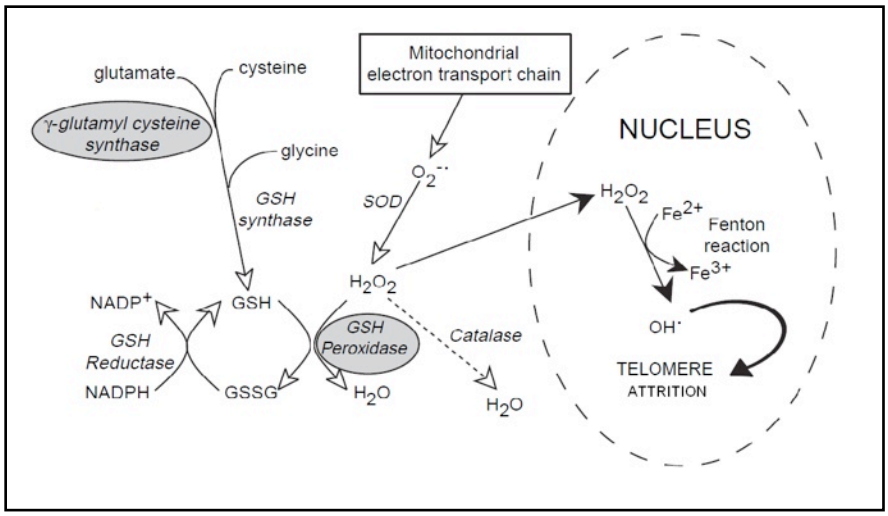


Figure 1. Depiction of how a compromised glutathione (GSH) redox cycle inhibits detoxification of peroxides (H_2O_2) leading to telomere attrition in human cells. Reference: Kurtz et al 2004.

Evidence indicates that chronic oxidative stress not only causes progressive damage to cellular membranes, proteins and molecules, but also induces an arrest of existing telomerase activity and accelerates telomere attrition (1&2).

Chronic oxidative stress develops into a state of progressive telomere attrition induced by elevated homocysteine levels, and reduced glutathione, or an otherwise compromised GSH-redox cycle.

Lower amounts of reduced glutathione, and diminished activity of the enzymes GSH peroxidase and catalase, cause a failure to protect cell components from damaging peroxides (1-3). The mitochondria become dysfunctional, producing increasing amounts of free radicals and less ATP energy (1-3). Together, these effects lead the cell to cease division or appropriate function, known as replicative senescence.

Because the GSH-antioxidant system is the predominant guardian against oxidative stress, it is proposed that maintaining its integrity can support against telomere erosion and "stress-induced" premature onset of accelerated aging.

Continued on Page 3.

ROLE OF DIET AND LIFESTYLE AND TELOMERE LENGTH

Telomere length, the new and exciting "marker" of health and longevity, is a complex trait that is shaped by genetics, epigenetics and environmental factors. The longer the telomeres, the better people are aging!

Already, medical and nutritional researchers are measuring telomeres in white blood cells (leukocytes) to see how diet and lifestyle impacts telomere length.

A study published in the *American Journal of Clinical Nutrition* in 2010 analyzed data from 2,284 women who are part of the Nurses Health Study—an ongoing prospective study that has been following 121,700 nurses since 1976 to see how their diets are impacting their health status.

This cross-sectional study (1) evaluated blood samples from the participants and compared dietary components, body composition and lifestyle parameters gathered from self-reporting or questionnaires administered in 1990.

Based on earlier studies (2-6), the researchers hypothesized that dietary factors associated with increased inflammation or oxidative stress would be associated with shorter telomeres. Interestingly, their data confirm that diet and lifestyle do influence telomere length!

The findings are welcome news for anyone who is interested in adopting behaviors of a healthier lifestyle that can ultimately slow the aging process.

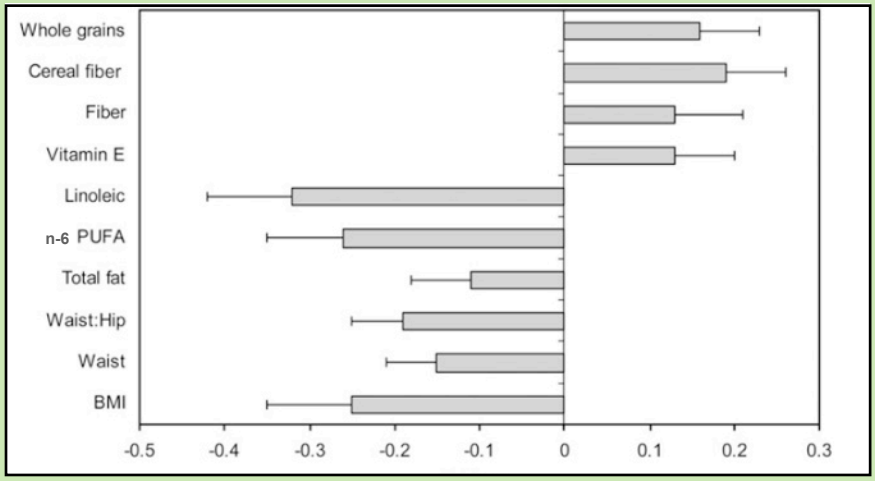


Figure 2. Relative effect of body composition and dietary factors on telomere length (change in z score) in Nurses' Health Study. Reference: Cassidy et al. Am J Clin Nutr *2010 (adapted).*

For example, the researchers found that women with the *highest intake of whole grains, specifically of insoluble (cereal) fiber, and vitamin E* had the longest telomeres.

Conversely, women with a *high fat intake (predominately from linoleic acid, the major fatty acid—omega-6—from corn and safflower oils), increased waist and higher BMI had the shortest telomeres* (see Figure 2). The strength of the associations were modest ($p < 0.05$) but support the hypothesis that dietary factors and body composition are related to telomere length.

"Telomere shortening is accelerated by oxidative stress and inflammation, and diet affects both of these processes," the authors report.

References

1. Cassidy A et al. Associations between diet, lifestyle factors, and telomere length in women. *Am J Clin Nutr* 2010;91:1273-80.
2. Blackburn EH. Telomere states and cell fates. *Nature.* 2000;408:53-6.
3. Harley et al. The telomere hypothesis of cellular aging. *Exp Gerontol* 1992;27:375-82.
4. Blackburn EH. Telomeres and telomerase: their mechanisms of action and the effects of altering their functions. *FEBS Lett.* 2005;579:859-62.
5. von Zglinicki T. Oxidative stress shortens telomeres. *Trends Biochem Sci* 2002;27:339-44.
6. Serra et al. Extracellular superoxide dismutase... slows telomere shortening. *J Biol Chem.* 2003;278:6824-30.

Continued from Page 1, "How Oxidative Stress Shortens Telomeres".

Scientific research suggests that a variety of consistent behaviors in humans in-vivo are available to alter the amount of oxidative stress placed on cells of the body.

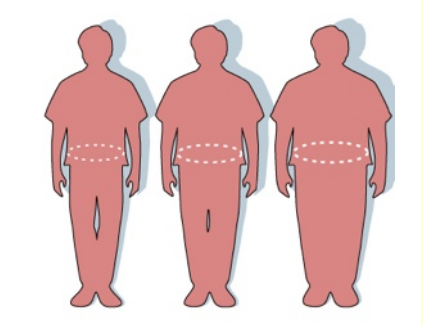
Among factors thought to adversely affect telomeres are smoking, drinking heavily, obesity, and chronic psychological stress (1-3). On the other hand, meditation, socialization, and regular exercise are associated with longer telomeres (1-3).

In addition, studies suggest diet and supplementation habits can be help preserve telomere integrity. Some choices linked with longer telomeres are: consuming higher amounts of omega-3 fatty acids, obtaining higher amounts of vitamin D, maintaining a healthy weight, eating a diet higher in dietary fiber (particularly insoluble fiber), drinking green tea regularly, and taking a quality multivitamin (containing sufficient amounts of B vitamins, vitamins A, C, and E) daily (4).

References

1. Kurz et al. Chronic oxidative stress compromises telomere integrity and accelerates the onset of senescence in human endothelial cells. *J Cell Sci* 2004.
2. Tchirkov & Lansdorp. Role of oxidative stress in telomere shortening in cultured fibroblasts from normal individuals and patients with ataxia-telangiectasia. *Hum Mol Genet* 2003.
3. Sahin E, Colla S, Liesa M et al. Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature* 2011;470:359-65.
4. Xu Q, Parks CG, DeRoo LA, Cawthon RM, Sandler DP, Chen H. Multivitamin use and telomere length in women. *Am J Clin Nutr* 2009;89:1857-63.

OBESITY AND TELOMERES



Weight gain during adulthood may reduce the length of your telomeres, researchers from the National Institute of Environmental Health Sciences find.

This cross-sectional study (1) revealed that weight gain, obesity and weight cycling were all predictors of telomere length in women. Published in *Cancer Epidemiology Biomarkers & Prevalence*, researchers gathered data from 647 women ages 35 to 74 years.

In addition to finding that current weight was a predictor of telomere length, the researchers reported that "higher BMI at ages 30 to 39 years, adult weight gain and frequent weight cycling were inversely associated with telomere length."

The authors discussed how telomere length is often reduced by chronic exposures to oxidative stress and inflammation, both of which are commonly induced by obesity (see Figure 3). "Accumulating adiposity increases oxidative

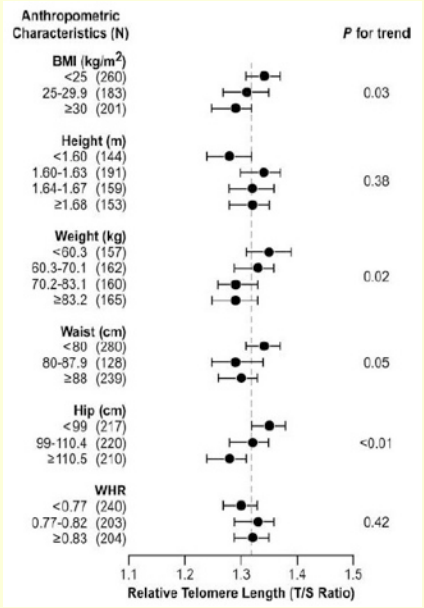


Figure 3. Telomere length according to anthropometric measurements. Reference: Kim et al. 2009.

stress and causes deregulation of inflammatory cytokines," the researchers explained. This highly destructive cascade, initiated by weight gain, is particularly hazardous for telomeres.

The researchers showed that the shortest telomeres were seen in women that both had a history of obesity and were currently overweight or obese. While fluctuations in weight adversely affect telomere length, the authors suggest that "the duration of obesity may be more important than weight change."

Previous research on obesity and its relationship with telomere length has yielded conflicting data (2 & 3).

An epidemiological study in 2008 published in *Obesity* investigated the link between cardiovascular disease (CVD) and obesity with short telomere length in peripheral blood.

Swedish researchers analyzed a large set of known risk factors for CVD in relation to telomere length in blood cells on a cohort of 989 individuals. They found a significant or borderline association between obesity parameters and telomere length in women after age and center adjustments. In men, they found a positive borderline correlation to high-density lipoprotein (HDL) and a negative correlation to two-hour post-oral glucose tolerance test.

The researchers found no association between telomere length and cholesterol, triglycerides, low-density lipoprotein, plasma insulin, blood pressure, pulse pressure, or smoking.

References

1. Kim S et al. Obesity and weight gain in adulthood and telomere length. *Cancer Epidemiology Biomarkers & Prevention*. 2009; 18: 816-20.
2. Weinberg CR et al. Telomere length is associated with obesity parameters but with a gender difference. *Obesity* (Silver Spring) 2008;16:2682-9.
3. Valdes AM et al. Obesity, cigarette smoking, and telomere length in women. *Lancet*. 2005;366:662-4.

MULTIVITAMINS AND PRESERVATION OF TELOMERE LENGTH

National Institute of Health researchers were the first to report, in a study (1) published in the March 2009 issue of *American Journal of Clinical Nutrition*, epidemiological evidence that regular multivitamin use was associated with longer telomeres among women.

The study found that when compared to non-users of multivitamins, women who used multivitamins had an average of 5 percent longer telomeres, which can translate to nearly a decade of age-related telomere loss.

To eliminate any variables that might have confounded their results, the authors were careful to exclude women who smoked, were obese, suffered from diabetes or cardiovascular disease, or who had reported a "fair or poor" health status.

In their report, the researchers write, "sixty-five percent of the women had used multivitamins at least once per month, and most (74 percent) took multivitamins on a daily basis." Additionally, multivitamins accounted for a significant amount of their total vitamin and mineral intake.

The micronutrients most likely to have an important role in preserving telomeres, wrote the scientists, were vitamins C, D, E and most of the B vitamins.

Based on prior cell-culture and animal studies (2 & 3), the authors suggest that higher dietary intake of vitamins C and E is thought to have made an impact on slowing telomere loss due to protection against free radicals, which cause oxidative stress.

Telomere biology is an active area of research among scientists who are seeking to understand more about the aging process and how to improve the quality of life for older adults.

Vitamin D and Preservation of Telomere length

Vitamin D has long been linked with calcium for developing strong bones; however, researchers from the London School of Medicine (4) suggest that vitamin D may also affect every cell in the body and support telomere length. Coming to the forefront in preventative nutrition, vitamin D has been shown to mediate the immune system and possibly reduce inflammation, the authors report (5-7). "The inhibitory effect of vitamin D on the inflammatory response also points to a potential link between this vitamin and telomere dynamics in leukocytes," they suggest.

The researchers explained that leukocyte telomere length (LTL) is a multifactorial marker of cellular aging. Affected by habits and conditions ranging from smoking to obesity, the authors state that LTL may also reflect chronic stress and inflammation.

Results from this study showed both LTL and vitamin D concentrations decrease with age when markers of inflammation increase (see Figure 4).

The researchers analyzed C-Reactive Protein (CRP), a marker of inflammation, LTL and Vitamin D concentrations in 2,160 women. The average woman was 49 years of age, ranging from 18 to 80 years of age. After adjusting for age, season, life-stage, use of hormone replacement therapies and physical activity level, the researchers found that the women who supplemented with Vitamin D had longer telomeres.

The authors suggest that while some lifestyle factors affecting LTL may be difficult to change, "vitamin D concentrations are easily modifiable through nutritional supplementation or sunshine exposure."

Correlating negatively with CRP and positively with Vitamin D, LTL varied with levels of inflammation. "The present study further supports the concept that LTL may serve as a cumulative index of an individual's lifelong burden of oxidative stress and inflammation," the authors conclude.

Increased Homocysteine Levels Linked to Shorter Telomeres

Researchers from King's College London School of Medicine hypothesized that elevated blood homocysteine, which is a risk factor for cardiovascular disease, may be linked to shorter leukocyte telomere length (LTL) because of

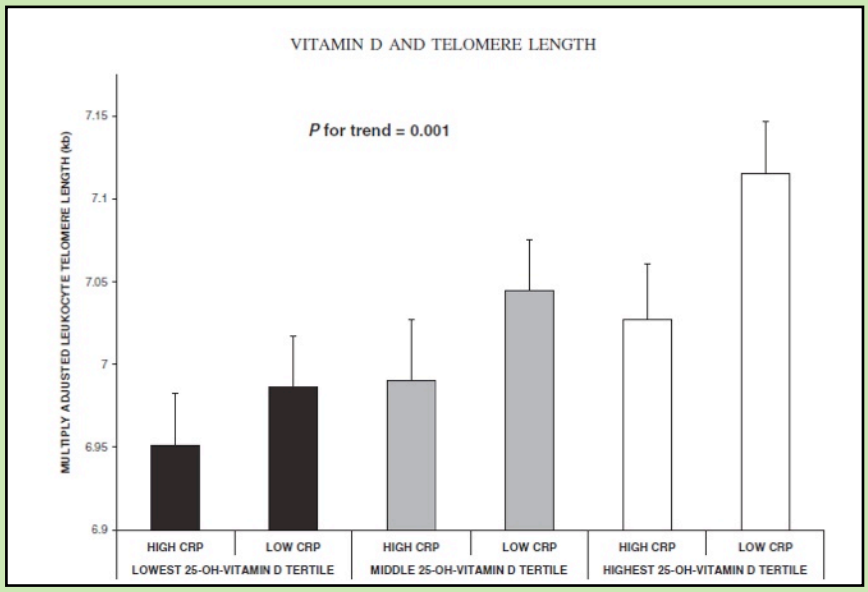


Figure 4. Associations of vitamin D (25-HO-vitamin D) and leukocyte telomere length stratified by C-reactive protein (CRB) concentrations (n=2160). Reference: Richards et al. 2007.

possible increased oxidative stress (8 & 9).

The population-based cohort study (8) included 1,319 people from the UK. The researchers measured the subjects' blood homocysteine, leukocyte telomere length and C-reactive protein (CRP), a marker of inflammation.

The study, published in *Atherosclerosis* in 2008, confirmed that "shortened LTL is independently associated with high plasma homocysteine in a large population of healthy women and men."

B vitamins folate and B12 play a large role in regulating homocysteine levels (as shown in Figure 5). Folate and B12 deficiencies are common cause of high blood homocysteine levels.

The researchers explained that "the common threads that link elevated plasma homocysteine levels with shortened LTL may be oxidative stress and inflammation." Increases in oxidative stress and inflammation may shorten the biological life of white blood cells.

CRP was highest in the subjects with high blood

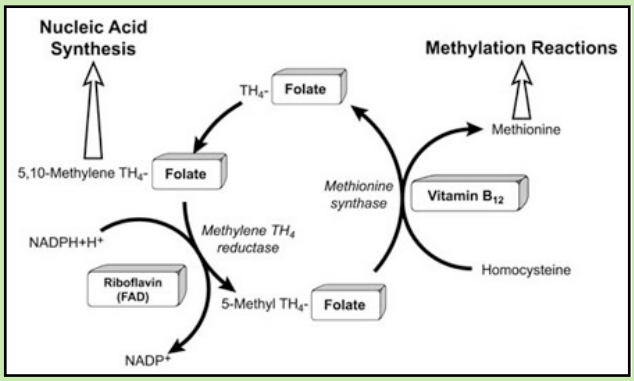


Figure 5. Role of B vitamins and methylation of homocysteine, an inflammatory marker. Reference: Linus Pauling Institute.

homocysteine and negatively associated with LTL. This relationship "between LTL and homocysteine by CRP further supports the role of homocysteine-mediated inflammation in leukocyte telomere dynamics" noted the researchers.

"By reducing homocysteine levels, folate supplementation may attenuate telomere attrition" the researchers propose.

References

1. Xu Q et al. Multivitamin use and telomere length in women. *Am J Clin Nutr* 2009;89:1857-63.
2. Houben JMJ et al. Telomere length assessment: biomarker of chronic oxidative stress? *Free Radic Biol Med* 2008;44:235–46.
3. Furumoto K et al. Age-dependent telomere shortening is slowed down by enrichment of intracellular vitamin C via suppression of oxidative stress. *Life Sci* 1998;63:935–48.
4. Richards JB et al. Higher serum vitamin D concentrations are associated with longer leukocyte telomere length in women. *Am J Clin Nutr* 2007; 86: 1420-5.
5. Provvedini DM et al. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. *Science* 1983;221:1181-2.
6. D'Ambrosio D et al. Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3 in normal human peripheral blood lymphocytes. *J Clin Invest* 1987;79:1700-5.
7. Manolagas et al. Interactions of 1,25-dihydroxyvitamin D3 and the immune system. *Mol Cell Endocrinol* 1985;43:113-22.
8. Richards JB et al. Homocysteine levels and leukocyte telomere length. *Atherosclerosis* 2008; 200: 271-77.
9. Milani RV et al. Homocysteine: The Rubik's Cube of Cardiovascular Risk Factors. *Mayo Clin Proc* 2008; 83(11): 1200-02.

DEPRESSION LINKED TO SHORTER TELOMERES

People who suffer from major depression have a higher risk of age-related illness and earlier mortality (1 &2). Researchers from University of California, San Francisco (UCSF), investigated (1) telomere length in depressed individuals versus matched controls and assessed other biological factors associated with telomere shortening.

Led by Nobel laureate Elizabeth Blackburn, Ph.D., the team of researchers published their findings in the March issue of *PLos One.* Their hypothesis was that not all depressed subjects would show shortened telomeres equally because of a large variance in depressive episodes over a lifetime. However, they predicted that those who suffered from depression for long durations would have shorter telomeres due to longer exposure to oxidative stress and inflammation induced by psychological stress.

The scientists recruited 18 subjects diagnosed with Major Depressive Disorder (MDD), excluding those with psychosis or bipolar histories, as well as those with Post-Traumatic Stress Disorder to eliminate confounding variables due to interferences with stress hormone regulation. Results from depressed individuals were compared to those of the matched control group.

Blood samples were taken to measure leukocyte (white blood cell) telomere length, as well as oxidative stress markers (F2-isoprostanes and vitamin C) and inflammation (IL-6).

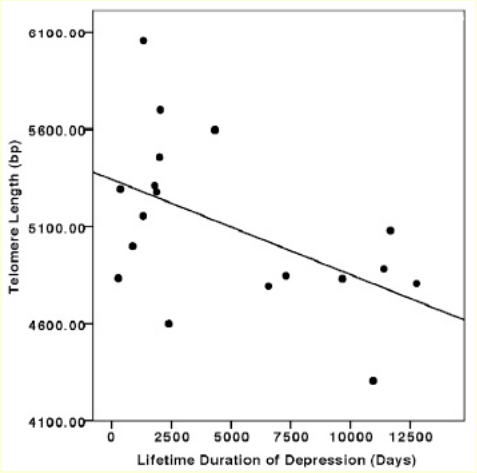


Figure 6. Relationship between cumulative lifetime duration of depression and leukocyte telomere length (in base pairs, bp). Reference: Wolkowitz et al. 2011 March.

The severity of MDD was determined using the standard Hamilton Depression Rating Scale and total lifetime duration of depression was estimated using a life history method interview. The history-taking and telomere assays were performed blind to each other.

The average age (ranging 36 to 47 years) of the depressed and control subjects in the study didn't differ significantly, nor did the sex of the subjects, ethnicity distribution, or body mass index. The subjects also did not differ significantly in current or past consumption of alcohol or nicotine, marital status, or highest educational level or socioeconomic status.

The authors reported that, across the broad range of chronic depression types, the "depressed individuals did not significantly differ from controls in leukocyte telomere lengths. However, those individuals with longer courses of major depression had significantly shorter leukocyte telomeres than controls.

Additionally, regardless of depressed status, plasma vitamin C concentrations were significantly correlated with telomere length as was F2-isoprostane levels (a marker of oxidative stress).

"Importantly, the relationship between telomere length and lifetime duration of depression was significant after age was controlled, the authors wrote.

The researchers concluded that, since telomere length is a proposed biomarker of cell aging, their findings could explain why chronically depressed individuals are at higher risk of disease and mortality.

References

1. Wolkowitz et al. Leukocyte Telomere Length in Major Depression: Correlations with Chronicity, Inflammation and Oxidative Stress - Preliminary Findings. *PLos One*. 2011 March:6(3):e17837.
2. Brown et al. Association of depression and medical illness: Does cortisol play a role? *Biol Psychiatry* 55:1-9.

EXERCISE PROTECTS AGAINST STRESS-INDUCED TELOMERE SHORTENING

Stress is a well-known factor that can negatively affect health and studies are suggesting that chronic psychological stress can adversely affect telomere length. However, exercise may serve as an effective buffer against psychological stress.

According to a recent study (1) published in *PLoS One*, at least 14 minutes daily of vigorous exercise protected older women from the effects of high amounts of perceived stress. Conversely, women with high stress who do not engage in any exercise have shorter telomeres.

Similar results were found in another study (2) published in the *Archives of Internal Medicine* in 2008. Researchers discovered that participants who engaged in physical activity had increased telomere length compared to those who led sedentary lifestyles (see Figure 7). The subjects who participated in physical activity averaging approximately 200 minutes per week had telomere length that was 200 nucleotides longer than those who engaged in minimal exercise (less than 16 minutes per week). This increase in length corresponded to a *biological age* of approximately ten years, further confirming the protective role of exercise on cellular aging.

These findings further illuminate the many benefits exercise can have on our health. Leading a sedentary lifestyle can accelerate the progression of many age-related diseases by negatively affecting telomere length, especially in the presence of stress. Participating in regular physical activity can slow this progression by protecting our telomeres and promoting healthy aging.

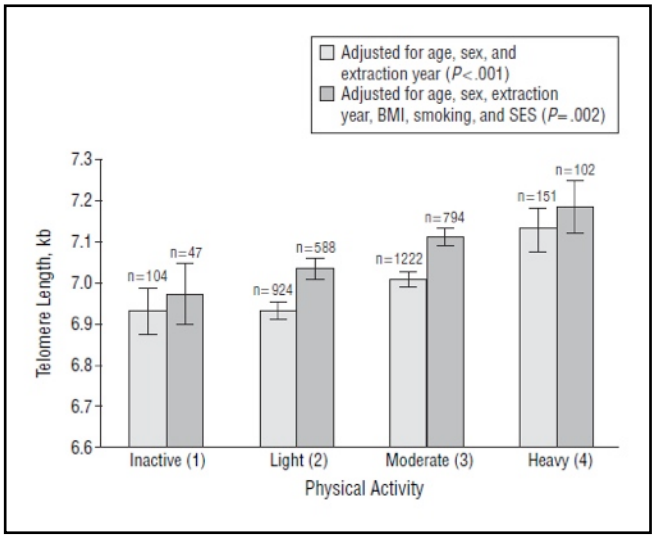


Figure 7. Mean telomere length and standard error bars by physical activity and leisure time. Reference: Cherkas et al. 2008.

References

1. Puterman E et al. The power of exercise: buffering the effect of chronic stress on telomere length. *PLos One*. 2010 May 26;5 (5):e10837.
2. Cherkas L et al. The Association Between Physical Activity in Leisure Time and Leukocyte Telomere Length. *Arch Intern Med.* 2008;168(2): 154-158.

MEDITATION: DE-STRESS TO DEFY AGING

A little bit of stress is important to keep you awake, active, and motivated. However, when we experience chronic periods of intense stress, our bodies, including our telomeres, begin to feel the burden. Telomerase, the enzyme primarily involved in elongation and maintenance of chromosomal telomeres, can be increased with extensive meditation, researchers from UC Davis report.

The study showed that positive changes in psychological well-being through mindful meditation contribute to increases in telomerase activity. Mindfulness, a Buddhist concept that emphasizes conscious and compassionate observance and attentiveness, was measured following a period of prolonged meditation.

Sixty men and women with a history of meditative experience were assigned to either a retreat group or the wait-list control group. The groups were randomized by age, gender and years practicing meditation. The retreat group underwent three months of instruction and meditative practice 6 hours per day with the intention of cultivating a more benevolent state of mind.

In addition to *mindfulness*, the researchers measured established *purpose in life, perceived control*, and *perceived negativity*. "Here," the researchers explained, "we consider the possibility that enhanced purpose in life is one of the mediators of the relation between meditation practice and perceived control and negative affectivity and telomerase activity."

Reference: Jacobs TL et al. Intensive meditation training, immune cell telomerase activity, and psychological mediators. *Psychoneuroendocrinology*. 2010.

GREEN TEA PROTECTS TELOMERES FROM OXIDATIVE STRESS

Drinking more than 3 cups of green tea daily is associated with longer telomere length in elderly chinese men, according to researchers from the Centre for Nutritional Studies, Chinese University of Hong Kong.

Supported by a grant from the National Institute of Health, USA, the scientists examined the association of food groups and telomere length in 2,006 elderly Chinese (976 men and 1030 women). They found that in men, only tea consumption was significantly associated with telomere length after adjustment for demographics and lifestyle factors.

The study was published in 2010 in the *British Journal of Nutrition.*

The men with the highest tea consumption -- more than three cups or 750 ml per day -- had a telomere length that corresponded to a difference of five years of life.

In the women, the intake of dietary fats was borderline and negatively associated with telomere length after adjustment for demographic and lifestyle factors.

The researchers suggested that the antioxidant properties of tea and its constituent nutrients may help protect telomeres from oxidative stress during the normal aging process. They note that prior work has found an association of processed meat and shorter telomeres reasoned to be due to higher amounts of oxidative stress.

The next year, in 2010, another study (2) from Hong Kong Polytechnic University supported the antioxidant protection hypothesis through controlled trial of supplementation in humans.

The study's authors state that the "genoprotective effects of green tea lend support to its use as a functional food and provide scientific evidence for the more confident recommendation of regular intake of green tea for health promotion."

The researchers collected blood samples and tested cells before and after supplementation when exposed to hydrogen peroxide. Tea drinkers had a 30 to 35 percent decrease in DNA oxidation.

Green tea's protective effects are thought to be dependent on its content of antioxidant polyphenols, which include its main polyphenol, epigallocatechin gallate (EGCG).

Numerous studies in animals and humans have linked EGCG to positive health outcomes including better weight management, cellular health, heart health, and even longer life.

References

1. Chan R et al. Chinese tea consumption is associated with longer telomere length in elderly Chinese men. *Br J Nutr* 103(1): 107-13. Epub 2009 Aug 12.

2. Han KC et al. Genoprotective effects of green tea (*Camellia sinensis*) in human subjects: results of a controlled supplementation trial. *Br J Nutr*. 2010 Sep 1:1-8.

OMEGA-3 FATTY ACIDS AND TELOMERES

Higher levels of omega-3 fatty acids helps to preserve telomere length in patients with Coronary Heart Disease, UCSF researchers report (1).

A study published in the January issue of *JAMA* last year showed that leukocyte telomere length (LTL) was positively associated with higher blood levels of omega-3 fatty acids (shown in Figure 8).

The researchers report that "omega-3 fatty acids may protect against cellular aging in patients with coronary heart disease."

This longitudinal study followed 608 patients with stable coronary artery disease for five years. LTL was measured at baseline and again five years later. The baseline levels of omega-3 fatty acids were then used to compare the rates of telomere attrition over the five-year period.

The authors suggest that the "association of omega-3 fatty acids with decelerated telomere attrition may lie in the paradigm of oxidative stress, a powerful driver of telomere shortening."

Omega-3 fatty acids have been shown to increase levels of catalase and superoxide dismutase (enzymes that serve important antioxidant roles in the body).

The researchers hypothesize that omega-3s may increase the activity of telomerase, the enzyme responsible for the addition of base pairs to DNA during replication.

Citing other work, the authors write that "the adoption of comprehensive lifestyle changes, which included daily supplementation with omega-3 fish oil, was associated with a significant increase in telomerase activity."

Higher levels of omega-3 fatty acids have been associated with more favorable outcomes for cardiovascular health, brain health, and vision health (2). Their role in preservation of telomeres appears as an added benefit for their inclusion in a healthy diet.

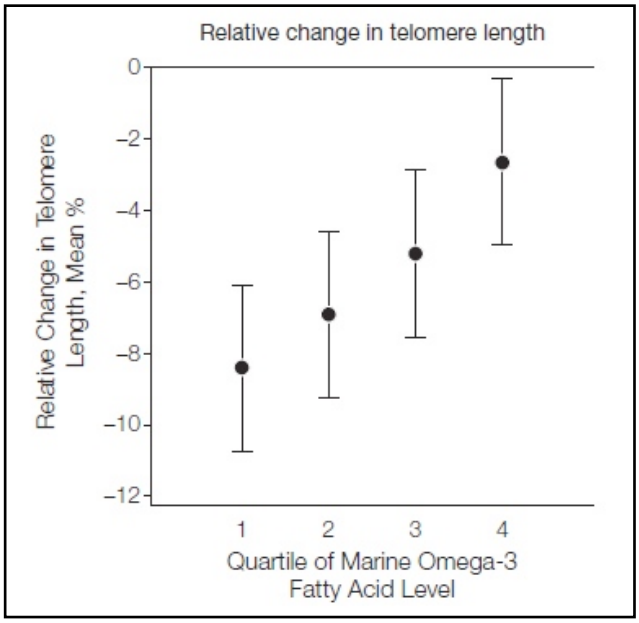


Figure 8. Relative mean changes in telomere length over five years by quartile of omega-3 fatty acid level, adjusted for age and baseline telomere length. Reference: Farzaneh-Far et al. 2010.

Editorial

Managing Editor

David Despain, MS
Sr. Mgr. of Science Communications

Contributions and Copyediting

Suk Cho, PhD
Chief Science Officer

Pierre Teissier, PhD
VP of Global Product Development

Susie Rockway, PhD
Director of Research and Science

Dalia Blunt, MS

Amanda Jensen

Leigh Flynn

www.isagenixhealth.net

References

1. Farzaneh-Far R et al. Associations of Marine Omega-3 Fatty Acid Levels with Telomeric Aging in Patients with Coronary Heart Disease. *JAMA* 2010; 303(3):250-7.
2. Lee JH et al. Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc*. 2008;83(3): 324-332.