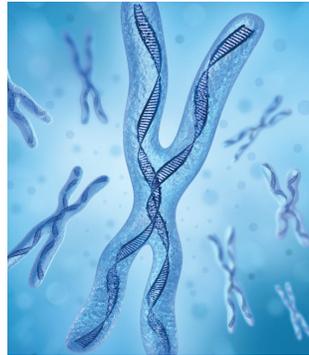
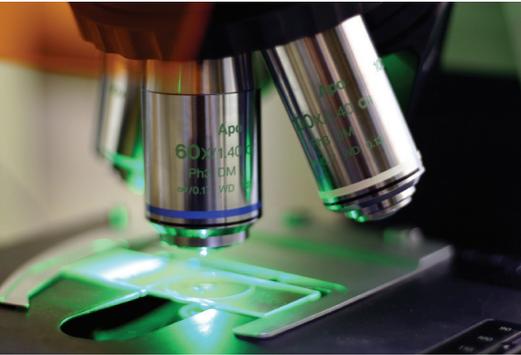


Telomere Testing



Clinical Applications

“Telomeres are special functional complexes, located at the ends of chromosomes, that are involved in maintaining genetic stability and in regulation of cellular life span. Telomere homeostasis is relevant to normal aging and a wide range of disease states, including cancers, cardiovascular diseases and age-related disorders. As somatic cells proliferate, telomeres progressively shorten and the measurement of telomere length has emerged as an important determinant of replicative senescence and cell fate-an important indicator of the aging process. For the first time, we have the ability to measure human biological age accurately, follow the progression and actually intervene with various treatments that may slow the aging process in humans.”

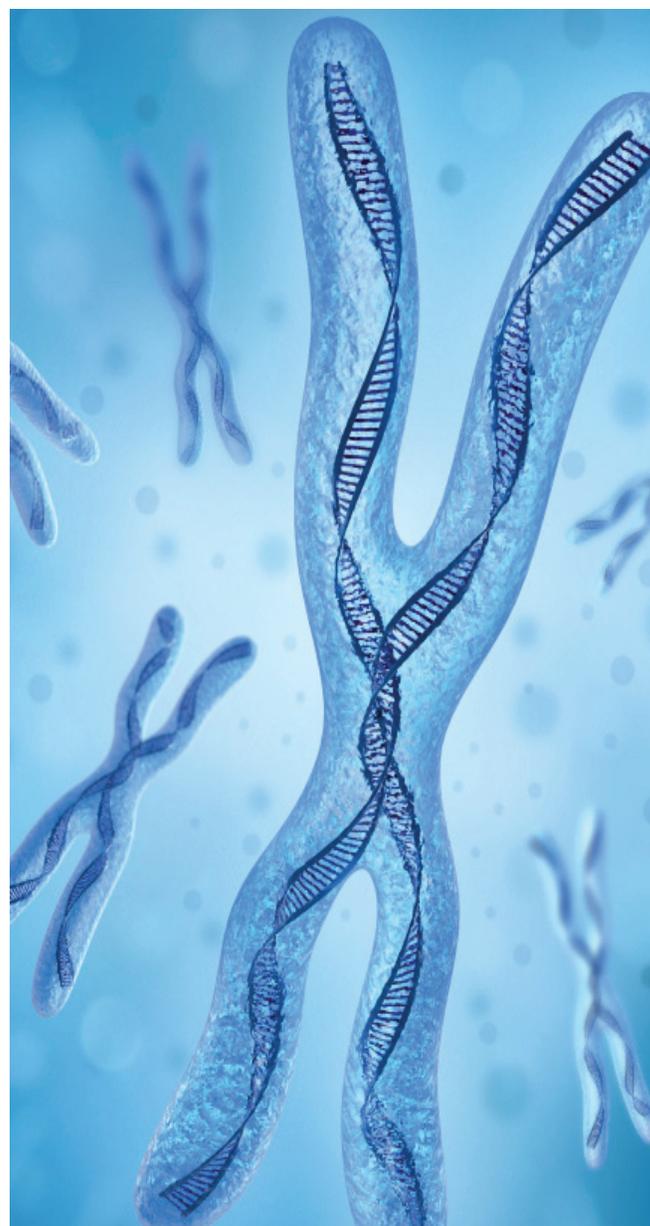
- **Mark Houston, MD, MS, FACP, FAHA**
Associate Clinical Professor of Medicine
Vanderbilt University School of Medicine
Director, Hypertension Institute
Saint Thomas Hospital

Established in 1993, SpectraCell Laboratories, Inc. has been a pioneer in the field of laboratory functional testing for micronutrients. Unlike traditional serum testing, SpectraCell's patented, ground breaking technology, micronutrient testing, offers the practitioner a true window to intracellular function with a long-term analysis of nutrient status. By supporting the practitioner in identifying

subclinical nutritional deficiencies, micronutrient testing aids the development of optimal interventions to assist patients in their quest for lasting health. As medicine progresses in the pursuit of health and wellness, patient care is taking on a broader and deeper perspective. With that in mind, SpectraCell has introduced the ONLY commercially available telomere analysis in the United States.

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Telomere Testing

from SpectraCell Laboratories

TELOMERE MEASUREMENT

An individual's chronological and cellular age may be different, and SpectraCell's Telomere Test can measure and quantify this difference. Age adjusted telomere length is the best method to date to assess biological age using structural analysis of chromosomal change in the telomere.

Just as serial evaluation of other diagnostic tests tends to be more relevant than any one test result, serial evaluation of telomere length is an indicator of how rapidly one ages relative to a normal population. Increases in telomere loss may point to an increase in immunoproliferation, inability to handle oxidative stresses, or progression of chronic disease and metabolic abnormalities. SpectraCell recommends testing to be done once per year to evaluate the rate of aging.

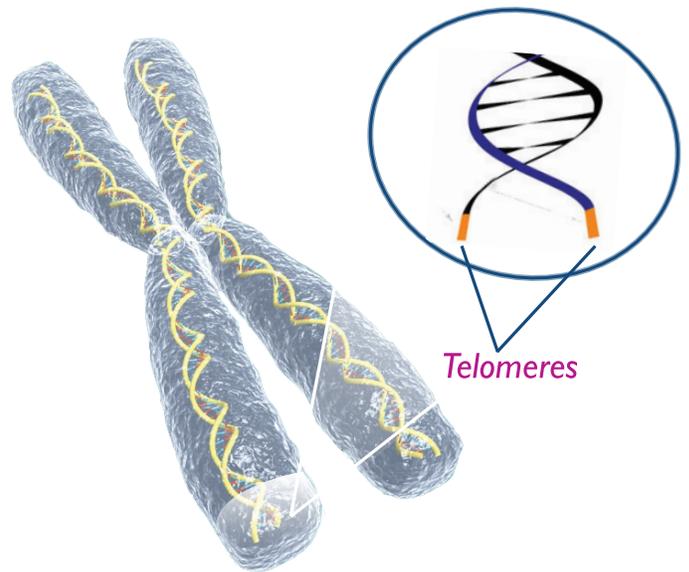
Several therapies such as those listed below which slow the loss of telomere length may slow aging and age-related diseases. Knowing the rate of telomere loss allows a patient and clinician to work together to make adjustments in nutrition and other lifestyle modifications known to influence telomere length.

CORRECT MICRONUTRIENT DEFICIENCIES

Micronutrient status has direct implications on telomere length. A single micronutrient deficiency can profoundly affect the rate of telomere shortening:

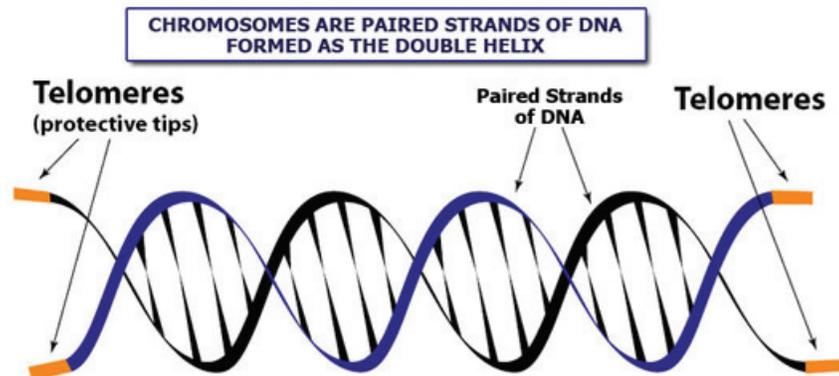
- **Copper** – Copper is a known cofactor to the powerful antioxidant superoxide dismutase, which affects a cell's potential to resist oxidative stress, one of the major causes of telomere attenuation.^{1,2}
- **Folate** – Folate affects the integrity of DNA by providing precursors to nucleotide synthesis via methylation pathways. Research has shown a positive association between folate status and telomere length.³
- **Glutathione** – This antioxidant plays a key role in preserving telomere function in endothelial cells by regulating intracellular oxidation homeostasis.⁴
- **Magnesium** – Researchers measured a decrease in telomere length in magnesium deficient rat liver cells, when compared to a control group with no induced magnesium deficiency.⁵
- **Selenium** – Its antioxidant properties ultimately affects a cell's ability to resist oxidative stress. At least one experiment has shown that the administration of selenium in vivo significantly extended the telomere length of liver cells.⁶
- **Zinc** – When the relationship between telomere shortening and zinc status was investigated, researchers found that impaired zinc homeostasis, which is linked to an increase in inflammatory markers, was associated with critical shortening of telomeres.⁷
- **B Vitamins** – Increased homocysteine levels are associated with shortened telomeres.^{8,9} Deficiencies in vitamins B6, B12 or folate can impair homocysteine metabolism, raising its level in blood and linking it with accelerated telomere loss. Administration of vitamin B3 to human fibroblasts decreases the rate of telomere shortening, extending their lifespan.¹⁰
- **Vitamin C** – Administration of vitamin C to human epithelial cells mitigates telomere loss via reduction of reactive oxygen species.^{11,12}
- **Vitamin D** – A potent inhibitor of the proinflammatory response, higher vitamin D concentrations have been associated with longer telomere length in leukocytes.¹³
- **Vitamin E** – Repression of age-dependent telomere shortening has been demonstrated with vitamin E administration, especially when combined with vitamin C.¹⁴

The synergistic effect of micronutrients on the various systems of the body creates a complex web of metabolic pathways that can be profoundly affected by a single nutrient deficiency. This makes it especially important to correct specific deficiencies and maintain nutritional balance. Measuring total antioxidant capacity (SPECTROX™) is equally important as the body's ability to handle oxidative stress contributes significantly to telomere length.



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REDUCE OXIDATIVE STRESS

Oxidative stress shortens telomeres by inducing single-stranded damage in telomeric DNA. Unlike other genes, such chromosomal damage is not repaired in telomeric DNA, and consequently ages the cell.¹⁵ Overwhelming evidence links oxidative stress with reduced telomere length, and consequently accelerated cellular aging. Since the etiology of oxidative stress is so complex, measuring the body's ability to resist oxidative damage is key. Antioxidant supplements can potentially reduce oxidative stress very effectively, which will ultimately improve oxidative defenses, mitochondrial function, reduce inflammation and slow vascular aging. However, targeted supplementation is necessary, as antioxidants work synergistically and must be balanced to work most effectively and avoid inducing a pro-oxidant effect. Increasing antioxidant capacity at the cellular level is critical to maintaining telomere length. Reducing oxidative stress is a multi-faceted issue:

- **Diet** – An inflammatory diet, or one that increases oxidative stress, will shorten telomeres faster. This includes refined carbohydrates, fast foods, processed foods, sodas, artificial sweeteners, trans fats and saturated fats. A diet with a large amount and variety of antioxidants that improves oxidative defense will slow telomere shortening. Consumption of 10 servings of fresh and relatively uncooked fruits and vegetables, mixed fiber, monounsaturated fats, omega-3 fatty acids, cold water fish and high quality vegetable proteins will help preserve telomere length.
- **Minimize Emotional Stress** – Studies have linked psychological distress to reduced telomerase activity in immune cells.¹⁶ In fact, exposure of lymphocytes to cortisol from emotional distress has been directly associated with telomere attrition.¹⁷
- **Minimize Physiological Stress** – Chronic infections will induce oxidative stress and ultimately shorten telomeres. Anything that makes your cells divide (infection, inflammation, routine division for replacement due to oxidative damage or wound healing) will decrease their telomere length.
- **Increase Antioxidant Defenses** – Powerful antioxidants such as glutathione, resveratrol and superoxide dismutase function to slow telomere

shortening at the cellular level.² Proper function and balance of various antioxidants in the body is critical for telomere health.

- **Reduce Inflammation** – Chronic oxidative stress plays a major role in the pathophysiology of several chronic inflammatory and autoimmune diseases. In fact, research links telomere attrition to inflammatory markers such as hs-CRP and interleukin.^{6,34} Inflammation promotes an increase in white blood cell turnover, which also enhances telomere attrition.¹⁸
- **Caloric Restriction** – The normal metabolic process of digesting food is a significant generator of oxidative stress. Not only will excess caloric intake lead to overweight, but it creates additional oxidative stress during digestion, especially of inflammatory foods.

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REDUCE CARDIOVASCULAR RISK FACTORS

The link between accelerated telomere shortening and cardiovascular disease is well established. Individuals with shorter white blood cell telomeres have greater than 3-fold higher mortality rate for heart disease,¹⁹ and telomeres are shorter in patients with atherosclerosis.²⁰ Reducing CVD risk factors is imperative to maintaining telomere integrity:

- **Blood Pressure** – Hypertension is linked with shorter telomeres, possibly due the endothelial dysfunction and oxidative stress in vascular tissue that occurs commonly with high blood pressure.^{21,22}
- **Carotid Intima Thickness** – Shortened telomere length is a powerful marker of increased carotid intimal medial thickness in obese men.²⁰
- **Endothelial Dysfunction** – Aging in vascular endothelial cells is induced by telomere shortening and contributes to atherogenesis.²³
- **Homocysteine** – A recent study that measured telomere length in over 1300 people found that, after adjusting for several other cardiovascular risk factors, people with the highest levels of homocysteine had on average 111 less base pairs in their telomeric DNA, corresponding to six years of telomeric aging.⁸ Similarly, studies demonstrate that the telomere length of lymphocytes is adversely affected by homocysteine levels.⁹
- **Hs-C Reactive Protein** – High levels of hs-CRP, a diagnostic marker for systemic inflammation, have been specifically linked with shorter telomeres.³⁴
- **HDL Levels** – Slower rates of telomere shortening is associated with higher HDL cholesterol.²⁴
- **LDL Levels** – Increases in telomerase activity are associated with decreases in LDL cholesterol.¹⁶
- **Vascular Dementia** – Telomere length may be an independent predictor for the risk of vascular dementia.²⁵ Specifically in lymphocytes, there is a strong correlation between short telomeres and the incidence of vascular dementia.²⁶

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INCREASE PHYSICAL ACTIVITY

Although the mechanism is not totally clear, very strong evidence links longer telomeres with people who exercise regularly (at least 30 minutes daily). The converse is also true; a sedentary lifestyle is linked to shorter telomeres and higher risk for age-related diseases. Although exercise itself can cause oxidative stress, research shows that moderate exercise training will increase the activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase to compensate for the physical activity, and this ultimately protects telomeres.²⁷

Interestingly, when the telomeres of identical twins that had different levels of physical activity were measured, the telomeres of the active twin were longer, by about 88 nucleotide pairs. Even after adjusting for age, BMI and smoking, a difference of about 200 nucleotide pairs was seen in people who regularly exercised and those who did not. This difference suggests that inactive subjects may be biologically older by 10 years compared with more active subjects.²⁸

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MAINTAIN HEALTHY WEIGHT

Overwhelming evidence suggests that obesity accelerates aging. Weight gain is associated with accelerated telomere loss,¹⁸ and body mass index (BMI) and hip circumference are inversely associated with telomere length.²⁹

Decreasing visceral fat is very important. Although obese adults have shorter telomeres than their normal-weight counterparts, this phenomenon is not present in childhood.³⁰

One should achieve ideal body weight and body composition with low body fat (less than 22% for women and less than 16% for men). Obesity is also associated with increased inflammation because fat tissue is a major source of inflammatory cytokines.¹⁸ Since body fat reflects both caloric consumption as well as energy expenditure, which are both directly linked to telomere length, maintaining ideal weight is a fundamental and necessary remedy to reduce telomere attrition.

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CORRECT INSULIN RESISTANCE

Obesity often coincides with metabolic abnormalities, including insulin resistance and glucose dysregulation, both of which are linked to telomere length. Research demonstrates that a rise in insulin resistance, which is associated with heightened oxidative stress, accelerates telomere attrition. In fact, when a group of patients were studied for over a decade, a strong relationship between insulin resistance and telomere shortening was demonstrated, especially when it coincided with a gain in body mass index.¹⁸ Similarly, research has demonstrated short telomeres to be independent predictors of certain diabetic complications, such as kidney disease.³¹

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IMMUNITY AND TELOMERES

The immune system is highly sensitive to shortening of telomeres since its effectiveness depends on immune cells', specifically white blood cells, ability to proliferate during times of immunological stress. Although cells of the immune system are unique in that they can up-regulate telomerase unlike other somatic cells, when telomeres of lymphocytes reach a critical minimum length, the ability to activate telomerase in lymphocytes is diminished and adaptive immunity becomes compromised.³² Less effective immune response means more infections and less defenses against cellular stresses, which then increases oxidative stress and inflammation, ultimately contributing to even more telomere attrition. Individuals with shorter white blood cell telomeres have an 8-fold higher mortality rate for infectious disease.¹⁹

The expansion of lymphocytes when confronted with an antigen results in major cell proliferation. Each immune response typically results in 15-20 cell divisions. Once these cells eliminate the antigen, they will usually undergo apoptosis although a few will remain which gives a person life-long immunity to various pathogens. Research has shown that the telomeres of these lymphocytes which have undergone major cell division, but still remain as memory cells do, in fact, have shorter telomeres. Since the immune system depends on the ability of lymphocytes to undergo cell division in response to antigens, telomere shortening can severely limit a person's immunological defenses.³³

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Clinical Update

Vitamin D May Slow Aging

Evidence links vitamin D levels to telomere length

(American Journal of Clinical Nutrition, November 2007)

Vitamin D, produced naturally by the body through exposure to sunlight, may help slow the aging of cells and tissues, say researchers at King's College London. Researchers measured telomeres in women and found that women with higher levels of vitamin D had longer telomeres. They studied 2,160 women, ages 18 to 79 and measured leukocyte telomere length (LTL). LTL is a predictor of ageing-related disease and decreases with each cell cycle and increased inflammation, the scientists said.

However, the study -- published in the American Journal of Clinical Nutrition -- did not prove a direct cause and effect between vitamin D levels and aging.

"These results are exciting because they demonstrate for the first time that people who have higher levels of vitamin D may age more slowly than people with lower levels of vitamin D," said study leader Professor Brent Richards.

"This could help to explain how vitamin D has a protective effect on many aging-related diseases, such as heart disease and cancer," Richards said.

The scientific community has already called for an increase in the recommended level of vitamin D intake.

Currently, the recommended daily intake is set at 400 IU, and the tolerable upper intake level (UL) in Europe and the US is set at 2000 International Units (IU), equivalent to 50 micrograms per day. Research, particularly from clinical trials, suggests that this should be raised.

A recent risk assessment by the US-based trade organization, the Council for Responsible Nutrition (CRN) concluded that the UL could be raised to 10,000 IU (250 micrograms per day).

Vitamin D refers to two biologically inactive precursors - D3, also known as cholecalciferol, and D2, also known as ergocalciferol. The former, produced in the skin on exposure to UVB radiation, is said to be more bioactive. The latter is derived from plants and only enters the body via the diet.

Both D3 and D2 precursors are hydroxylated in the liver and kidneys to form 25- hydroxyvitamin D, the non-active 'storage' form, and 1,25-dihydroxyvitamin D, the biologically active form that is tightly controlled by the body.

Clinical Update

Multivitamins linked to younger 'biological age': Study

The cells of multivitamin users may have a younger biological age than cells from non-users, according to new research from the US.

(American Journal of Clinical Nutrition, June 2009)

Researchers led by Honglei Chen, MD, PhD from National Institute of Environmental Health Sciences looked at the length of telomeres, DNA sequences at the end of chromosomes that shorten as cells replicate and age.

The ageing and lifespan of normal, healthy cells are linked to the so-called telomerase shortening mechanism, which limits cells to a fixed number of divisions. During cell replication, the telomeres function by ensuring the cell's chromosomes do not fuse with each other or rearrange, which can lead to cancer. Elizabeth Blackburn, a telomere pioneer at the University of California San Francisco, likened telomeres to the ends of shoelaces, without which the lace would unravel.

With each replication the telomeres shorten, and when the telomeres are totally consumed, the cells are destroyed (apoptosis). Previous studies have also reported that telomeres are highly susceptible to oxidative stress.

Dr Chen and his co-workers noted that telomere length may therefore be a marker of biological ageing, and that multivitamins may beneficially affect telomere length via modulation of oxidative stress and chronic inflammation. According to results published in the new issue of the American Journal of Clinical Nutrition, the telomeres of daily multivitamin users may be on average 5.1% longer than in non-users.

According to a National Institutes of Health (NIH) State-of-the-Science Panel, half of the American population routinely use dietary supplements, with their annual spend estimated at over \$20 billion. Recent results of the National Health and Nutrition Examination Survey showed that 35% of the US adult population regularly consumes one or more types of multivitamin product (Am. J. Epidemiol., 2004, Vol. 160, Pages 339-349).

New study

Dr Chen and his co-workers analysed multivitamin use and nutrient intakes, as well as telomere length of 586 women aged between 35 and 74 in the Sister Study. A 146-item food-frequency questionnaire was used to determine multivitamin use and nutrient intakes.

Compared to non-multivitamin users, the researchers noted that that telomeres were on average 5.1 per cent longer for daily multivitamin users.

In an attempt to identify specific nutrients that could be behind the observations, a positive relationship between telomere length and intakes of vitamins C and E from foods was observed.

Being the first study to report such an association, Dr Chen and his co-workers emphasized that the evidence is only preliminary and that additional epidemiologic studies are required to further explore the association. The implications of the findings in terms of ageing and the etiology of chronic diseases should be carefully evaluated.

Source: www.nutraingredients.com

