Association of Marine Omega-3 Fatty Acid Levels With Telomeric Aging in Patients With Coronary Heart Disease

Ramin Farzaneh-Far, MD
Jue Lin, PhD
Elissa S. Epel, PhD
William S. Harris, PhD
Elizabeth H. Blackburn, PhD
Mary A. Whooley, MD

Context Increased dietary intake of marine omega-3 fatty acids is associated with prolonged survival in patients with coronary heart disease. However, the mechanisms underlying this protective effect are poorly understood.

Objective To investigate the association of omega-3 fatty acid blood levels with temporal changes in telomere length, an emerging marker of biological age.

Design, Setting, and Participants Prospective cohort study of 608 ambulatory outpatients in California with stable coronary artery disease recruited from the Heart and Soul Study between September 2000 and December 2002 and followed up to January 2009 (median, 6.0 years; range, 5.0-8.1 years).

Main Outcome Measures We measured leukocyte telomere length at baseline and again after 5 years of follow-up. Multivariable linear and logistic regression models were used to investigate the association of baseline levels of omega-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) with subsequent change in telomere length.

Results Individuals in the lowest quartile of DHA+EPA experienced the fastest rate of telomere shortening (0.13 telomere-to-single-copy gene ratio [T/S] units over 5 years; 95% confidence interval [CI], 0.09-0.17), whereas those in the highest quartile experienced the slowest rate of telomere shortening (0.05 T/S units over 5 years; 95% CI, 0.02-0.08; $P<.001$ for linear trend across quartiles). Levels of DHA+EPA were associated with less telomere shortening before (unadjusted β coefficient $\times 10^{-3}=0.06$; 95% CI, 0.02-0.10) and after (adjusted β coefficient $\times 10^{-3}=0.05$; 95% CI, 0.01-0.08) sequential adjustment for established risk factors and potential confounders. Each 1-SD increase in DHA+EPA levels was associated with a 32% reduction in the odds of telomere shortening (adjusted odds ratio, 0.68; 95% CI, 0.47-0.98).

Conclusion Among this cohort of patients with coronary artery disease, there was an inverse relationship between baseline blood levels of marine omega-3 fatty acids and the rate of telomere shortening over 5 years.

JAMA. 2010;303(3):250-257 www.jama.com

Multiple epidemiologic studies, including several large randomized controlled trials, have demonstrated higher survival rates among individuals with high dietary intake of marine omega-3 fatty acids and established cardiovascular disease.[1-4] On this basis, the American Heart Association recommends increased oily fish intake and the use of omega-3 fatty acid supplements for the primary and secondary prevention of coronary heart disease.[5] The mechanisms underlying this protective effect are poorly understood but are thought to include anti-inflammatory, antiplatelet, antihypertensive, antiarrhythmic, and triglyceride-lowering effects.[6] There is ongoing interest in the identification of novel mechanisms of cardiovascular benefit from omega-3 fatty acids.

Telomeres are tandem repeat DNA sequences $(TTAGGG)_n$ that form a protective cap at the ends of eukaryotic chromosomes.[7] During somatic cell division, DNA polymerase cannot fully replicate the 3′ end of linear DNA, resulting in an obligate and progressive loss of telomeric repeats. This process may eventually result in cellular senescence or apoptosis.[8] These observations have led to telomere length emerging as a novel marker of biological age, which integrates the cumulative lifetime burden of genetic factors and environmental stressors independent of chronological age.[9] Moreover, a robust association between short telo-

Author Affiliations: Division of Cardiology, San Francisco General Hospital (Dr Farzaneh-Far), Departments of Medicine (Drs Farzaneh-Far and Whooley), Biochemistry and Biophysics (Drs Lin and Blackburn), Psychiatry (Dr Epel), and Epidemiology and Biostatistics (Dr Whooley), University of California, San Francisco, and Veterans Affairs Medical Center (Dr Whooley), San Francisco; and Sanford Research/USD and Sanford School of Medicine, University of South Dakota, Sioux Falls (Dr Harris).
Corresponding Author: Ramin Farzaneh-Far, MD, Division of Cardiology, Room 5G1, San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94110 (rfarzanehfar@medicine.ucsf.edu).