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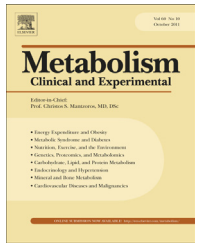

Review

Nutrients, foods, dietary patterns and telomere length: Update of epidemiological studies and randomized trials☆

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ABSTRACT

Identifying simple strategies to prevent or delay age-associated pathologies is a major public health concern. Attrition of telomeres, chromatin structures that help maintain genome stability, leads to cell death or senescence. Thus telomere length is a reliable hallmark of biological aging and the risk of developing age-related chronic diseases through common oxidation and inflammation mechanisms. Variability in telomere shortening that is independent of chronological age suggests that it is a modifiable factor, which may be explained in part by lifestyle variables such as smoking, adiposity, physical exercise, and diet. Here we summarize data from published studies focused on nutrition (nutrients, foods, and dietary patterns) and telomere length. Research on the topic is incipient and most data comes from epidemiologic studies, often cross-sectional in design. Consistent with well-known evidence of benefit or harm for chronic age-related diseases, dietary antioxidants and consumption of antioxidant-rich, plant-derived foods help maintain telomere length. In contrast, total and saturated fat intake and consumption of refined flour cereals, meat and meat products, and sugar-sweetened beverages relate to shorter telomeres. Data on alcohol and dairy products is controversial. There is evidence that adherence to the Mediterranean diet is associated with longer telomeres. Randomized clinical trials are limited to seafood-derived long-chain n-3 polyunsaturated fatty acids, with promising results. To fill the many gaps in our knowledge of the aging process and confirm nutrition as a useful tool to counteract biological aging more research is warranted, particularly observational studies using repeated measurements of telomere length and randomized trials of foods and dietary patterns with sequential telomere analyses.

Abbreviations: LTL, leukocyte telomere length; NHS, Nurses' Health Study; PUFA, polyunsaturated fatty acids; RCT, randomized clinical trial.

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1. Introduction

The rapid pace of population aging coupled with the raising prevalence of metabolic diseases is expected to increase the rate of age-associated pathologies such as type 2 diabetes, cardiovascular disease and neurodegenerative disorders [1]. Given the social and economic burden of treating such chronic conditions, identifying simple strategies to prevent them or at least delay their onset is a major public health concern [2]. Molecular mechanisms of mammalian aging remain to be elucidated, but there is increasing evidence of interplay between the genetic background, biochemical and metabolic pathways, and lifestyle behaviors. This overall has prompted the search for candidate biomarkers of biological aging, aiming at filling the many gaps in our knowledge of this momentous process and tracking the effects of exogenous interventions intended to slow it. A comprehensive list of hallmarks of biological aging has been proposed, which includes genomic instability, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communications, and telomere attrition [3]. There is growing evidence that lifestyle factors may influence these biomarkers, particularly telomeres [4,5]. This review will focus on diet effects on telomeres, a field of increasing interest in human biology, albeit still in its infancy.

Telomeres are located at the end of chromosomes, contributing to genome stability. They consist of long stretches of TTAGGG-DNA repeats associated with specific proteins. Telomere length is particularly sensitive to cellular replication, since the 5′ end of the lagging strand becomes shorter in each DNA replication (a process termed "end-replication problem"). The enzyme telomerase synthesizes additional telomeric repeats, preventing loss of important genomic information, cellular senescence and apoptosis. The issue of whether telomere length is a cause or a mere consequence of biological aging is a matter of dispute, but there is robust evidence of its role as a primary hallmark of aging [3]. This has paved the way to use telomere length as an outcome in epidemiologic research to investigate both its predictive role in age-related diseases and mortality and whether lifestyle can modulate it beyond the genetic background [6]. Indeed, a substantial variability in the rate of telomere shortening that is independent of chronological age suggests that telomere attrition is likely a modifiable factor [7]. As in most age-related conditions, oxidative stress leading to chronic inflammation is believed to play a major role in aging [8] and, as could be forecasted, in telomere attrition [9].

Given that lifestyle factors noticeably influence the oxidation–inflammation pathway, it comes as no surprise that they might relate to telomere biology [4,5]. Thus, smoking has been associated with shorter telomeres cross-sectionally and with a greater shortening prospectively compared to nonsmokers [4,10–12], although the recent results of a large cohort study nested in the Copenhagen City Heart Study could not relate smoking to 10-year telomere changes [13]. Physical inactivity and obesity are believed to relate to shorter telomeres compared with exercising and lean individuals, respectively, but recent meta-analyses of epidemiological studies on these outcomes show only weak associations, with important study heterogeneity [14,15]. Several studies have focused on nutrition and telomere length usually measured in circulating white blood cells as leukocyte telomere length (LTL). Findings from published epidemiologic studies and randomized clinical trials (RCTs) investigating the relationship between LTL and nutrients, foods, and dietary patterns are the subject of this review. To identify all relevant literature published on the topic, MEDLINE and SCIENCE CITATION INDEX searches were performed, ending September 28, 2015. The keywords used were (LTL OR telomer*) AND (intake OR consum* OR diet* OR nutri*). In addition, references cited in published original and review articles were examined until no further study was identified.

2. Caloric Restriction

There is a large body of evidence from experimental models, mostly rodents and non-human primates, indicating that decreasing energy intake beginning in early life protects from DNA damage through a general slowing of metabolism and mitochondrial activity, resulting in an increased lifespan [16]. Data in humans are lacking, but a recent report of the CALERIE randomized trial, a two-year study conducted in 218 normal-weight and moderately overweight subjects, shows that, compared to subjects eating *ad libitum*, those who decreased by 25% their calorie intake improved cardiometabolic risk factors (blood pressure, cholesterol, and insulin resistance), although primary pre-specified endpoints (resting metabolic rate adjusted for weight change and core temperature) remained unaffected [17].

Notwithstanding the robust link between caloric restriction and biological aging derived from animal models, whether restraining calories modulates telomere length has been barely explored. In this regard, calorie limitation by 40% from the third month of life prevented telomere shortening in different tissues of wild type mice compared to similar animals fed a control diet (not *ad libitum*). This translated into a delayed onset of age-related diseases and death, although not sufficient to significantly increase lifespan compared to control mice [18]. The authors justified the latter finding by the age of the mice (3 months), much younger than mice usually used in calorie restriction studies. There are no clinical trial data on caloric restriction and telomere length; hence we must rely on much less reliable cross-sectional data on energy intake derived from food-frequency questionnaires in epidemiological studies. A cross-sectional analysis of 840 white, black, and Hispanic adults 45 to 84 years old from the Multi-Ethnic Study of Atherosclerosis found no significant association between energy intake and LTL [19]. Similarly, cross-sectional studies conducted in 2884 American women aged 35–50 years from the Nurses' Health Study (NHS) [20], 2006 Chinese individuals >65 years old [21], and 287 Spanish children and adolescents 6 to 18 years old [22] also failed to uncover an association between LTL and energy intake. The detection of a significant association between energy intake and LTL in humans is limited to a longitudinal study conducted in 609 young adults (age 28–32 years) from Israel who provided dietary data at baseline and were followed for a mean of 13 years [23]. The authors found that, in men (particularly in those who never smoked), energy intake