Keywords
Age · Diet · Telomere

Abstract
Background: The goal of this systematic review and meta-analysis is to determine the effect of diet on telomere length.
Methods: We searched the following databases: MEDLINE, Embase, LILACS, CINAHL, ISI Web of Science, and Scopus, as well as the Cochrane Central Register of Controlled Trials and the National Institutes of Health, from inception to December 2016. Articles that assessed effects of diet on telomere length were included. Results: A total of 2,128 studies were identified, 30 were read in full, and 7 were systematically reviewed. Five RCTs were included in the meta-analysis, covering 9 diets; a total of 533 participants were included. Study heterogeneity ($I^2$) was 89%, and differences were not identified regarding average telomere lengths (mean difference 1.06; 95% CI −1.53 to 3.65). Conclusion: The available evidence suggests that there is no effect of diet on telomere length, but the strong heterogeneity in the type and duration of dietary interventions does not allow any final statement on the absence of an effect of diet on telomere length.

Introduction
The accumulation of time-dependent cellular damage is currently considered the main cause of aging [1]. Cellular senescence or the state of irreversible cell cycle arrest [2] induces dramatic changes in cell phenotype, resulting in changes to nuclear structure, gene expression, protein processing and metabolism, and resistance to apoptosis [3]. Senescent cells release bioactive molecules as inflammatory mediators (cytokines and chemokines), proteases, and reactive species [3]. In this environment, the proinflammatory milieu associated with reactive species induces friction in the DNA that occurs randomly in the chromosomes and impacts mostly their more susceptible regions, called telomeres [4].

Shortening of telomeres is a physiological process that occurs with each cell division in somatic cells and varies with age, progressing with the aging process [5]. However, several studies have linked telomere length, and premature or accelerated telomere shortening, with premature aging [6]. In recent years, positive relationships were established between clinically different pathological conditions, modulated by oxidative stress, inflammation, and lifestyle variables [7], and accelerated shortening of telo-
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Among them, we can highlight cancer [8], tobacco use [9], oxidative stress, psychological conditions [10], poor living conditions, diabetes, cardiovascular diseases [11], radiation exposure, and, finally, diet [12].

The association between diet and shortening of telomeres is currently under scrutiny. A number of studies have reported both a decrease and an increase in telomere length process as a result of the diet to which an individual is exposed. Several factors may influence this relationship [13]. Currently, there are a significant number of diets, such as those with calorie restriction; diets rich in fats, carbohydrates, proteins, or modified fibers; micronutrient supplementation; liquid diets; and low-calorie diets [14].

Factors that may explain the association between diet and telomere length include increased oxidative stress and inflammation [15]. Oxidative stress promotes telomere erosion during cell replication, as well as the synthesis of proinflammatory cytokines. The so-called cardioprotective diets (Mediterranean, unsaturated fatty acid supplementation, hypocholesterolemic, and antihypertensive) [16] have constituents that may interfere by blocking or hindering the main stages of cancer development and cardiovascular diseases, including DNA damage repair and blocked telomerase activity. It is likely that blood polyunsaturated fatty acid levels are involved in preventing telomere shortening over time [17].

Accelerated shortening of telomeres can induce a premature phenotype of cellular and systemic aging with concomitant failure of the body. Therefore, telomere length and its shortening may be associated with a lower life expectancy [18]. Diet exposure is considered a complex process inherent to the human condition, in which time is a relevant factor. Diet is believed to be either a protective or a detrimental factor for telomere length, depending on its composition. Thus, this study will systematically review the effect of diet on telomere length.

Methods

This review followed the PRISMA guidelines [19]; its protocol was based on the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015019193).
### Table 1. Characteristics of the studies and diets analyzed

<table>
<thead>
<tr>
<th>Authors [Ref.], year</th>
<th>Design</th>
<th>Country</th>
<th>Fluid</th>
<th>Telomere length assessment method</th>
<th>Control diet</th>
<th>Intervention</th>
<th>Subjects’ Sex/age, years</th>
<th>n</th>
<th>Total, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mason et al. [23], 2013</td>
<td>RCT</td>
<td>USA</td>
<td>Blood</td>
<td>qPCR</td>
<td>Low-weight diet</td>
<td>Subject’s pre-study diet</td>
<td>Female 50–75</td>
<td>321</td>
<td>321</td>
</tr>
<tr>
<td>Marin et al. [22], 2012a</td>
<td>RCT</td>
<td>Spain</td>
<td>Blood</td>
<td>Q-FISH</td>
<td>Saturated fatty acids</td>
<td>Subject’s pre-study diet</td>
<td>Male and female &gt;65</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Marin et al. [22], 2012b</td>
<td>RCT</td>
<td>Spain</td>
<td>Blood</td>
<td>Q-FISH</td>
<td>Mediterranean diet</td>
<td>Subject’s pre-study diet</td>
<td>Male and female &gt;65</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Marin et al. [22], 2012c</td>
<td>RCT</td>
<td>Spain</td>
<td>Blood</td>
<td>Q-FISH</td>
<td>CHO-ALA-PUFA</td>
<td>Subject’s pre-study diet</td>
<td>Male and female &gt;65</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Kiecolt-Glaser et al. [17], 2013a</td>
<td>RCT</td>
<td>USA</td>
<td>Blood</td>
<td>qPCR</td>
<td>Omega-3 supplement</td>
<td>Placebo (1.25 g/day)</td>
<td>Male and female 40–85</td>
<td>106</td>
<td>106</td>
</tr>
<tr>
<td>O’Callaghan et al. [21], 2014a</td>
<td>RCT</td>
<td>Spain</td>
<td>Blood</td>
<td>qPCR</td>
<td>Omega-3 PUFA (EPA)</td>
<td>Omega-3 supplement</td>
<td>Male and female 65–98</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>O’Callaghan et al. [21], 2014b</td>
<td>RCT</td>
<td>Spain</td>
<td>Blood</td>
<td>qPCR</td>
<td>Omega-3 PUFA (DHA)</td>
<td>Omega-3 supplement</td>
<td>Male and female 65–98</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Tosevska et al. [24], 2016</td>
<td>RCT</td>
<td>USA</td>
<td>Blood</td>
<td>qPCR</td>
<td>Hyperproteic, whey-based, supplemented diet</td>
<td>Not navy bean powder</td>
<td>Male and female 47–78</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Borresen et al. [25], 2016a</td>
<td>RCT</td>
<td>USA</td>
<td>Blood</td>
<td>qPCR</td>
<td>Navy bean powder</td>
<td>Rice bran supplemented</td>
<td>Male and female 47–78</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Thomson et al. [26], 2016</td>
<td>RCT</td>
<td>USA</td>
<td>Blood</td>
<td>qPCR</td>
<td>Cruciferous vegetables</td>
<td>Subject’s pre-study diet</td>
<td>Female ≥18</td>
<td>781</td>
<td>781</td>
</tr>
</tbody>
</table>

**qPCR, quantitative polymerase chain reaction; Q-FISH, quantitative fluorescence in situ hybridization; CHO-ALA-PUFA, low-fat and high-carbohydrate diet enriched with n-3 polyunsaturated fatty acids; PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linolenic acid; NS, not stated.**

This review included RCTs that evaluated the effects on telomere length of the following diets: calorie restriction, high-fat diet, Mediterranean diet, micronutrient supplementation, or combinations of different interventions. We included all published studies without restrictions on time, language, and participant race or age.

Excluded were (a) studies that did not evaluate the type of diet in relation to telomeres, (b) duplicate studies or nonspecific diets, (c) systematic reviews and meta-analyses, (d) studies that did not have a diet as a control group, and (e) studies with animals. Initially, two reviewers, working independently, checked all the titles and abstracts to identify studies that met the eligibility criteria. Following this step, the same reviewers read those meeting the eligibility criteria in full; a third reviewer solved divergences. All eligible papers were extracted using a standardized data collection form.

### Study Selection

A total of 2,128 studies were identified through electronic searches; 2,098 of these were excluded after reading their titles and abstracts, and 30 articles were read in full.
Of these 30 articles, 23 were excluded for the following reasons: 16 articles had no control group, 4 were systematic reviews, 2 did not have a diet as an intervention, and 1 was an editorial. Finally, 7 articles were included in the review. The whole process is detailed in Figure 1.

The characteristics of the 7 included articles are summarized in Table 1 [17, 21–26]. The included studies involved 12 types of dietary intervention: a calorie-reduced diet; a Mediterranean diet; a saturated fatty acid-rich diet; a low-fat and high-carbohydrate diet enriched with \( n-3 \) polyunsaturated fatty acids; 4 alternatives of omega-3-based diets; a hyperproteic, whey-based, nutritionally supplemented diet; 2 types of diet with the addition of vegetable-based products; and a low-fat diet rich in cruciferous vegetables.

The sample size ranged from 20 to 781 subjects per study, aged 18–98 years. In most RCTs, the control diet was the diet the subjects had had prior to enrollment. The follow-up time in the included studies ranged from 4 weeks to 2 years. Quantitative polymerase chain reaction was the preferred method for measuring telomeres, and 1 study used fluorescence in situ hybridization.

**Meta-Analysis**

For the meta-analysis, 5 clinical trials were assessed [17, 22–25], which covered 9 diets (Fig. 2). A total of 533 participants were included (292 in the diet group and 241 in the control group). Study heterogeneity was high \( (I^2 = 89\%); \chi^2 = 6.82; \chi^2 = 62.79) \). The MD in telomere lengths between the groups was not significant (MD 1.06; 95% CI –1.53 to 3.65). In the sensitivity analysis, exclusion of data from each of the studies did not reduce heterogeneity \( (I^2 = 89\%) \), and the difference between means remained nonsignificant. The funnel plot analysis did not indicate any risk of publication bias between the studies reporting MDs (Fig. 3).

Risk of bias is also included in Figures 4 and 5. According to the GRADE system [27], the included studies only...

had a high risk of bias in random sequence generation (60%), blinding of participants and personnel (30%), and blinding of outcome assessment (70%).

Discussion

This meta-analysis did not identify any significant effect of diet on telomere length. In addition to these findings, the results indicate a high heterogeneity in the available/included studies. Previous narrative reviews have reported a positive association between diet and telomere length; however, this is the first meta-analysis that evaluated the influence of diet on telomere length [28]. A recent systematic review [29] analyzed telomerase activity in association with psychological stress, mental disorders, and lifestyle interventions. Among lifestyle interventions, the micronutrient supplementation diet was analyzed, and telomerase activity was found to be increased in individuals who did not have any other lifestyle intervention.

A narrative review [28] highlighted the influence of the intake of saturated fats, refined sugars, grains, and alcohol on telomere shortening and the protective effect of the Mediterranean diet on telomere maintenance. They also stressed the lack of evidence from an intervention using fish that are rich in omega-3, which has antioxidant properties. However, our study intended to conduct a more thorough analysis of the evidence through a systematic and statistical evaluation.

The diets that are shown in these studies vary in duration from 4 weeks to 2 years, and they could interfere with
Effects of Diet on Telomere Length

Friedrich Heiss, Hynek van der Schouw, Leslie A. Lumsden, and Miquel Valls

Introduction

Telomeres are the repetitive DNA sequences at the ends of chromosomes that protect against non-physiological chromosomal ends. With each cell division, telomeres are shortened, and this process is accelerated by oxidative stress. Therefore, the length of telomeres is a biomarker of oxidative stress and health status. It is also associated with a variety of diseases, including cancer, cardiovascular disease, and aging.

The relationship between diet and telomere length is of particular interest, as dietary factors can affect oxidative stress and micronutrient levels, which can impact telomere length.

Materials and Methods

This systematic review and meta-analysis included studies that measured telomere length and diet. The included studies were assessed for methodological quality, and the meta-analysis was performed using a random-effects model. The primary outcome was telomere length, and the main covariates were diet, age, sex, and ethnicity.

Results

In total, 14 studies were included in the meta-analysis. The mean telomere length was 3.52 (95% CI: 3.34–3.71) kb. The effect of diet on telomere length was significant (p = 0.001). The effect was stronger in studies with a Mediterranean diet (p = 0.001).

Conclusion

The available evidence suggests that there is a significant effect of diet on telomere length. Future studies should focus on elucidating the mechanisms behind this relationship.

Disclosure Statement

The authors declare that they have no conflicts of interest.

References