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Review

The potential nutrigeroprotective role of Mediterranean diet and its functional components on telomere length dynamics

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ABSTRACT

The Mediterranean diet (MD) is a gold standard for nutrition and the most evidence-based diet to delay the onset of age-associated pathologies. Telomeres are the heterochromatic repeat regions found at the ends of eukaryotic chromosomes, whose length is considered a reliable hallmark of biological ageing. Telomere shortening is, at least in part, a modifiable factor and there is evidence that adherence to the MD is associated with longer telomeres. Data from several studies indicate an association between "inflammatory/oxidative status" and telomere length (TL). The MD, as a complex exposome with thousands of nutrients and phytochemicals, may positively influence telomere attrition by reducing inflammation and oxidative stress. However, it is unclear whether the protective effects on TL provided by the MD result from its individual constituents or some combination of these. Furthermore, these properties of the MD and its components are not yet fully validated by clinical endpoints in randomized trials or observational studies. Here, we summarize the data from experimental and population-based studies on the effects of the MD on TL maintenance. We will both highlight the possible role of the MD in the prevention of age-associated diseases, and attempt to identify certain aspects of the diet that are particularly important for telomere maintenance.

1. Introduction

Modern civilization was born around the basin of the Mediterranean Sea and the regions surrounding this area have seen the rise and fall of many great civilizations. The geographic and evolutionary origins of the Mediterranean diet (MD) encompass the history of Western civilization. Extensive archeologic evidence derived from food debris, pottery, and tools dates the origin of the MD to the Neolithic periods and the Bronze Age (Nestle, 1995). Paleobotanical studies already indicate a dietary pattern with high quantities of cereals and legumes. Cultivation of cereals and legumes began in Syria, Palestine, and Southern Turkey and subsequently spread to Greece and southern regions of Italy and Spain between 6000–4000 BCE (Grigg, 1999). The MD was a part of ancient Egyptian civilization as is illustrated by a sculpture on the tomb of Ramses II showing the association of cereals, olive trees and vine (Nestle, 1995; Gerber and Hoffman, 2015). In 1614, Giacomo

Abbreviations: MD, Mediterranean diet; CVD, cardiovascular diseases; CHD, coronary heart disease; BMI, body mass index; LTL, leukocyte telomere length; TL, telomere length; ROS, reactive oxygen species; ω-3, omega-3; SSB, single-stranded breaks; OO, olive oil; MUFA, monounsaturated fatty acids; PREDIMED, Prevención con Dieta Mediterránea; EVOO, extra virgin olive oil; IL-, interleukin-; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; F2-IP, F2-Isoprostane; 8-oxo-dG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; VOO, virgin olive oil; hTERT, human telomerase reverse transcriptase; NHS, Nurses' Health Study; PUFA, polyunsaturated fatty acids; ALA, α-linolenic acid; LC, long chain; NHNES, National Health and Nutrition Examination Survey; AMD, age-related macular degeneration; SIRT, sirtuins; NF-κB, nuclear factor kappa-B; PGC1α, PPAR-gamma co-activator 1α; FOXO, forkhead box transcription factors; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; RCT, randomized controlled trial; MDS, Mediterranean Diet Score; MedDietScore, Diet Score; MAI, Mediterranean Adequacy Index; FFQ, food frequency questionnaires; WELL, Wellbeing, Eating and Exercise for a Long Life; GWAS, genome-wide association studies; SNPs, single nucleotide polymorphisms; TERC, telomerase RNA component; PPARγ2, PPAR-gamma 2; DII, dietary inflammatory index; SFA, saturated fatty acids; AA, arachidonic acid; WAHA, Walnuts and Healthy Aging; RBC, red blood cells

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Castelvetro, an Italian refugee exiled in England, in his essay, “Breve racconto di tutte le radici, di tutte le erbe e di tutti i frutti che crudi o cotti in Italia si mangiano,” exhorted the local population to eat less meat and more vegetables and cereals, in order to attain better health. Castelvetro was the first to praise the MD as a model of healthy eating (Nowak, 2015; Haber, 1997). In the second part of the twentieth century, the government of Greece invited the Rockefeller Foundation to conduct an epidemiologic study on the island of Crete. The results, published in 1953 (Allbaugh, 1953), showed that in the Cretan diet 61% of total energy came from plant foods and only 7% of calories came from animal foods such as meat, fish, eggs, and dairy products. Additionally, the researchers made the unexpected observation that people on Crete, although living in extreme poverty, were quite healthy and had one of the highest life expectancy levels in the world (Nestle, 1995). In 1952, Ancel Keys, a pioneer advocate of the MD, initiated a series of studies known as the Seven Countries Study to examine the relationship between diet and health in Italy, Greece, the USA, Japan, Finland, the Netherlands, and Yugoslavia. The term “Mediterranean diet” was coined in 1960 by Keys and his wife, Margaret, in their book “How to Eat Well and Stay Well: the Mediterranean Way” (Keys and Keys, 1975). However, the MD, as defined following the Keys study, is not a specific diet, but rather a lifestyle, a cultural model, and a collection of eating habits, determined by conviviality, intergenerational transmission and intercultural dialogue (Trichopoulou and Lagiou, 1997; Moro, 2016). The Seven Countries Study, which lasted for nearly three decades and included about 12,000 men ages 40–59 years, showed that lower rates of cardiovascular disease (CVD) were observed among participants with low consumption of saturated fats. Based on pioneering studies such as “Coronary Heart Disease in Seven Countries”, the dietary patterns of countries around the Mediterranean basin became associated with longevity as well as reduced rates of coronary heart disease (CHD) morbidity and mortality, cancers, and other chronic diseases (Keys, 1980). These studies initiated scientific interest in the health benefits of the MD. During the past few decades, the MD has emerged as an appropriate plant-centered dietary pattern that may affect mechanisms underlying ageing phenotype and reduce the main risk factors involved in the etiology of multiple age-associated diseases, including cancer, CVD, and neurodegeneration (Corella et al., 2018; Trichopoulou et al., 2003; Benetou et al., 2008; Estruch et al., 2018; Scarmeas et al., 2006). Numerous observational studies have illustrated the positive impact of a MD pattern on chronic conditions affecting the health of older adults. These benefits include reductions in blood pressure, blood cholesterol, diabetes, inflammatory markers, coronary syndromes, CVD, body mass index (BMI), and obesity (Roman et al., 2008; Schroder et al., 2004). Moreover, the MD has been linked to healthy ageing (Haveman-Nies et al., 2002), greater longevity (Trichopoulou, 2004), and potentially longer leukocyte telomere length (LTL) and telomerase activity (Boccardi et al., 2013; García-Calzón et al., 2016). In this review, we aimed to explore how a MD may positively affect telomere length (TL). Furthermore, the available studies on the association between MD and TL were systematically reviewed.

1.1. Telomeres, Mediterranean diet, and ageing

Telomeres are specialized dynamic nucleoprotein structures that maintain the structural integrity of chromosomes (Stewart and Weinberg, 2006). At birth, human telomeres are typically 10 to 15 kilobases in length, with substantial inter-individual heterogeneity (Palm and de Lange, 2008). TL shortens with age due to incomplete replication of DNA ends with each cell division. On average, human telomeres lose 50 to 100 base pairs per mitotic division, thus limiting the cell's replicative capacity (Allsopp et al., 1992). Once telomeres shorten to a critical length, the cell encounters a proliferation block where it either ceases to divide (cellular senescence) or undergoes programmed cell death (apoptosis). TL is considered a sort of biological clock that measures the lifespan of a cell and an organism. Shorter telomeres are associated with decreased life expectancy and an increased rate of developing age related chronic diseases (Heidinger et al., 2012). Studies suggest that it is possible to modify telomere attrition, as substantial variability exists in the rate of telomere shortening that is independent of chronological age (Aviv, 2006; Blackburn, 2000). The rate of telomere loss is influenced by factors other than the mitotic replication rate. Telomere attrition can also occur through damage incurred by reactive oxygen species (ROS) released in the inflammation process or by chemical alterations to purines and pyrimidines from oxidative stress (Correia-Melo et al., 2014). Since accelerated telomere attrition may underlie many chronic diseases, it is important to identify modifiable factors that may affect telomere dynamics. Systemic exposures that contribute to oxidative stress and age-related disease, e.g., smoking, obesity, and chronic stress, have been associated with shorter TL in white blood cells (Shammas, 2011). Additionally, an accelerated telomere shortening in humans has been linked with increased intake of red meat, processed meat, sweetened carbonated beverages, sodium, and white bread (Lee et al., 2015; Nettleton et al., 2008; Leung et al., 2008; Zhu et al., 2015). On the other hand, healthy lifestyle choices such as tobacco abstinence, moderate physical activity, lower BMI, and healthy dietary patterns have been hypothesized to promote more stable TL presumably via enhanced antioxidant and anti-inflammatory activities (Sun et al., 2012). Given that fruits, vegetables, and nuts, key components of the MD, have well known antioxidant and anti-inflammatory effects, and that TL is affected by both these processes, it follows that a greater adherence to the MD would likely be associated with longer TL. Considerable evidence suggests that consumption of antioxidant-rich foods and/or a diet rich in fruits and vegetables may play a role in telomere biology maintenance and thus impact overall health status and longevity (Lian et al., 2015; Hou et al., 2009). It has been shown that TL in humans is positively influenced by dietary factors such as the MD, higher intake of phytochemicals, nutritional status of vitamin and minerals, and higher consumption of omega-3 (ω-3) fatty acids (Paul, 2011). A wide variety of bioactive compounds of the MD have been shown to influence TL and telomerase regulation (see Table 1). Additionally, many of these food components can reduce inflammation and decrease oxidative stress, and thus could protect telomeres from damage (Martucci et al., 2018). In recent years, a growing body of literature has emerged showing a potential connection between telomere maintenance and MD. Although it is crucial to better elucidate how different components of MD exert their protective effects (individually and/or synergistically), it is thought that the MD as a whole may have a greater influence on TL rather than its individual nutrients and/or food groups (Boccardi et al., 2013). In the next sections, using the current knowledge regarding the potential association between TL and MD, we discuss the latest findings on the effects of the MD and its specific components on telomeric stability.

2. Food groups in the Mediterranean diet and their effects on telomere length maintenance

Due to the high guanine-cytosine content and long stretches of repetitive DNA, telomere sequences suffer disproportionately higher rates of damage by oxidative stress compared to nontelomeric sequences. Single-stranded breaks (SSB) of telomeric DNA, caused either directly by ROS or indirectly as part of the DNA repair process, are not efficiently restored by repair mechanisms (Lee et al., 2017). Additionally, an important development associated with ageing is the proinflammatory phenotype that accompanies ageing in mammals. Low-grade inflammation is strictly connected to oxidative stress, and both are linked to the onset of age-associated diseases and telomere shortening (Zhang et al., 2016). The possibility of maintaining telomeres in normal cells, through diet and lifestyle interventions, has generated widespread interest as a means of increasing healthspan (Cassidy et al., 2010; Boccardi et al., 2016). The traditional MD consumed in Greece

Table 1
Overview of selected bioactive compounds from foods of the Mediterranean diet affecting telomere biology.

Author, year	Compounds	Food source	Model	Outcome
Lopez et al. (2018)	MUFA	VOO	Male Wistar rats	Overexpression of genes associated with TL pathway and antioxidant response
Tanaka et al. (2007)	Vitamin E (α-tocopherol)	VOO, EVOO, and nuts	Brain microvascular endotheliocytes	Inhibition of telomerase activity
Rafehi et al. (2012)	Hydroxytyrosol	VOO and EVOO	Myelogenous leukemia K562 cells	Downregulation of hTERT subunit
Chakrabarti et al. (2013)	Apigenin	Common fruits, vegetables, legumes, and herbs	Neuroblastoma SK-N-DZ and SK-N-BE2 cells	Downregulation of hTERT subunit
Chen et al. (2011)	Quercetin	Common fruits, vegetables, legumes, and herbs	HepG2 cells, lung cancer cell lines, and gastric cancer cell lines	Reduction of telomerase activity and downregulation of hTERT gene expression
Guo et al. (2004)	Daidzein	Common fruits, vegetables, legumes, and herbs	Cervical cancer HeLa cells	Downregulation of hTERT subunit
Kashafi et al. (2017)	Kaempferol	Common fruits, vegetables, legumes, and herbs	Cervical cancer HeLa cells	Downregulation of hTERT subunit
Meeran et al., (2010)	Sulforaphane	Cruciferous vegetables	Breast cancer cell lines	Epigenetic repression of hTERT expression
Chau et al. (2007)	Genistein	Common legumes	Prostate cancer cells	Enhancement of telomerase activity
Xia et al. (2008)	Resveratrol	Grapes, and red wine	Endothelial progenitor cells	Activation of telomerase
Sen et al. (2014)	Carotenoids (lutein and zeaxanthin)	Green leafy vegetables	Elderly adults	Higher lutein and zeaxanthin concentrations in plasma were associated with longer TL
Min and Min (2017)	Carotenoids (α-carotene, β-carotene, and β-cryptoxanthin)	Common fruits and vegetables	Adults (20 years and older)	Higher α-carotene, β-carotene, and β-cryptoxanthin in blood associated with longer TL

Abbreviations: MUFA = Monounsaturated Fatty Acids; VOO = Virgin Olive Oil; TL = Telomere length; EVOO = Extra Virgin Olive Oil; hTERT = Human telomerase Reverse Transcriptase; ω-3 fatty acids = Omega-3 fatty acids; ω-6 fatty acids = Omega-6 fatty acids; PUFA = Polyunsaturated fatty acids; CHD = coronary heart disease.

and other countries in Southern Europe, e.g., Italy and Spain, is characterized by a high intake of vegetables, fruits, nuts, legumes, and (mainly unrefined) grains; a high intake of olive oil (OO), but low intake of saturated lipids; a moderately high intake of fish; a low intake of dairy products, meat, and poultry; and a regular but moderate intake of alcohol (specifically wine with meals) (Bach-Faig et al., 2011). Multiple studies have found positive correlations between some of the food groups typically consumed in the MD and TL (see Table 2). These food groups contain a wealth of chemical compounds, including monounsaturated fatty acids (MUFA), vitamins, minerals, and a complex group of thousands of plant metabolites known as phytochemicals (Davinelli et al., 2012, 2016). Observational studies and intervention trials have consistently shown the health benefits of a high degree of adherence to the MD (Bonaccio et al., 2018), including reduction of oxidative stress, inflammation and telomere attrition. In the "Prevención con Dieta Mediterránea" (Prevention with Mediterranean Diet) (PREDIMED) study, an intervention trial comparing the MD to a control diet, a MD supplemented with extra virgin olive oil (EVOO) and/or with nuts lowered proinflammatory mediators such as interleukin-1β (IL-1β), IL-6, IL-12, tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ) as well as oxidative stress biomarkers such as F2-Isoprostane (F2-IP) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) (Casas et al., 2017). Participants selected from a different PREDIMED sub-study had an increase in TL after a 5-year of MD intervention (García-Calzón et al., 2014).

2.1. Monounsaturated fatty acids and phytochemicals from olive oil

The main bioactive constituents of virgin olive oil (VOO) and EVOO are MUFA, and more than 250 phytochemical compounds ("minor constituents") (Lopez et al., 2014). Recently, many health claims have been considered for the main antioxidants and bioactive phenolic compounds found in VOO and EVOO, e.g., vitamin E (α-tocopherol), hydroxytyrosol, tyrosol, and oleuropein. (EFSA, 2010; EFSA, 2011).Data from the microarray analysis show that aged rats fed with VOO, rich in MUFA, displayed a higher expression of genes associated with the TL pathway and antioxidant response (Varela-Lopez et al., 2018). The vitamin E (α-tocopherol), which is largely present in VOO, EVOO, and nuts, prevented age-dependent telomere shortening and decreased telomerase activity (Tanaka et al., 2007). Hydroxytyrosol, a minor polyphenolic constituent of VOO and EVOO, has been shown to downregulate human telomerase reverse transcriptase (hTERT) *in vitro*, suggesting that this compound may modulate TL (Rafehi et al., 2012).

2.2. Phytochemicals from common legumes

Legumes belong to the family *Leguminosae* also called *Fabacae*. Recommendations for legume intake range from every meal to at least twice a week (Davis et al., 2015). The most consumed legumes of MD are beans (*Phaseolus vulgaris*), chickpeas (*Cicer arietinum*), lentils (*Lentis esculenta*), peas (*Pisum sativum*), broad beans (*Vicia faba*), peanuts (*Arachys hipogea*), and soybeans (*Glycine max*) (Bouchenak and Lamri-Senhadji, 2013). It has been suggested that several phytochemicals derived from common legumes that are part of the MD may inhibit telomerase activity in various cancer cells. These substances include flavonoids such as apigenin, quercetin, daidzein, and kaempferol (Chakrabarti et al., 2013; Chen et al., 2011; Guo et al., 2004; Kashafi et al., 2017). The isoflavone genistein, derived from common legumes such as chickpeas, has a dual effect on telomerase activity in cancer cells. This compound may activate telomerase activity at low concentrations and inhibit telomerase activity at higher treatment concentrations (Chau et al., 2007). Although few observational studies have examined the effects of legumes on TL, Lee et al. found a significant positive association between consumption of legumes and TL in 1958 middle-aged Korean adults (Lee et al., 2015). In another study, a higher intake of legumes was correlated with longer telomeres (García-

Table 2
Human studies exploring the associations between consumption of food groups of the Mediterranean diet and telomere length.

Author, year	Food groups	Study design	Population and sample size	Outcome	Variables of adjustment	Findings associated with telomere length
Lee et al. (2015)	Legumes	Prospective, 10-year follow up	1958 middle-aged and older Korean adults	LTL	Age, sex, BMI, other potential confounders	Longer LTL with higher intake of legumes
García-Calzón et al. (2015a)	Legumes	Cross-sectional	287 Spanish subjects aged 6-18 years (55% males)	LTL	Age, sex, BMI-SDS, and total energy intake	Significant direct associations: between legume intake and longer LTL
Tiainen et al. (2012)	Legumes	Cross-sectional	1942 Finnish men and women aged 57–70 years	LTL	Age, energy intake, other potential confounders	No association between legume intake and LTL
Chan et al. (2010)	Legumes	Cross-sectional	2006 Chinese men and women aged 65 years and over	TL	Age, BMI, energy intake, other potential confounders	No association between legume intake
Cassidy et al. (2010)	Cereals	Cross-sectional	2284 US women within the NHS aged 43-69 years	LTL	Age, smoking, postmenopausal hormone use, BMI, physical activity, energy intake	Positive association between dietary fiber intake and LTL especially cereal fiber and whole grain intake
García-Calzón et al. (2015a)	Cereals	Cross-sectional	287 Spanish subjects aged 6-18 years (55% males)	LTL	Age, sex, BMI-SDS, and total energy intake	Shorter telomeres with higher cereal consumption (white bread having the major adverse effects on LTL)
Lee et al. (2015)	Fruits	Prospective, 10-year follow up	1958 middle-aged and older Korean adults	LTL	Age, sex, BMI, other potential confounders	Longer LTL with higher intake of fruits
Hou et al., (2009)	Fruits	Case–control	300 cases of gastric cancer and 416 age and gender-matched controls	LTL	Age, gender, smoking status	Protective effect of fruit intake on TL
Tiainen et al. (2012)	Fruits	Cross-sectional	1942 Finnish men and women aged 57–70	LTL	Age, energy intake, other potential confounders	Direct association between fruit intake and LTL in women
Tucker (2017)	Nuts	Cross-sectional	5582 men and women within the NHANES	LTL	Smoking, alcohol use, BMI, other potential confounders	Consumption of nuts was significantly related to TL
Marcon et al. (2012)	Vegetables	Cross-sectional	56 Italian men and women (31 women)	LTL	Age, gender, energy intake	Significantly higher mean TL with higher consumption of vegetables (especially root vegetables such as pepper, carrot and tomato)
Bekaert et al. (2007)	Vegetables	Cross-sectional	2509 women and men Volunteers aged 35–55 years	TL	Age	Positive association between TL and low vegetable intake (combined with fruits)
Gong et al. (2017)	Vegetables	Cross-sectional	553 Chinese adults (50.8% men) aged 25-65 years	TL	Age, smoking, energy intake, other potential confounders	Longer TL with higher intake of vegetables
Song et al. (2013)	Dairy products	Cross-sectional	4029 US women postmenopausal	LTL	Age, race-ethnicity, BMI, smoking, daily alcohol intake, physical activity, and daily intakes of energy, fruit and vegetables	No association between milk intake and TL. Inverse association between non-skim milk and TL. Inverse association for butter and TL. No association between total cheese intake and TL
Lee et al. (2015)	Dairy products	Prospective, 10-year follow up	1958 middle-aged and older Korean adults	LTL	Age, sex, BMI, other potential confounders	Longer LTL with higher intake of dairy products
Farzaneh-Far et al. (2010)	Fish ω-3 fatty acids	Prospective, 5-year follow up	608 patients with CHD	LTL	Age, sex, race/ethnicity, education level, other clinical, and biochemical confounders	Inverse relationship between baseline levels of marine ω-3 fatty acids and the rate of telomere shortening over 5 years
Kiecolt-Glaser et al. (2013)	Fish ω-3 fatty acids	Randomized intervention trial	106 healthy sedentary overweight middle-aged and older adults (46-85 years)	LTL	N/A	Lower ω-6:ω-3 PUFA ratios were associated with longer LTL

Abbreviations: LTL = leukocyte telomere length; BMI = Body mass index; BMI-SDS = Standard deviation score for body mass index; TL = Telomere length; NHS = Nurses' Health Study; NHANES = National Health and Nutrition Examination Survey; CHD = Coronary heart disease; ω-3 = omega-3; ω-6 = omega-6; PUFA = Polyunsaturated fatty acids; N/A = Not Applicable.

Calzón et al., 2015a), but several observational reports have not shown any significant association between consumption of legumes and TL (Tiainen et al., 2012; Chan et al., 2010).

2.3. Micronutrients, phytochemicals, and dietary fiber from cereals

The people of the Mediterranean basin consume high amounts of cereal products (one or two servings per meal) such as bread (wheat, mixture, whole, corn and rye), pasta, potatoes and rice. The health benefits of whole cereal products may be attributed to the synergistic effect of micronutrients (monosaccharides, vitamins, and minerals) and phytochemicals (phenolic acids, sterols, tocols, tannins, and anthocyanins) as well as the effect of dietary fiber (Kaur et al., 2014). Phytochemicals of cereal grains possess antioxidant properties which prevent oxidative damage to cellular components such as membranes, proteins, and nucleic acids, thus reducing the rate of cell death and the effects of ageing (Masisi et al., 2016). To date, there are limited data and no robust evidence on the influence of cereals and grains on TL in humans. However, some studies observed that shorter TL was related to consumption of cereals and/or grains. In a cross-sectional study of 2284 female participants from the Nurses' Health Study (NHS), a diet high in fiber, specifically cereal fiber, was positively associated with longer TL (Cassidy et al., 2010). An inverse correlation between cereal intake and TL was also confirmed in a study conducted on 287 children and adolescents. In contrast, white bread appeared to have the most adverse effect on TL (García-Calzón et al., 2015a). This may be due to the use of refined flour cereal products because the refining process removes the outer layer and the germ of grains that are rich in antioxidant compounds.

2.4. Bioactive compounds of fruits

Some of the health protective effects of the MD have been attributed to high levels of beneficial components which are abundant in fruits (one or two servings per meal – fruit should be chosen most frequently as dessert) (Ortega, 2006). Indeed, fruits provide a range of nutrients and different bioactive compounds including phytochemicals (polyphenols, flavonoids, and carotenoids), vitamins (vitamin C, folate, and pro-vitamin A), minerals (potassium, calcium, and magnesium), and fibers. Many of these compounds affect multiple biological pathways and can alter cellular function by modulating transcription factors and altering the expression of genes associated with antioxidant response and anti-inflammatory pathways (Traka and Mithen, 2011). Fruits may contain up to 200–300 mg polyphenols per 100 g fresh weight (Aguilera et al., 2016 Fruit intake has also been associated with positive changes in gut microbiota, including increases in Bifidobacteria and Lactobacilli, probiotic bacterial species that downregulate the expression of various proinflammatory genes (Lopez-Legarrea et al., 2014; Plaza-Diaz et al., 2014). A positive relationship with TL and fruit intake was observed in a population of middle-aged and older adults who consumed high amounts of fruit (Lee et al., 2015). This association was also confirmed in a case-control study with 300 gastric cancer cases and 416 age and gender-matched controls (Hou et al., 2009). Another study, conducted in Finnish elders, reported a direct association between fruit consumption and TL in women, but failed to find an association for men (Tiainen et al., 2012).

2.5. Nutrient content of nuts

Nuts are energy-dense and an important source of fats and unsaturated fatty acids in the MD. Nuts contain variable amounts of polyunsaturated fatty acids (PUFA), including high content of α-linolenic acid (ALA), which is known to be a precursor of long chain (LC) ω-3 PUFA (Ros and Mataix, 2006). Although fatty acids play a central role in mediating the health properties of nuts, the micronutrients, fiber, antioxidant phenolic compounds and minerals found in nuts are also important. Several human studies suggest that nuts may positively affect inflammatory conditions due to their high levels of phytochemicals (proanthocyanidins, gallic acid, ellagic acid, ellagitannins, flavonoids, and stilbenes) (Alasalvar and Bolling, 2015; Jiang et al., 2002; O'Brien et al., 2014). Recently, consumption of nuts was linearly and significantly related to TL in a random sample of 5582 men and women representing adults within the National Health and Nutrition Examination Survey (NHANES) (Tucker, 2017).

2.6. Phytonutrients from vegetables

In addition to its emphasis on fruits and nuts, the MD is rich in vegetables (two servings per meal, at least one serving should be raw). The MD consists of fruiting vegetables (tomato, eggplant, zucchini, cucumber, pepper, artichoke), leafy vegetables (spinach, chard, lettuce), root vegetables (carrot, pumpkin), and other vegetables such as cabbage, cauliflower, broccoli, and asparagus. Beyond basic nutrition, the plant-based foods may also help reduce the risk of chronic disease (Liu, 2004). The most important dietary phytochemicals contained in these vegetables are phenolic compounds, alkaloids, nitrogen-containing compounds, organosulfur compounds, phytosterols, and carotenoids. Cruciferous vegetables, such as cabbage, cauliflower, and broccoli, are important sources of isothiocyanates, which have antioxidant and anti-inflammatory properties (Higdon et al., 2007). Sulforaphane, the organosulfur derived from cruciferous vegetables, has been shown to cause epigenetic regulation, resulting in a decrease of hTERT expression, as well as the phosphorylation of hTERT, which prevents translocation to the nucleus in cancer cells (Meeran et al., 2010). Marcon et al. found that vegetable intake was significantly associated with TL, and that root vegetables, peppers, and carrots were the vegetables most significantly correlated with TL (Marcon et al., 2012). However, a large Belgian cross-sectional study found no association between TL and (combined) fruit and vegetable intake, but when a low fruit and vegetable intake was assessed as part of an unhealthy lifestyle score, a positive association was found (Bekaert et al., 2007). Recently, Gong et al. investigated whether a vegetable-rich dietary pattern was associated with TL in 553 Chinese adults. Although no significant relations were observed in men, a dietary pattern characterized by high intake of fruits, whole grains, various vegetables, and nuts was positively related to TL in women (Gong et al., 2017). Additionally, orange and yellow vegetables like carrots and red peppers are rich sources of carotenoids, particularly β-carotene. Dark green leafy vegetables, like spinach, kale, turnip greens, and broccoli are rich sources of lutein and zeaxanthin, pigments that may protect against age-related macular degeneration (AMD) by reducing oxidative stress (Wu et al., 2015). Data from epidemiological studies support the idea that a high intake of carotenoid-rich food may play a role in protecting telomeres and regulating TL. A population-based cohort study of 786 healthy older subjects found that higher plasma concentrations of lutein and zeaxanthin were strongly associated with longer LTL, suggesting a protective role for carotenoids in telomere maintenance (Sen et al., 2014). More recently, a study on 3660 US adults who participated in the 2001–2002 NHNES found a significant, positive association between leukocyte telomere shortening and blood carotenoid levels, especially for α-carotene, β-carotene (trans + cis), β-cryptoxanthin (Min and Min, 2017).

2.7. Resveratrol in red wine

Some of the beneficial effects of the MD have been attributed to the polyphenols in red wine. However, the bioactive component that has received the most attention is resveratrol (a stilbene polyphenol). This compound has been characterized as an inducer of autophagy as well as a calorie restriction mimetic. Resveratrol is an activator of the small protein family sirtuins (SIRT). SIRT1, which has been proposed to be a central target of resveratrol in mammals, regulates cellular processes

Table 3
Human studies on the association between whole Mediterranean diet and telomere length.

Author, year	Study design	Population and sample size	Outcome	Variables of adjustment	Findings associated with telomere length	Method of telomere length measurement
Crous-Bou et al. (2014)	Cross-sectional	4676 disease-free women within the NHS	Association between relative TL and alternate MD score	BMI, smoking, total calorie intake, physical activity	Greater adherence to the MD associated with longer telomeres	RT-qPCR
Boccardi et al. (2013)	Cross-sectional	217 elderly subjects	Association between adherence to the MD, TL, and telomerase activity	Gender, age and smoking	Retrospective association between high adherence to the MD style and telomere maintenance	RT-qPCR
Gu et al. (2015)	Cross-sectional	1743 multi-ethnic community residents within the WHICAP study	Association between MD and TL	Age, gender, ethnicity, education, caloric intake, smoking status, leisure/physical activities and vascular, cognitive, and functional status	No association between adherence to the MD and TL. Higher intake of vegetables associated with longer TL, and higher intake of cereal associated with shorter TL	RT-qPCR
Milte et al. (2018)	Cross-sectional	679 participants within the WELL study	Associations between three indices of diet quality including MDS and TL in older men and women	Age, sex, education, smoking, physical activity and BMI	Greater diet quality and adherence to the MD were not associated with longer TL	RT- qPCR
Gomez-Delgado et al. (2018)	Randomized, controlled, dietary intervention trial	926 CHD patients within the CORDIOPREV study	Interaction between MD, TERC gene locus, and TL	N/A	TERC rs12696304 SNP interacts with MD, improving TL	RT-qPCR
García-Calzón et al. (2015a, 2015b)	Randomized, controlled, dietary clinical trial (5 year follow-up)	521 high CVD risk subjects within the PREDIMED-NAVARRA study	Interaction between the gene variant of PPARγ2 (Pro/Ala (rs1801282), MD, and TL	Age, sex, BMI, TL, smoking habit, physical activity, total energy intake, the MD tool score and for each initial dietary component.	Association between PPARγ2 rs1801282, and TL. A higher adherence to MD increases TL in Ala carriers	RT-qPCR
García-Calzón et al. (2014)	Randomized, controlled, dietary clinical trial (5 year follow-up)	521 high CVD risk subjects within the PREDIMED-NAVARRA study	Assessment of the relationship between TL and changes in adiposity indices	Age, sex, BMI, WC, smoking habit, diabetes, hypertension, dyslipidaemia, physical activity, total energy intake	TL inversely associated with changes in obesity parameters	RT-qPCR
García-Calzón et al. (2015c).	Randomized, controlled, dietary clinical trial (5 year follow-up)	520 high CVD risk subjects within the PREDIMED-NAVARRA study	Association between DII and TL	Sex, BMI, physical activity, smoking, hypertension, dyslipidemia, and intervention group assignment	DII scores were inversely associated with TL	RT-qPCR
García-Calzón et al. (2016)	Randomized, controlled, dietary clinical trial (5 year follow-up)	520 high CVD risk subjects within the PREDIMED-NAVARRA study	Association between MD and TL in high CVD subjects	Age, sex, BMI, total energy intake, adherence to the MD, physical activity, smoking, diabetes, hypertension dyslipidaemia, and TL	A higher baseline adherence to the MD is cross-sectionally associated with longer TL only in women. No effect on TL after 5 years	RT-qPCR
Marin et al. (2012)	Randomized, crossover, intervention study	20 free-living elderly subjects	Association between MD and TL associated with cellular senescence	N/A	MD prevents cellular senescence and telomere shortening	FISH and flow cytometry
Freitas-Simoes et al. (2018)	Cross-sectional randomized controlled trial	344 Mediterranean elder subjects within WAHA trial	Associations between TL and the PUFA composition of RBC	Sex, age, education years, APOE4 genotype, smoking, BMI, energy intake, physical activity, diabetes, hyperlipidemia, and hypertension	Inverse association between TL and the RBC content of C20:4n-6, a fatty acid associated with inflammation	FISH

Abbreviations: NHS = Nurses' Health Study; TL = Telomere length; MD = Mediterranean Diet; BMI = Body Mass Index; RT-qPCR = Real Time quantitative Polymerase Chain Reaction; WHICAP = Washington Heights-Inwood Community Aging Project; WELL = Wellbeing, Eating and Exercise for a Long Life; MDS = Mediterranean Diet Score; CHD = Coronary heart disease; TERC = Telomerase RNA Component; CORDIOPREV = Coronary Diet Intervention With Olive Oil and Cardiovascular Prevention; N/A = Not Applicable; SNP = Single-nucleotide polymorphism; CVD = Cardiovascular disease; WC = Waist; PREDIMED = Prevención con Dieta Mediterránea; PPARγ2 = Peroxisome proliferator–activated receptor γ 2; Circumference; DII = Dietary Inflammatory Index; FISH = Fluorescent in situ hybridization; WAHA = Walnuts and Healthy Aging; PUFA = Polyunsaturated fatty acids; RBC = Red blood cells; APOE4 = Apolipoprotein E 4.

such as DNA repair, fat differentiation, glucose output, insulin sensitivity, fatty acid oxidation, and neurogenesis, through deacetylation of a number of key histone and protein targets including H3-K9, H4-K16, H1-K26, nuclear factor kappa-B (NF-κB), PPAR-gamma co-activator 1α (PGC1α), forkhead box transcription factors (FOXO), and numerous others (Bhullar and Hubbard, 2015; Davinelli et al., 2013). While telomerase inhibition is an attractive goal for cancer cell treatment, it is important to highlight that activation of telomerase in normal somatic cells may be beneficial for maintaining TL. Resveratrol, isolated from a variety of dietary sources of MD, has been shown to activate telomerase in human mammary epithelial and endothelial progenitor cells, reducing senescence through mechanisms of self-renewal (Pearce et al., 2008; Xia et al., 2008).

2.8. *Probiotic bacteria from dairy products*

The moderate intake of dairy products is a characteristic of the MD. Probiotics are nonpathogenic microorganisms able to modulate the proper composition of human gut microbiota and its immune system. Yogurt, cheese, and other fermented milk products are usually prepared using lactic acid bacteria of four general species: *Lactobacillus* sp., *Bifidobacterium* sp., *Enterococcus* sp., and *Streptococcus* sp (Parvez et al., 2006). Although the efficacy of probiotics remains in dispute, Pprobiotics have been shown to lower inflammatory mediators (Thushara et al., 2016). Dairy products contain high-quality protein and vitamins (A, D, B2, B12) and may contribute to telomere maintenance but their effect on TL remains controversial. Milk intake was inversely related to TL in healthy women who usually chose non-skim milk (whole milk or reduced fat milk) compared with those who usually chose skim milk. In addition, intake of fat containing cheese compared with low or no fat cheese resulted in shorter TL (Song et al., 2013). The consumption of dairy products was associated with maintained TL in middle-aged Koreans but this finding was not confirmed on multi-ethnic populations (Lee et al., 2015; Nettleton et al., 2008; Chan et al., 2010; Marcon et al., 2012).

2.9. *Omega-3 polyunsaturated fatty acids and fish consumption*

A Mediterranean-style eating pattern includes moderate to high fish and seafood intake. Fish is the one of the main dietary source of LC ω-3 PUFA, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). There is substantial evidence that ω-3 PUFA are capable of inhibiting many mechanisms associated with inflammation, including leucocyte chemotaxis, adhesion molecule expression and leucocyte–endothelial adhesive interactions, and eicosanoid production. For example, these ω-3 fatty acids may have benefits on inflammatory conditions such as rheumatoid arthritis, asthma, and psoriasis. A slower telomere attrition was predicted by higher baseline levels of EPA and DHA in a prospective cohort study of 608 patients with CHD who completed the 5-year follow-up examination (Farzaneh-Far et al., 2010). A small pilot study on subjects with low-risk prostate cancer found that intensive lifestyle modification, including supplementation with ω-3 PUFA from fish oil, led to an increase in telomerase levels and telomere lengthening 5 years after the intervention, for those subjects who adhered to the program (Ornish et al., 2008, 2013). More significantly, a randomized controlled trial (RCT) on 106 healthy sedentary, overweight, middle-aged and older adults assessed the impact of ω-3 PUFA supplementation on LTL, telomerase, oxidative stress, and ω-6:ω-3 ratio. Although telomerase activity level did not change in this study, for the first time, the authors provided evidence that TL increased with a decreasing ω-6:ω-3 PUFA ratio (Kiecolt-Glaser et al., 2013). These data suggest that LC ω-3 PUFA may reduce the burden of oxidative stress and inflammation with positive consequences for TL in healthy subjects.

3. Mediterranean diet, telomere length and human population studies

Although epidemiological studies are by nature observational rather than experimental, and the observed associations do not imply a causal relationship, many large epidemiological studies have recently focused their attention on the link between the whole MD and TL and its health impact on the general population (see Table 3). To analyze this and other health benefits of MD, several indices were developed to measure adherence to the MD. There are over ten different MD scoring indices; however, the indices used most frequently are the MD Score (MDS), Diet Score (MedDietScore), and the Mediterranean Adequacy Index (MAI). Randomized trials with a lifestyle/diet intervention based on the MD may provide a definitive answer to the findings reported by observational studies. In the following section we provide a review of population and intervention studies that have examined whether MD led to increases in telomerase levels and telomere lengthening.

3.1. *Population studies*

A robust epidemiological confirmation of a positive influence of the MD on TL has been obtained within the NHS, an ongoing prospective cohort study of 121700 nurses enrolled in 1976, which is one of the largest research studies into the risk factors for major chronic disease in women (Townsend et al., 2016). Specifically, 4676 healthy, middle-aged women who completed food frequency questionnaires (FFQ) were assessed. After adjustment for potential confounders, a greater adherence to the MD by study subjects was associated with longer telomeres. The authors also suggest that a three point change in the Alternative MDS would correspond on average to 4.5 years of ageing based on TL (Crous-Bou et al., 2014). Although the use of elderly subjects is considered questionable due to “survivor bias” (i.e., the fact that the necessary characteristics to attain a healthy old age may include longer telomeres), a cross-sectional study conducted in 217 older subjects (mean age 78 years) showed that adherence to the MD was associated with LTL after adjusting for several cardiovascular risk factors. The group was stratified according to the MDS in low adherence (MDS ≤ 3), medium adherence (MDS 4–5), and high adherence (MDS ≥ 6) groups. The high adherence group showed longer LTL and higher telomerase activity compared to the others (Boccardi et al., 2013). Gu et al. conducted a cross-sectional study among 1743 individuals aged 65 years or older from the Multi-Ethnic Study of Atherosclerosis. Analysis of completed FFQ by participants showed that MD score was not associated with LTL in the overall study population. However, there was a significant correlation between MD score and LTL in non-Hispanic whites. The authors also explored whether specific food groups of MD were associated with LTL. They found that vegetable and cereal intake above the sex-specific population median was associated with 89 bp longer and 94 bp shorter LTL, respectively, in the whole population. Additionally, among whites, the intake of dairy or meat below the sex-specific population median was associated with 155 bp and 241 bp longer LTL, respectively. Other food components such as fish, legumes, and nuts were not associated with LTL among whites (Gu et al., 2015). Very recently, a different scenario was reported by Milte et al. who conducted a study with 679 adults aged 57–68 years participating in the Wellbeing, Eating and Exercise for a Long Life (WELL) study in Victoria, Australia. In this prospective, population-based longitudinal cohort study the associations between three indices of diet quality and TL were assessed. Higher adherence to MD assessed via MDS was not cross-sectionally associated with longer TL. However, this study had several limitations, e.g., modest sample size, dietary intake assessed by a non-quantified FFQ, suspected survivor bias, and a short follow-up (2 years) (Milte et al., 2018).

3.2. Dietary intervention studies

A nutrigenetic/nutrigenomic approach may uncover new knowledge on the link between MD and TL that could lead to more personalized strategies for maintaining telomere integrity throughout the lifespan. In the past ten years, genome-wide association studies (GWAS) have highlighted the relationship between LTL and single nucleotide polymorphisms (SNPs) associated with the telomerase RNA component (TERC) gene. The CORDIOPREV study was designed to investigate the efficacy of the MD in the secondary prevention of CHD with an average follow-up of 7 years. Interestingly, from a personalized nutrition perspective, a genetic variant of TERC (rs12696304 SNP) interacts with MUFA, improving inflammation status and telomere attrition related with CHD in CC individuals (Gomez-Delgado et al., 2018). Furthermore, in a cohort of 521 men and women aged 55–80 years following a 5-year MD intervention, telomere shortening appeared to be reduced with greater adherence to the MD in individuals carrying the Pro12 Ala polymorphism in the PPAR-gamma 2 (PPARγ2) gene (García-Calzón et al., 2015b). These studies show the first evidence of the role of nutrition in genes related to LTL. García-Calzón et al. also observed an association between TL and changes in adiposity indices in the context of the PREDIMED-NAVARRA trial (García-Calzón et al., 2014). Studies investigating inflammation may be promising in finding a treatment for age-associated diseases and comorbidity with short TL. A further study, from a subgroup of 520 participants in the PREDIMED-NAVARRA trial with 5-year follow-up, shows both cross-sectional and longitudinal associations between the inflammatory potential of the Western-type diet, measured by dietary inflammatory index (DII) score, and telomere shortening in older subjects at high cardiovascular risk (García-Calzón et al., 2015c). The most recent findings from PREDIMED-NAVARRA trial specifically assessed the association between TL and the MD. It was reported that a higher baseline adherence to the MD is cross-sectionally associated with longer telomeres only in women. Moreover, no beneficial effects of the MD on TL were observed at 5-year follow-up, and a higher risk of telomere shortening was observed in the MD and nuts group (García-Calzón et al., 2016). A RCT evaluated changes in the TL of human umbilical endothelial cells incubated with serum from 20 subjects who consumed a MD enriched with MUFA from VOO, a saturated fatty acids (SFA) rich diet, and a high-carbohydrate diet enriched with a plant-derived ALA ω-3 PUFA for 4 weeks each. The MD supplemented with VOO group maintained TL and showed decreased oxidative stress and apoptosis, as well as reduced cellular senescence, compared to the groups on the other two diets (Marin et al., 2012). Recent nutritional surveys carried out in Mediterranean countries confirm that a rapid and progressive shift from the traditional MD towards a Western dietary pattern has been linked to increased amounts of ω-6 PUFA and inflammation. High intake of ω-6 is associated with long-term production of proinflammatory eicosanoids from arachidonic acid (AA) and the development of CVD and diabetes (Simopoulos and DiNicolantonio, 2017). A recent RCT within the context of the Walnuts and Healthy Aging (WAHA) trial reinforced the concept of an interplay between inflammation and accelerated telomere shortening. In this cross-sectional study conducted in healthy Mediterranean elders (344 subjects; mean age 68.8 years), an inverse association has been observed between LTL and the red blood cell (RBC) content of AA, while no significant associations were found for other exposures (Freitas-Simoes et al., 2018).

4. Conclusions

To our knowledge, this review is the first to examine the literature on the potential link between MD and telomere maintenance. The primary aim of this review was to address the question of whether or not the MD is a feasible nutritional approach to slow down telomere attrition. Given that physiological ageing is provoked, at least in part, by telomere shortening, a greater adherence to a healthy dietary pattern may be used not only to counteract telomere shortening but also to prevent multiple age-related diseases. Although the association between diet and shortening of telomeres is currently under investigation, the importance of telomere maintenance in conferring chromosomal stability and prevention of cell senescence has triggered immense interest in the field of human nutrition. Diet may be either a protective or a detrimental factor for TL, depending upon its composition. The first advantage of the MD appears to lie in its synergy among bioactive nutrients belonging to several food groups (Jacobs et al., 2009). Indeed, the evidence highlighted here indicates that the MD possesses a unique cocktail of multiple phytochemical compounds with remarkable biological properties, including the ability to target telomere maintenance. Synergistically, at a molecular level, the interaction between these components may exert a multifactorial protective effect that is capable of reducing disease risk through attenuating specific ageing mechanisms (i.e., inflammation and oxidative stress) (Mendez and Newman, 2018). Although more longitudinal studies of greater sample size are necessary to provide definitive evidence on the influence of the MD on TL, the above summary of preliminary human studies indicates that the MD may be considered a potential nutritional tool for preserving TL throughout the lifespan. However, since most studies on MD and TL are cross-sectional in design, it is difficult to determine a cause and effect relationship. Findings from more RCTs may provide more evidence on how to optimally apply this dietary pattern to maintain telomere integrity. Genetic factors are also involved in the regulation of TL. There is evidence that polymorphisms associated with telomerase activity and metabolism of nutrients may also modify the effects of dietary factors on telomere structure and function. Thus, although TL represents a measureable outcome, a nutrigenetic/nutrigenomic approach may add new information to fill the many gaps in our knowledge on the link between MD and TL. Future epidemiological studies and clinical trials should include a more comprehensive and personalized assessment, beyond estimation of TL, in order to gain deeper insights on the potential benefits of MD on telomere maintenance.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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