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Longevity and Diet. Myth or pragmatism?

Christina Chrysohoou*, Christodoulos Stefanadis

First Cardiology Clinic, Hippokration Hospital, School of Medicine, University of Athens, Greece

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ABSTRACT

Longevity is a very complex phenomenon, because many environmental, behavioral, socio-demographic and dietary factors influence the physiological pathways of aging and life-expectancy. Nutrition has been recognized to have an important impact on overall mortality and morbidity; and its role in extending life expectancy has been the object of extensive scientific research. This paper reviews the pathophysiological mechanisms that potentially link aging with diet and the scientific evidence supporting the anti-aging effect of the traditional Mediterranean diet, as well as of some specific foods. The diet and several of its components have additionally been shown to have beneficial effects on the co-morbidities typical of elderly populations. Furthermore, the epigenetic effects of diet on the aging process – through calorie restriction and the consumption of foods like red wine, orange juice, probiotics and prebiotics – have attracted scientific interest. Some, such as dark chocolate, red wine, nuts, beans, avocados are being promoted as anti-aging foods, due to their anti-oxidative and anti-inflammatory properties. Finally, an important moderator in the relationship between diet, longevity and human health remains the socio-economic status of individual, as a healthy diet, due to its higher cost, is closely related to higher financial and educational status.

1. Introduction

People have always looked for ways to extend both their life span and their quality of life. Longevity, through, is a complex phenomenon, because many environmental, behavioral, socio-demographic and dietary factors influence the physiological pathways of aging and life-expectancy. The aging process has been characterized by multiple alterations in organ function, energy metabolism and cellular apoptosis, which all have an impact on morbidity. One of the most important changes that elderly individuals have to face is the reduction of their lean body mass, especially from skeletal muscles, which reduces muscle strength. Furthermore, renal function, after the age of 80 years old, deteriorates due to a 50% loss of nephrons. A deficiency in sex-hormones leads to increased rates of dementia, osteoporosis, cardiometabolic syndrome and atherosclerosis [1]. The cardiovascular system of elderly individuals undergoes many alterations, as the number of myocytes is reduced, their mass is increased and the formation of fibrin leads to the increased prevalence of heart hypertrophy. This causes progressive stiffness, dilatation and lengthening of the arteries; leading to low arterial distensibility, altered autonomic system function [2] and future cardiovascular events [3,4]. One direct consequence is hypo-perfusion of the brain, among other organs. Also, the associated perforation of small cerebral vessels and the augmentation of vascular resistance, are related to dementia [5]. The incidence of cardiac hypertrophy also seems to be influenced by some of the physiological factors associated with aging, such as changes in the levels of growth differentiation factor 11 and the chemokine CCL11 (eotaxin) [6]. Additionally, lifestyle factors such as diet, daily caloric output, amount of physical activity, smoking and maintenance of an adequate body mass index seem to modify aging through epigenetic mechanisms [7,8].

Nutrition has long been recognized having an impact on overall morbidity and mortality in all species, including human. Many scientific studies assessing both the quality and the quantity of food intake have confirmed its importance; these have looked at overall dietary patterns as well as specific foods and groups of nutrients [9–12]. The purpose of this review article is to discuss the pathophysiological mechanisms that may link diet with human longevity and quality of life in old age.

2. Mediterranean diet and longevity

Quality of diet is key to human health. In this regard, the Mediterranean type of diet has been extensively studied [13]. The traditional Mediterranean lifestyle is characterized by daily physical activity and the consumption of particular seasonal foods; the main source of fat is olive oil. What is now termed the Mediterranean diet was described in the early 1960s in the northern

* Corresponding author at: 46 Paleon Polemiston Street, Glyfada, 166 74 Attica, Greece. Tel.: +30 210 9603116; fax: +30 210 9600719.
E-mail address: chrysohoou@usa.net (C. Chrysohoou).

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Mediterranean basin. With that diet, the consumption of fat is primarily from foods high in monounsaturated fatty acids. The Mediterranean diet is characterized by the consumption of large amounts of fruit, vegetables, legumes, nuts and whole grain cereals, and moderate amounts of fish, poultry and wine, but low amounts of red meat and meat products. Adherence to the traditional Mediterranean diet is associated with low mortality and reduced risk of chronic illnesses like cancer, metabolic syndrome and depression, as well as of cardiovascular and neurodegenerative diseases [14–17].

The Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain) evaluated the relationship between Mediterranean diet and longevity in 40,622 participants (37.7% males), aged 29–69 years who were recruited from five Spanish regions in 1992–1996. During a mean follow-up of 13.4 years, when 1855 deaths were documented, greater adherence to the Mediterranean dietary pattern was associated with a 21% reduction in mortality from all cause, by a 34% reduction in cardiovascular mortality; but there was no significant impact on overall crates of cancer [18]. In addition, a Mediterranean diet was shown to increase longevity in the HALE project (Healthy Aging: a Longitudinal study in Europe) [19]. Several components of this diet, including olive oil, antioxidants, omega-3 and -6 polyunsaturated acids, polyphenols and flavonoids, show anti-aging effects.

Recently, five places (i.e., Okinawa, Japan Sardinia, Italy, Loma Linda, California, Ikaria, Greece and Nicoya, Costa Rica) have been recognized as having a very high prevalence of octogenarians [20], and have joined the Blue-Zones, a National Geographic project [21]. Among the lifestyle habits that are common to those populations are high levels of daily physical activity (e.g., gardening and walking), positive attitude (e.g., an ability to articulate a sense of purpose and enriching their day with periods of calm and mid-day siesta) and a wise diet-high consumption of fruit, wild plants and vegetable and low consumption of meat products. That diet is similar to the Mediterranean type of diet [22].

In addition to studies of the overall Mediterranean diet, several of components have been evaluated for their beneficial effects. Among them, olive oil [23], due to its high concentration to polyunsaturated fatty acids and phenolic compounds, has been associated with decreased risks of cardiovascular disease, obesity, metabolic syndrome, type-2 diabetes and hypertension; it also improves endothelium function and oxidative stress, thereby promoting healthy aging and longevity. Additionally, the consumption of fruit and vegetable has been linked with reduced mortality among elderly populations [24,25], mainly due to their high concentration in polyphenols, carotenoids, folate acid and vitamin C. Much of the longevity advantage of Okinawa (one of the Blue Zones mentioned above) is thought to be related to this healthy dietary pattern, as the traditional diet is low in calories, but high in nutritional density, as it is rich in vegetable and fruit (and therefore rich in phytonutrients and antioxidants) but low in meat, refined grains, saturated fat, sugar, salt, and full-fat dairy products [26].

3. Mediterranean diet and co-morbidities

Advanced age is associated with a high prevalence of medical conditions; notable osteoporosis, dementia, atherosclerosis, cancer, arthritis, Dementia and depression have an incremental effect on both morbidity and mortality. A recent meta-analysis of 22 studies evaluated diet and the risk of stroke, depression, cognitive impairment and Parkinson's disease. It found that adherence to a Mediterranean diet was consistently associated with reduced risk for stroke and cognitive impairment; even only moderate adherence to the diet was associated with a reduced risk of depression and cognitive impairment, but its protective effect concerning stroke was only marginal [27].

In a recent cross-sectional study of an elderly Korean population, a modified traditional dietary pattern (rich in fruits, legumes and diary products), was related to decreased levels of functional disability, after adjustments were made for several covariates including energy intake [28]. Furthermore, in an epidemiological longevity study on Ikaria Island, Greece, moderate consumption of fish, due to the anti-inflammatory and antioxidative effects of omega-3 essential fatty acids, was related to a lower prevalence of depressive symptoms among elderly individuals [16]. Kidney dysfunction is one of the major co-morbidities of elderly individuals, and is related to cardiovascular and overall mortality (the annual incidence of end stage kidney disease of 1 per 1000 elderly adults). This has been mainly attributed to the association between chronic kidney disease and increased circulating levels of inflammatory markers, phosphate retention with medial vascular calcification, increased concentrations of parathyroid hormone, valvular calcification and dysfunction, anemia and left ventricular hypertrophy. The Ikaria study revealed that long-term fish consumption was independently associated with improved kidney function among elderly individuals, as it increased creatinine clearance levels, even after adjusting for overall dietary habits through the MedDietScore and other potential confounders [15].

A100 g/day increase in fish consumption can increase by 121% the likelihood of having well preserved renal function with creatinine clearance levels above 60 mL per min. A possible explanation for this association relates to the anti-inflammatory effects of essential omega-3 fatty acids that have shown to prevent diabetic nephropathy, albuminuria, glomerulosclerosis, tubulointerstitial fibrosis, inflammation and arterial hypertension – all long-term complications of diabetes [15]. Hyperuricaemia is another common medical problem in elderly populations. Increased uric acid levels are linked with uric arthritis; they have been recognized as markers of oxidative stress and have been linked with increased cardiovascular morbidity and mortality. The adoption of Mediterranean Diet, with its low amounts of animal purine and large quantities in vitamin C and E, carotenoids and polyphenols, has been shown to decrease the levels of uric acid, especially in male elderly individuals [21].

Heart failure has prevalence above 10%, in elderly population, and therefore constitutes an economic burden as well as a medical one. The Mediterranean diet has been shown to decrease the probability of heart failure, and even to improve diastolic heart function. Olive oil, which is rich in oleuropein, has been shown to reduce the size of infarct and to protect reperfused myocardium from oxidative damage after an acute coronary event. Furthermore, high levels of several serum antioxidants (including vitamins C, E and extracellular glutathione peroxidase) are associated with preserved systolic and diastolic left ventricular function [29].

4. Calories restriction and longevity

Besides nutrition, another aspect of diet that has been associated with longevity is energy intake. Calories restriction appears to be associated with extended life span, delay onset of age-related changes and a lower incidence of chronic diseases, such as cancer, atherosclerosis, diabetes mellitus and neurological diseases [30]. Studies have shown that lifelong calorie restriction can decrease the prevalence of cardiovascular risk factors, like lipid level and inflammatory factors, and can improve the sympathetic–parasympathetic balance by lowering overall heart rate and increasing heart rate variability [29]. Furthermore, oxidation processes are decreased by 20% calorie restriction or 20% expenditure by exercise.

Cellular interactions seem to be involved, as calorie restriction modulates signaling pathways, including those involving IGF1 insulin, DNA methylation, histone acetylation, and adiponectin and

genes related to mitochondria metabolism. Adiponectin, levels of which are increased by calorie restriction, suppresses the metabolic rearrangements that lead to the appearance of type 2 diabetes mellitus, promotes the oxidation of fatty acids in adipose tissue, thereby reducing fatty acid accumulation in other tissues, and regulates mitochondrial energy production; it also suppresses the formation of inflammatory factors, like TNF-a and inhibits the synthesis of adhesion molecules on endothelial cells (adhesion molecules promote atherosclerosis).

Calorie restriction also regulates FOXOs (an O subclass of the forkhead family of transcription factors), which control various cellular functions: apoptosis, cell cycle differentiation, the expression of genes involved in DNA repair and oxidative stress resistance, and the deposition of amyloid in Alzheimer disease [8]. Furthermore, calorie restriction seems to modulate the signaling pathways of sirtuins, which are NAD(+)-dependent enzymes that play an important role between epigenetic and genetic paths, and the activation of those responses may prevent cellular apoptosis.

Calorie restriction also prevents obesity, which itself appears to accelerate the aging process. Restriction of food intake is a well-known way to prolong life in laboratory animals. The comparatively few studies that have been conducted with humans have shown that food restriction lowers core temperature and basal metabolism energy expenditure, and thus energy is saved for critical conditions. Although there is a body of evidence suggesting a connection between age-related changes in human and calorie restriction, there is no scientific evidence that calorie restriction leads to longevity [30–32].

5. The mimetics of calories restriction: epigenetic implications of diet

Although calorie restriction has been shown beneficial effect on health and mortality, it is usually difficult to implement. Alternatives that (potentially) provide the same beneficial effects without requiring food restriction have therefore been investigated, in what might be termed a mimetic of calorie restriction. These alternatives should activate the same metabolic pathways but without the need to limit food intake and should have the same beneficial effects on morbidity and mortality. For instance, the combination of a healthy diet with exercise could have the same beneficial effects as calorie restriction on anti-inflammatory and anti-oxidative response, that is, over and above what could be achieved by a healthy diet alone [32].

Another proposed alternative is to modify the quality (as opposed to overall quantity) of the diet by reducing protein intake. The restricted methionine intake could decrease the degeneration of mitochondrial reactive oxygen species and thereby oxidative damage in mitochondrial DNA, lipids oxidation and the formation of inflammatory factors and thus reduce overall cardiovascular risk [33].

Alternate-day fasting, even for short periods, has also shown to have beneficial effects on both insulin and levels of inflammatory markers [32].

Specific components of the diet have also been investigated in this context. For example, resveratrol, a plant-derived polyphenol found in red grapes, seems to activate Sir2, a SIRT1 homolog, thereby mimicking the benefits of calorie restriction and expanding life span in several species [34]. Even in the case of high-fat dietary intake in human studies, resveratrol supplementation decreased the levels of circulating inflammatory factors and improved glucose tolerance and insulin sensitivity [33].

Recently, the Mediterranean diet has been shown to affect telomere length, independently of other biological and environmental cofounders. It seems that higher adherence to that diet was associated with leukocyte telomere length variability and telomerase activity among elderly people. Higher telomerase activity was also associated with a lower incidence of chronic ill-death, like hypertension, myocardial infarction, dementia, vascular diseases and heart failure [34,35]. This suggests another protective mechanism of the traditional Mediterranean diet.

6. Anti-aging diets

Recently, several foodstuffs have been claimed as “anti-aging”, principally on the basis of their anti-inflammatory and anti-oxidative properties: berries; dark chocolate; beans (due to their high concentration in low-fat protein, protease inhibitors, fibrins, genistein and minerals); fish; vegetables; nuts; whole grains; garlic (due to the high amount of garlic-derived polysulfides that undergo catabolism to hydrogen sulfide promoting vasodilatation); and avocados (as a great source of monounsaturated fat, vitamins and antioxidants).

Recent data on chocolate consumption suggest it reduces the risk of cardiovascular disease. This is mainly attributed to the flavonoids found in cocoa, which protect cells from free radicals; lower blood cholesterol and blood pressure, inhibit platelets adhesion and improve blood flow. Although some of the beneficial flavonoids are lost during the processing of chocolate, the addition of dark chocolate to daily nutrition still has beneficial effects. However, the calorie intake is rather high, about 500 calories per 100 g of dark chocolate, and there are other foods that are rich in flavonoids bur are less calorific, such as apples, grapes, peanuts, orange juice, red wine and tea. Orange juice drinking seems to disrupt the adverse inflammatory mechanisms that are activated after consumption of a high-carbohydrate, high-fat meal. Such meals suppress cytokine signaling 3, and interfere with insulin secretion and metabolism; therefore orange juice consumption during meals might be expected to help prevent the development of insulin resistance and diabetes mellitus, and eventually to reduce cardiovascular events and stroke. The same beneficial effects have been reported with moderate consumption of wine, due to the large amount of flavonoids found on the surface of red grapes. Additionally, alcohol intake is associated with a modest increase in HDL-cholesterol; it also helps to prevent arterial thrombus formation. Eating nuts is another nutritional habit that, as a part of a balanced diet, can beneficially affect blood lipids levels and reduce the risk of coronary heart disease, up to 40%. The high ratio of unsaturated to saturated fatty acids found in nuts has been held to be largely responsible for any anti-inflammatory and anti-oxidative properties [36–39].

There are several alterations to gut function with aging, and these affect the microbial balance of the colon, in turn potentially leading to increased inflammation, chronic infections and cancer. Several studies have evaluated the role of ingesting probiotic and prebiotic foods and supplements on the health of elderly people. Among the probiotics, species of *Lactobacilli* and *Bifidobacteria*, due to their non-pathogenic profile, are the most commonly used to modulate the microbial environment of the gut. They affect the biosynthesis of vitamin K; they alter the metabolic effects of indigestible dietary fiber; they increase colon peristalsis; they compete with pathogenic microbes for both nutrients and binding sites on mucosal epithelial cells; and finally, they also modify the host’s immune response [40,41]. Prebiotics are defined as natural or processed ‘functional foods’ as they contain biologically active compounds. It seems that their clinical benefits range from the prevention of colorectal cancer prevention to the modulation of host defenses against viral and bacterial infection. The most extensively studied prebiotics are the fructans (inulin, fructo-oligosacharides (FOS)) and galacto-oligosaccharides (GOS), and these have been

shown to have beneficial effect in irritable bowel syndrome, as well as on osteoporosis in elderly women; lactulose has been used to treat constipation [42].

7. Socio-economic implications on the diet–longevity relationship

Socio-economic status is an important moderator of the relationship between diet and longevity, as a healthy diet is associated with financial and educational status. This is mainly attributed to the higher cost of healthy foods compared to unhealthy food and the lack of time for food preparation in modern societies, even among elderly individuals [43]. In the light of the financial crisis presently being experienced in many countries around the world, food cost need to be taken into account. Reduced family incomes, increased taxes and indirect expenses, and high unemployment rates will all affect dietary behavior at the population level. Where individuals face an economical crisis, they tend to reduce the quality of their diet and to turn to unhealthy dietary choices by consuming foods rich in saturated fat and sugars, and low in antioxidants and essential fatty acids [44]. Public health policy should focus on the most vulnerable segments of society, in order to improve the quality of their diet and, consequently, their health status.

8. Conclusion

Diet has been considered as a non-pharmaceutical therapy for several chronic diseases. A healthy lifestyle – especially avoiding cardiovascular disease and its risk factors – should include a healthy diet. The guidelines for cardiovascular disease prevention include dietary recommendations (made on the basis of the specific characteristics of several foodstuffs) and behavior modification [11]. Diet may play a substantial role in promoting human health and prolonging life; however, the role of decision makers is crucial, especially under the current economic circumstances.

Contributors

Christina Chrysohoou wrote the manuscript; and Christodoulos Stefanadis critically reviewed the manuscript.

Competing interest

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