DERLEME

Diyet Biyolojik Yaşlanmayı Kronolojik Yaştan Ayırabilir Mi?

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ÖZ

Beslenme, organizmada meydana gelen biyolojik ve metabolik süreçler için gerekli olan besin ögelerinin vücuda alınması ve kullanılmasıdır. Yeterli ve dengeli beslenme; kardiyovasküler ve nörolojik fonksiyonların desteklenmesi, homeostazın sürdürülmesi ve sağlıklı yaşlanma sürecinin desteklenmesi ile ilişkilidir. Bireye ait beslenme durumu, organizmada biyolojik yaşlanma süreçleri ile ilişkili olan rapamisinin mekanistik hedefi kompleks 1 (mTORC1), AMP ile aktive olan protein kinaz (AMPK), sirtuinler ve insülin/insülin benzeri büyüme faktörü sinyal yolağı (IIS) gibi çeşitli metabolik yolakları modüle edebilir. Beslenme durumu ayrıca hücre bölünme kapasitesinin bir göstergesi olan telomer uzunluğu ile immün yanıt süreçleri üzerinde potansiyel etkileriyle yaşlanma sürecinde rol oynayabilir. Bu noktada, farklı bölgelerde benimsenen beslenme modellerinin ve spesifik diyet yaklaşımlarının, hastalık riskleri ile beklenen yaşam süresi üzerine etkilerinin aydınlatılması büyük önem taşımaktadır. Bu bağlamda bu derlemenin amacı; Batı tipi diyet, Akdeniz diyeti ve Okinawa diyeti gibi beslenme modelleri ile aralıklı oruç, enerji, protein ve amino asit kısıtlaması gibi diyet yaklaşımlarının yaşlanma süreçleri ile ilişkisini mevcut literatür temelinde incelemek ve sentezlemektir.

Anahtar Kelimeler: Beslenme durumu; Diyet; Uzun ömürlülük; Sağlıklı yaşlanma

Can Diet Dissociate Biological Aging from Chronological Age?

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ABSTRACT

Nutrition is the intake and utilization of nutrients required for the biological and metabolic processes of the organism. Adequate and balanced nutrition is linked to regulating cardiovascular and neurological functions, maintaining homeostasis and promoting healthy aging. Nutritional status may modulate metabolic pathways associated with biological aging processes, including mechanistic target of rapamycin complex 1 (mTORC1), AMP-activated protein kinase (AMPK), sirtuins and insulin/insulin-like growth factor signaling (IIS) pathway. This may also play a role in aging process through its potential effects on immune response and telomere length, an indicator of cell division capacity. In this context, it is important to elucidate the effects of specific dietary interventions and dietary patterns adopted in different regions on disease risk and life expectancy. Therefore, the objective of the present study is to examine and synthesize current literature regarding the relationship between aging process and dietary patterns such as the Western diet, the Mediterranean diet and the Okinawan diet as well as dietary interventions like intermittent fasting and calorie, protein and amino acid restriction.

Keywords: Diet; Healthy aging; Longevity; Nutritional status

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INTRODUCTION

Aging is the gradual process of natural changes that occur throughout the human lifespan, beginning at conception and continuing across all stages of life (1). Chronological age is the amount of time that have passed since a birth to a given date and is the main way of defining age (2). Beginning in early adulthood, as chronological age progresses, DNA errors become more common, both cellular perception and communication abnormalities and mitochondrial dysfunction develop (3). As telomere structures are located in the terminal parts of chromosomes, which function to protect DNA, shorten with each cell division and lose their protective capacity, human diploid cells can divide only for a limited number of repetitions. The cells that are damaged but remain viable, initiate the aging process by triggering the release of immune system-dependent activated factors such as proteases, growth factors, and proinflammatory cytokines, thereby causing harm to other healthy cells (4). As the aging process advances cellular and molecular damage accumulates over time, leading to a decline in the functional capacity of tissues and organs, alongside rising morbidity and mortality rates (5). This progressive loss of systemic integrity within the organism is defined as biological aging (6).

The healthy progression of the aging process is crucial for both individuals and society. The World Health Organization (WHO) defines the healthy aging process as the maintenance of functional ability to live with well-being and health, despite aging (7). An extended lifespan is defined as the survival status of the elderly population (8). An extended lifespan or healthy lifestyle, longevity, has long been a subject of curiosity and has been associated with having regular exercise, avoiding smoking, having no or less alcohol consumption, managing stress, having a successful marriage and living in moderation (9). Over the past few decades, the age threshold used to define long life has increased to 85 years, and a recent study considered this threshold to be 100 years (8). In modern societies, parallel to developments in the fields of technology and health, the average life expectancy has increased (8). Since 1990, the global average life expectancy has risen by 6.2 years, particularly as a result of the reduction in lower respiratory tract infection, stroke, cancer and ischemic heart disease mortality rates (10). According to a report published by the WHO in 2024, both average life expectancy and healthy life expectancy consistently increased over a 20-year period beginning in 2000; but decreased markedly after the COVID-19 pandemic. A report indicated that the global average life expectancy was 71.4 years, and healthy life expectancy was 61.9 years (60.9 years in men, 63.0 years in women) in 2021 (11). According to the 2025 Turkish Statistical Institute (TURKSTAT) report, the average life expectancy is 78.1 years, and healthy life expectancy is 57.6 years (58.9 years in men, 56.3 years in women) in Turkey (12). The global average life expectancy is estimated to increase by 4.6 years over the next 30 years (10), and the population aged above 65 is expected to reach 1.6 billion in 2050 (8). In developed countries, the morbidity and mortality rates associated with an increasing rising elderly population increase the load and cost related to health services, and this situation is beyond a personal objective (8). Therefore, to improve the quality of life of elderly people and help to maintain health services, investigations of factors related to healthy life are needed (3). The management of various outcomes that are associated with nutritional status, such as elevated blood glucose levels, body mass index (BMI) and obesity, is expected to further improve global health. Consequently, nutritional interventions have a great potential and importance for this purpose (10). All living organisms adapt to available food sources, and nutrients, and nutrient-sensitive signaling pathways can regulate cell metabolism and processes such as growth and aging (13). Therefore, diet is considered one of the main pillars of the healthy aging process, with physical activity and social-cognitive interactions (14). The importance of nutrition for health and longevity has been demonstrated in many studies (8,15). Healthy eating patterns may have major potential for improving healthy outcomes in elderly people (16). The objectives of this review were to examine the effects of several dietary patterns, such as the Western diet, the Mediterranean diet, and the Okinawan diet; specific dietary interventions, including calorie restriction, intermittent fasting (IF), protein and amino acid restriction; and aging-related metabolic signaling pathways and to investigate the potential associations between diet and healthy aging processes.

METHOD

In this review study, a comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases for articles up to 2026. The search utilized the keywords “longevity,” “nutrient-sensing mechanisms and pathways,” “Western diet,” “Mediterranean diet,” “Okinawan diet,” “Intermittent fasting,” “calorie and protein restriction.” In the selection process, original research articles were primarily included to evaluate clinical and specific metabolic outcomes, while comprehensive, up-to-date review articles were integrated to elucidate complex molecular mechanisms and signaling pathways.

Nutrition in Aging Processes

Nutrition is defined as the process and the physiological state by which a living organism obtains and utilizes food from the environment to support growth and development, sustain life, and maintain health through substances called nutrients (17). Nutrients have a crucial effect on telomeres, which are located in the protein-containing terminal regions of chromosomes in the DNA structure (18). Optimal nutrition, may protect against some chronic diseases, including hypertension, diabetes mellitus, cancer, and cardiovascular diseases, and delays the aging process through various mechanisms and is associated with longevity (5). Today, many food product with labels such as antiaging, protection against inflammation, and enhancement of brain health are available on the market. However, several factors should be taken into account, such as differences in food harvest, production stages, changes in nutrient composition, and overall nutritional status. Considering these factors and the limited potential of a single food to independently affect health, these unscientific claims are misleading and made primarily for marketing purposes. In this context, instead of focusing on the effects of one food product, investigations and subsequent dietary interventions, such as calorie restriction, time-restricted eating, amino acid restriction or healthy dietary patterns including the Western diet, the Mediterranean diet and the Okinawan diet, are promising and realistic approaches for healthy aging processes and longevity (14). To understand how holistic dietary approaches decelerate cellular aging, it is first essential to examine the four nutrient-sensing mechanisms and pathways through which cells detect nutrient availability or scarcity.

Nutrient-Sensing Mechanisms and Pathways

Nutrient-sensing mechanisms and pathways promote anabolism and storage during periods of nutrient abundance, whereas during scarcity, homeostatic mechanisms, including the mobilization of internal stores via autophagy, are triggered. Nutrient sensing can occur either directly through the binding of a molecule to a sensor or indirectly via a 'surrogate' molecule that reflects nutrient abundance (19). Nutrient-sensing is regulated through the insulin/insulin-like growth factor signaling (IIS), mechanistic target of rapamycin complex 1 (mTORC1), AMP-activated protein kinase (AMPK) and sirtuins pathways, which are considered molecular regulators of aging (20).

The mechanistic target of rapamycin (mTOR) signaling supports cell division, proliferation, and protein synthesis by integrating nutrients, growth factors and amino acids. Its overactivation suppresses autophagy and plays a progressive role in aging, age-related neurological diseases, diabetes and malignancies (21). It has been established that suppressing the mTORC1 complex with the pharmacological agent rapamycin extends lifespan in mice, highlighting its link to aging processes (13). Moreover, the inhibition of mTORC1 signaling is associated with improved immune response, prevention of age-related neurodegeneration, cancer and metabolic disorders (21).

Insulin and insulin-like growth factor-1 (IGF-1) - the latter synthesized in response to pituitary growth hormone- share a common intracellular cascade, known as the IIS pathway (22). This network integrates nutrient availability with metabolism, growth, development, longevity, and cellular behavior (23). The IIS pathway suppresses the activity of longevity-associated FOXO transcription factors by phosphorylating them and excluding them from the nucleus (24), while supporting the activation of MTOR (22). In animal models, the inhibition of IIS signaling pathway has been associated with an extended lifespan through FOXO activation, leading to improved mitochondrial function, activation of brown adipose tissue, and a coordinated decrease in cellular metabolic rate and oxidative damage (22).

AMPK and sirtuins are energy-sensing molecules that have co-evolved within cellular networks throughout evoloution (25). AMPK is an enzyme that senses cellular energy status and is activated by decreases in energy (26). In response to cellular energy depletion, it stimulates fatty acid oxidation while concomitantly suppressing non-essential ATP-consuming processes, including triglyceride synthesis, protein translation, and cellular proliferation (25). AMPK also regulates food intake and energy expenditure in mammals by mediating the effects of hormones and other agents that act on neurons in different hypothalamic regions (26). AMPK can reduce oxidative stress and other potentially harmful cellular events in the long term by inducing changes in mitochondrial biogenesis and function (25).

Sirtuins comprise a family of NAD^+-dependent histone and protein deacetylases, with seven distinct members (SIRT1-SIRT7) identified in mammals (25). Sirtuins respond to dietary changes such as IF diet and calorie restriction, as well as environmental changes such as DNA damage and oxidative stress. Sirtuin activation triggers transcriptional programs that increase metabolic efficiency, enhancing mitochondrial oxidative metabolism and resistance to oxidative stress (27). Sirtuins act as critical mediators of the lifespan extension associated with caloric restriction across diverse species, ranging from yeasts and nematodes to mammals. Among these, silent information regulator 1 (SIRT1) is the most extensively investigated family member and is centrally implicated in the regulation of longevity (25). Despite extensive research, the intricate crosstalk and precise molecular dynamics of nutrient-sensing pathways have yet to be fully elucidated (19).

Unhealthy Dietary Patterns

Western Diet

The Western diet is a hypercaloric and hyperglycemic diet that is rich in total carbohydrates, simple carbohydrates such as fructose and glucose, sodium, saturated fatty acids and omega-6 polyunsaturated fatty acids (18). The combination of higher energy intake with meals and preferred nutritionally poor snacks leads to regularly elevated levels of substrate and insulin in the circulation, increases reactive oxygen species (ROS) and free radicals, and causes a low-grade chronic inflammation (28). The daily requirements for dietary fiber, which has anti-inflammatory and antihypertensive effects, are generally not met by Western diets (29,30). Additionally, the omega-6/omega-3 polyunsaturated fatty acid ratio is generally 20:1, which is considerably higher than the optimal ratio and can promote the progression of proinflammatory and prothrombotic processes (28). Moreover, obesity which is strongly associated with the Western diet, may influence pathways to those related with cellular senescence (31). Human telomere length, an indicator of cellular senescence, are decreased by 30% in healthy obese individuals, similar to normal-weight or obese elderly individuals (29). The Western diet disrupts carbohydrate and lipid metabolism, increasing oxidative and endoplasmic reticulum stress. Additionally, this diet is associated with changes in the composition of the microbiota and through these pathways, may reduce life expectancy (31). In a study by Shively et al (32), the effects of a Western diet and a Mediterranean diet applied for 31 months to Macaca fascicularis monkeys on the composition of the specific microbiota of the breast tissue were investigated. The study revealed a significant increase in body weight (18.43±4.70% vs. 2.60±3.04%), and BMI (20.76±4.15% vs. 5.90±2.86%) after dietary intervention in monkeys following a Western diet. In a Western diet-fed monkey group, the increase in commensal Lactobacillus spp. was nearly 10-fold lower, while significantly higher levels of Lachnospiraceae, Oscillospira and Coprococcus were detected in the microbiota of breast tissue. In this study, the composition of breast tissue-specific microbiota was shown to be modulated by various dietary patterns, thereby exerting either beneficial or detrimental effects on overall health (32). In addition to its detrimental effects on the microbiota, the Western dietary pattern also establishes a pro-tumorigenic microenvironment. Indeed, in a study by Imbroisi Filho et al (31), the effects of a 26-week Western diet (65.4% kcal from fat and 19.6% kcal from sucrose) and a standard rodent diet (4.4% kcal from fat, 3.6 kcal/g energy density) on tumor progression were investigated in an adult mice. A Western diet-fed mice presented a nearly 2-fold increase in total body weight and a significantly greater increase in tumor weight and size. The level of the tumor-associated macrophage marker F4/80 was 38-fold greater among a Western diet-fed mice. Moreover, the Western diet promote tumor growth by increasing the metastatic potential of tumors, the insulin response and mitogenesis (31).

Healthy Dietary Patterns

Mediterranean Diet

The history of nutritional approaches for delaying the aging process derives from ancient times (33). Particularly, in the Mediterranean region, nutritional habits were closely associated with health and healthy aging. The word "diet" originates from the Greek word "díaita", which means "lifestyle". Hippocrates, known as the father of medicine, who also lived in the Mediterranean region, regarded food as medicine, whereas Plato, the philosopher, recommended a diet consisting of sufficient grains, legumes, fruits, and fish, with limited red meat and wine. The Mediterranean diet has evolved and developed throughout history around the local food resources of ancient civilizations such as the Greeks and Romans in the Mediterranean region (34). The main characteristic that distinguishes the Mediterranean diet is the use of extra virgin olive oil, which historically dates back thousands of years BCE and is called "God's gift", as the main source of fat (35). Four tablespoons (approximately 60 ml) of extra virgin olive oil are recommended for consumption daily as a part of the diet (36). Frequent consumption is observed for vegetables and fruits, legumes, whole grains, seeds and fish; moderate consumption is reported for dairy products such as cheese, yogurt and poultry; and limited consumption is reported for red meat, processed meats and wine in this diet (18). The Mediterranean diet is related to longevity in various aspects (9). The islands of Sardinia (Italy) and Ikaria (Greece) are two of the five regions called the Blue Zones, regions characterized by exceptional longevity. These two regions, where the Mediterranean diet is practiced, have the lower chronic disease incidence rates and the higher life expectancy compared with other societies (37). Specifically, as the main dietary fat source, olive oil is hypothesized to be one of the drivers of this exceptional longevity, owing to its high monounsaturated fatty acid content and a diverse array of polyphenols, phytosterols and other antioxidants (18). Olive oil may play a role in reducing the risk of dementia and some cancer types, such as the breast, endometrium, and ovary, by affecting the basic biological pathways of aging, and protecting telomere length (3). As a component of this diet, resveratrol, obtained from grapes and red wine, promotes longevity in animal models by mimicking calorie restriction (9). Also nuts which are rich in protein, unsaturated fatty acids, vitamin E and vitamin B6 have been shown to have a protective effect against cardiovascular diseases in humans (18). The Mediterranean diet, which is rich in antioxidants and bioactive compounds, acts as a natural preservative for telomere structures (18). Given its strong relevance to health and longevity, the Mediterranean diet was included in the list of "Intangible Cultural Heritage of Humanity" by UNESCO in 2010 (38).

Okinawan Diet

The Okinawan diet is based on the traditional dietary practices of the local population of Okinawa Island, Japan (9). Okinawa Island, located in southern Japan, is the region with the highest proportion of people aged 100 and over and the longest average healthy lifespan in the world (37). Compared with those living in Western Europe, North America and Japan, adult and elderly individuals living on Okinawa Island are less likely to suffer from neurodegenerative diseases and cardiovascular diseases (39). This diet, characterized by moderate consumption of locally grown produce, has been identified as one of the most important factors affecting the health and longevity of the local population. In particular, the principle of "food we get from the land and sea" has great importance for these people (16). Nutrient-dense carbohydrates, especially fresh vegetables, constitute approximately 90% of the energy intake in the traditional Okinawan diet (35). Sweet potatoes, together with other root vegetables, soy-based products, green and yellow vegetables, and various plants, are included in nearly every meal (16). Individuals on the island of Okinawa are reported to consume an average of 300 grams of vegetables daily (35). Purple sweet potato, which is a source of anthocyanin, contributes to the inhibiton of ROS and proinflammatory cytokines (40), and by activating sirtuin proteins, it exerts a calorie restriction-like effect (35). The turmeric contained in the herbal tea suppresses proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) by regulating the nuclear factor-kappa B

(NF-kB) signaling pathway and supports the production of antioxidant enzymes, including glutathione peroxidase and superoxide dismutase (40). Vegetables harvested from Japanese volcanic soil have inherent protective properties against free radicals due to their polyphenol, phytochemical, and vitamin C concentrations (35). Kombu seaweed, which is frequently consumed, is important for meeting the need for omega-3 fatty acids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA); iodine, and dietary fiber (37). The preference for low glycemic index food consumption along with the calcium- and magnessium-rich composition of water as a result of geological properties may play a role in lowering the risk of mortality associated with cardiovascular diseases (37). This diet includes moderate consumption of seafood, lean meats, fruit, and alcohol, but limited consumption of dairy products and eggs (16). In addition to fish consumption, pork is consumed as a terrestrial animal source into a limited extent. The consumption of pork cartilage and tendons provides benefits for cell proliferation and differentiation, and wound healing due to the collagen and elastin content (37). The population living on the island also frequently uses healthy cooking methods that combine braising, boiling and sauteing instead of harmful methods such as grilling or deep frying (16). This population follows the "Hara Hachi Bu" nutritional philosophy, which entails leaving the table after approximately 80% satiety; with these characteristics, Okinawan people differ from other populations that they practice calorie restrictions (35). Compared with the general population of Japan, Okinawan individuals have a lower average daily energy intake (37). This reduced energy intake can delay aging via a mechanism known as "hormesis," which induces low-dose stress in the organism (41). The Okinawan diet may contribute to the effective utilization of cognitive functions, closely linked to healthy aging, through various pathways (39). In a study by Ćurčić-Blake, brain activation during executive functions were investigated using fNIRS in 80 healthy individuals aged 65–80 years (41 from the Netherlands and 39 from Okinawa) (39). Although participants from both groups demonstrated similar levels of cognitive performance, Okinawans showed lower activation in task-related frontal regions. These findings suggest more efficient neural processing and the presence of different cognitive strategies in elderly Okinawan individuals (39). It should be noted that, in addition to healthy nutritional habits, factors such as a highly active outdoor lifestyle, sufficient vitamin D levels from sunlight, and a stress-free way of life are collectively thought to contribute to the general health status and exceptional longevity of the Okinawan people (35). Currently, Okinawa-inspired dietary interventions adopted in modern populations exert beneficial effects on body composition, gut microbiota composition and overall health (42). In a study by Manoharan et al, a 12-week Okinawa-based Nordic diet intervention was applied to 30 patients with type 2 diabetes (17 women, mean age 57.5 ± 8.2 years, duration of diabetes 10.4 ± 7.6 years, 90% overweight). The daily diet averaged total 1866 kcal (42% carbohydrates, 6% fiber, 35% fat, 23% protein) across three meals and two between meals. Each main meal started with a raw vegetable or salad portion (100 g for breakfast; 150 g for lunch and dinner). After the 12-week intervention, participants exhibited mean reductions of 6.8% in body weight and 6.1% in waist circumference, accompanied by statistically significant decreases in systolic and diastolic blood pressure, fasting glucose, HbA1c, insulin, cholesterol, and triglyceride levels. The intervention altered gut microbiota beta diversity, enriching Actinobacteria, Firmicutes, and Verrucomicrobia while depleting Bacteroidetes. Following a subsequent 16-week return to an ad libitum diet, participants experienced a rebound in BMI, systolic and diastolic blood pressure, fasting glucose, HbA1c, and insulin levels (42).

Restrictive Dietary Interventions

"Calorie restriction", which related to severely limiting energy intake during the day, and IF diet, which refers to consuming food only during restricted periods within a certain period, are two restrictive dietary interventions associated with longevity (5).

Calorie Restriction

Calorie restriction is a quantitative nutritional intervention designed to limit food consumption and reduce total energy, protein and other macronutrient intake (15). Among various dietary interventions, calorie restriction is recognized as one of the promising strategies for enhancing lifespan in healthy adults without a risk of malnutrition (43,44). Calorie restriction without causing malnutrition may improve metabolic health and promotes longevity (13). Due to the inherent challenges of conducting long-term calorie restriction trials in humans, its lifespan extending effects have been demonstrated in animal models (44). The health-promoting effects of calorie restriction include reducing oxidative damage; regulating blood glucose and cholesterol levels (9); modulating the metabolism of endogenous substrates, such as glycerol, ketone bodies, and fatty acids (5); stimulating autophagy, which typically declines with age; and preserving stem cell function. The leading effect of calorie restriction on extending lifespan is its ability to prevent or treat obesity, which is closely related to epigenetic aging, by controlling body weight (44). Evidence from animal models indicates that the most effective strategy for lifespan extension involves reducing total caloric intake by 50% while deriving 20–30% of those calories from protein (45). Post-weaning caloric restriction significantly prolongs lifespan in different mouse strains, provided its duration and severity are progressively increased without inducing starvation or death (46). Similarly, research conducted on C. elegans, demonstrated that continuous dietary restriction and AMPK activation promoted longevity by preserving mitochondrial network homeostasis and orchestrating critical mitochondria-peroxisome crosstalk to upregulate fatty acid oxidation (47). Indeed, while the traditional Okinawa diet must be understood holistically -encompassing both specific dietary compositions and broader lifestyle factors- it is reasonable to suggest that moderate protein restriction is an inherent component of this dietary pattern (44). Indeed, it has been reported that daily energy intake among certain Okinawan individuals over 100 years old was calculated as 1096 kcal/day for women and 1407 kcal/day for men (37). However, it must be strongly emphasized that long-term calorie restriction has been associated with low sex drive, decreased fertility, abnormal menstruation, impaired wound healing in young individuals, unexplained weight loss and increased health care requirements in the elderly population (9). And findings from animal studies cannot be directly generalized to human populations.

Intermittent Fasting (IF)

IF, which is defined as limiting food consumption during certain periods of the day or week and consuming food only during limited time intervals, is a promising nutritional intervention for healthy aging and longevity (5). IF includes different patterns, such as alternate-day fasting, modified alternate-day fasting and time-restricted feeding. Alternate-day fasting is based on an energy intake of only 25% of usual consumption after a day without any limit on food consumption (48). Modified alternate-day fasting involves following a normal dietary routine for five days and severely reducing energy intake on two nonconsecutive days a week (49). Time-restricted feeding entails restricting nutrient intake to only certain time intervals within the day (14). The most recognized models of time-restricted feeding are the 16/8, 12/12, and 20/4 protocols, which restrict the daily eating window to 8, 12, and 4 hours, respectively (48). IF patterns have been reported in many studies as safe eating patterns, providing metabolic benefits with only mild or no side effects (48,50). Compared with calorie restriction, which is a relatively difficult nutritional intervention, IF is more likely to be integrated consistently into daily life (49). Following an 8–12 hour fasting, circulating glucose levels decrease, prompting the hepatic β-oxidation of free fatty acids into acetyl-CoA. This acetyl-CoA is then converted into circulating ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone) that drive metabolism through ketolysis (48). Ketone body levels in the circulation increase to 0.2-0.5 mM in the initial period of fasting and to 1-2 mM after 48 hours of fasting (49). Beyond their primary role as energy substrates, the fasting-induced elevation of ketone bodies exerts profound physiological benefits by promoting the clearance of damaged proteins and organelles (49). Furthermore, these metabolites function as powerful signaling molecules that inhibit anabolic nutrient-sensing pathways, such as mTORC1 and IIS, while activating the sirtuin network to regulate cellular aging and promote overall longevity (48). IF has been shown to improve metabolic health with respect to insulin sensitivity and glucose tolerance, decrease the risk of age-related pathology and prolong the lifetime of various organisms such as yeast, bacteria and mice (5). Beyond the promising findings observed in animal models, recent clinical investigations reveal that IF also confers metabolic benefits in humans. In a study involving 25 healthy adult men, Erlangga et al. evaluated the genetic implications of a 30-day prolonged IF (17–19 hours of Ramadan fasting) by investigating the mRNA expression of key genes mediating autophagy, inflammasome activation, and cellular senescence (51). Their findings demonstrated that this fasting model can profoundly induce autophagy while promoting a downward trend in TNF-α levels and senescence markers. After two weeks from IF intervention, the expression levels of autophagy markers ULK1 (from 0.97 to 2.60; $p = 0.05$) and ATG5 (from 0.73 to 1.05; $p = 0.002$) showed a significant increase compared to baseline levels, while the change in BECN1 levels was not statistically significant ($p>0.05$). Specifically, ULK1 expression levels continued to increase statistically significantly until the end of the first month (from 2.60 to 6.21; $p<0.001$) and returned to almost basal levels in the first week after fasting. Although the expression levels of senescence markers (p16INK4A, p21, and p53) fluctuated over time, no statistically significant difference was found at any point in time. Among the inflammasome markers, an increase in NLRP3 and IL-1β expression was observed in the second week of fasting and at the end of the first month, and they returned to basal levels in the first week after fasting. Although TNF-α expression did not change significantly, it showed a decreasing trend during the intervention (51). In a randomized crossover study conducted with 24 healthy, non-obese young adults, the effects of isocaloric IF on the expression of genes associated with aging and metabolism were examined (52). This study shows that the IF protocol can stimulate protective biological responses even independently of weight loss. As part of the study design, participants completed two different 21-day intervention periods, including a 14-day washout period, in a randomized sequence of IF alone and IF supplemented with antioxidants vitamins, vitamin C and E (IFAO). Expression levels of SIRT1, SIRT3, SOD2, and TFAM genes were evaluated in venous blood samples taken before and after the intervention. It was found that the IF protocol alone resulted in a non-significant upward trend in all target genes, but only the increase in SIRT3 expression showed borderline significance (p = 0.07). In the IFAO combination, a non-significant upward trend was recorded only in SIRT1 and SIRT3 expression, while no change was observed in SOD2 and TFAM levels (52).

Dietary Protein and Amino Acid Restriction

In addition to various dietary patterns and nutritional interventions, the relationships between protein and amino acid restriction and longevity are also discussed in the literature (53). One of the potential effects of amino acids on aging processes is based on their relationship with the mTORC1 pathway (54). Branched-chain amino acids (leucine, isoleucine and valine) play significant roles in the regulation of protein synthesis, metabolism and aging processes, are the most potent stimulants that activate the mTORC1 pathway (53,54). S-adenosylmethionine, the active form of methionine, in combination with the amino acids leucine and arginine, activates the mTORC1 pathway and thereby inhibits autophagy. As a result, protein degradation products and damaged organelles lead to cellular toxicity (13). 3-hydroxyisobutyric acid, a catabolic intermediate of valine, may lead to insulin resistance by being transported to the vascular endothelium, thereby increasing the risk of sarcopenia in elderly animals (53). In various animal species, long-term calorie restriction and reduced intake of branched-chain amino acids and methionine have been shown to prolong lifespan by exerting positive effects on mitochondrial stress and inflammatory markers (43). According to the National Health and Nutrition Examination Survey (NHANES), protein restriction in individuals under 65 years of age reduces all cause mortality risk (49). While the extended longevity of the Okinawan population cannot be attributed solely to protein restriction by disregarding other dietary and lifestyle factors, the markedly limited protein intake (9% of total energy) of this cohort nonetheless provides compelling support for this NHANES report (13). On the other hand, it is critical to highlight that older individuals face an elevated risk of malnutrition and anabolic resistance (55). Inadequate protein intake is known to be associated with severe adverse outcomes, including the loss of muscle mass and strength, as well as an increased risk of cardiovascular diseases, stroke, and hypertension (54). Consequently, implementing protein restriction in this older population is highly contraindicated (55). A different study showed that even minimal amino acid intake in elderly individuals can increase protein synthesis and improve health by stimulating the mTORC1 pathway (54). Tryptophan serves as a precursor for the synthesis of nicotinamide adenine dinucleotide (NAD+), which is necessary for structural enzymes (46). Tryptophan may also improve cognitive ability and protect against dementia by participating in serotonin metabolism; it supports immune function by participating in the kynurenine pathway; and adequate intake through diet is recommended (54). Both endogenous branched-chain amino acid production and serum branched-chain amino acid levels have been shown to delay the aging process by preserving leukocyte telomere length (53,56). In conclusion, while protein and amino acid restriction has been shown to prolong lifespan in various animal models, it is imperative to recognize that such interventions can be highly contraindicated in humans, particularly in older populations. And considering both positive and negative effects the relationships between dietary protein amino acid intake and lifetime are remain controversial (53).

CONCLUSIONS

The aging process is a multifactorial phenomenon shaped by a complex interplay of genetic, environmental, and behavioral determinants, resulting in significant interindividual variability. Dietary patterns dynamically shape biological aging by regulating fundamental metabolic signaling networks, including the mTORC1, AMPK, sirtuin, and IIS pathways. By acting through these nutrient-sensing pathways, diet orchestrates critical downstream mechanisms -including autophagic flux, insulin sensitivity, and telomere maintenance- thereby profoundly impacting cellular homeostasis and the trajectory of senescence. While extensive preclinical research has highlighted the potent anti-aging effects of various dietary interventions in animal models, these findings cannot be directly extrapolated to human populations due to inherent biological and metabolic complexities. Nonetheless, such animal studies provide an indispensable mechanistic foundation to guide and support future clinical investigations. Ultimately, optimizing dietary habits remains a paramount strategy for enhancing human health, delaying the onset of age-related pathologies, and achieving a prolonged, healthy lifespan.

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