Role of Olive Oil and Monounsaturated Fatty Acids in Mitochondrial Oxidative Stress and Aging
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The free radical theory of aging argues that free radicals produced by the mitochondria are responsible for the damage that affects all biological tissues and leads to the aging phenotype. High olive oil intake is related to lower mitochondrial oxidative stress, including that which happens during aging. The degree of fatty acid unsaturation of mammalian tissues is also negatively correlated with greater longevity, and olive oil leads to less polyunsaturated biological membranes. Finally, monounsaturated fatty acids (such as those of olive oil) have been associated with greater longevity and a high degree of protection against age-related cognitive decline in humans.

Key words: aging, cognitive decline, free radicals, longevity, reactive oxygen species

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INTRODUCTION

In recent years, a large body of evidence has shown that nutritional factors may play a role in the etiology of chronic diseases, suggesting a link between dietary patterns and increased longevity. Higher consumption of olive oil is regarded as the hallmark of the traditional Mediterranean diet, and a growing knowledge suggests that olive oil, with its high levels of monounsaturated fatty acids (MUFA) and phenolic compounds, plays a role in the prevention of coronary artery disease and several types of cancer and is inversely associated with both systolic and diastolic blood pressure.

Aging, usually defined as the progressive loss of function accompanied by decreasing fertility and increasing mortality, has a great deal of significance for both society and science. Among the theories of aging, the free radical theory is currently supported by several lines of evidence. In principle, oxidative stress could be related to aging through variations in the generation of reactive oxygen species (ROS), ROS elimination, or both. However, although they may be involved in protection against various age-related diseases, antioxidants do not seem to control the rate of aging, because: 1) long-lived animals have low levels of tissue antioxidants and 2) experimentally increasing antioxidant concentrations does not increase life span. The impact of the diet and dietary components on aging and age-associated degenerative diseases has become widely recognized in recent years. However, most studies on this subject have focused on the effect of caloric restriction or antioxidant nutrient supplementation. In spite of the fact that dietary lipids modulate the membrane lipid profile and peroxidation rate, their effects on aging have been only partially studied. Studies have focused primarily on short-term treatments based on n-3 polyunsaturated fatty acids (PUFA).

Although fat is no longer the dirty word for consumers that it was just a few years ago, there is still a great deal of interest in healthy eating because of raised consumer awareness about the importance of limiting and selecting the consumption of fat and fatty foods. Current topics of research concern the relative nutritional disadvantages of consuming fats, focusing on which are the better or healthier fats. Therefore, not only is the correct use of fats always advisable in terms of ingested amounts (percentage of calories from fats as a proportion of total calories delivered), but so is the consumption of...
the right type of fat. But what does the "right fat" really mean? It means a barely damaging fat, possibly enriched with active and healthy molecules.

In this sense, virgin olive oil (technically a "fruit juice" and not a product of solvent extraction) possesses special features that make it unique: it is characterized by very high contents both of MUFA (mainly oleic acid) and antioxidant molecules (mainly phenolic compounds but also α-tocopherol and even coenzyme Q). Virgin olive oil may thus be a key component of successful dietary manipulations aimed at partially modifying the structure, and consequently the features, of biological membranes in the daily struggle against free radicals and oxidative stress-induced damage.

**MITOCHONDRIAL OXYGEN RADICAL GENERATION AND LONGEVITY**

Although antioxidants do not determine the rate of aging, their negative correlation with maximum longevity indicates that the endogenous rate of free radical production must be lower in long-lived than in short-lived animals. Free radicals can be generated at many cellular sites, but in healthy tissues the main source is the mitochondrial respiratory chain. Almost every study performed to date has shown that the rate of ROS production of mitochondria isolated from post-mitotic tissues is indeed lower in long-lived than in short-lived species.19 This occurs in all kinds of long-lived homeothermic animals independent of their relative rates of oxygen consumption, which are low in mammals of large body size and high in birds of small size. That characteristic can explain why endogenous tissue antioxidants correlate negatively with maximum longevity: long-lived animals have constitutively low levels of antioxidants simply because they produce ROS at a low rate.

The site in the respiratory chain where ROS production is lower in long-lived animals has been also studied. ROS generation in the respiratory chain occurs both at complex I and complex III.20,21 However, the respiratory complex responsible for the reduced mitochondrial ROS generation of long-lived animals is complex I, not complex III. Where the identity of the ROS generator inside complex I is concerned, various studies point to the FeS clusters. Since all of the FeS clusters of complex I are situated in the hydrophilic matrix domain of complex I, ROS generation originating in them will damage targets situated in the mitochondrial matrix, such as mitochondrial DNA (mtDNA), and this is thought to be especially relevant for aging.22

ROS can attack many different kinds of cellular macromolecules, including proteins, lipids, and DNA, and the latter is the most important for aging. mtDNA is situated very close to the site of mitochondrial ROS production. Since long-lived vertebrates have low rates of mitochondrial ROS generation, this would affect the level of oxidative damage in their mtDNA. In agreement with this notion, it has been found that brain and heart mtDNA oxidative damage, estimated as 8-hydroxy-2'-deoxyguanosine, correlates negatively with greater longevity in mammals and birds, and this does not happen in the case of nuclear DNA (nDNA). Moreover, levels of 8-hydroxy-2'-deoxyguanosine are higher in mtDNA than in nDNA in the brain and heart of a large number mammalian and bird species, in agreement with the location of mtDNA as very close to the sites of ROS production in the mitochondria.23 The relatively higher rate of mitochondrial ROS production of short-lived animals could be an important cause of their much faster rate of accumulation of mtDNA mutations during aging. Mutations in mtDNA, both deletions and point mutations, are known to occur with aging in post-mitotic tissues and to reach high levels in elderly individuals, especially in the control region responsible for mtDNA replication and transcription. Most interestingly, caloric restriction, the only experimental manipulation known to slow aging, also decreases the rate of ROS production at complex I and lowers oxidative damage in mtDNA.20,24

**FATTY ACID UNSATURATION AND LONGEVITY**

In addition to ROS production, there is another constitutive characteristic of long-lived animals that links aging with oxidative stress: the degree of fatty acid unsaturation of tissue cellular membranes. Unsaturated fatty acids are the cellular macromolecules most sensitive to oxygen radical damage due to the presence of highly unstable electrons near their double bonds, and their sensitivity to lipid peroxidation greatly increases as a function of the number of double bonds per molecule. Thus, a low level of fatty acid unsaturation (e.g., that of oleic acid) will decrease cellular oxidative stress. Detailed studies have shown that the degree of fatty acid unsaturation of mammalian tissues is indeed negatively correlated with maximum longevity.25 It has been suggested that the function of the low fatty acid unsaturation of mammals of large body size would be to decrease their metabolic rates, because low unsaturation will diminish the rates of passive ion leaks through the membranes. However, birds, which are much longer-lived than mammals of similar body size, have lower tissue fatty acid unsaturation than do mammals despite their high metabolic rates. Instead, fatty acid unsaturation is low both in birds and in mammals of large body size, in agreement with their high longevity. This characteristic constitutively protects them against lipid peroxidation. Moreover, lipid peroxidation products can cause detrimental

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protein covalent modifications. In accordance with this, lower levels of malondialdehyde-lysine and carboxymethyl-lysine protein adducts have been found both in mitochondria and tissues of the long-lived mammals and birds that display a low degree of fatty acid unsaturation. Recent studies indicate that experimentally induced decreases in liver and brain fatty acid unsaturation also lower oxidative damage in mtDNA. Further investigations are needed to clarify whether the same occurs for mtDNA lipoxidation markers such as malondialdehyde-deoxyguanosine.

The low degree of fatty acid unsaturation of long-lived animals is a parameter that tends to be homeostatically regulated at a different level in each species depending on its maximum longevity. Detailed analysis of fatty acid composition suggests that the main reason fatty acid unsaturation is low in slowly aging species is their possession of low tissue delta-5 and delta-6 desaturase activities, which are the main limiting factors in the biosynthesis of highly unsaturated long-chain n-6 and n-3 fatty acids (e.g., 20:4n-6 and especially 22:6n-3) from their precursors, 18:2n-6 and 18:3n-3. What changes between species with different longevities is not the total amount of unsaturates but their degree of unsaturation. Maintaining this at a low level minimizes oxidative damage to lipids, proteins, and mtDNA.

**DIETARY FAT TYPE AND MITOCHONDRIAL OXIDATIVE STRESS**

Over the past 15 years, we have accumulated a good deal of evidence on the effectiveness of dietary virgin olive oil in strengthening membranes by increasing their resistance to free radical-induced modifications following xenobiotic uptake or during physical training. We have also demonstrated that the oxidative modifications produced by the ingestion of fried fats may be successfully buffered by the use of virgin olive oil.

**Protection Against Oxidative Damage Induced by Adriamycin**

Because of the usefulness of doxorubicin in chemotherapy for the treatment of many types of cancer, researchers have expended great effort in trying to prevent or attenuate the side effects of Adriamycin administration. Several strategies have been adopted, including dosage optimization, synthesis and use of analogs, and combined therapy. In relation to combined therapy, although the anti-tumor action of Adriamycin may be mediated by a wide range of mechanisms, free radical production is among the main causes of cardiotoxicity mediated by this drug. This permits the use of strategies to reduce the toxic effects of doxorubicin without interfering with its anti-tumor properties.

The most effective approach has been the combination of drug delivery together with an antioxidant to reduce oxidative stress. Our laboratory has been working on the effects of antioxidant-rich virgin olive oil in relation to Adriamycin toxicity in rats for the past 15 years. Several aspects of metabolism, particularly those related to mitochondrial composition, function, and free radical generation have been studied in relation to Adriamycin and the intake of virgin olive oil or other types of edible oil. We found that when consumed as a dietary fat, virgin olive oil produces lower levels of peroxidation in both liver mitochondria and microsomes and attenuates the toxic effects of the drug in several components of the electron transfer chain. The effectiveness of virgin olive oil in protecting biological membranes is greater than that of either sunflower or corn oil. To study the relative importance of antioxidants present in virgin olive oil, we compared it with a low-antioxidant "refined" olive oil enriched with vitamin E. Supplementing refined olive oil with vitamin E greatly improved the effects of this edible oil against Adriamycin toxicity in rats. In fact, the levels of hydroperoxides produced by intraperitoneally injected Adriamycin were higher in refined olive oil than in virgin olive oil or refined olive oil with added vitamin E.

**Physical Training and Protection Offered by Diet**

Although it has many other advantages to the organism, physical exercise generates free radicals that affect both tissues and blood. For this reason, it is commonly used to study the effects of free radical generation in a quasi-physiological model. In this context, mitochondria are regarded as the main source of damaging species due to electron leakage from the electron transport chain following the increased electron flow required to meet the higher energetic requirements generated by physical exercise. Concomitantly, dietary fats also play a key role in the dissemination and amplification of oxidative stress-mediated damage in the main core of biological membranes. These latter features can be ascribed to several main causes: 1) unsaturated dietary fats are more susceptible to oxidation and to the production of lipid peroxides; 2) the lipid composition of biological membranes is modified according to the type of fat eaten; and 3) fats may be an important source of antioxidants. Therefore, the extent of oxidative damage occurring during and after exercise depends on the rate of oxygen consumption, the availability of unsaturated fats, and the dynamic balance of antioxidant/prooxidant cellular mechanisms.

In systematic studies performed during the past decade, we have also demonstrated that oxidative dam-

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age to tissues depends not only on training intensity but also on the type of exercise performed. We found that hydroperoxides in plasma, skeletal muscle, and liver mitochondrial membranes increased when rats were subjected to physical training, and this increase was higher when animals were fed a polyunsaturated-based diet.32 Trained animals fed a virgin olive oil-enriched diet had lower blood triacylglycerol and cholesterol values and a modified fatty acid profile in both plasma and tissue according to the fat ingested.33,34 Coenzyme Q, vitamin E, vitamin A, and uric acid all underwent dramatic changes, with sharp decreases in blood and concomitant increases at the mitochondrial level, suggesting a mobilization of these molecules among body compartments depending on local needs during and after training.32,35 Physical exercise and dietary fat also raised levels of several components of the mitochondrial respiratory chain.36 Finally, sedentary rats also showed clear differences in their ability to counteract lipid peroxidation, depending on the mono- or polyunsaturated diet they had consumed.37

**The Consequences of Frying Oils**

Thermal stressing of PUFA-rich culinary oils generates high levels of cytotoxic aldehydeic products arising from the fragmentation of conjugated hydroperoxydiene precursors. Such aldehydic products are harmful to human health. Moreover, several minor but pivotal components (such as antioxidant vitamins) may be lost during the frying process. Because worldwide consumption of frying oils is high, the dangers of thermally modified oils are of growing interest. We found that the frying process decreased the content of vitamin E and phenolics in the oils while enhancing total polar materials. These effects were markedly higher in sunflower oil than in virgin olive oil. Furthermore, rats fed fried oils had higher levels of lipid peroxidation and lower concentrations of plasma antioxidants. Rats fed a fried, sunflower oil-rich diet displayed a higher degree of lipid peroxidation in liver microsomes in vivo than rats fed fried virgin olive oil.38 Moreover, we found that the intake of fried oil greatly affected the hydroperoxide and thiobarbituric acid-reactive substance (TBARS) content of liver mitochondrial membranes, both being enhanced after the dietary treatments. Again, several mitochondrial respiratory chain components were affected.39

**VIRGIN OLIVE OIL IN THE ATTENUATION OF AGING-RELATED MITOCHONDRIAL OXIDATIVE STRESS**

As pointed out above, the type of dietary fat determines several biochemical parameters at the mitochondrial membrane level, since mitochondrial membranes, like the rest of the biological membranes, are able to adapt to some extent their lipid composition to dietary fat.38,33,40 On the other hand, adaptations of the electron transport system to dietary fat type have been widely reported.50,36 Moreover, oxidative stress is related to biological membrane composition. In that sense, a source of PUFA will lead to membranes being more prone to oxidation than a saturated or a monounsaturated source, as mentioned above. Thus, the type of dietary fat affects the structure and function of the mitochondria as well as their susceptibility to oxidative stress. Therefore, if we build "customized" biological membranes matched to a particular type of dietary fat, we may be able to modify in a positive direction the way and the degree to which different organs undergo aging.

Although the way that the membrane fatty acid profile adapts to the dietary lipid source has been previously reported, we were the first to report a lifelong adaptation to type of dietary fat type in a range of rat tissues using a large sample size (20 animals per group).41 Our results showed that adaptation of this sort effectively occurred during aging, with animals fed olive oil showing the highest proportion of MUFA in their mitochondrial membranes, and those fed sunflower oil registering the highest percentages of n-6 PUFA. This result is noteworthy because any benefit or damage derived from the intake of the two lipid sources is maintained throughout life, which suggests that there is a possibility of modulating the aging process through diet.

We tried to test this possibility by studying mitochondrial function; tissues with the ability to regenerate their cells, such as the liver, were able to buffer at least in part the effects of aging or changes in type of dietary fat, as has been suggested by the lack of changes in mitochondrial function in terms of cytochrome c oxidase activity.42 However, a loss of function was found in post-mitotic tissues such as skeletal muscle, heart, and brain. These tissues lack the capacity to replace damaged cells and probably possess a less-effective repair system (differences between liver and heart concerning repair mechanisms for mtDNA damage have been already reported).43 This loss of function was reflected in the large decrease in cytochrome c oxidase activity, which led to the decoupling of the mitochondrial electron transport chain, with further bioenergetic inefficacy and an increase in ROS production.41,42

Mitochondria from post-mitotic tissues try to buffer the unfavorable situation by increasing some elements of the mitochondrial electron transport chain, such as cytochrome b or PUFA. The increase in polyunsaturation attempts to enhance membrane fluidity and cytochrome c oxidase activity by the presence of a more polyunsaturated cardiolipin.50 However, both actions lead to a rise in ROS production. Apparently, the role of dietary fat in
this mechanism may lie in the building of an environment more or less prone to the generation and propagation of ROS, especially when, as the result of events such as aging, failures in the mitochondrial electron transport chain, take place. Moreover, dietary fat may modulate the phenomenon through variations in the antioxidant system and overall either upgrade or attenuate the process. Thus, since post-mitotic tissues are those most seriously affected by aging, diet should be particularly important in these tissues. Therefore, when dietary fat is dispensed as virgin olive oil rather than sunflower oil, a better general state at the mitochondrial function level was found, with lower ROS production, reduced loss of mitochondrial function and, in consequence, a delay in the occurrence of the aging phenotype.

Other results support the use of virgin olive oil instead of PUFA sources against mitochondrial oxidative stress during aging. We have previously reported that animals fed through life on virgin olive oil-based diets showed an improvement in the aging-related increase in blood lipids and DNA double-strand breaks at the level of peripheral blood lymphocytes, as well as in the fall in the antioxidant capacity of plasma with aging, compared with those fed on sunflower oil. In a different study, male Wistar rats were fed throughout their life on virgin olive or sunflower oil-based diets. At 6 and 24 months, liver mitochondria were analyzed for a deletion at the mitochondrial DNA level (in particular in two of the subunits from the mitochondrial electron transport chain, complex I), reactive oxygen species, antioxidants, and ultrastructural alterations. An aging-related increase in the relative amount of the deletion was observed in both dietary groups, but was higher in animals fed sunflower oil. Oxidative stress was lower in animals fed virgin olive oil; aging led to higher superoxide dismutase, catalase and glutathione peroxidase activities and increased α-tocopherol and coenzyme Q. Mitochondria from aged animals fed sunflower oil exhibited a lower number of cristae and a higher circularity. Overall, these results allow us to conclude that, from the point of view of aging, the intake of virgin olive oil presents important advantages compared with other dietary sources of PUFA.

Olive Oil, Monounsaturated Fatty Acids, Survival, and the Age-Related Cognitive Process

In an older southern Italian population with a typical Mediterranean diet, high MUFA energy intake appeared to be associated with a high degree of protection against age-related cognitive decline. The Italian Longitudinal Study on Aging (ILSA), a randomized, cohort study with a median follow-up period of 8.5 years, explored the hypothesis that high MUFA intake could protect against the development of cognitive impairment over time, the question of whether this protection is MUFA dependent, the role of PUFA intake in mild age-related cognitive decline, and whether MUFA and/or PUFA intakes in older persons are associated with protection against all-cause mortality. The study covered eight Italian municipalities, and each cohort comprised 704 subjects between 65 and 84 years of age. A standardized test assessing global cognitive functions (Mini-Mental State Examination, MMSE) was performed and a semi-quantitative food frequency questionnaire evaluating macronutrient energy intakes was administered. The subjects of our cohort that participated in the study were 278, 186, and 95 non-demented elderly subjects evaluated during the first (1992–1993), second (1995–1996), and third survey (2000–2001), respectively.

High MUFA, PUFA, and total energy intake were significantly associated with better cognitive performance over time. Total energy intake should be regarded as an important confounder of the relationship between diet and age-related cognitive decline, as we proposed in our methodological approach, suggesting that the association between macronutrient intake and cognition should be adjusted by total energy intake. No other individual dietary components of our study population were significantly associated with cognitive impairment over time. The association between high MUFA and PUFA intakes and cognitive performance remained robust even after adjustment for potential confounding variables such as age, sex, educational level, Charlson Comorbidity Index, body mass index, and total energy intakes. Our evidence of a protective role of unsaturated fatty acids against age-related cognitive decline confirms very recent findings that have shown that high intakes of MUFA and n-6 PUFA may protect against Alzheimer’s disease, whereas intake of saturated or trans-unsaturated fats may increase risk. Dietary intake of n-3 PUFA and weekly consumption of fish may reduce the risk of Alzheimer’s disease. In the recent Rotterdam Study, after a mean follow-up period of 6.0 years, intakes of total fat, MUFA, and PUFA were significantly associated with a lower risk of Parkinson’s disease.

On the other hand, in a recent study on the same ILSA sample, higher MUFA intake was associated with an increase of survival, and a higher ratio of unsaturated fatty acids to SFA increased total mortality only marginally, while no effects of other selected food groups were found. In particular, a higher MUFA intake was significantly associated with a reduction in all-cause mortality of about 20%. The evidence that the unsaturated to SFA ratio is only marginally associated with all-cause mortality should suggest that the estimated increase in mortality is
essentially due to the PUFA component. In fact, taking into account the fact that the term unsaturated fatty acids includes fatty acids with widely differing numbers of double bonds (from as few as 1 in oleic to as many as 6 in docosahexaenoic acid), which are known to have very different chemical and biological effects in tissues (positive or negative depending on the kind of fatty acid family involved), a clear distinction between the more consistent results in MUFA and the marginal ones in the unsaturated/SFA ratio should be made.

The mechanisms by which a high unsaturated fat intake might protect against cognitive decline in healthy older people are still unknown. This effect may be related to the role played by fatty acids in maintaining the structural integrity of neuronal membranes, determining the fluidity of synaptosomal membranes and thereby regulating synaptic neuronal transmission. Furthermore, essential fatty acids can modify the activity of certain membrane-bound enzymes (phospholipase A2, protein kinase C, and acetyltransferase) and the function of the neurotransmitters’ receptors. Moreover, free fatty acids, lipid metabolites, and phospholipids modify the functions of membrane proteins, including ion channels. Finally, the fatty acid composition of neuronal membranes in advancing age demonstrated an increase in MUFA content and a decrease in PUFA content, and rats administered diets high in SFA or PUFA were impaired in various tests of learning and memory.

Several studies on human infants have related breast-feeding, which leads to higher n-3 PUFA (docosahexaenoic acid, DHA) concentrations in the brain, and n-3 PUFA supplementation to better cognitive performance later in life. Finally, there is also evidence that associates a dietary deficiency in n-3 PUFA with changes in cortical dopaminergic function. While there are biologically plausible mechanisms to link n-3 and cognitive functioning, findings on the possible role of n-6 PUFA, as shown above, are controversial. In fact, high linoleic acid intake (n-6 PUFA) may increase the susceptibility of low-density lipoprotein cholesterol (LDL-C) to oxidation, which makes it more atherogenic, even if the association between linoleic acid and atherosclerosis is controversial. The ratio of dietary n-3/n-6 PUFA intake may therefore influence the potential role of PUFA on age-related cognitive decline; the optimal ratio of n-6:n-3 should be under 5:1.

One of the principal mechanisms by which MUFA could exert a beneficial effect on longevity is by decreasing the sensitivity of the cellular membranes to lipid peroxidation, a destructive process that also generates many mutagenic, carcinogenic, and DNA-modifying short-chain organic compounds. That sensitivity increases exponentially with the number of double bonds per fatty acid molecule. MUFA should thus be ideal as a means of avoiding the negative effects of both saturated and unsaturated fatty acids (e.g., n-6 PUFA). Moreover, they can protect membranes against oxidative damage while still maintaining them with a certain and necessary degree of fluidity. This offers a very likely connection between human and animal experimental studies. In fact, recent studies have shown that the longer the life span of mammals, the lower the degree of unsaturation of their cellular membranes, and this occurs by substitution of highly unsaturated fatty acids (such as 22:6n-3 and 20:4n-6) for less unsaturated fatty acids (such as 18:2 or 18:1n-9) without changing the total amount of PUFA.

Our findings on the effect of unsaturated fatty acids on longevity confirm those from 15 cohorts of the Seven Countries Study comprising 11,579 men between 40 and 59 years of age and considered to be healthy at entry. In this study, death rates were related positively to the average percentage of the dietary energy obtained from SFA, negatively to the dietary energy percentage from MUFA, and unrelated to the dietary energy percentage from PUFA, proteins, carbohydrates, and alcohol. All death rates were negatively related to the ratio of MUFA to SFA, while in the present study this association only approached statistical significance. However, only men were included in the analysis of the Seven Countries Study and their mean age was considerably lower than that of our sample.

Furthermore, in a recent large population study, although the follow-up period was only 44 months, adherence to a traditional Mediterranean diet was associated with significantly lower total mortality, mortality from coronary artery disease, and mortality from cancer. Interestingly, in this study, unlike ours, olive oil was associated with only a small and nonsignificant reduction in mortality, whereas the inverse association between mortality and the ratio of MUFA to SFA was stronger and statistically significant.

There are strong indications that intake of n-3 PUFA from fish reduces the risk of heart disease, possibly preventing cardiac arrhythmia and sudden death after myocardial infarction. In laboratory animals, n-6 PUFA can promote chemical carcinogenesis and suppress the immune system. As shown above, limited epidemiological data also suggest that high PUFA consumption may increase the risk of human cancer, atherosclerosis, and hypertension. Health recommendations refer to the ratio of PUFA/SFA, but the ratio of n-3 to n-6 could be more important. Although these are promising findings, further studies are needed in larger samples of elderly subjects to determine the role of unsaturated fatty acid intake in age-related cognitive

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decline and survival in relation to other environmental
and genetic factors.

SUMMARY

Nutritional factors may play a role in the etiology of
chronic diseases and probably in longevity. Important
evidence suggests that olive oil plays a role in the
prevention of coronary artery disease, several types of
cancer, and high blood pressure. During the past 15
years, we have accumulated a good deal of evidence on
the effectiveness of dietary virgin olive oil in strengthen-
ing membranes by increasing their resistance to free
radical-induced modifications following xenobiotic up-
take, physical training, and the ingestion of fried fats.
Unsaturated fatty acids are the cellular macromolecules
most sensitive to oxygen radical damage due to the
presence of highly unstable electrons near their double
bonds. A low level of fatty acid unsaturation decreases
cellular oxidative stress.

Detailed studies have shown that the degree of fatty
acid unsaturation of mammalian tissues is negatively
correlated with maximum longevity, and that virgin olive
oil may attenuate oxidative stress related to aging. High
MUFA intake has been significantly associated with
better cognitive performance over time. This evidence
confirms very recent findings showing that high intake of
monounsaturated fatty acids may protect against Alzhei-
mer’s disease, whereas intake of saturated or trans-
unsaturated fats may increase risk. On the other hand, in
a recent study, higher monounsaturated fatty acid intake
was associated with increased survival, and a higher ratio
of unsaturated fatty acids to saturated fatty acids in-
creased total mortality only marginally, while no effects
of other selected food groups were found. Although these
findings are promising, further studies are needed in
larger samples of elderly subjects to determine the role of
monounsaturated fatty acids in age-related cognitive de-
cline. Of particular importance will be the development
of experiments with humans designed to confirm the
promising finding on mitochondrial oxidative stress
found in animals.

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REFERENCES

1. Keys A. Coronary heart disease in seven countries.
Circulation. 1970;41:201–211.
2. World Cancer Research Fund. Food, Nutrition and
the Prevention of Cancer: A Global Perspective.
between eating patterns recommendations and subse-
4. Osler M, Schroll M. Diet and mortality in a cohort of
elderly people in a north European community. Int J
5. Lasheras C, Fernandez S, Patterson AM. Mediter-
renean diet and age with respect to overall survival
in institutionalized, nonsmoking elderly people.
study of diet quality and mortality in women.
patterns and mortality in Danish men and women: a
prospective observational study. Br J Nutr. 2001;85:
219–225.
8. Trichopoulou A, Costacou T, Bamia C, et al. Adher-
eence to a Mediterranean diet and survival in a Greek
study of association of monounsaturated fat and other
types of fat with risk of breast cancer. Arch Intern
10. Stoneham M, Goldacre M, Seagroatt V, Gill L Olive
oil, diet and colorectal cancer: an ecological study
and a hypothesis. J Epidemiol Comm Health. 2000;
54:756–760.
11. Psaltopoulou T, Naska A, Orfanos P, Trichopoulos
D, Mountokalakis T, Trichopoulou, A. Olive oil, the
Mediterranean diet, and arterial blood pressure: the
Greek European Prospective Investigation into Can-
13. Barja G. Aging in vertebrates, and the effect of
caloric restriction: a mitochondrial free radical pro-
duction-DNA damage mechanism? Biol Rev Camb
14. Meydani M. Nutrition interventions in aging and
15. Sohal RS, Mockett RJ, Orr WC. Mechanisms of aging:
an appraisal of the oxidative stress hypothe-
16. Mataix J, Ochoa JJ, Quiles JL, Olive oil and mito-
chondrial oxidative stress. Int J Vit Nutr Res. 2005;In
press.
17. Carrie I, Guesnet P, Bourre JM, Frances H. Diets
containing long-chain n-3 polyunsaturated fatty ac-
ids affect behaviour differently during development
18. Battino M, Ferreiro M.S. Ageing and the Mediterra-
nean diet: a review of the role of dietary fats. Public
19. Orr WC, Sohal RS. Does overexpression of Cu,Zn-
SOD extend life span in Drosophila melanogaster? Exp
restriction decreases mitochondrial free radical
generation at Complex I and lowers oxidative dam-

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