CHAPTER 17

DIETARY FATS AND AGE-RELATED DISEASES

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Abstract: Balanced diet, which includes fats and oils, is one of the important factors for attaining and maintaining a healthy life. Numerous clinical studies have shown the detrimental effects of trans- and saturated-fats in the origin and progression of various age-related diseases, such as coronary heart disease, diabetes, cancer and neurodegenerative diseases. This article reviews the role of dietary lipids in various age-related diseases, and discusses the appropriate dietary fat requirements for the prevention of such diseases

Keywords: Polyunsaturated fatty acids, saturated fats, diseases, antioxidants

1. INTRODUCTION

Fats and oils, as a specific component of diet, provide essential fatty acids and facilitate the delivery of various other nutrients that are vitally important for normal physiological functions. As structural units, fats and lipids are the integral parts of the cellular and organellar membranes, and of the nerve sheathing. Normal physical and mental growth, development and maturation depend on the optimal availability of dietary fats. Additionally, body fat or adipose tissue helps to protect vital organs from injuries and shocks, and provides a source of energy during prolonged exercise. Fats have the highest caloric density among foodstuffs (9 kcal/g), and are also the carriers of vitamins such as A, D, E and K. Vegetable oils are important sources of natural antioxidants, such as tocopherols, tocotrienols and carotenoids. Dietary lipids also play an important role in the immune function by modulating eicosanoid production (Formo, 1979; Lands, 1986; Robert, 1990).

Oils and fats are consumed for caloric reasons and also for their non-caloric functions such as flavour, palatability, appearance, consistency and texture. Intake of oils and fats is primarily through cooking oils, baked products, margarines and

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spreads, various fried products, chocolate and sugar confectionery, dairy products and desserts, salad oils, mayonnaise and other dressings. Fats are also consumed when meat, poultry or fish are eaten. All these sources make up a complex matrix of various visible and invisible oils and fats that end up in our body.

The content and composition of dietary fat, especially the carbon chain length, degree of saturation, positioning of the double bonds and cis and trans configuration of the unsaturated fatty acids and region-specific distribution of the fatty acids in the triacylglycerols have significant contribution to human health. Good health is dependent not only on the quantity but also on the quality of the fat. Several diseases such as hypercholesterolemia and related cardiovascular disorders, type 2 diabetes, inflammation, certain types of cancer, renal diseases and Alzheimer's disease are directly or indirectly related to dietary fats. Very often such diseases are associated with excessive and improper intake of dietary fats or deficiency of essential fatty acids. Excessive amounts of free radicals generated from oxidised oils are also related to the origin of various diseases. This chapter discusses the effects of different types of dietary fats on the origin and progression of various age-related diseases.

2. TYPES AND SOURCES OF DIETARY FATS

Fats and oils of animal and plant origin consist almost exclusively of the simple lipid class triacylglycerols (often termed "triglycerides"). They consist of a glycerol moiety with each hydroxyl group esterified to a fatty acid. Triacylglycerols are synthesised by enzyme systems, which determine that a centre of asymmetry is created about carbon-2 of the glycerol backbone, so they exist in enantiomeric forms, i.e. with different fatty acids in each position. The positions of the fatty acids in the glycerol backbone are denoted by sn-1 or sn-3, the two terminal positions and sn-2, the middle position. (The abbreviation 'sn' stands for 'stereospecific numbering'). Generally, in case of vegetable oils, unsaturated fatty acids are situated in the sn-2 position while SFA's occupy the sn-1 and sn-3 positions (Hunter, 1992). The naturally occurring fatty acids are mainly straight-chain compounds containing an even number of carbon atoms. Fatty acids can be divided into the following three groups: (i) saturated; (ii) monounsaturated and polyunsaturated; and (iii) branched-chain. Unsaturated fatty acids may contain one or more double or triple bonds and can be classified as monounsaturated, polyunsaturated, and acetylenic fatty acids.

The distribution of the fatty acids in triacylglycerols can be rearranged or 'structured' and if desired, new fatty acids can also be introduced through a process called interesterification. The rationale behind the development of structured lipids is based on the effects of dietary fatty acids and the importance of their relative position (sn-1 or sn-3 and sn-2) in triacylglycerol molecules. Triacylglycerols can be tailored to contain appropriate proportions of n-3, n-6, n-9 and SFAs which are beneficial in lowering serum LDL cholesterol and triacylglycerol levels, preventing thrombosis, enhancing immune system, reducing the risk of cancer and improving nitrogen balance (Akoh, 2002).

The nomenclature omega-9, omega-6 and omega-3 fatty acids are related to the position of the first unsaturation in the fatty acid chain relative to the methyl end. Position of the double bond can also be denoted in the form (n-x), where n is the chain-length of the fatty acid and x is the number of carbon atoms from the double bond in the terminal region of the molecule. In case of linoleic acid, it lies at the sixth carbon and as regards linolenic acid it lies at the third carbon atom from the methyl end of the molecule. Thus linoleic acid is termed omega-6 (or n-6) and alpha-linolenic acid is called omega-3 (n-3) fatty acid.

2.1 Saturated fatty acids (SFA)

Saturated alkanoic acids have the general formula R-COOH where R represents straight-chain hydrocarbons having the formula C_nH_{2n+1} or $CH_3(CH_2)_nCOOH$. SFA range from short-chain volatile liquids to waxy solids. Common saturated fatty acids are lauric, (C_{12}), myristic (C_{14}), palmitic (C_{16}) and stearic (C_{18}). Milk fats are characterised with C_4 to C_{10} fatty acids while C_{12} to C_{24} occur in fats and oils. Higher members up to C_{38} are found in waxes. SFA are present in appreciable amounts (50–90% of total fatty acids) in milk fat, coconut oil, palm oil and palm kernel oil.

2.2 Monounsaturated fatty acids (MUFA)

Monounsaturated fatty acids contain one double bond which is present mostly at the ninth carbon atom from the methyl end. They are referred to as omega-9 or n-9 fatty acids. Though more than 100 monounsaturated fatty acids are known, oleic acid (cis-9-octadecaenoic acid) is the most widely distributed of all fatty acids. It acts as the precursor of biosynthesis of omega-9 families of fatty acids. Petroselinic, vaccenic and erucic acids are some examples of other commonly found MUFA. Two most common sources of oleic acid are olive oil and rapeseed oil. However, genetic mutation and selective breeding have developed 'high-oleic' version of commodity oils such as sunflower, safflower, peanut, soybean and canola oil. These 'high-oleic' oils typically contain more than 70% oleic acid and are commercially available for various food applications (Kristott, 2003).

2.3 Polyunsaturated fatty acids (PUFA)

PUFA contain more than one carbon-carbon unsaturation. There are two major PUFA families: one based on linoleic acid (delta-9,12-18:2 omega-6) and the other on alpha-linolenic acid (delta-9,12,15-18:3 omega-3). The importance of PUFAs in human health and nutrition was postulated first in the 1920s. Linoleic acid and alpha-linolenic acid were termed essential fatty acids (EFA) since these cannot be synthesised in vivo by animals, including humans. Therefore EFA must be consumed from plant-derived dietary sources. Once consumed, both linoleic

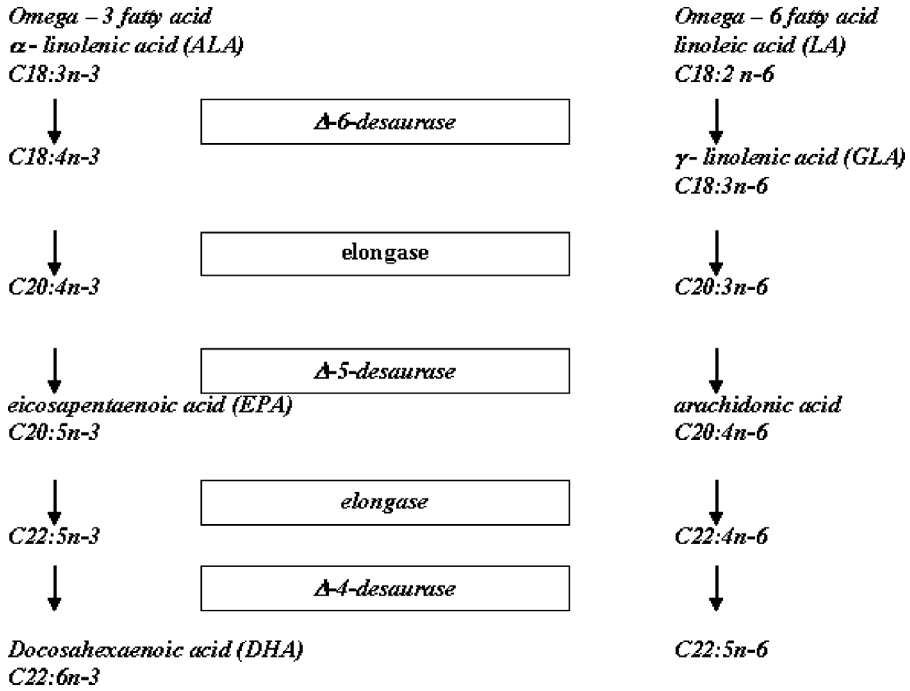

Figure 1. Metabolic pathways of conversion of linoleic and linolenic acid (Adapted from Ref 7)

and alpha-linolenic acid are converted to other long chain omega-6 and omega-3 fatty acids by metabolic pathways in mammals through enzymatic catalysis (see Figure 1).

These changes require chain-elongation and desaturation. The most important omega-6 metabolite is arachidonic acid (AA, 20:4) and the most important omega-3 metabolites are eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6). EPA and DHA are the most bioavailable forms of omega-3 for humans. Linoleic acid is the major fatty acid in vegetable oils such as soybean, sunflower, safflower, peanut and corn. Vegetable oils such as flax, blackcurrant, rape, perilla and chia contain moderate to high amounts of alpha-linolenic acid. Soybeans, navy beans and walnuts are also sources of alpha-linolenic acid. It is also present in phytoplankton, zooplankton and many marine species.

2.4 Trans fatty acids

Trans fatty acids are those fatty acids that contain double-bond geometry in the trans (E) configuration, i.e. the hydrogen atoms are placed on the opposite sides of the double bond (Hunter, 1992). They naturally occur in small amounts (<1%) in unmodified vegetable oils and fats. The majority of trans fatty acids in our diets

come from partially hydrogenated oils. Hydrogenation is a chemical reaction in which hydrogen is added to the ethylenic linkages (double bonds) of unsaturated fatty acids (Hastert, 1996). Small amounts of trans fatty acids occur naturally in milk, butter and tallow as a result of biohydrogenation in ruminants. Blends of hydrogenated and non-hydrogenated oils and fats have been used to produce base stocks for margarine, frying oils and a variety of general purpose fats where solid and stable fats are required. Hydrogenated fats have been given the generic name "vanaspati" in India, and are used for numerous edible applications. The most abundant of the trans fatty acids in partially hydrogenated oils is elaidic acid, the trans isomer of natural cis-oleic acid.

3. FATS AND AGE-RELATED DISEASES

The detrimental effects of improper dietary fats are not observed overnight but the damages undergo a slow, yet certain cumulative pattern and surface at later stages of life. Thus, very often the root causes of various diseases during old age stem from the dietary habits at the young age. The effects of dietary fats on the major age-related diseases are discussed in the following sections.

3.1 Cardiovascular diseases

Early epidemiological observations suggested an association between dietary fat and cardiovascular diseases (Keys et al., 1957; Keys et al., 1959). One of the major risk factors for cardiovascular disease is hypercholesterolemia. Coronary heart disease (CHD) is caused by atherosclerosis, a process characterized by endothelial dysfunction, in connection with cholesterol deposition macrophages and smooth muscle cells in the arterial walls and various other factors. The risk of CHD increases proportionally with serum levels of total and low density lipoprotein (LDL) cholesterol and decreases with increase in high density lipoprotein (HDL) cholesterol (Martin et al., 1986; Castelli et al., 1986). The increased ratio of total cholesterol to HDL is associated with a rise in risk for all-cause mortality in men aged 65 years and above. When considered alone, an elevated level of HDL seems to be protective against mortality from all causes in men aged 65–74 years but this effect diminishes over the age of 75 years (Chyou et al., 2000).

3.1.1 Effect of saturated fatty acids on cholesterol

Saturated fatty acids are reported to be cholesterol-raising but not all acids in this class show the same effect (Mensink et al., 2002). Alkanoic acids can be divided into three major classes: (i) fatty acids having less than 12 carbon atoms; (ii) fatty acids with 12, 14 or 16 carbons atoms; and (iii) the 18 carbon homologue, stearic acid. It has been suggested that the first group slightly reduces LDL cholesterol relative to palmitic acid but raises it when compared to oleic acid (Cater et al., 1997). From the second group, lauric acid has been reported (Denke and Grundy 1992) to increase

plasma total cholesterol and LDL cholesterol concentrations compared to oleic acid but to a lower extent relative to palmitic acid while effects on HDL cholesterol were not observed. However, an increase of total cholesterol due to an increase of HDL cholesterol as compared to palmitic acid has also been reported (Temme et al., 1996). Myristic acid has an increasing effect on both LDL cholesterol and HDL cholesterol and hence on total cholesterol concentration relative to palmitic acid (Zock et al., 1997). Despite being hypercholesterolemic compared to stearic acid (Mensink et al., 2002), palmitic acid has not been labeled in all cases as a cholesterol-elevating saturated fatty acid (Ng et al., 1992; Choudhury et al., 1995). This holds true when dietary cholesterol intake is less than 300 mg/day and 6–7% of daily energy comes from linoleic acid. Stearic acid had been shown not to elevate plasma total cholesterol concentration (Keys et al., 1965; Grande et al., 1970). In fact, later studies revealed that stearic acid has a neutral effect on plasma lipoproteins similar to that of cis-monounsaturated oleic acid (Bonanome and Grundy, 1988). Overall, it can be concluded that, saturated fatty acids such as lauric, myristic and palmitic acids raise the levels of both total and LDL cholesterol.

3.1.2 Effect of trans fatty acids on cholesterol

Trans monounsaturated fatty acids, raise LDL cholesterol concentrations (Katan et al., 1995) and decrease HDL cholesterol concentrations (Mensink et al., 2002) in contrast to intake of cis-monounsaturated fatty acids. Investigations on whether TFAs from ruminant sources differ from those resulting from partial hydrogenation with respect to CHD have shown that below an intake level of 2.5 g/day, there were no differences in effects on CHD between the two sources of TFAs but that at total intake levels of above 3 g/day industrial TFAs cause bigger risk of CHD (Weggemans et al., 2004).

3.1.3 Effect of PUFA on CHD

In the recent years, the beneficial cardiac health effects of PUFA, especially omega-3 fatty acids have attracted considerable scientific and public interest. The present consensus is that the cardio protective effects of EPA and DHA at the low dosage used in recent secondary prevention trials mainly results from an effect on the ischemic myocardium and probably not from an effect on blood lipids and hemostasis. On the other hand, dietary α-linolenic acid, the precursor of EPA and DHA may be protective through mechanisms other than the myocardial (anti-arrhythmic) ones (De Lorgeril and Salen, 2004a). Epidemiological studies and dietary trials in humans suggest that α-linolenic acid is a major cardio-protective nutrient (De Lorgeril et al., 2004b).

One of the studies showing the effect of alpha-linolenic acid on heart was the Multiple Risk Factor Intervention Trial (MRFIT). It involved 12,000 men aged between 35 and 57 years who had high risk of heart diseases. It was found that risk of death from CHD was lowest in subjects with highest intakes of alpha-linolenic acid (Dolecek, 1992). The Lyon Diet Heart Study had shown the effect of alpha-linolenic acid on people who had survived one heart attack. Participants in the test group had

an increased intake of alpha-linolenic acid by 68% and had lower blood cholesterol and triglyceride levels. In fact, alpha-linolenic acid rich diets were associated with a 70% reduction in coronary problems and cardiac deaths (De Lorgeril et al., 1999). Other investigations indicate that dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women, possibly by favourably changing vascular inflammation and endothelial dysfunction (Zhao, 2004). These authors have also reported that high-PUFA diets (diets rich in linoleic acid and alpha-linolenic acid) decrease serum total cholesterol, LDL cholesterol and triglycerides.

Fish oils, rich in long-chain omega-3 fatty acids, have been found to reduce plasma triacylglycerols of hyperlipidemic subjects, especially in patients with elevated triglyceride concentrations (Harris, 1989). In the case of normocholesterolemic subjects, long-chain PUFA from fish oils do not induce any changes in plasma LDL cholesterol or HDL cholesterol concentrations but have a lowering effect on plasma triacylglycerols and the concentration of cholesterol in very low density lipoprotein (VLDL) (Harris et al., 1983).

3.2 Effect of PUFA on cardiac mitochondrial membranes

Biological membranes are made of complex matrices of lipids, proteins, lipid-proteins complexes, glycolipids and glycoproteins. With aging, both the hormonal status and lipid component of a membrane change and the remodelling of myocardial cell membrane is a major occurrence. Age-related mitochondrial changes include increase of membrane rigidity, cholesterol, phosphatidylcholine, omega-6 fatty acids, and decrease in omega-3 fatty acids and cardiolipin (Pepe, 2005). Studies have shown how specific age-related changes of phospholipids and fatty acid composition in the cardiac mitochondrial membranes can influence vital mitochondrial processes and the heart's adaptive response to stress and survival. The various constitutive changes that occur in heart cells with increased age reduce the cellular capacity to tolerate and adapt to ischemic stress.

The primary PUFA in myocardial membranes are omega-6 linoleic and arachidonic acid and omega-3 DHA. With abundant use of linoleic acid rich oils such as, soybean, sunflower and corn, and low consumption of fish in the western world, there is a much higher intake of linoleic acid and a very low amount of omega-3 fatty acids. Such vast excess of omega-6 fatty acids compete with the omega-3 fatty acids and utilise the delta-5 and delta-6 desaturase enzymes to a greater extent for subsequent conversion into higher homologues of the omega-6 series. Delta-5 and delta-6 desaturase enzymes are crucial for the conversion of linoleic acid to arachidonic acid and conversion of α-linolenic acid into EPA and DHA. The activity of microsomal delta-6 desaturase is less than that of delta-5, making it the rate limiting step involved in two stages of DHA production (Cho et al., 1999). Thus, α-linolenic acid cannot be converted into adequate levels of EPA and DHA (Sprecher et al., 1995). In a situation where there is excess linoleic acid and insufficient omega-3

fatty acids, there occurs a reduction of omega-3 fatty acids in cell membranes. Such deficiency of PUFA in cell membranes is further augmented during senescence.

It has been reported that there is an age-related increase in sarcolemmal and michondrial membrane content of aracidonic acid and reduction in DHA in the heart (Pepe, 2005). The decline in the content of cardiac cell membrane omega-3 fatty acids with aging may result in increased vulnerability to Ca^{2+} overload induced by high work stress, ischemia and reperfusion or oxidative stress itself. However, these age-related qualitative changes in membrane fatty acid composition can be reversed and rectified through dietary manipulation. Studies with young and senescent rats indicate that diets enriched with omega-3 fatty acids can prevent the age-related decline in omega-3 fatty acids in cardiac mitochondrial membranes (Pepe et al., 1999). Reports (Pepe et al., 1999; Demaisson et al., 1994) show that higher ratio of omega-3: omega-6 fatty acids in cardiac mitochondrial membranes displayed greater capacity to recover contractile functions after ischemia and reperfusion compared to that with low ratio of omega-3: omega-6 fatty acids.

Membrane ion permeability is also associated with the PUFA present in the membrane phospholipids. A common aspect of cardiac ischemia and reperfusion during advanced age is increased vulnerability to the perturbation of Ca^{2+}-management systems resulting in highly elevated intracellular Ca^{2+} that precipitates systolic and diastolic contractile dysfunctions (Hano et al., 1995). A higher omega-3/omega-6 ratio in the membrane phospholipids modifies the relative activity of Ca^{2+}-Mg^{2+} -ATPase, Ca^{2+} uptake into sarcoplasmic reticulum, voltage dependence of inactivation of Na^{+} current, and Na^{+} -Ca^{2+} exchanger activity (Phillipson and Ward, 1985; Swanson et al., 1989; Taffet et al., 1993; Leifert et al., 2000).

It is suggested that immunosenescence through increased inflammatory cytokines play important roles in promoting cardiac infections and heart failure (Watson et al., 2005). It is suggested that cytokine polarization due to aging directly dysregulates fibroblasts, leading to altered cardiac structure and dysfunction (Watson et al., 2005). Elderly people with heart diseases have high cytokine levels in the T-helper 2 cells due to suppressed resistance to cardiotrophic pathogens. It is also suggested that reduction of T-helper 2 cells and increase of T-helper 1 cytokines by supplementation with omega-3 fatty acids might provide a way to treat and prevent excessive inflammatory cytokines and their detrimental effects on the heart (Watson et al., 2005).

The recommended intake of omega-3 fatty acids for primary prevention of CHD could be 2–3 g/day of fish oil. This will occur if there is a regular consumption of 200–300 g fish and shellfish per week (Connor and Connor, 1997). The present knowledge of omega-3 fatty acids justifies that physicians in the context of secondary prevention of CHD suggest their patients to increase their consumption of these fatty acids. Apart from advising them to adequately adapt their diet, the systematic prescription of capsules containing oils enriched in α-linolenic acid, EPA and DHA should become a common practice.

4. IMMUNE RESPONSE AND INFLAMMATORY DISEASES

The immune system provides us protection from pathogens but the immunologic vitality has been shown to diminish with age. Immune cells such as lymphocytes contain high amounts of PUFA in their membrane phospholipids. Numerous studies have shown that diets high in fat content suppress immune function (Wu et al., 1999). This is more pronounced, at least in animal studies, when the fat belongs mainly to the omega-6 family of PUFA (Boissonneult and Hayek, 1992). However, the effect of dietary fats is related much more to its quality i.e. the degree of its saturation and unsaturation.

Effects of hydrogenated fats on immunity of human subjects with moderate hypercholesterolemia have been studied. Though trans fatty acids have not been reported to directly affect cellular immunity, they increase the production of inflammatory cytokines (such as interleukin-1beta) known to be associated with atherosclerosis (Han et al., 2002). have Investigations (Mozaffarian et al., 2004) on the correlation between the trans fatty acids content and inflammatory marker concentrations in the red blood cell membranes of 86 patients with established heart failure suggest that trans fatty acids are strongly associated with systemic inflammation in patients with cardiac problems.

The role of eicosanoids in immune regulation is well documented. However, excessive omega-6 eicosanoid signalling has been associated with numerous inflammatory/immune vascular disorders, thrombic heart attacks and cardiac arrhythmic events, arthritis, asthma, cancer proliferation and various other chronic illnesses in aging adults (Lands, 2004). Dietary lipids are capable of influencing the fatty acid composition of membrane phospholipids. Such alterations are largely responsible for changes in immune function, through either influences on membrane-bound enzyme activity or the availability of fatty acid precursors of immune-modelling eicosanoids (Boissonneult and Hayek, 1992). Among the different fatty acid types, omega-3 and omega-6 fatty acids are most capable of influencing eicosanoids production. The omega-6 fatty acids are precursors to the 1- and 2-series prostaglandins and leukotrienes of 3- and 4-series while omega-3 fatty acids are the precursors to the 3-series prostaglandins and leukotrienes of 5-series. Leukotriene B_4 is known to enhance natural killer cell activity compared to less potent leukotriene B_5. It is also a powerful inducer of inflammation and leukocyte chemotaxis and adherence (Simopoulos, 1999).

Intake of omega-3 fatty acids either as α-linolenic acid or as EPA or DHA results in the accumulation of these fatty acids into the membrane lipids of the tissues, including cells of the immune system such lymphocytes and phagocytes (Conroy et al., 1986; Marshall and Johnston, 1983; Bankey et al., 1989). In fact, ingestion of EPA partially replaces the omega-6 fatty acids (particularly AA, 20:4) in the cell membranes of platelets, erythrocytes, neutrophils, monocytes and liver cells (Simopoulos, 1999). Intake of EPA and DHA decreases production of prostaglandin E_2 metabolites; reduces formation of leukotriene B_4; lowers the concentrations of throboxane A_2, which is a powerful platelet aggregator and vasoconstrictor;

and increases the concentrations of leukotriene B_5 (Simopoulos, 1999). Selective inhibition of inflammatory responses without inhibiting T- and B-cell functions by DHA supplementation has also been reported (Kelly, 2001).

Production of proinflammatory eicosanoids through metabolic pathways of fatty acids modulates the course of inflammatory diseases such as arthritis and psoriasis. Dietary supplements ranging 1–8 g per day of omega-3 PUFA have been reportedly beneficial in the treatment of inflammatory bowel disease, eczema, psoriasis and rheumatoid arthritis. In addition, experimental studies in rats with experimental ulcerative colitis, induced by intrarectal injection of trinitrobenzene sulphonic acid, have documented that treatment with long-chain omega-3 PUFA reduces mucosal damage as assessed by biochemical and histological markers of inflammation (Gil, 2002).

Psoriasis is one of the most common inflammatory diseases of the skin which can happen at all ages. The epidermis and scale chamber fluid of psoriatic lesions contain several lipoxygenase compounds such as leukotriene B_4, leukotriene C_4, leukotriene D_4, 12-HETE (hydroxy fatty acids) and 15-HETE (Fogh, 1990). Modulation of eicosanoid and lipoxygenase production, through dietary lipids provides a therapeutic treatment. A number of trials have demonstrated the anti-inflammatory effects of fish oils. Various studies (Ziboh et al., 1986) demonstrate the mild to moderate improvement of psoriatic patients from fish oil supplements (11–14g EPA/day for 8 weeks). The improvement in clinical response was associated with the incorporation of EPA and DHA present in the fish oils into the epidermal tissues. Successful reduction of itching, scaling and erythema from 8 week supplementation with fish capsules (1.8g EPA/day) has also been reported (Bittiner et al., 1988). Following similar trials with 3.6g EPA ethyl-ester/day for 3–6 months, significant improvement of scaling and erythema in their patients was reported (Terano et al., 1989). Reduction in neutrophil production of leukotriene B_4 was observed from one month after start of the study along with marked increase of leukotriene B_5 and 5-HETE. These reports demonstrate the potency of omega-3 fatty acids in prevention and treatment of inflammatory skin disorders like psoriasis.

Rheumatoid arthritis is a chronic inflammatory disease of the joints which trouble a large number of the elderly population. It is characterised by inflammation of the synovium and infiltration of the joint by neutrophils, macrophages and T lymphocytes and subsequent erosion of articular cartilage and bone (Boissonneult and Hayek, 1992). Eicosanoids derived from the metabolic pathways of omega-6 fatty acids, arachidonic acid, and the cytokines interleukin-1beta and tumour necrosis factor-alpha are related with the symptoms of inflammatory joint disease, as well as the cartilage degradation seen in established rheumatoid arthritis (James et al., 2003). The presence of leukotriene B_4 and 5-HETE in the synovial fluid from patients with rheumatoid arthritis (Fogh, 1990) suggest that restricting the production of these eicosanoids can probably slow down the inflammatory processes associated with rheumatoid arthritis. The use of omega-3 fatty acids as a part of dietary treatment of rheumatoid arthritis had been investigated by various researchers. Rheumatoid

arthritis patients who consumed a supplementation of 1.8g of EPA/day showed fewer clinical symptoms of their disease after 12 weeks (Kremer et al., 1985). Similar improvement of symptoms of rheumatoid arthritis in patients supplemented with omega-3 fatty acids have been observed by others (Sperling et al., 1987; Magaro et al., 1988).

5. CARCINOGENESIS

The correlation between dietary fats and cancer has been investigated through epidemiological and experimental studies in several organs such as the skin, liver, colon, pancreas and mammary gland. Most of the experimental studies concerning dietary fats have been on the rat model system, and have been followed up till complete carcinogenesis induced by polyaromatic hydrocarbons (PAH) or ultra-violet (UV) light. However, non-conforming results, even from similar studies have also been reported.

The incidence of skin cancer has been undergoing a steady increase in recent years. Skin cancer is most common among the elderly, but is now also more frequently found in younger people (Tarstedt et al., 2005). Early studies have shown the effect of fatty acids on the initiation and promotion of skin carcinogenesis. Daily application of lauric acid (20:0) and oleic acid (18:1) on mouse skin after a single administration of 7,12-dimethylbenz[a]anthracene (DMBA) showed cancer promoting activity. Stearic acid (18:0) and palmitic acid (16:0) however showed no effect. In case of DMBA-initiated carcinogenesis, high fat diets slightly inhibited initiation but enhanced the promotion (Birt et al., 1989). Such enhancing effect has been attributed mostly to the increased consumption of calories. While reports show that high fat diets increased UV induced skin carcinogenesis in rats, others found no such effects (Black et al., 1983). On the contrary, they concluded that diets containing saturated fatty acids inhibited tumorigenesis.

Occurrence of colon cancer in the industrialized countries has risen since the early 1970's and it is estimated that more than one-third of such cases are diet related (Roynette et al., 2004). Though a number of correlational and case control epidemiological studies have established a positive association between dietary fats and development of colon cancer many prospective epidemiological studies have concluded otherwise (Glauert, 1992). However, interpretations of such studies are complicated by the total energy intake which has been correlated to colon cancer in various correlational and case control studies (Kolonel, 1987; Lyon et al., 1987). Studies on the effect of different dietary fatty acids show that the promotional phase of colon carcinogenesis (induced by multiple injections of azoxymethane) is affected more by PUFA compared to saturated fatty acids (Sakaguchi et al., 1984). The initiation of colon carcinogenesis, however, is affected more by increasing the level of saturated fats and not by the amount of PUFA (Reddy and Sugie, 1998). It has been hypothesized that dietary fats increase the concentration of metabolites with carcinogenic or promoting activity in fecal stream (Glauert, 1992).

Several researchers have reported the effect of dietary fats on initiation and promotion of carcinogenesis in liver. Increase in fat content of the diet enhanced the development of artificially induced tumors in rat livers (Reddy and Sugie, 1998). The enhancement of hepatocarcinogenesis by dietary fats is primarily due to the effect on initiation of carcinogenesis and polyunsaturated fats have greater effect then saturated fats (Glauert, 1992).

Pancreatic carcinogenesis in humans has been connected with dietary fats (Baldwin and Parker, 1986) and detailed investigations have been carried out in animal models with rats and hamsters. Since the tumors are derived primarily from ductal cells in both hamsters and humans, the hamster model may be considered to be more pertinent to human pancreatic cancer. Higher dietary fat intake increases the incidence of pancreatic carcinogenesis in hamsters (Birt et al., 1989) with polyunsaturated fats having greater enhancing effect, compared to saturated fats. Conversely, one study (Birt et al., 1990) showed that intake of a saturated fat (beef tallow) promoted pancreatic carcinogenesis more than that by polyunsaturated fat (corn oil) in hamster model.

Prostate cancer is the second major cause of cancer related death in men in the US (Pienta and Esper, 1993). Epidemiological studies have demonstrated that men with higher dietary intake of omega-3 fatty acids have a lower incidence of prostate cancer. Moreover, omega-6 and omega-3 fatty acids have respectively displayed promotional and inhibitory effects in prostate cancer cell lines as studied by Pandalai et al. (Pandalai et al., 1996). Their results revealed that EPA inhibits prostate cell growth at high concentration.

Most of the polyunsaturated oils such as corn and safflower, used in various carcinogenic studies are rich in LA i.e. omega-6 fatty acids (typically 55% for corn and 75% for safflower) and have a very low content of omega-3 fatty acids (typically 0–1% for both). Fish oils, rich in long chain omega-3 PUFA however have beneficial effects. Substitution of corn oil with oils rich in omega-3 fatty acids (such as fish oils) generally has inhibitory effects on chemically induced carcinogenesis (O'Connor et al., 1989). Various researchers have observed similar effects in the colon, mammary glands and the pancreas of their animal subjects. Radiation therapy and chemotherapy drugs such as doxorubicin, epirubicin, tamoxifen etc. show higher efficacy when omega-3 fatty acids are included in the diet (Hardman, 2004). Data from 24 European countries indicate that a high ratio of omega-6/omega-3 fatty acids in diet has greater risk for colon cancer (Caygill and Hill, 1995). The mechanisms of action of omega-3 fatty acids on colon carcinogenesis is proposed to be that n-3 PUFAs are able to influence colon carcinogenesis by altering enzyme expression and/or activity and, therefore, the concentrations of end-products or by modulating the levels of available precursors for biosynthetic pathways (Roynette et al., 2004). Other probable mechanisms for the effect of omega-3 fatty acids against carcinogenesis include modulation of eicosanoid production and inflammation, angiogenesis, proliferation, susceptibility for apoptosis, and estrogen signalling (Hardman, 2004).

6. DIABETES

One of the silent killers of modern times is diabetes mellitus. Hyperglycemia and dyslipidemia (a condition marked by abnormal concentrations of lipids or lipoproteins in the blood) are two main abnormalities associated with both insulin-dependent diabetes mellitus (IDDM, type 1) and non-insulin-dependent diabetes mellitus (NIDDM, type 2). Diabetes mellitus is characterised by hyperglycemia in presence of insulin resistance, hypertriglyceridemia, increased VLDL, altered lipogenesis and accelerated lipolysis (Bhathena, 1992). High intake of dietary fats has been correlated with development of insulin resistance in both animals and humans with different types of fats having different effects on insulin action. Saturated fats and trans fats cause insulin resistance while monounsaturated and polyunsaturated fats improve it (Rivellese and Lilli, 2003).

Recent evidence from epidemiological studies show that risk factors for type 2 diabetes is connected to high trans fatty acid and low ratio of unsaturated: saturated fat intake (Parillo and Riccardi, 2004). Increased levels of palmitic acid and palmitoleic (16:1n-7) and reduced levels of linoleic acid have been linked with insulin resistance and consequent complications (Vessby, 2000). Animal studies using primates reveal that similar to saturated fatty acids, trans fatty acids affect the insulin receptors by reducing their numbers and increasing their affinity (Barnard et al., 1990). Markedly higher proportions of saturated fats and decreased PUFA have been observed in the phospholipids of red blood cells of both IDDM and NIDDM subjects (van Doormaal et al., 1984; Prisco et al., 1989). A study involving more than 84,000 women aged between 34–59 years was conducted to examine the relations between dietary fat intakes and risk of type 2 diabetes in USA (Salmeron et al., 2001). None of the subjects had any cardiovascular problems, cancer or diabetes at start. From the data collected over a period of 14 years, it was concluded that total fats and saturated and monounsaturated fatty acids do not increase the risk of type 2 diabetes in women, but trans fatty acids enhance, whereas PUFAs reduce the risk. Trans fatty acids are incorporated into cell membrane phospholipids causing decrease in membrane fluidity and binding of insulin to its receptor, leading to impaired insulin action, insulin resistance and hyperinsulinemia (Simopoulos, 1999).

Most of the studies concerning human diabetic subjects have used linoleic acid rich vegetable oils. Linoleic acid has a protective effect on diabetic retinopathy (Howard-Williams et al., 1985). However, some have reported increased insulin resistance in liver and muscle in diabetic rats from saturated fatty acids and linoleic acid rich diet (Storlien et al., 1987). γ-linolenic acid (GLA), an omega-6 metabolite, has been reported to have many beneficial effects in both NIDDM and IDDM such as prevention and treatment of distal diabetic polyneuropathy (Jamal and Carmichael, 1990). Feeding animal subjects an essential fatty acid deficient diet which lowers the concentration of AA, decreased the incidence of spontaneous diabetes. It has been hypothesised that AA or its eicosanoid metabolites may be responsible for the inflammatory conditions of autoimmune diabetes in the experimental rat model system (Lefkowith et al., 1990), which is similar to human IDDM.

Hyperinsulinemia and insulin resistance are inversely linked with the content of C20 and C22 fatty acids in the phospholipids of muscle cell membranes (Borkman et al., 1993). A reduction of EPA in the livers of diabetic patients was also observed (Singer et al., 1980). In another study, a higher EPA content was reported in the liver triglycerides of diabetic subjects without hyperlipoproteinemia (Singer et al., 1984). Chronic deficiency of EPA may lead to complications of diabetes such as retinopathy, peripheral neuropathy and nephropathy (Sinclair, 1962). Dietary fish oils have various beneficial effects on diabetic subjects, for example, an augmentation of 20- and 22-carbon PUFAs leads to increase in membrane fluidity, the number of insulin receptors and insulin action (Harris, 1996).

People suffering from diabetes mellitus have an increased cardiovascular morbidity and mortality. The most consistent beneficial effect of long chain PUFAs is the reduction of triglyceride levels in serum. There is also considerable evidence that fish oils lower cholesterol/phospholipids ratio and cholesterol/HDL ratio which is considered to be a measure of atherogenic index (Bhathena, 1992). Fish oil also increases lipoprotein lipase activity in NIDDM but has no effect in IDDM (Kasim et al., 1988; Bagdade et al., 1990). Dietary omega-3 fatty acids reportedly reduce blood viscosity (Rillaerts et al., 1989), lower blood pressure (Kasim et al., 1988) and increase neutrophil in diabetic subjects (Schmidt et al., 1989).

Despite the physiological benefits on diabetic subjects, unrestricted or unmonitored use of omega-3 fatty acids is not recommended. Omega-3 fatty acids have detrimental effects on carbohydrate metabolism and inversely affect glycemic control even though insulin sensitivity is improved. Plus, the positive effects on lipid metabolism cannot be sustained by prolonged use of fish oil and are reversed when fish oil supplementation is discontinued (Bhathena, 1992). Another concern for excessive use of omega-3 fatty acids is their susceptibility to oxidation. This aspect of PUFA is discussed in later sections.

7. ALZHEIMER'S DISEASE (AD)

AD is the most common dementing illness of the aged and is characterised by global impairment of cognitive functions. Though the environmental risk factors for AD have not been identified with certainty, a number of dietary elements have been reported to be associated with the development of dementia. Evidence shows that oxidative stress, homocysteine-related vitamins, dietary fats and alcohol play a role in the pathogenesis of AD (Luchsinger and Mayeux, 2004). It has been postulated that AD may be promoted by insulin resistance, excess free radicals, inflammatory metabolites, homocysteine and oestrogen deficiency (Berrino, 2002). Vascular risk factors such as type 2 diabetes, hypertension, high dietary fat intake, high cholesterol, and obesity are also suspected of increasing the risk of both vascular and AD (Haan and Wallace, 2004).

Based on epidemiological risk factors, it has been suggested that dietary lipids may be the principal risk factors for the development of late-onset AD (Cooper, 2003). The nature of saturation and unsaturation of fatty acids are crucial

in determining the effect on AD. The Mediterranean diet comprising mostly of oleic acid rich olive oil appear to provide high protection against cognitive decline as observed for the aged population in Southern Italy (Solfrizzi et al., 2003). Omega-3 fatty acids offer some protection against AD while saturated and omega-6 fatty acids increase the risk (Cooper, 2003).

DHA is the principal fatty acid of neurological and retinal membranes and it makes up more than 30% of the structural lipid of the neuron (Kyle et al., 1999). Reduced blood levels of omega-3 fatty acids have been related to many neuropsychiatric disorders such as attention deficit (hyperactivity) disorder, AD, schizophrenia and depression (Young and Conquer, 2005). Innvestigations have been made on the protective relationship between fish consumption and intake of different types of omega-3 fatty acids against AD (Morris et al., 2003). A total of 815 subjects, aged 65 to 94 years, who were initially unaffected by AD completed a dietary questionnaire on average 2.3 years before clinical evaluation of incident disease. It was concluded that participants who consumed fish once per week or more had 60% less risk of AD compared with those who rarely or never ate fish. Total intake of omega-3 PUFA was associated with reduced risk of AD, as was intake of DHA. EPA was not associated with AD. Other clinical studies with DHA have also shown to bring improvement in senile dementia (Yazawa, 2004).

Some investigations have shown reduced levels of AA and DHA in phospholipids fractions such as phosphatidylcholine (PC) and phosphatidylethanolamine (PE) from various parts of the brain (frontal grey frontal white, hippocampus, pons) of patients suffering from AD (Söderburg et al., 1991; Prasad et al., 1998). However, senescence itself has no influence on the fatty acid composition of PC and/or PE in these areas of the brain (Söderburg et al., 1991). The plasma fatty acid analysis of various phospholipids fractions of patients suffering from AD (mean age 82.7 yrs) and other forms of cognitive impairment (but nondemented) (mean age 83.3 yrs) and dementia (mean age 79.4 yrs) show lower levels of EPA, DHA, total omega-3 fatty acids and omega-3/omega-6 ratio in plasma phospholipids, PC and PE (Conquer et al., 2000). No other differences in the fatty acid composition of the different phospholipids fractions were noted in this study.

Kyle et al. (1999) have investigated the correlation between circulating DHA of 1188 elderly American subjects (mean age 75 yrs) and AD diagnosis and scores on the Minimental State Exam (MMSE). The serum PC was used as the biomarker. Their data present low levels of circulating PC-DHA as a risk factor for low scores on the MMSE and development of AD in the elderly patients. Due to the declining activity of the delta-6-desaturase enzyme it is difficult for the elderly to maintain a healthy level of serum DHA. Thus it is very important for the elderly to have DHA supplementation or eat adequate amounts of fish. A relatively small pilot study with 10 elderly subjects (average age 83 yrs) suffering from senile dementia of cerebrovascular disorders has been performed (Terano et al., 1999). They administered DHA (0.72g daily for 1 year) to the subjects and evaluated the effect on dementia using psychometric tests such as MMSE and Hasegawa's Dementia rating scale. Their findings show that DHA supplementation improved

the dementia scores in the elderly suffering from moderately severe dementia from thrombotic cerebrovascular disorders.

Thus, one may conclude that, dietary intake of omega-3 fatty acids and weekly consumption of fish may reduce the risk of incident AD. However, there cannot be any compromise with the oxidative quality of the omega-3 supplements and the freshness of the fish, as discussed below.

8. OXIDATION OF LIPIDS AND USE OF ANTIOXIDANTS

Though by and large, PUFAs have numerous beneficial effects on human health, their susceptibility to autoxidation is a serious concern associated with all forms of their intake. Exposure to air, heat and light causes the unsaturated moieties of the fatty acids to undergo a spontaneous free radical-initiated chemical reaction called autoxidation. It proceeds in three steps, initiation, propagation and termination. Autoxidation is commonly characterised by an induction period during which very little change occurs in lipids. After the end of the induction period, oxidative deterioration of the lipids occurs much more quickly. It is well known that the greater the number of unsaturated sites, the greater is the tendency of oxidation. For example, if the rate of oxidation for oleic acid (18:1) is 1, then the relative rates of oxidation for linoleic acid and alpha-linolenic acid are 12 and 25 respectively.

Autoxidation of PUFAs generates hydroperoxides as primary oxidation products and further oxidation leads to cyclic peroxides as secondary oxidation products. Monocyclic peroxides, bicyclic endoperoxides, serial cyclic peroxides, and a new class of endoperoxides (dioxolane-isoprostane peroxides) have been identified from the oxidation of arachidonate (Yin and Porter, 2005). These oxidation products are a potential source of free radicals which may cause damaging effects in vivo. The excess free radicals may react with proteins, DNA and other molecules and these reactions represent pathways whereby cancer, CHD and a host other disorders can develop. Thus it is vitally important that oils and fats are protected from oxidation.

Addition of antioxidants to oils and fats prevent oxidation by extending the induction period. However, use of antioxidants after the end of this period is generally ineffective because by that time, the oil or fat has developed considerable degree of rancidity. Storage of oils and fats in closed containers and in cool, dark places away from heat sources also prolongs the induction period.

Antioxidants can be both synthetic and natural. The major synthetic antioxidants which are widely used in various food products are t-butylhydroquinone, butylated hydroxy toluene, butylated hydroxy anisole and propyl gallate. However, possible harmful side effects of the synthetic antioxidants have created a demand for natural antioxidants. Various herb extracts, spices, teas, oilseeds and oils, cereals, legumes, fruits and vegetables contain minor components that act as natural antioxidants. The different types of natural antioxidants investigated include: (i) tocopherols and tocotrienols; (ii) phenolic acids (carnosic acid and rosmarinic acid) found mainly in the Lamiaceae family of herbs; (iii) flavonoids (e.g. quercetin, kaemferol, luteolin, morin, myricetin) from plant sources; and (iv) catechins or phenols

(carnosol, rosmanol, epirosmanol) from tea and Labiatae family of herbs. Several beneficial properties have been attributed to these dietary compounds, including anti-inflammatory and anticarcinogenic effects (Galati and O'Brien, 2004). Though these natural phenolics/flavonoids are generally regarded safe, controlled clinical trials to show efficacy and potential for toxicity of many of these natural antioxidants are still required. These natural compounds are generally lipophilic and dietary lipids can act as the carrier of such active ingredients which would provide multiple benefits.

9. CONCLUSIONS AND FUTURE PERSPECTIVES

It is evident that dietary fats have significant contribution to our well being during all stages of life. It is never too late to initiate and benefit from the nutritive effects of dietary lipids. Modern life style is making us increasingly dependant on bulk-prepared foods. When designed with healthy and top quality oils, the innumerable varieties of prepared foods available can play an important role in the diet schemes. However, dietary fats have to be consumed with prudence and in moderate amounts. Nordic Nutrition Recommendations suggests a limitation of the intake of saturated plus trans fatty acids to about 10% of the total energy intake (E%), and of the total fat intake to 30E%. It is also recommended that cis-MUFA should provide 10–15E% and PUFA 5–10E% including approximately 1E% from omega-3 fatty acids.

Direct consumption of EPA and DHA for vegetarian people is almost non-existent due to absence of fish in their diets and alpha-linolenic acid from plant sources is the primary omega-3 fatty acid in their diet. Although alpha-linolenic acid is transformed to EPA and DHA, consistent quantification seems to be a debatable issue. Though DHA from algal sources is now available in encapsulated forms, future research should concentrate on incorporating such long chain PUFAs into the seed oils. Such development might even require genetic modification. Scientific studies from both academic and industrial areas will continue to discover newer benefits of specific lipids and at the same time caution us about some. Simultaneously, conscious effort has to be made to translate scientific findings into a language understood by consumers who need to feel confident and comfortable about what they eat.

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QUERIES TO BE ANSWERED (SEE MARGINAL MARKS)

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Chapter-17

Query No.	Page No.	Line No.	Query
AQ1	343	14	The sentence is incomplete. Please check.