The Role of Omega-3 Fatty Acids Contained in Olive Oil on Chronic Inflammation

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ABSTRACT

Nowadays, people have been eating lots of unhealthy dietary excesses, that make them have chronic inflammatory diseases or known as chronic diseases. Countless millions of people worldwide can not help eating selectively massive quantities of unhealthy foods, until they become sick, often mortality. The omega-6 fatty acids account for the majority of PUFA (Poly Unsaturated Fatty Acids) in the food supply. They are the pre-dominant PUFA in all diets, especially the western diets, which produce pro-inflammatory metabolic products. The persistent antigenic or cytotoxic effects will lead to chronic inflammation. Olive tree is native to the Mediterranean basin and parts of Asia Minor. Its compression-extracted oil from the fruit has a wide range of therapeutic and culinary applications. It had been used as aphrodisiacs, emollients, laxatives, nutritives, sedatives, and tonics. In the later part of the 20th century, several studies had revealed that the olives in the Mediteranian diet is linked to a reduced incidence of degeneratives diseases. It is one of phytomedicine which has omega-3 fatty acid as its constituent, may inhibit inflammation composing chronic inflammatory proccess in many chronic diseases, such as coronary artery disease, rheumatoid arthritis, hypertension, and even cancer.

Key words: *unhealthy dietary excess,chronicinflammatory diseases, chronic diseases, olive oil, omega-3 fatty acid.*

INTRODUCTION

Chronic diseases are now the major cause of death in practically all nations of the world, with arround 60% of all cause of deaths. Several factors may cause chronic inflammation leading to the chronic diseases events, but one important cause is the unhealthy dietary excesses, since people eat kind of diets that are currently suspected of producing chronic diseases, that is, those rich in calories, fat, and animal products, and almost devoid of all vegetal components and especially fibres. It is designated as CANF (Calories-Animal products-No fibre) diets.[1,2]

On the basis of estimates from studies on Paleolithic nutrition and modern-day hunter-gatherer populations, it appears that human beings had been consuming a diet that was much lower in saturated acids than in today's diet.[3] Over the past 10,000 years with the development of agriculture, changes began to take place in food supply, but it was especially during the last 100 – 150 years that nutritional changes have led to an increase in saturated fats from grain-fed cattle, an increase in trans-fatty acids from the hydrogenation of vegetable oils and enormous in omega-6 fatty acids, which produce pro-inflammatory metabolic products.[4] In several years different sources of lipid dietary mixtures have been used to improve general health for inflammatory disorders. Although not every clinical study has found health benefits from supplementing specific lipids in the diet, most studies have documented the value of dietary supplements, commonly the omega-3 fatty acids, especially which are found in many plant oils, such as olive oil.[5,6]

OLIVE OIL

Olive oil is made from the olive (*Olea europaea*), a species from the Oleaceae family, a native plant,

growing widely in the east Mediteranian region, from Lebanon, Syria and Northern part of Iraq. It has silvery green leafs, little white flowers, and green small fruits when used to produce oil and they are 1-2.5 cm in length. The plant is 8-15 m in height and 1-3 cm in width.[7] References to the olive oil date back to Biblical and Roman time and to Greek mythology, that it had been used as aphrodisiacs, emollients, laxatives, nutritives, sedatives, and tonics. In the later part of the 20th century, several studies had revealed that the olive in the Mediteranian diet is linked to a reduced incidence of degeneratives diseases.[8]

The content of minor components with biological properties varies, depending on cultivar, climate, ripeness of the fruits at the time of haversting, and the processing system for the type of olive oil. There are several types of olive oil: extra virgin which is the the best, least proccessed and comprising the oil, without using heat or cold pressing or chemicals, virgin olive oil which is produced by the second direct press or centrifugation methods then submitted to a refination process, pure olive oil which is produced through filtering and refining, extra light olive oil which undergoes considerable proccessing and only retains a very mild olive flavour, and pomace olive oil, to which a certain quantity of virgin olive oil is added.[9] Every 100 g of olive oil contains the following fatty acids: monounsaturated fatty acids/MUFA 73.3 g (n-9 oleic acid 18:1); saturated fatty acids/SFA 13.5 g (16:0 palmitic acid); polyunsaturated fatty acids/PUFA 7.9 g (n-6 linoleic acid/LA 18:2 and n-3 alpha-linolenic acid/ALA 18:3).[10]

THE OMEGA-3 FATTY ACIDS IN OLIVE OIL AND CHRONIC INFLAMMATION

There are many causes of chronic diseases, but the overabundant diet and physical inactivity are the most cause of chronic diseases, such as: cardiovascular diseases, asthma, cancers, rheumatoid arthritis, diabetes, and many others. Countless millions of people worldwide can not help eating selectively massive quantities of unhealthy foods, until they become sick, often result in mortality **(Figure 1)**.[1] The omega-6 fatty acids account for the majority of PUFA in the food supply. They are the pre-dominant PUFA in all diets, especially the western diets, which produce pro-inflammatory metabolic products. The persistent antigenic or cytotoxic effects will lead to chronic inflammation.[11,12]

Besides inhibit the inflammatory proccess caused by omega-6 fatty acids, the omega-3 fatty acids may clear the plasm from chylomicron lipoprotein and also possibly from very low density lipoprotein (VLDL), reducing trigliceride and β-apolipoprotein production in the liver, as the main part of lipid and protein in VLDL. The omega-3 fatty acids are related to the prevention of coronary artery disease and arthritis.[13] The omega-3 fatty acids may also act as antioxidants through oxidation of the double bond parts of the omega-3 fatty acids.[8]

The omega-3 fatty acids (ALA) contain in olive oil may inhibit the inflammatory proccess caused by omega-6 fatty acids (LA). Dietary omega-3 may decrease tissue concentrations of AA. Alpha-linolenic acid can endogenously be metabolized

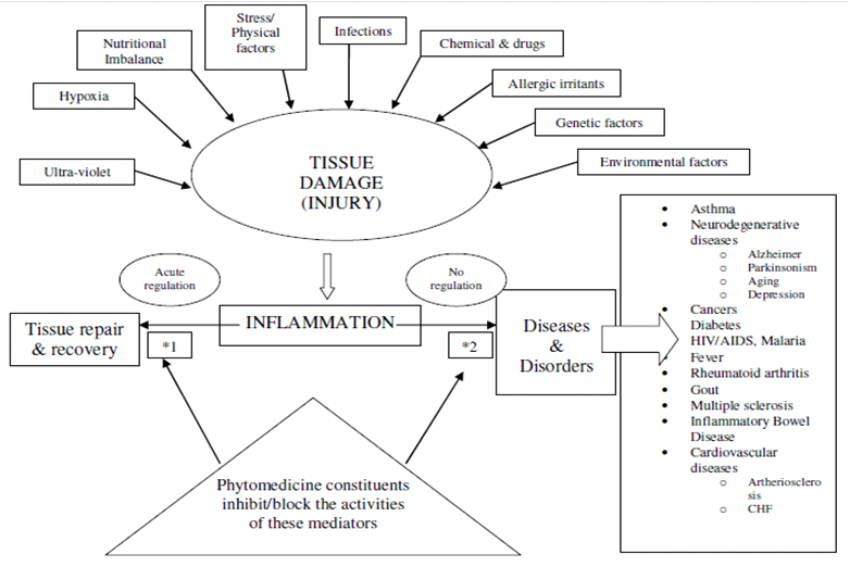

Figure 1. The sketch diagram shows the pathways of tissue damage and inflammatory diseases and disorders.[1]

into eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), while LA into arachidonic acid (AA,20:4n-6).11 Cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) are enzymes required for prostaglandins (PG) and leukotrienes (LT) synthesis. Competition between omega-3 fatty acids and omega-6 fatty acids using this two enzymes occurs for both PG and LT synthesis **(Figure 2)**. Some omega-3 fatty acids derived eicosanoids may counteract their AA derived counterparts.[11]

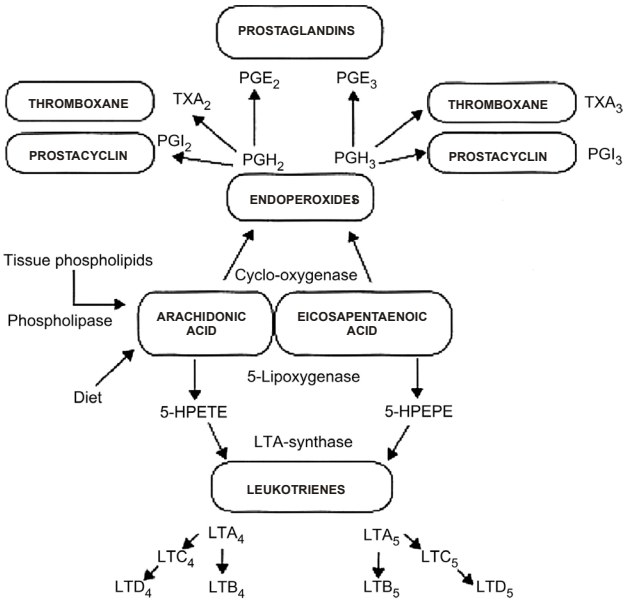

Figure 2. Oxidative metabolism of arachnoid acid and eicosapentaenoic acid by cyclooxygenase and 5-lipoxygenase pathways.[12]

When humans ingest EPA or DHA, it will lead to decrease prostaglandin E_2 (PGE_2) metabolites (vasodilator), decrease in thromboxane A_2 (TXA_2), a potent platelet aggregator and vasoconstrictor, decrease in leukotriene B_4 (LTB_4) formation, an inducer of inflammation and a powerful inducer of leukocyte chemotaxis and adherence, increase in thromboxane A_3 (TXA_3), a weak platelet aggregator and a weak vasoconstrictor, increase in prostacyclin (PGI_3), leading to an overall in total prostacyclin by increasing PGI_3 without decrease in PGI_2 (both PGI_2 and PGI3 are active vasodilators and inhibitors of platelet aggregation), and increase in leukotriene B5 (LTB_5), a weak chemotactic agent.[11,14,15] The PGE1 may increase intracellular cyclic AMP (cAMP) and it also may increase in polymorphonuclear leukocyte cAMP that reduce the release of lysosomal enzymes, reduce polymorphonuclear leukocyte chemotaxis, migration and, adherence of leukocytes in the blood vessel, inhibit both in vitro function of lymphocytes and in vivo responses mediated by lymphocytes. It has been suggested to have negative feedback role in chronic diseases.[16]

A substantial amount of data, primarily from in vitro studies, indicated that omega-3 fatty acids are important regulators and act as natural ligands of peroxisome proliferator activated receptors (PPAR), which is a transcription regulator. There are 4 PPAR isoforms : alpha (α), beta (β), delta (δ), and gamma (γ). The EPA had been reported to bind at least to PPARα and PPARγ. The PPARα is expressed in many types of human cells, such as macrophages as well as in atherosclerotic plaques macrophages.[17,18]

The PPARγ is expressed in various tissues and cell types, including the immune cells (eg,lymphocytes, monocytes, and macrophages), and dendritic cells (DCs).[19] The PPARγ activation by omega-3 fatty acids may play a role in innate or adaptive immunity by affecting DC migration that could contribute to the initiation and modulation of immune responses, and their subsequent accumulation in lymphoid organs.[20] It may also inhibit the expression of some costimulatory markers and the secretion of important regulatory cytokines, as well as limiting the lymphocytes stimulatory capacity of DCs, reducing the inflammatory cytokines in DCs and can inhibit several other pro-inflammatory pathways such as inducible nitric oxide synthetase (iNOS) or matrix metalloproteinase-9.[19,21]

The PPARγ activated human monocyte-derived DCs have an elevation in expressing CD1d, that is coupled to the enchanged capacity to activate a CD1d-dependent cell type, the iNKT (invariant natural killer T) cells. The lack of iNKT cell activation has been implicated in the development of autoimmune conditions, suggesting that iNKT cells are intimately linked to sustaining immunological tolerance.[22] The expression and activation of PPARγ inhibit T cell activation by scavenging the transcription factor, nuclear factor of activated T cells (NF-AT), known to be responsible for interleukin-2 (IL-2) expression and reducing its production in whole splenocyte or human peripheral blood lymphocyte populations. Moreover anti-CD3-induced expression of interferon-γ (IFN-γ) was suppressed in CD4+T cells in response to PPARγ activation. In addition, it is acknowledged that activated protein-1 (AP-1) and nuclear factor-kappa beta (NF-κβ) are attenuated by PPARγ in T cells.[23,24]

Besides anti-inflammatory effect, PPARγ is known to induce T cells apoptosis. Thus, the anti-inflammatory effects of omega-3 fatty acids may be the combined with indirect suppression of Th1 cells by the enchanged cross-regulatory function of Th2 cells, to make the balance of Th1 and Th2.[23,24] The omega-3

fatty acids is also associated with the reduction of IFN-γ-activated monocytes to present antigen to autologous lymphocytes, and this may lead to reduce helper T cell activation. The stricking inhibition of major histocompability complex (MHC) class II molecules and intercellular adhesion molecule-1 (ICAM-1) expression on IFN-γ-stimulated monocytes, and this may be relevant to the rheumatoid arthritis.[25] A dose dependent of omega-3 fatty acids on the inhibition of vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, and to a lesser extent, ICAM-1 gene expression will attenuate inflammatory responses that are important in the initiation of atherosclerosis.[26]

The omega-3 fatty acids may alter the pro-inflammatory cytokine genes expression, perhaps by altering the intracellular signaling mechanisms that lead to activation of pro-inflammatory cytokine genes. This might occur through inhibition of activation of transcriptional factors, such as NF-κβ, which regulate activation of tumour necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and interleukin-6 (IL-6). The NF-κβ is activated by phosphorylation, often by protein kinase C, and subsequent dissociation of its inhibitory subunit. The omega-3 fatty acids have been shown to directly inhibit protein kinase C from brain, spleen lymphocytes, and macrophages, and so these fatty acids might prevent the activation of NF-κβ by this mechanism. This effect could account for the reduced plasma TNF-α, IL-1β, and IL-6.[27,28] There is also a link between activated PPARγ by omega-3 fatty acids and NF-κβ that already has been established. The activated PPARγ can inhibit the NF-κβ pathway by directly binding the NF-κβ components p50 and p65.[29]

The reduction of plasma level in TNF-α, IL-1β, and IL-6, will reduce the production of C-reactive protein (CRP) in the liver. The IL-6 is a main inductor for the production of CRP, through the induction of RNACRP transcription, and IL-1 is also synergistic with IL-6 in the production of CRP.[30,31] The CRP activates the endothelial cells to express several adhesion molecules, ICAM-1, VCAM-1, selectin and chemokines, monocyte chemotactic protein-1 (MCP-1), increasing the secretion of IL-6 and endothelin-1, reducing the expression and bioavailability of endothelial nitric oxide synthetase, increasing the activation of macrophages to express cytokines and tissue factors and low density lipoprotein (LDL), also strengthning the pro-inflammatory effect from other mediators including endotoxin. Those whole proccesses are related to the coronary artery disease events and its severity level. [26,30-32]

THE CLINICAL USE, SAFE DOSE, AND THE SAFETY OF OLIVE OIL

The epidemiological studies demonstrate the Mediterranean diet reduces the incidence of coronary heart disease, by blocking the inflammation process occuring prior to the formation of fatty streaks and atherosclerotic lesions causes alterations to the endothelial cell wall which increases the adhesion of leukocytes, LDL cholesterol, and platelets. There is also a reduced incidence of hypertension in the populations that consume the Mediterranean diet. The olive oil will reduce the systolic and diastolic pressure, since the olive oil may act as a calcium channel antagonist, improve endothelial function by reducing the reactive oxygen species (ROS), and decreasing the vascular tone and changes to the fatty acid and phospholipid composition of the aorta, with the dose of 30 g/day for women and 40 g/day for men.[9] The olive oil may contribute to the lowering of LDL cholesterol with the dose of 25 ml/day.[33] The olive oil also may reduce the incidence of cancer by acting as anti-oxidant reducing the risk of mutagenesis and carcinogenesis. The women that had intake of olive oil more than 30.5 g/day were 30% less likely to be associated with greater breast risk cancer.[9] Besides the omega-3 fatty acids contained in the olive oil, the MUFA/ omega-9 fatty acid also acts as an anti-oxidant. There is an antimicrobial activity of olive oil, especially against *Helicobacter pylori* as the primary cause of gastric ulcers and linked to gastric carcinoma, by inhibiting the bacterial growth. It may also activates the secretion of bile and pancreatic hormones.[8,9,11] The olive oil also has a benefit in the rheumatoid arthritis, with the dose of 6 g/day, that inhibit the production (competitive metabolism inhibition between omega-3 fatty acids and omega-6 fatty acids) and neutralize the ROS produced during inflammation.[34]

The olive oil regimen may also help to eliminate the gallstones by promoting the passage of the multiple gallstones (1-2 cm in diameters), which is also known as gallbladder flush or liver cleansing regimen. The first day purge usually consist of an overnight fast, then eating apples in the morning and than drinking a warm mixture of olive oil (2/3 cup) and fresh lemon juice (1/3 cup). The patients are instructed to lie on the right side and it is claimed that in the morning the gallstones will pass in the stool. This regimen is repeated, usually for a week or so.[35,36]

The healthy daily diets and tolerated should contain omega-3 fatty acids and omega-6 fatty acids in the ratio of less than 1 : 5.[37] In this condition, not only does the rate of triglyceride decrease, but also inflammation

of the entire organisms and the arteries without any harmful side effects, especially bleeding event, since intake of omega-3 fatty acids more than 3 grams per day or greater may decrease platelet aggregation, prolong bleeding time, increase fibrinolysis, and may reduce von Willebrand factor, reducing blood pressure which appear to be dose related, the higher dose may produce the greater effect, higher low density lipoprotein which is likely to occur at the consumption of 1 gram per day or greater omega-3 fatty acids, mild elevation in liver function (alanine aminotransferase), restlessness and formication (the sensation of ants crawling), and higher calories intake. Each 100 g of olive oil contains the following fatty acid: MUFA 73.7 g (n-9 oleic acid 18:1), Saturated Fatty Acids (SFA) 13.5, Polyunsaturated fatty acids (PUFA) 7.9 g (n-6 linoleic acid 18:2, and n-3 alpha-linoleic acid 18:3).[11] It is suggested to take 25 ml/ day of virgin olive oil daily.[38] The standarization of omega-3 fatty acids contained in olive oil is 0.1 grams/ tablespoon. It is important to keep out the olive oil from light in a tightly sealed bottle, since it can easily go rancid when exposed to air, light, or high temperature.[33,38-39]

CONCLUSION

The humans unhealthy diets and lifestyle nowdays will produce the chronic inflammation condition, leading to the chronic disease events. Diet is the main cause of it, since there is an imbalance proportion of daily intake of omega-3 fatty acids and omega-6 fatty acids. The olive oil intake, with omega-3 fatty acid contained in it, may help to prevent and reduce the chronic inflammation and diseases.

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