

## Multiple Effects of Omega-3 P.U.F.A. on Some Important Life Processes

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### ABSTRACT

Omega-3 fatty acids are essential compounds for health. They play a crucial role to avoid and/or delay many cardiovascular alterations such as inflammation, arrhythmic effect, endothelial dysfunction, thrombosis, etc.. Their supplementation can induce a reduction of post-prandial dysmetabolic “spikes”, responsible for a rapid progression of atherosclerosis. Daily giving of PUFA omega-3, by lowering triglycerides serum levels, may induce a slowing of the age-dependent atherosclerosis’ progression reducing the cardiovascular risk. On the other hand, the high serum concentration of Poly-Unsaturated Fatty Acids (PUFA) omega-3 is associated with prolonged survival in patients mediated by telomeres’ lengthening. In fact, an inverse relationship between baseline blood levels of omega-3 fatty acids and the length of telomeres was demonstrated. An anti-depressant effect of PUFA omega-3, for its action on neuronal membrane stability was also evidenced. In addition, omega-3 PUFA seems to exert a positive effect on squamous cells carcinoma, even though they can increase the cancer prostate growth. Thus, besides several positive effects of high serum levels of PUFA omega-3 concentration, their detrimental action on prostate cancer growth must be considered too.

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**Key words:** PUFA omega-3; Cardiovascular impairments; Post-prandial dysmetabolism; Telomere’s length; Depression; Cancer

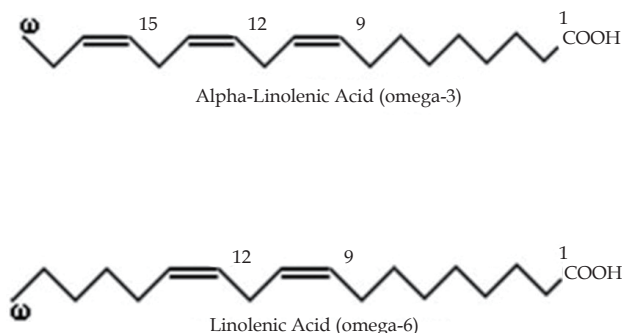
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### INTRODUCTION

Essential Fatty Acids (EFAs) are necessary fats that humans cannot synthesize but may be obtained through the diet. Two families of EFAs there are: omega-3 and omega-6 fatty acids. These families belong to a group of polyunsaturated fats called “essential” because they are necessary for life. Biochemically, both omega-3 and omega-6 have more than a double bond in the carbon chain. The omega-6 fatty acids contain their double bond between the 6<sup>th</sup> and 7<sup>th</sup> carbon atoms (counted from a methyl terminal carbon atom). Omega-3 fatty acids have their first double bond between the 3<sup>rd</sup> and 4<sup>th</sup> carbon atoms (Figure 1). The hormones derived from two classes of fatty acids have opposite effects. Those coming from omega-6 fatty acids tend to increase the inflammatory processes, the blood clotting and the cell proliferation. Contrarily, the hormones deriving from omega-3 fatty acids reduce these same effects. Both hormones’ families must be dynamically balanced to obtain a fair effect. Some reports have referred a significant risk lowering for heart disease and certain forms of cancer prevalently ingesting oil of omega-3 fatty acids. Concerning this, recent studies have reported that certain cultural eating styles with prevalence in omega-3 PUFA, such as Asian and Mediterranean diets, appear to lower risk factors for heart disease and certain forms of cancer as well. Eskimo diet is another diet-type, mainly containing marine fish-oils omega-3 fatty acids, that exert a protective effects on some, important pathologic processes influencing the life’s duration.

Omega-3-Poly-Unsaturated Fatty Acids (PUFA), such as Eicosapentaenoic Acid (EPA) and Docosa-Hexaenoic Acid (DHA) were prevalently employed for their multiple arterial and cardioprotective properties evidenced in Eskimo people since early ’60-’70 years<sup>[1]</sup>. The dietary consumption of marine fish oils by this population was believed to be responsible for that<sup>[2]</sup>.

Protective cardiovascular effects of omega-3 PUFA are mediated by several mechanisms<sup>[3,4]</sup>. But, this drug owns many others properties, able to significantly improve the state of health and to extend the length of life (Table 1).



**Figure 1** Chemical structure of omega-3 and omega-6 PUFA. from: Harris WS, Mozaffarian D, Rimm E *et al* *Circulation* 2009 119: 902-907

Table 1 Different actions performed by PUFA omega-3 in humans.	
Actions of PUFA omega-3 in humans	
<b>A-Anti-atherosclerotic Actions</b>	
	Lowering triglyceride serum levels,
	Anti-inflammatory effects,
	Modulation of endothelial function,
	Anti-thrombotic activity
	Reduction of post-prandial dysmetabolic status
<b>B-Other Effects</b>	
	Metabolic syndrome,
	Anti-arrhythmic action
	Alzheimer's disease,
	Anti-depressive (or depressant) action
	Telomere's lengthening,
	Cancer effects

## EFFECTS

The drug exerts several actions on cardiac rhythm-disturbances, endothelial function, coagulative system, some metabolic pathways and on inflammatory mediators, altogether opposing to the atherosclerotic process and so inducing a protective effect on cardiovascular system.

### Triglycerides levels

A firstly described effect of Omega-3 fatty acids is the lowering of triglycerides' serum levels. It is known that triglycerides, such as the major component of Very Low Density Lipoproteins (VLDL) and chylomicrons, play an important role in the metabolism of energetic sources and transporters of dietary fat. They are stored in the body fat after digestion and are formed by combining glycerol and three molecules of fatty acids. When physiological conditions dictate the need to use the triglycerides, hormones or a neurotransmitter signal their release. An enzyme called lipase breaks down the triglyceride molecule into glicerol and fatty acids (this process is called lipolysis and happens in the interstine). Free fatty acids are used as an energy source when the body requires that. In the human body, high levels of triglycerides in the bloodstream have been linked to atherosclerosis and the risk of heart disease and stroke. Particularly, triglyceride-rich remnants of VLDL were able to penetrate the artery wall and take up residence in the sub-intimal space, despite their size. Retention of these large particles below the endothelium induces the formation of foam cells having a share in the pathogenesis of atherosclerosis. That especially happens in the post-prandial phase, exerting most important damages in the intimal layer of the vessels' wall. A recent clinical study described that post-prandial triglyceride levels are related to the most important angiographic progression of coronary and carotid atherosclerosis<sup>[5]</sup>. But, the pathogenesis of post-prandial lipid abnormalities is only partially known. Certainly

it mainly depends on insulin resistance progressively establishing with advancing age in individuals also without overt diabetes. Many conditions related to lifestyle factors such as dietary habits, physical inactivity, and smoking have also been associated with abnormal post-prandial lipemia. In addition, exaggerated post-prandial "spikes" in glucose and lipids generate excess of free radicals that can trigger biochemical cascade resulting in inflammation, endothelial dysfunction, and sympathetic activity.

The American Heart Association (AHA) evidenziated that the fish oil acids DHA and EPA are useful in decreasing triglyceride serum levels. The mechanisms by which such effect happens is still a matter for controversy, but a recent report supposes that triglyceride synthesis could be reduced by n-3 fatty acids in three ways: (1) reduced substrate (i.e. fatty acids) availability, which could be secondary to increase in  $\beta$ -oxidation, decreased free fatty acids delivery to the liver, decreased hepatic fatty acids synthesis; (2) increased phospholipid synthesis; (3) decreased activity of triglyceride-synthesizing enzymes<sup>[6]</sup>.

Omega-3 fatty acids has been found to suppress hepatic lipogenesis, reduce the hepatic output of triglycerides, enhance ketogenesis, and induce fatty acid oxidation in both liver and skeletal muscle. The drug also induces a consistent reduction of VLDL, with rise in high density lipoproteins (HDL) and reduction in Low Density Lipoproteins (LDL). These beneficial effects support the opinion that omega-3 fatty acid intakes are associated with reductions in cardiovascular disease risk.

### Anti-arrhythmic action

Another important action of PUFA-omega-3 is their anti-arrhythmic activity. Some meta-analyses demonstrated that the consumption of fish oil has beneficial effects on survival for reduction of the arrhythmic death, particularly in patients with ischemic substrates. The most important anti-arrhythmic effect of PUFA omega-3 consists in its protective action towards Atrial Fibrillation (AF). Possible mechanisms for this benefit appear to be multiple and likewise include the effects of omega-3 fatty-acids on cardiac ion currents, their actions on cardiac autonomic properties, and the rise in atrial fibrillation threshold. In addition, the alterations in cell membrane properties by inclusion of fish oil derivatives may have a prominent part for reduction of supra-ventricular arrhythmias<sup>[7]</sup>. Concerning that, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione performed a study in 11.323 patients suffered from previous myocardial infarction and treated with a dose of 1.0 gr/day of omega-3 PUFA for 3.5 years. The results of the trial clearly demonstrated that in patients who have had a previous myocardial infarction, PUFA omega-3 supplements reduced long-term complications. In particular, the combined primary end-point of death, non fatal myocardial infarction and non fatal stroke were significantly reduced by this daily treatment<sup>[8]</sup>. Possible mechanisms for the anti-arrhythmic benefit of fish oil therapy appear to be multiple and may include effects on cardiac ion currents, effects on cardiac autonomic and electrical properties and effects on alteration cell membrane.

### Anti-inflammatory effect

There is increasing evidence that acute hyper-triglyceridemia state and dyslipidemia happening in the post-prandial period are the most important metabolic conditions contributing to the progression of atherosclerotic process by the inflammatory action. The possible mechanism seems to be the following: hypertriglyceridemia induces a rapid increase of triglyceride remnants levels favouring the

serum increase in C-reactive protein, cytokines, InterLeukin (IL)-1B, IL-6, IL-8 and endothelin-1<sup>[9]</sup>. In turn, this inflammatory environment contribute to degenerative process at expense of vascular wall (atherosclerosis). Some studies reported that the administration of omega-3 fatty acids at individuals having pro-inflammatory proteins is able to induce reduction of tumor necrosis factor-A, interleukin levels, cytokines, and other inflammatory mediators<sup>[10]</sup>. Omega-3 fatty acids may exert their anti-inflammatory properties through multiple pathways. They are able to suppress monocyte adhesion to human endothelial cells and to reduce the production of messenger chemicals called cytokines, interleukines and tumor-necrosis factor-A. Another anti-atherosclerotic effect carried out by n-3 PUFA in respect to n-6 PUFA was recently illustrated by Thies *et al.* These demonstrated that atherosclerotic plaques readily incorporate n-3 PUFAs from fish-oil supplementation show changes that can enhance their stability (thick, fibrous caps and no signs of inflammation), in comparison with plaques of patients receiving n-6 PUFAs. Furthermore, in the group being treated with n-3 PUFAs longer than the median duration, there were more characteristically stable plaques than in these with increased consumption of n-6 PUFAs. That happens because the number of macrophages in the plaques from patients receiving n-3 PUFAs was lower than in those of n-6 group. Stability of plaques (treated with omega-3 PUFA) could explain reductions in fatal and non-fatal cardiovascular events<sup>[11]</sup>.

#### Effects on endothelium

It is known that the endothelial layer such as the major regulator of vascular homeostasis, exerts a number of vasoprotective effects. That happens by maintaining the balance between vasodilation and vasoconstriction (respectively due to the inhibition and the stimulation of smooth muscle cell) and preserving the dynamic equilibrium between thrombogenesis and fibrinolysis. On the other hand, the increased triglyceride levels (inducing the decrease in HDL and the inflammatory, pro-arrhythmic and pro-thrombotic activities) favours an impaired endothelial dysfunction. This condition is related to minor and/or impaired release of Nitric Oxide (NO). The positive effect of omega-3 fatty acids on endothelial dysfunction was associated with higher DHA levels that antagonize this disorder<sup>[12]</sup>. Concerning that, a recent study of Engler *et al* demonstrated that DHA supplementation in hyperlipemic children restores endothelial dependent flow-mediated dilation, consistent with the hypothesis that Omega-3 PUFA induces the NO increase<sup>[13]</sup>. It was also demonstrated that the chronic supplementation with fish oil in type 2 diabetes mellitus-patients, improves fasting endothelium-dependent vascular reactivity by enhancing NO release and formation of prostaglandins<sup>[14]</sup>. Another potential mechanism of restoration of normal endothelial function induced by omega-3 PUFA supplementation includes the increased vascular smooth muscle relaxation dependent from reduced calcium<sup>[15]</sup>. In a recent paper was also demonstrated that in patients with dyslipidemia both omega-3 PUFA and Rosuvastatin, improve endothelial dependent and independent vasodilatation as well as the lipide profile<sup>[16]</sup>.

#### Anti-thrombotic activity

In addition, omega-3 PUFA supplementation is able to induce a reduction of Thromboxane-2 (TXA2) production, a prolongation of bleeding time, a reduction of platelet adhesiveness, and an increase in red cell deformability. The reduction of the platelet's TXA2 production may be ascribed to the decrease in arachidonate (AA) content of platelets' membrane, the inhibition of AA release, and the competitive inhibition of AA at level of cyclo-oxygenase.

Other studies indicated that diets rich in fish or supplemented with fish oils may increase Plasminogen-Activator Inhibitor-1 (PAI-1) plasma levels. In addition, EPA-administration increases ProstaGlandin (PG12) production in rat thoracic aorta, and in rat aorta smooth muscle cell. This may be explained by EPA-derived peroxide stimulation of cyclo-oxygenase activity. Finally, EPA-administration decreased platelets' growth factor (PDGF) production in rat peritoneal macrophages, and suppressed foam cell formation<sup>[17]</sup>. This last effect was also demonstrated that the addition of omega-3 ethyl esters to the combination of Aspirin and Clopidogrel significantly potentiates platelets' response of anti-thrombotic activity after coronary intervention, in comparison to one of two drugs alone<sup>[18]</sup>.

#### Post-prandial disorders

Several data evidenced that increased levels of glucose and lipids are present in the serum during the post prandial phase, producing an unpaired metabolism in this period. Some evidences demonstrated that post-prandial dysmetabolism is important to be an independent predictor of future cardiovascular events both in diabetic and non-diabetic subjects<sup>[19]</sup>. Particularly, transient increase in free radicals acutely triggers inflammation, endothelial dysfunction, hypercoagulability, sympathetic hyperactivity, and cascade of other atherogenic changes<sup>[20]</sup>. To these main effects, must be also added to the unfavourable increase of post-prandial hyperglycemia and the negative effects of post-prandial hyperlipemia (showing besides the elevated triglyceride levels, the raise in serum chylomicrons, and remnant lipoproteins). Accumulated evidences concerning non-fasting triglyceride levels suggest that the atherosclerosis progression happening in the post-prandial phase is a phenomenon in which intestine-derived triglyceride-rich lipoproteins, would play an important role<sup>[21,22]</sup>. These negative actions are responsible for the atherosclerotic progression mainly happening in this period (post-prandial phase). On the contrary, the reduction of post-prandial "spikes" in glucose and in lipids obtaining with the omega-3 PUFA giving improves the inflammatory processes, the thrombogenic tendency, and the endothelial dysfunction, slowing the atherosclerotic progression.

#### Metabolic syndrome

Metabolic Syndrome (MetS) is a cluster of interrelated factors, such as central obesity, high blood pressure, impaired glucose metabolism and elevated triglyceride serum levels. It must be considered as an important predictor of cardiovascular disease and is associated with gene variations, insulin resistance and dyslipidemia. Recently, Jimenez-Gomez *et al* demonstrated that the adverse postprandial triglyceride effects may be avoided by concomitant long chain ( $n=3$ ) PUFA supplementation<sup>[23]</sup>. It was also demonstrated that the obesity-associated metabolic syndrome is a significant health care concern today. Levels of the adipocyte-derived peptide hormone leptin are highly correlated with adipose tissue mass (for leptin resistance) and are reduced in both humans and mice after weight loss<sup>[24]</sup>. Oils from marine sources containing omega-3 PUFA, such as EPA and DHA, have been shown to reduce the adipocyte diameter and thus the adipose tissue, for the reduction of leptin serum levels<sup>[25]</sup>. In addition, Carpentier *et al* suggested that the benefits of n-3 fatty oil supplementation could be caused by a reduction of inflammatory conditions, improvement of endothelial function, and increase of antioxidant status<sup>[26]</sup>. On the other hand, Mori *et al* showed that DHA significantly reduced 24 h blood pressure. The potential role of omega-3 PUFA in blood pressure prevention and management was

also evidenced by Borghi and Coll. that underlined as this compound reduce Angiotensin-Converting Enzyme (ACE) activity, Angiotensin II formation and enhance eNO generation activating the parasympathic nervous system<sup>[27]</sup>. In addition, the compound favours the NO release, as well as the ADP release, acts on vasoactive prostanoids (as TXA2), and endothelium-derived hyperpolarizing factor<sup>[28]</sup>.

## OTHER EFFECTS

### Alzheimer's Disease

Some studies performed at the Department of Veteran Affairs and the University of California have found that a diet rich in DHA dramatically slowed the progression of Alzheimer's Disease (AD) in mice. A recent research found that the DHA consumption cut the harmful brain plaques that mark the disease by up to 70%<sup>[29]</sup>. On the contrary, cross sectional and prospective cohort data have demonstrated that reduced dietary intake or low DHA brain levels are associated with accelerated cognitive decline and AD. But several trials, investigating the effects of PUFA-omega-3 supplementation, failed to demonstrate its efficacy in the AD prevention. But, these trials suggested that beneficial effects of omega-3 PUFA on AD depend perhaps on the specific stage of the disease<sup>[30]</sup>. Specifically, it is known that AD is a multifactorial neurodegenerative disease. Some clinical studies have shown that nutrition can affect the risk of its development and DHA appears to play an important role in that. In fact, DHA incorporation into neuronal membranes increases their fluidity. It also improves neurotransmission and signaling via increased receptor binding, and the the function of ion channels<sup>[30,31]</sup>. In addition, the DHA supplementation is able to lower the beta amyloid and tau proteins levels, reducing the amount of neuronal loss. These are the mainly manners of intervention of DHA in the AD pathogenesis.

An adjunctive modality of intervention is related to Resolvins and Protectins respectively derived from EPA and DHA. These compounds seem to play an important role in AD derived by their anti-inflammatory and immunoregulatory actions<sup>[32]</sup>. In fact, they are part of the molecular mechanisms that contribute to removal the inflammatory effect in neuronal cells and to restore tissue integrity. In particular, a protective effects in animal models of stroke and in AD, and the ability to promote the cells-apoptosis were found for (neuro) Protectins<sup>[33]</sup>. In addition, both Resolvins and Protectins may mitigate the sepsi-effects and may positively intervene in the recovery process from acute inflammation. Nevertheless, the mechanisms by which such effects are exerted are controversial too.

### Anti-depressant action

Some evidences showed that DHA deficiency is associated with dysfunction of neuronal membrane stability connected to the aetiology of mood cognitive depression and cognitive function<sup>[34,35]</sup>. Meanwhile, EPA is important in to balance the immune function and physical health, by reducing the membrane arachidonic acid and prostaglandin E2 synthesis and might be associate with medical comorbidity and somatic symptoms in depression<sup>[36]</sup>.

The phospholipid hypothesis of depression is promising and supported by numerous data on n-3 PUFAs and immunomodulation, signal transduction, neurotransmission and neuroprotection. It seems that a lack od DHA acts by increasing corticotropin-releasing hormone that moderates emotionality. This, in turn, acts on hypothalamic pituitary adrenal axis (an important neuroendocrine system) that regulates mood and anxiety. Other data suggest that Omega-3 fatty acid intake increases attention, and reduces aggression by reducing cognitive processes. Probably, PUFA omega-3 PUFA

will be a common antidepressant treatment in several populations, including those with bipolar disorders<sup>[37]</sup> and in depressant patients with somatic symptoms<sup>[38,39]</sup>. Thus, emerging researches suggest that the omega-3 PUFA and the balanced n-3/n-6 PUFA ratio may be effective for people with mild depression, means by an innovative but unknown mechanism.

### Telomere's length

Independently from their cardiovascular actions but by mechanisms referring to these same, Omega-3 PUFA fatty acids seem also to act on the life-lengthening. In fact, a previous report referred on the association between telomere's length, coronary disease, and Omega-3 fatty acids consumption. The hypothesis explaining these findings is that cardiac ischemia results in an intracellular redox shift, responsible for accelerated telomere's attrition<sup>[40]</sup>. On the other hand, telomere's shortening results to be associated with an increased likelihood of mortality favoured by heart disease. Concerning this, Starr *et al* showed that telomeres' shortening in peripheral blood leukocytes is a reliable index of ischemic heart disease risk<sup>[41]</sup>. More recently, Farzaneh-Far and al. found a significant association between omega-3 fatty acid blood levels and telomere's length in ischemic patients<sup>[42,43]</sup>. These results highlighted the presence of an inverse relationship between baseline blood levels of marine omega-3 fatty acids and the rate of telomere shortening. Nevertheless, the mechanisms involved in this process remain incompletely understood, even though there seems to be an increasing evidence that omega-3 fatty acids exert some direct effects on aging and its related diseases<sup>[44]</sup>. Particularly, omega-3 fatty acids supplementation seems to be associated with attenuation of age-associated rises in pulse-wave velocity, that is a key marker of vascular stiffness<sup>[45]</sup>. Another possibile explanation is that the decelerated telomere attrition depends from the oxidative stress<sup>[46]</sup>. Both actions seem to reduce the activity of enzyme telomerase, responsible for life duration<sup>[47]</sup>. Other factors, such as systemic inflammation, obesity, and lack of physical activity, are also invoked in to define the telomere's length by different and unspecified mechanisms. Finally, recent data suggest that lower n-6:n-3 omega PUFA ratio (obtained by omega-3 supplementation) impacts on inflammation, oxidative stress, immune cell aging and some cardiovascular diseases reducing the length of telomerase<sup>[48]</sup>.

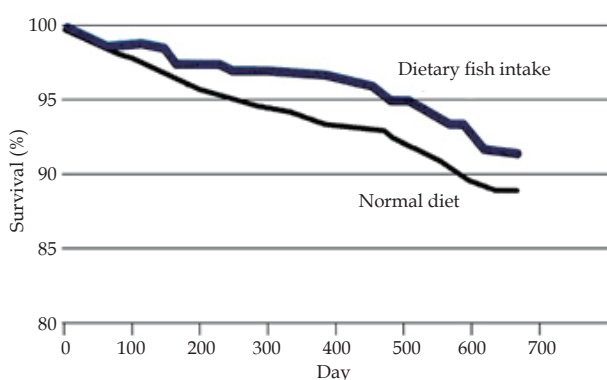
### Cancer effects

Omega-3 fatty acids selectively inhibit cell-growth and favour cell-death in squamous-cell carcinoma. Squamous cells are mainly present in skin cancer. But, they also occur in tumours of the digestive tract, lungs and of other areas of the body. Particularly, omega-3 fatty acids selectively inhibited the growth of the malignant and pre-malignant cells at doses which did not affect the normal cells, by an unknown mechanism<sup>[49]</sup>. On the contrary, a study found that men with high levels of omega-3 PUFA in their blood were at greater risk of prostate cancer than those with low concentrations. But, previous studies regard to the prostate cancer have produced different results, even though it is unclear why omega-3 PUFA increased the risk of the prostate cancer. Recent data evidenced that the effect could be related to the body's conversion of fatty acids into compounds which can damage cells and DNA<sup>[50]</sup>.

## CONCLUSIONS

Omega-3 PUFAs have been shown to exert a range of actions which include numerous positive effects slowing the atherosclerotic process. To delay that, their supplementation against the "spikes" of

metabolic disorder induced by the post-prandial phase, could be also considered. Other beneficial actions are performed in varied fields, such as telomere's length, depressive state, Alzheimers' disease, some malignants characterized by the presence of squamous cells. Referring to these favourable effects, the American Heart Association recommends eating fish (particularly fatty fish) at least two times a week. Each serving is 3-5 once cooked or about ¼ cup of fish. Of these, fishes like salmon, mackarel, herring, sardines and albacore tuna are particularly high in omega-3 fatty acids. In addition, a balanced diet is composed by 40% of carbohydrates; 25% of proteins, 25% of fats and 10% of mineral, vitamins and water. Finally, for a balanced weight loss diet, 1,200-1,500/day calories are requested (Figure 2). For all these favourable activities, the serum levels of omega-3 PUFA must be high. But, this condition could be avoided in men for the capability of omega-3 PUFA to favour the cancer-prostate growth. Thus, their daily supplementation is conflicting



**Figure 2** Survival (%) in individuals following dietary fish intake (two days by the week), in comparison with those receiving normal diet. Derived and modified from: *Circulation* 2002; 106, 2747-2757 and *Journ. Acad. Nutr. Diet* 2013; 113, 307-317

#### Abbreviations

PUFA=Poly-Unsaturated Fatty Acids  
 CAD=Coronary Artery Disease  
 EFAs=Essential Fatty Acids  
 EPA=Eicosa-Pentaenoic Acid  
 DHA=Doicosa-Hexaenoic Acid  
 VLDL=Very Low Density Lipoproteins  
 AHA=American Heart Association  
 LDL=Low Density Lipoproteins  
 AF=Atrial Fibrillation  
 GISSI=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico  
 IL=InterLeukin  
 AD=Alzheimer's Disease  
 NO=Nitric Oxide  
 TXA2=Thromboxane-2  
 AA=Arachidonic Acid  
 PAI-1=Plasminogen Activator Inhibitor-1  
 PG12=Prostaglandin-12  
 PDGF=Platelets' Growth Factor  
 MetS=Metabolic Syndrome

#### REFERENCES

- Sagild U, Littauer J, Jerpersen CS, Andersen S. Epidemiological studies in Greenland 1962-1964 I. Diabetes mellitus in Eskimos. *Acta Med. Scand* 1966; **179**: 29-39
- Lee JH, O'Keefe JH, Lavie CJ, Marchioli R, Harris WS. Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc* 2008; **83**: 324-332
- Das UN. Beneficial effect(s) of n-3 fatty acids in cardiovascular diseases: but, why and how? *Prostaglandins Leukot. Essent Fatty Acids* 2000; **63**: 351-362
- Calder PC. n-3 Fatty acids and cardiovascular disease: evidence explained and mechanism explored. *Clin Sci (London)* 2004; **107**: 1-11
- O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. *JACC* 2008; **51**: 249-255
- Harris WS, Deepti B. Why do omega-3 fatty acids lower serum triglycerides? *Curr Opin Lip* 2006; **17**: 387-393
- Reiffel JA, McDonald A. Antiarrhythmic effects of omega-3 fatty acids. *Am J Cardiol* 2006; **98**: 50i-60i
- Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Frantosi MG, Geraci E, Levatesi G, Maggiori AP, et al. Early protection against sudden death by omega-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 2002; **105**: 1897-1903
- Blum S, Aviram M, Ben-Amotz A, Levy Y. Effect of a Mediterranean meal on post-prandial carotenoids, paraoxonase activity and C-reactive protein levels. *Ann Nutr Metab* 2006; **50**: 20-24
- Oh R. Practical applications of fish oil (omega-3 fatty acids) in primary care. *J Am Board Fam Pract* 2005; **18**: 28-36
- Thies F, Garry JMC, Yaqob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PC, Grimble RF. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003; **361**: 477-485
- Bazan NG. Neuroprotectin D1-mediated anti-inflammatory and survival signaling in stroke, retinal degenerations, and Alzheimer's disease. *J Lipid Res* 2009; **50**: S400-S405
- Mindrescu C, Gupta RP, Hermance EV, De Voe MC, Soma VR, Coppola JT, Staniloae CS. Omega-3 fatty acids plus rosuvastatin improves endothelial function in South Asians with dyslipidemia. *Vasc Health and Risk Management* 2008; **4**: 1439-1447
- Tamura Y, Terano T, Saitoh H. Anti-thrombotic and anti-atherogenic action of eicosapentaenoic acid. *Nippon Tindho* 1992; **50**: 403-407
- Gajos G, Rostoff P, Undas A. Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary interventions. *JACC* 2010; **55**: 1671-1678
- Hilpert KF.; West SG.; Etherton PMK.; Hecker KD.; Simpson NM.; Alanpovic P.: Post prandial effect of n-polyunsaturated fatty acids on apolipoprotein B-containing lipoproteins and vascular reactivity in type-2 diabetes. *Am J Nutr* 2007; **85**: 369-376
- O'Keefe J, Bell D. Postprandial hyperglycemia/hyperlipidemia (postprandial dysmetabolism) is a cardiovascular risk factor. *Am J Cardiol* 2007; **100**: 899-904
- Huff MW. Dietary cholesterol, cholesterol absorption, postprandial lipemia and atherosclerosis. *Can J Clin Pharmacol* 2003; **10**: 26A-32A
- Fujioka Y, Ishikawa Y. Remnant lipoproteins as strong key particles to atherogenesis. *J Atheroscl Thromb* 2009; **16**: 145-154
- Jimenez-Gomez Y, Marin C, Perez-Martinez P, Hartwich J, Malczewska-Malec M, Golabek I et al. A low-fat, high-complex carbohydrate diet supplemented with long chain (n=3) fatty acids alters the post-prandial lipoprotein profile

- in patients with metabolic syndrome. *J Nutr* 2010; **140**: 1595-1601
- 21 Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA obese and weight-reduced subjects. *Nat Med* 1995; **1**: 1155-1161
  - 22 Parra D, Ramel A, Bandarra N, Kiely M, Martinez JA, Thosdottir I. A diet rich in long chain omega-3 fatty acids modulates satiety in overweight and obese volunteers during weight loss. *Appetite* 2008; **51**: 676-680
  - 23 Carpentier YA, Portois L, Malaisse WJ. N-3 fatty acids and the metabolic syndrome. *Am J Clin Nutr* 2006; **86**: S1499-S1504
  - 24 Mori TA, Bao DQ, Burke V, Pruddey IB, Bellin LJ. Docosahexenoic acid but not eicosapentenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension* 1999; **34**: 253-260
  - 25 Starr JM, McGrun B, Harris SE, Whalley LJ, Deary IJ, Shield PG. Association between telomere length and heart disease in a narrow age cohort of older people. *Exper Geront* 2007; **42**: 571-573
  - 26 Farzaneh-Far R, Lin J, Epel ES, Harris ES, Blackburn EH, Whooley MA. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA* 2010; **303**: 250-257
  - 27 Borghi C, Cicero AFG. Omega-3 polyunsaturated fatty acids: their potential role in blood pressure prevention and management. *Heart Int* 2006; **98**: 98-105
  - 28 Fuster JJ, Andres V. Telomere biology and cardiovascular disease. *Circ Res* 2006; **99**: 1167-1180
  - 29 Pauwels EK, Volterrani D, Mariani G, Kairemo K. Fatty acids facts, Part IV: docosahexanoic acid and Alzheimer's disease. A story of mice, men and fish. *Drug News Perspec* 2009; **22.4**:1367709
  - 30 Jicha GA, Markesbery WR. Omega-3 fatty acids: potential role in the management of Alzheimer's disease. *Clin Inter Aging* 2010; **5**: 46-61
  - 31 Mori TA, Watts GF, Burke V, Hilme E, Puddley IB, Beilin LJ. Differential effects of eicosapentenoic acid and docosahexanoic acid on vascular reactivity of the forearm microcirculation in hyperlipemic, overweight men. *Circulation* 2000; **102**: 1264-1269
  - 32 Engler MM, Engler MB, Malloy M, Chiu E, Besio D, Paul S et al. Docosahexanoic acid restores endothelial function in children with hyperlipemia: results from the EARLY study. *Int J Clin Pharmacol* 2004; **42**: 672-679
  - 33 Stirban A, Nandreaan S, Gotting C, Tamler R, Pop A, Negrean M, Gawlowski T, Stratmann B, Tschoepe D. Effects of n-3 fatty acids on macro- and microvascular function in subjects with type 2 diabetes mellitus. *Ann J Clin Nutr* 2010; **13**: 10.3945/ajcn.2009.28374
  - 34 Chin JP, Dart AM. How do fish oils affect vascular function? *Clin. Exp. Pharmacol Physiol* 1995; **22**: 71-81
  - 35 Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentenoic acid in bipolar depression: report of a small open-label study. *J Clin Psychiatry* 2005; **66**: 726-729
  - 36 Hamilton M. Frequency of symptoms in melancholia (depressive illness). *Br J Psychiatry* 1989; **154**: 201-206
  - 37 Bourre JM, Dumont O, Piciotti M, Clement M, Chaudiere J, Bonneil M, Nalbhone G, Lafont H, Pascal G, Durand G. Essentially of omega-3 fatty acids for brain structure and function. *World Rev Nut Diet* 1991; **66**: 103-117
  - 38 Heron DS, Shinitzky M, Hershkowitz M, Samuel D. Lipid fluidity markedly modulates the binding of serotonin to mouse brain membranes. *Proc Natl Acad Sci USA* 1980; **77**: 7463-7467
  - 39 Ariel A, Serhan CN. Resolvins and protectins in the termination program of acute inflammation. *Trends Immunol* 2007; **28**: 176-183
  - 40 Visioli F, Hagen TM. Nutritional strategies for healthy cardiovascular aging: focus on micronutrients. *Pharmacol Res* 2007 **55**: 199-206
  - 41 Tomiyama H, Takazawa K, Osa S, Hirose K, Hirai A, Iketani T, Monden M et al. Do eicosapentenoic acid supplements attenuate age-related increases in arterial stiffness in patients with dyslipidaemia? A preliminary study. *Hypertens Res* 2005; **28**: 651-655
  - 42 Farzaneh-Far R, Cawthon RM, Na B, Browner WS, Schiller NB, Whooley MA. Prognostic value of leukocyte telomere length in patients with stable coronary artery disease: data from the heart and Soul study. *Arterioscl Thromb Vasc Biol* 2008; **28**: 1379-1384
  - 43 Chan SR, Blackburn EH. Telomeres and telomerase. *Philos Trans R Soc Lond B Biol Sci* 2004; **359**: 109-121
  - 44 Freeman MP, Hibbein JR, Wisner KL, Davis JM, Mishoulon D, Peet M, Keck PE Jr et al. Omega-3 fatty acids evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry* 2006; **67**: 1954-1967
  - 45 Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry* 2006; **163**: 1098-1100
  - 46 Su KP. Biological mechanism of antidepressant effect of Omega-3 fatty acids: how does fish oil act as a "mind-body interface?" *Neurosignal* 2009; **17**: 144-152
  - 47 Farooqui AA, Ong WY, Horrochs LA. Inhibitors of brain phospholipase A2 activity: their neuropharmacologic effects and therapeutic importance for the treatment of neurologic disorders. *Pharmacol Rev* 2006; **58**: 591-620
  - 48 Kiecolt-Glaser JK, Epel ES, Belury MA, Andridge R, Lin J, Glaser R et al. Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: a randomized controlled trial. *Brain Behav. Immun* 2013; **28**: 16-24
  - 49 Nikolakopoulou Z, Nteliopoulis G, Michael AT, Titus AT, Parkinson EK. Omega-3 polyunsaturated fatty acids selectively inhibit growth in neoplastic oral keratinocytes by differentially activated ERK1/2 Carcinogenesis 2013 DOI: 10.1093/carcin/bgt 257
  - 50 Brasky TM, Darke AK, Song X, Tangen CM, Goodman PJ, Thompson IM, Meykens FL et al. Plasma phospholipids fatty acids and prostate cancer risk in the SELECT Trial. *JNCI Natl. Cancer Inst.* 2013 DOI: 10.1093/jnci/djt174
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