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Why Fish Oil Fails to Prevent or Improve CVD: A 21st Century Analysis

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ABSTRACT

In May 2013, The Risk and Prevention Study Collaborative Group (Italy) released a conclusive negative finding regarding fish oil for those patients with high risk factors but no previous myocardial infarction. Fish oil failed in all measures of CVD prevention—both primary and secondary. This study was so conclusive that Eric Topol, MD, editor-in-chief of Medscape and Medscape's Heartwire for cardiologists, issued a new directive to patients to stop taking fish oil, *i.e.*, long-chain EFA metabolites of EPA/DHA. Fish oil's failure is shown to be consistent with known physiology and biochemistry: there should never have been any expectation of success. To the contrary, true EFAs, linoleic acid and alpha-linolenic acid, termed Parent Essential Oils (PEOs), fulfill fish oil's failed promise. Fish oil supplements contain supra-physiologic amounts of EPA/DHA. Recommendations are often paramount to pharmacologic overdose. Unlike fish oil, which failed to decrease 19 markers of inflammation, PEOs do decrease inflammation. The first screening experiment comparing fish oil with Parent EFA oils, the seminal IOWA experiment utilizing pulse wave velocity, demonstrated unequivocally that fish oil contributes to hardening of the arteries, aging subjects by nearly 4 years ($P < 0.0001$). To the contrary, PEOs increase arterial compliance, making subjects' arteries "biologically younger" (increased arterial compliance) by more than 11 years compared to subjects taking fish oil fish ($P < 0.001$).

Keywords: Fish Oil; EFAs; Parent Essential Oils; PEOs; LDL-C; PUFA; Arterial Compliance; Cardiovascular Disease; CVD; PGE_1; PGI_2; Prostacyclin; Endothelial; IOWA Experiment; Pulse Wave Velocity (PWV)

1. Introduction

CVD-related pathophysiology, including stroke, is by far the #1 killer in the United States. Fish oil, with its "active ingredients" EPA and DHA, has been recommended as a solution. While pre-2007 cardiovascular studies were associated with an improvement with fish oil, post-2007 studies show significant accumulated failure [1]. Confirmation of fish oil failure was independently summarized in a meta-analysis of 14 studies comprising 20,485 patients and published in 2012 [2].

Of their 1007 articles retrieved, only 14 met the criteria of randomization, double-blindness, and placebo-controlled. Clearly, an enormous number of poorly conducted studies in the journals have conclusions that can't be relied on and are misleading physicians worldwide. The researchers stated, "Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease". The final blow was in May 2013. This clinical trial, one of the most comprehensive and well-conducted trials to date, utilized over 12,000 patients and 860 general practitioners [3]. To understand its full impact, it is important to provide exact quotes of these researchers and reviewers of this landmark study: "In summary, we conducted a randomized trial of n-3 fatty acids [fish oil] in a large population of patients with multiple cardiovascular risk factors but no history of myocardial infarction. The trial incorporated systematic efforts to optimize medical therapies and control cardiovascular risk factors. On the basis of the results, we conclude that there was no significant benefit of n-3 fatty acids [fish oil] in reducing the risk of death from cardiovascular causes or hospital admission for cardiovascular causes."

This monumental failure caused editor-in-chief of Medscape, cardiologist Eric Topol, MD, to state, "I have an awful lot of patients that come to me on fish oil, and I implore them to stop taking it" [4]. The present study, with its efficacious dose, arms physicians with data to tell patients who have not had an MI and who don't have heart failure that n-3 fatty acid supplementation with fish oil is not effective. He called fish oil a "no-go", noting that if the supplement had no effect in this high-risk patient population, of whom just 40% were taking statins, it's hard to imagine that n-3 fatty acids [fish oil] would provide any benefit in lower-risk subjects. "Fish oil does nothing", continued Topol. "We can't continue to argue that we didn't give the right dose or the right preparation. It is a nada effect."

2. Physiologic Details of LDL and Parent Essential Oils (PEOs) in Arterial Plaque

2.1. Decreased NO by Oxidized LDL

Clearly, fish oil fails, but why? Are researchers looking in the wrong place? As a start, it is well known that nitric oxide (NO) is required for optimal vascular health. Chin and colleagues presented convincing evidence that a lipid component in *oxidized LDL inactivates nitric oxide* [5,6]. The key to improved cardiovascular health is in this lipid component. The answer becomes apparent by focusing on the established physiology and biochemistry of intimal (the matrix of tissue directly lining the artery) plaque. It will be proved how fish oil could never prevent or reverse CVD; there never should have been expectation for success. To the contrary, Parent Essential Oils (PEOs), the only true EFAs, will be shown to both prevent and reverse CVD via multiple metabolic pathways.

2.2. EFAs—Parents (PEOs) and Derivatives

There are only two true 18-chain carbon EFAs: linoleic acid (LA), with two double bonds, and alpha-linolenic acid (ALA) with three double bonds. Neither can be manufactured in the body; both must come from food. LA is termed "Parent" omega-6; ALA is termed "Parent" omega-3. Longer-chain metabolites are synthesized from LA and ALA. These long-chain metabolites, not essential and incorrectly termed "EFAs", are correctly termed "derivatives". For example, common derivatives of the omega-3 series are EPA (eicosapentaenoic acid) with five double bonds and DHA (docosahexaenoic acid) with six double bonds. To clarify the issue in this paper and in general, I term LA and ALA "Parent Essential Oils" (PEOs) or "Parents". I term all long-chain metabolites "derivatives". The body makes these important derivatives from Parents "as needed" in minute amounts. The literature often fails to clearly distinguish these two vastly different substances.

2.3. Variable Tissue Composition

The significant variable in tissue is its lipid structure. Although the genetics of a particular species precisely specify cellular structure, its lipid composition can vary significantly—in particular, when supra-pharmacologic amounts of long-chain metabolites are consumed, such as the case with fish oil supplements. A pharmacologic overdose can't all be oxidized away for energy or otherwise. Consequently, much of "the overdose" is forced into tissue composition, causing an improper structure—often in maintaining a linear relationship as does plasma, liver, and RBCs [7-9]. Cellular bilipid membrane structure and its LDL-C structure warrant intense investigation. Each of a human's 100 trillion cells consists of a bilipid membrane. Importantly, PEOs comprise 25% - 33% of their polyunsaturated lipids [10]. Additionally, every mitochondrion, typically a hundred to thousands per cell contain them too [11,12]. PEOs can be considered the "brick and mortar" of every cell, tissue, and organ, including mitochondria. In contrast, aside from the brain, eyes, and nervous system, most tissue and organs contain few derivatives like EPA/DHA.

2.4. Variability in LDL-C

The structure of LDL-C is complex. Its cholesteryl *ester* is key (**Figure 1**). The structure of cholesterol itself never changes, merely its esterified moiety—the acyl side chain. That's a big difference that many in the medical community may not appreciate. This is a simple condensation reaction, removing the water, catalyzed by the enzyme ACAT (Acyl CoA: Cholesterol Acyl Transferase) between a fatty acid and cholesterol. "R" symbolizes the hydrocarbon portion of the fatty acid. For example, if oleic acid were esterified with cholesterol, then R would be $-C_7H_{14}CH=CH-C_8H_{17}$ with the double bond in cis configuration.

Lipoproteins transport cholesterol and its esterified PEOs to the tissues via apoprotein B-100 ($ApoB_{100}$) (**Figure 2**). Although the molecule itself may become oxidized, that likelihood is extremely low. What is primarily oxidized are the fatty acids esterified to LDL-C (**Figure 1**). Quantities of esterified LA (Parent omega-6) are approximately 85% of its overall 50% fatty acid content [13].

2.5. Failure of LDL-Cholesterol to Prevent CVD

A review of a cholesterol/CVD causal effect categorically failed: Among 12 populations with similar cholesterol levels (clustered around "normal" levels—5.70 to 6.20 mmol per liter (220 to 240 mg per dl), the blood pressure readings and the serum cholesterol levels were not predictive of ischemic heart disease mortality [5]. If it were, a 10% reduction should have had significant positive effects; it didn't. Nothing has changed today regarding LDL-C's dismal success rate in both predicting

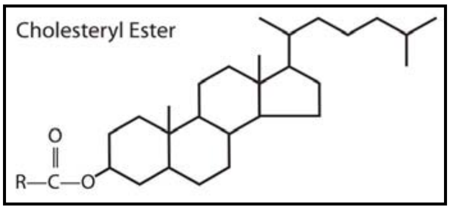

Figure 1. Cholesteryl ester.

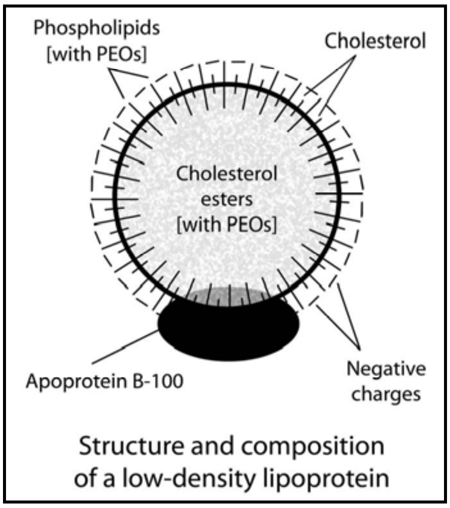

Figure 2. Structure and composition of a low-density lipoprotein showing the significance of its esterified cholesterol structure.

and lowering CVD by its general modification (lowering of LDL-C).

2.6. Esterified Cholesterol Detailed

The cholesterol molecule (better termed cholesteryl) is tied to a structure that *does change*—particularly, its EFA variable "R" component (**Figure 1**). It is well understood that the PEO LA dominates the esterified portion of cholesterol. The majority of the cholesteryl ester component is LA (Parent omega-6) [14]. The cholesterol ester portion is highly significant compared to free cholesterol or phospholipids (**Figure 2**). Approximately 70% of the cholesterol in the lipoproteins of the plasma is in the form of cholesterol esters attached to apolipoprotein B [15]. Of dietary cholesterol absorbed, 80% - 90% is esterified with long-chain fatty acids in the intestinal mucosa [16].

2.7. LDL-C Is NOT Oxidized in the Bloodstream

Cholesterol itself is extremely resistant to oxidization, whereas its main esterified component, Parent omega-6 (LA), is more easily oxidized, especially ex vivo. Dietary LA that has already become oxidized prior to ingestion ex vivo is ubiquitous through processing of foods or overheating, since heating in the presence of air enhances peroxidation of PUFA glycerol esters [17,18]. These insights suggest that looking in a new direction for the prevention of heart disease is warranted.

Strongly supporting this thesis is the fact that normal anti-oxidant levels are lower than would be presumed to be adequate and normal if analysis weren't performed. The sum molar ratio of all antioxidants to PUFA is a mere 1:165 (0.61%), with one antioxidant molecule having to protect the large number of 165 PUFA molecules. The total number of fatty acids bound in the different lipid classes of an LDL particle with a molecular mass of 2.5 million is on average 2700, of which about one-half (1/2) are polyunsaturated fatty acids (PUFAs), mainly linoleic acid (Parent omega-6), with small amounts of arachidonic acid and docosahexaenoic acid (DHA). It is highly unlikely than LDL can become oxidized in plasma to the extent that it causes foam cell formation and possesses chemotactic and cytotoxic properties. Furthermore, only minimal physical and chemical changes related to oxidation are produced by even a prolonged storage of LDL with oxygen or by incubation with low concentrations of copper ions. Clearly, the quantity of anti-oxidants is too small for oxidation in vivo to be a significant physiologic issue [5,13]. The sole logical conclusion is that the PUFA, in particular, LA, is being consumed and entering the body in an already oxidized state.

2.8. LDL-C Is Transporting a "Poison"

Prof. Gerhard Spiteller, who is Chairholder of Biochemistry, Institute of Organic Chemistry at the University of Bayreuth, Germany, has investigated EFAs and their degradation products—specifically, the influence of these substances in the physiology of mammals. He concluded that *consumption of oxidized PUFA-cholesterol esters* is responsible for the initial *damage to endothelial cells* and that cholesterol oxidation products are incorporated into LDL cholesterol in the liver [19]. LDL then carries these toxic compounds into the endothelial walls where they cause cell damage. Injury is not caused by an increase in free cholesterol but by an increase in cholesterol esters [20]. In atherosclerotic patients, LDL cholesterol is altered ex vivo by oxidation, and this altered LDL is taken up in unlimited amounts by macrophages. Dead macrophages filled with cholesterol's damaged, functionally impaired esters are then deposited in arteries. LDL-C is effectively transmitting a poison, *i.e.*, nonfunctional and harmful LA. We can now explain the significant failure of statins. By statin's lowering of LDL-C, its esterified PEOs are also lowered, both adulterated [good outcome] and fully functional [bad outcome]. This is problematic. By focusing on the ex vivo LA that has already become oxidized prior to ingestion through processing of foods, cooking, or overheating, a solution can be found to mitigate this damage.

2.9. Importance of Parent Omega-6 and Metabolites

The majority of the plasma fatty acids are LA (Parent omega-6). Mitigating the damage caused by *ex vivo* intake of already oxidized LA is possible. Compensation by ingesting fully functional, unadulterated, nonoxidized LA is a significant EFA-based anti-CVD solution. Additionally, the metabolites of LA—in particular, PGE_1 and PGI_2 (prostacyclin)—are significant vasodilators. PGE_1 is also a potent anti-inflammatory. If functional LA bioavailability is lowered, the potential for inflammation will rise, leading to atherosclerosis. Weiss, for example, has noted that PGE_1 (produced from functional Parent omega-6) reduces the fibrin deposition associated with the pathogenesis of atherosclerosis [21]. Membrane fluidity increases when more functional (undamaged) polyunsaturated fatty acids—in particular, linoleic acid—are available to incorporate into the membrane lipid bilayer.

If there is a deficiency of fully functional LA in the diet, the body will substitute into cell membranes nonfunctional LA or even a nonessential fatty acid, such as oleic acid (omega-9), found in olive oil. This forced substitution because of inadequate functional LA results in a marked decrease of cellular oxygen transport with adverse effects on cellular metabolism and function [22]. Because LDL cholesterol is the transport vehicle for PEO delivery into the cell, LDL cholesterol will transport any kind of LA into cells—defective or not—such as oxidized or trans entities.

2.10. Arterial Intima: Endothelial Tissue Comprised of Epithelial Cells

The innermost lining of arterial intima is endothelial tissue, comprised of epithelial cells containing significant LA, but no alpha-linolenic acid (ALA) [23,24].

A significant biologic effect of oxidized LDL is its cytotoxic effect on cultured endothelial cells directly lining the arterial wall [5]. Adulterated dietary LA, deposited in arterial intimal cell membranes, leads to abnormal oxidation at the vascular injury site, thus causing injurious inflammation. In this case, *abnormal oxidation*, caused by *ex vivo* adulteration of LA, involves formation of a hydroperoxide from LA by abstraction of a hydrogen atom as a radical from the doubly allylic methylene group between the two double bonds, followed by the addition of oxygen, a diradical, to make a hydroperoxide radical, which can then pick up another reactive hydrogen atom, perhaps from another LA molecule, to form the hydroperoxide. This, in turn, may break the O-O bond to form an alkoxide and a hydroxyl radical, which can continue to make more undesirable oxidized products [25]. Therefore, atherosclerosis can be prevented/arrested if endothelial cells are fully functional [26].

2.11. Parent Essential Oils—PEO Deficiency: Fully Functional vs. Adulterated

Not distinguishing an adulterated (processed) EFA against a fully functional unprocessed EFA—in particular, LA—is the prime cause of confusion leading to inconsistent clinical trials on cardiovascular health. From the above discussion, the criticality of distinguishing between the effects of adulterated versus unadulterated forms of LA is obvious. Failure to do so has led to the incorrect and misleading conclusion that dietary intake of LA increases CVD risk [27].

With functional LA deficiency there is an enormous increase in permeability of the skin (epithelial tissue) and an increase in capillary fragility, further explaining the pathophysiology of CVD and how it may be prevented [28]. Oxidation of LDL-C causes significant depletion of LA (Parent omega-6) [5].

With ingestion of fish oil (EPA/DHA) there was a corresponding decrease in tissue's LA, causing pathophysiologic deficiency [29].

2.12. PEOs in Plasma, Lipids, and Esterified Cholesterol

It is necessary to analyze the PEO content of plasma lipids (lipoproteins, triglycerides, and esterified cholesterol) to determine the specific "bad actor" in CVD and confirm LA's prime importance. LDL's esterified linoleic acid is the major source for lipid peroxidation products, yet linoleic acid is highly resistant in LDL against oxidation [30]. This is important to understand.

With all the focus on omega-3 series fatty acids today, both Parent and derivative, it is significant to note that the *free Parent fatty acids* (*non-esterified*) *in human plasma*, although minute in quantity, are ordinarily composed of about 15% LA (linoleic acid, Parent omega-6) and just 1% ALA (alpha linolenic acid, Parent omega-3) [30]. Derivatives such as EPA/DHA are naturally much less significant in quantity than LA. In sharp contrast to the high amounts of n-6 series PUFAs, n-3 series PUFA account for only 1.8% of the fatty acids in triglycerides, 3.5% in the phospholipids, and only 1.7% (ALA is 0.5%) in cholesterol esters. This high preponderance of LA is pervasive throughout: The LA/ALA ratio in triglycerides is 23:1; n-3 PUFA makes up only 1% - 2% of fatty acids in plasma [31]. Even in the brain, LA/ALA uptake is 100 times greater in favor of LA [31].

2.13. Composition of Arterial Plaque

Current anti-CVD recommendations lack a firm physiologic/biochemical basis. In 1994, using high-resolution chromatography, investigators found that plaque contained more than 10 different compounds, none of which were related to saturated fat [32,33]. Not surprisingly, cholesterol was found in the plaque. This key finding demonstrated that cholesterol, esterified with nonfunctional linoleic acid (LA)—adulterated Parent omega-6—was by far the most abundant component in plaques of arterial stenosis. Furthermore, it was also found that cholesterol esters are the predominant lipid fraction in all plaque types, and that oxidized derivatives are toxic to most types of arterial cells [34].

3. Fish Oil Is Expected to Cause CVD: Pathophysiology of Fish Oil

3.1. Fish Oil Spontaneously Oxidizes at Room Temperature and *in Vivo*

Fish oil is expected to contribute to CVD, not prevent it: a) Regardless of anti-oxidant level added to the fish oil supplement, rancidity/peroxidation upon ingestion is a very significant and problematic issue. Because of the five double bonds in EPA and six double bonds in DHA, these metabolites are highly sensitive to temperature. Spontaneous oxidation of EPA leads to generation of a mixture of aldehydes, peroxides, and other oxidation products. Highly polyunsaturated, long-chained EPA and more so with DHA, due to its additional double-bond, is readily oxidized at room temperature even in the absence of exogenous oxidizing reagents. Importantly, *in vivo*, a large increase in tissue and plasma accumulation of fatty acid oxidation products is noted in subjects consuming fish oil even after addition of antioxidant supplements to the diet. Again, this effect strongly suggests extensive oxidation of omega-3 fatty acids such as EPA *in vivo*. This led to a 14% decrease in life expectancy in those animals fed fish oil [35]. As shown above, PEOs don't suffer this problematic issue.

In primates and humans such as the monkey, no quantity of *in vivo* antioxidants will stop EPA/DHA damage as measured by lipofuscin, the peroxidized "age spots." Lipofuscin was three-fold (3Xs) greater in the livers of monkeys fed fish oil. Furthermore, another measure of oxidative damage, the basal thiobarbituric acid reactive substances (TBRS) levels, were four-fold (4Xs) greater than in the monkeys fed corn oil with no EPA/DHA. The researchers found that even a ten-fold (10Xs) increase in alpha-tocopherol, a potent antioxidant, was not fully able to prevent the peroxidative damage from fish oil [36].

3.2. Fish Oil Causes Decreased Prostacyclin Production

Prostaglandins are capable of both limiting thrombosis and reversing thrombosis in atherosclerotic patients [37]. Prostaglandin PGE_1 is the body's most powerful anti-inflammatory and vasodilator, and prostacyclin (PGI_2) is a vasodilator, and prevents both platelet adhesion and aggregation. These are both omega-6 metabolites. Fish oil increases *endothelial* platelet aggregation in heart patients [38]. In patients with atherosclerosis, prostacyclin (produced in endothelial tissue) biosynthesis fell by a mean of 42% during the fish-oil period [extremely bad outcome]. Synthesis of the platelet agonist thromboxane A_2 (produced in the platelets) declined by 58% [good outcome]. This may first appear a reasonably successful intervention, but that analysis is naïve and very wrong. Atherosclerotic patients require increased intimal PGI_2 output, as vessel wall thrombogenecity and not reduced platelet adhesion, is a much more significant factor for minimizing thrombosis [39]. Template bleeding times were significantly prolonged in all patients [bad outcome].

3.3. Fish Oil Raises Blood Glucose Levels and Decreases the Insulin Response

Elevated resting blood glucose levels are a diabetic's nightmare. Spontaneous auto-oxidation of blood glucose is a significant cause of diabetic patients' elevated increased risk of CVD. Both fish oil supplements and even "oily fish" itself are highly problematic for diabetics. In 2011, researchers looked at the effects on Type II diabetic patients eating more fish. Only from *non-fatty* fish, containing more Parent omega-6 and much less EPA/DHA, did the experiment show significantly decreased blood sugars [good outcome]. Further, those who ate "fatty" fish saw a decreased insulin output of 21% [bad outcome] compared to those not eating "fatty" fish [40]. "Fatty" fish (containing more EPA/DHA), not a supplement, caused the elevated blood glucose. EPA/DHA fish oil supplements cause elevated blood glucose and blunt the insulin response in diabetics. This deleterious finding was known years ago [41,42].

Since "fatty/oily" fish caused the same deleterious effects as the supplement, the only logical conclusion is that fish oil—in any form—is harmful to any diabetic. Diabetes is America's #1 epidemic and both oily fish and fish oil supplements exacerbate the condition.

3.4. Fish Oil Displaces Critical Omega-6 Metabolites Harming Tissue Structure

Importantly, fish oil potentially damages the brains of both infants and adults because critical omega-6 series metabolites are displaced [7]. The medical journal's authors specifically warned against feeding fish oil to human infants. This experiment was performed in rodents but the results are applicable to humans because EFA metabolism is similar and applicable to both mammals and rodents [9]. Systemic rises in fish oil's EPA is largely compensated by decreased Parent omega-6 [29].

3.5. Amounts of EPA/DHA in Fish Oil Supplements

An average 1000 mg health-food-grade fish oil capsule contains approximately 180 mg EPA and 120 mg DHA. Pharmaceutical-grade versions contain higher doses. The American Heart Association states that those with documented CHD are advised to consume about 1 gram of EPA + DHA per day. Is this advice rational? No.

3.6. Parent-to-Derivative Metabolism and Amounts

What percentage of PEOs becomes converted (naturally) to long-chain metabolites such as GLA, AA, EPA, DHA, etc.? The USDA and NIH provide these answers. The conversion amount is much less than the medical field assumes; it is less than 5%—often less than 1%—with at least 95% of PEOs staying in Parent form. This singular mistake in assuming very high conversion amounts, whereas in actuality they are extremely low conversion amounts, led to the irrational fish oil mania.

Contrary to wrong dogma, the enzymes that produce PEO derivatives (the delta-6 and delta-5 desaturase enzymes) are *not impaired* in the vast majority of patients [43]. Conversion of ALA [Parent omega-3] to DHA is unlikely to *ever normally exceed* 1% *in humans* [44]. Research at the United States Department of Agriculture's USDA food composition laboratory (2001) reported *a natural net conversion rate of a mere* 0.046% *of ALA to DHA* & 0.2% *to* EPA—not the highly misleading 15% conversion rate that is often-quoted [45].

NIH researchers determined the amount of DHA utilized in human brain tissue to be a mere 3.8 mg ± 1.7 mg/day. Therefore, brain tissue in 95% of all subjects, allowing for variation in brain size, would consume 0.4 mg - 7.2 mg of DHA per day [43]. New, twenty-first century quantitative research from both NIH and USDA show considerably lesser amounts of natural DHA conversion/usage from ALA than the medical community has been led to believe. These conversion amounts are extremely small and naturally limited. This mistake often leads to recommendations that are supra-pharmacologic and can potentially overdose patients by factors of 20-fold to 500-fold, depending on specific supplement and amounts consumed. The body cannot simply oxidize these tremendous overdoses of EPA/DHA; they are too great a quantity.

3.7. No Delta-6/-5 Desaturase Impairment in (Average) Patients

Highly accurate, quantitative experiments were performed showing that the average healthy person and animals are both quite capable of metabolizing adequate amounts of DHA from Parent omega-3 (ALA). In a key NIH experiment, rodents naturally produced 50-fold (50Xs) more DHA each day than their brains required [46]. Certainly, Nature would insure humans the same margin of safety shown to a rodent.

An *American Journal of Clinical Nutrition* article detailed over 60 firefighters and analyzed their conversion of omega-3 long-chain metabolites from Parent omega-3 (ALA) and found conversion adequate with sufficient intake of ALA [Parent omega-3] [47].

Even vegans consuming no animal food, including fish, a group that absolutely would be expected to manifest gross neurological abnormalities, including both visual impairment and cognitive impairment, do not. There is no clinical evidence of such abnormalities in vegetarians [48,49]. Confirmation in 2010 showed vegetarians with an intake of 0.3% DHA compared to fish eaters produced 85% of the EPA levels and 83% of the DHA levels that consumers of fish did. These amounts are within the "normal" ranges [48].

There is no widespread impairment in the typical patient whatsoever; the normal conversion amounts are simply very low.

4. The Most Predictive Physiologic Measurement of Cardiovascular Health

Blood markers have been less than ideal in predicting cardiovascular health. Utilization of LDL-C levels alone has been a dismal failure. The best noninvasive method of evaluating arterial health is pulse wave velocity (PWV). Hardening of the arteries, *i.e.*, arteriosclerosis, is a prime cause of cardiovascular disease and patient death. A stiff artery could result from either or both of the following conditions: 1) physiologic impairment of the arterial tissue, 2) occlusion inside the artery, *i.e.*, atherosclerosis.

Arterial stiffness is an accepted, strong, independent predictor of cardiovascular events and mortality [50]. While direct measurement of PWV is the "gold standard" requiring physician skill and time, a new method based on photoplethysmography is available. Digital pulse analysis (DPA) was the next evolution in photoplethysmography and is based on the measurement of reflected infrared light. Photoplethysmography has been validated for accurately calculating systemic arterial compliance (flexibility) [51]. Subject output is compared to an existing large population database by age. The computer matches the subject to the significant sample database and outputs a "biologic age." Inherent experimental error of the mean is ± 5 years.

Digital Pulse-Wave Analysis (DPA)

The Meridian DPA™ (Meridian Medical Co, Ltd., South

Korea) is an FDA 510(K) cleared device for diagnostic use. A non-invasive screening device, the Digital Pulse Wave Analyzer™, accurately measures arterial stiffness, a composite of both large and small arteries, along with aging based on prior population samples in their database. Because fish oil and plant-based EFA-containing oils are available in unlimited amounts without prescription, and this is also a noninvasive *screening study*, no IRB is required. A non-invasive finger probe (as used with a pulse oximeter) is utilized. The machine self-calibrates and a computer performs the analysis—no interpretation is required. The reading correlates to population biologic age samples—it is impossible to manipulate readings.

The only criteria for subject exclusion of the study was either a reading could not be accurately gained from the subject, e.g., weak pulse or impairment of light through fingernails or for reasons that would invalidate the DPA reading, *i.e.*, subject use of beta-blockers, ACE inhibitors, and all medications that artificially lower blood pressure so that the DPA reading would not be valid. Diabetes, high cholesterol, and all high-risk patients, if requested screening, were included. Both accuracy and repeatability of the machine are excellent.

5. Materials and Methods

Subjects were recruited in Iowa. A plant-based EFA supplement high in PEOs, [redacted], was used. Subject consumption amount was 725 mg per each 40 pounds per day of subject bodyweight; the average amount per patient per day being 2,900 mg.

Three (3) groups were screened: Group I—Long-term PEO users (34; 22 females and 12 males, aged 35 - 75 with median age 62; mean usage 90 months, median usage 24 months); Group II—Short-term PEO users (16; 9 females and 7 males, aged 46 - 84 with median age 64; mean usage 3 months, median usage 2.5 months); Group III—Fish oil to PEO usage (15; 8 females and 7 males, aged 46 - 74 with median age 60; mean usage 3.1 months, median usage 4 months).

Various brands of fish oil were used in the "Fish oil to PEO users" (Group III) leg of the screening. Since all oils used are commonly available in any quantity, no Institutional Review Board (IRB) is required. (Peskin is a consultant to Your Essential Supplements, Inc. and other companies.)

Investigating Oils with Respect to Arterial Health: IOWA Screening Experiment

To the author's knowledge, this is the first time PEOs were used to compare their arterial compliance (flexibility) improvements against fish oil. This is a broad-based population screening—the most realistic population to see effectiveness, if any.

6. Results

All statistical analyzes were independently performed by Alexander Kiss, PhD (Biostatistics). Group I (long-term PEOs only) statistics simply looked at the group's average chronologic age vs. their arterial compliance biologic age based on historical populations from the computer's database. For Groups 2 and 3, a "before/after" analysis, the paired t-test, was performed (**Table 1)**. Group I results were an average of 8.8 years decrease in "biological age" compared to their chronological age ($p = 0.001$); NNT = 1.4: 73% of all subjects improved their cardiovascular system. Group II results were an average of 7.2 years decrease in "biological age" ($p = 0.001$); NNT = 2.3: 43% of subjects improved in a very short time frame. Group III results were an average of 11.1 years decrease in "biological age" ($p = 0.0001$); NNT = 1.2: 87% of subjects improved in a very short timeframe; the most significant improvement in any population. Each group's results were highly statistically significant.

Results with Additional Patient Risk Factors

Seven subjects had "high" cholesterol levels while taking fish oil supplements before changing to PEOs. Six of the seven patients decreased their cardiovascular "biological age" by ceasing fish oil and converting to PEOs. NNT = 1.2: an 83% effectiveness rate in this sub-group. One subject with both "high cholesterol" and diabetes improved after replacing fish oil with PEOs. Two subjects taking statins decreased their cardiovascular biological age by 20 years after ceasing fish oil and replacing with PEOs (NNT = 1).

7. Discussion

Arterial compliance is the most accurate physiologic assessment of a subject's cardiovascular health. The highly statistically significant results and excellent NNTs confirm the theoretical predictions of both the failure of fish oil to increase arterial compliance, and the significant success of PEOs to improve arterial compliance across all populations.

Table 1. PEOs increase arterial compliance.

PEO Group	No. Subjects	Median Age	"Biologic Age Compared to Physical Age (yr)"	P-value
Long-term	34	62	−8.8	0.001
Short-term	16	64	−7.2	0.001
Ceasing fish oil/PEOs	15	60	−11.1	0.0001

The most remarkable finding was that subjects taking fish oil prior to PEOs obtained the most improvement. This was anticipated since those subjects started at a greater vascular deficit caused by the fish oil consumption. Ceasing fish oil use allowed the arterial system to revert to "normal". Once the vascular system was back to "normal", the expected improvement from PEOs, as shown by the other groups, was also achieved, resulting in an even greater decrease in biological age. Clearly, fish oil accelerates vascular aging.

It takes 18 weeks to fully rid patients of the negative effects of fish oil [52]. The subjects in the IOWA experiment were measured at an average of 13 weeks after ceasing fish oil usage. If they had been measured at the full 18 weeks, we would expect an even greater decrease in "biological age". Particularly significant is the positive effect of subjects' *additional* 54% *improvement in decreased cardiovascular* "*biological age*" *by merely discontinuing fish oil supplementation*. Furthermore, the greatest effectiveness both on a percentage basis and greatest endpoint effectiveness occurred in the ceasing fish oil/converting to PEO group (NNT = 1.2: an 87% population effectiveness both on a percentage basis and greatest endpoint effectiveness occurred in the ceasing fish oil/converting to PEO group (NNT = 1.2: an 87% population effectiveness), absolutely confirming fish oil's harm to the cardiovascular system when measured by arterial compliance.

Both the success of PEOs as well as the horrific failure and potential harm of fish oil supplements to negatively affect arterial compliance was predicted and consistently demonstrated.

Fish oil use decreased subject's arterial compliance, causing "hardening of the arteries"—a "biologic aging" of the subject group by nearly four years.

Compared to PEOs, fish oil users had an "11-year-older" cardiovascular system as measured by arterial compliance population scans—more than a decade's additional "hardening of the arteries" compared to their physical age.

8. Conclusion

Theoretically, it has been shown why fish oil supplementation with its EPA/DHA active components never had a physiologic or biochemical basis to either prevent or reverse CVD. Worse than doing nothing, fish oil causes harm. It has been explained physiologically what the correct EFA components must be (PEOs) to fulfill fish oil's failed promise and to positively effect cardiovascular health. IOWA is the first clinical screening experiment to measure arterial compliance in subjects using fish oil and PEOs. For the first time, using the most direct and effective physiologic measure, fish oil in the doses suggested, at least in regards to arterial compliance, is unequivocally shown to be an *anti* anti-aging substance.

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