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Clinical Overview of Algal-Docosahexaenoic Acid: Effects on Triglyceride Levels and Other Cardiovascular Risk Factors

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The cardiovascular benefits of fish-derived long-chain polyunsaturated fatty acids, docosahexaenoic acid (DHA), and eicosapentaenoic acid are well established. Less studied are specific effects of individual long-chain polyunsaturated fatty acids. Based on data from 16 published clinical trials, this review examines effects of DHA triglyceride (TG) oil derived from algae (algal-DHA) on serum TG levels and related parameters. Study populations included subjects with both normal and elevated TG levels including those with persistent hypertriglyceridemia treated with concomitant 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy. At doses of 1–2 g/d, algal-DHA significantly lowered plasma TG levels (up to 26%) either administered alone or in combination with statins. The reduction in TG levels was markedly greater in hypertriglyceridemic than in normal subjects. Algal-DHA modestly increased plasma levels of both high-density lipoprotein and low-density lipoprotein cholesterol. The increased plasma level of low-density lipoprotein cholesterol was associated with a shift of lipoprotein particle size toward larger, less atherogenic subfractions. In some subjects, blood pressure and heart rate were significantly reduced. Algal-DHA was safe and well tolerated. Unlike fish oil, algal-DHA seldom caused gastrointestinal complaints such as fishy taste and eructation, attributes of importance for patient compliance in high-dose therapy. Regression analysis that showed a linear relationship between baseline TG and magnitude of TG reduction suggests that a study of patients with very high TG levels (>500 mg/dL) is warranted. Future pharmacologic therapies for treating hypertriglyceridemia may include algal-DHA.

Keywords: docosahexaenoic acid, triglycerides, cardiovascular disease, omega-3 fatty acids

INTRODUCTION

Clinical trials have demonstrated that omega-3 long-chain polyunsaturated fatty acids (LC-PUFA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) provide important cardioprotective benefits. These LC-PUFA not only lower triglyceride (TG) levels but also provide modest lowering of both blood pressure and heart rate in normotensive and mildly hypertensive individuals,[1–3] reduce significantly the risk of sudden death,[4,5] reduce inflammation,[6] reduce the long-term risk of atherosclerosis and ischemic heart disease,[7] contribute to maintenance of graft patency after coronary artery bypass surgery,[8] and improve endothelial and vascular function.[9,10] Epidemiological studies have demonstrated an inverse association between the intake of LC-PUFA from fish and coronary heart disease mortality.[4,11–13] The cardioprotective effect of LC-PUFA is particularly strong among high-risk individuals with a previous myocardial infarction.[5] The American Heart Association recommends that individuals with documented coronary artery disease take at least 1 g/d of DHA plus EPA.[14] For individuals with hypertriglyceridemia (HTG), 2–4 g/d

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is recommended.[14] Fatty fish such as tuna, salmon, and mackerel contain the largest amounts of LC-PUFA, but pharmaceutical therapeutic options are also available for the treatment of HTG, including highly concentrated fish oil such as Lovaza (omega-3-acid ethyl esters; Reliant Pharmaceuticals, Inc, Liberty Corner, NJ).

Early investigations into the favorable effects of fish oils primarily attributed benefits to EPA, ignoring the presence of substantial amounts of DHA.[15,16] This was an understandable assumption as these early studies typically used menhaden oil, the only dietary source commercially available at the time.[16–18] Because menhaden oil consists of more EPA than DHA (18% vs. 9.6% of total fatty acids),[19] many researchers concluded that EPA rather than DHA delivered the benefits. The relative contribution of each omega-3 fatty acid to cardiovascular protection remained to be defined. Recent data, however, demonstrate that both DHA and EPA individually have important cardioprotective properties. Mori and Woodman[20] considered the independent effects of EPA and DHA on cardiovascular risk factors. Their review compared results of studies using DHA + EPA with those of DHA alone (including DHA from fish oil) and with one study of EPA alone (Epadel; Mochida Pharmaceutical Company, Tokyo, Japan). They identified important antiarrhythmic, antithrombotic, and antiatherogenic effects of DHA.[20] However, the review was limited to only 6 studies using DHA in healthy subjects.

This review summarizes the efficacy and safety of DHA TG oil derived from algae (algal-DHA) specifically for TG reduction and secondly for certain biomarkers and/or risk factors for cardiovascular disease in 16 clinical trials in humans in which algal-DHA–rich oils were derived from either 1 of 2 specific strains of microalgae: *Crypthecodinium cohnii* (DHASCO) and *Schizochytrium sp*. (DHASCO-S) (Martek Biosciences Corporation, Columbia, MD).

Eleven studies considered DHASCO and 5 evaluated DHASCO-S. The DHA in these algal oils is a TG form in the amount of approximately 35%–40% DHA by weight. Small amounts of saturated and monounsaturated fatty acids along with some minor amounts of nonsaponifiable materials are included in these oils (Table 1). These TG oils do not contain significant amounts of EPA. Compared with DHASCO, DHASCO-S has more docosapentaenoic acid (DPAn6, 22:5n-6) but the amount of DHA in each oil is approximately equivalent. Because algal-DHA is not derived from fish, it is essentially free of oceanic contaminants such as methylmercury, dioxins, or polychlorinated biphenyls. There are a number of ''DHA-enriched oils'' presently available, but those oils are derived from fish; consequently, studies with those oils were not considered for the present review. Algal-DHA may be considered for future therapeutic approaches for treating HTG.

Table 1. Composition of DHASCO and DHASCO-S.

Fatty acid composition (%)		DHASCO*	DHASCO-S†
10:0	Capric acid	2.1	0.0
12:0	Lauric acid	5.4	0.3
14:0	Myristic acid	15.5	7.7
16:0	Palmitic acid	14.6	23.1
16:1n-7	Palmitoleic acid	1.6	0.4
18:0	Stearic acid	0.6	0.7
18:1n-9	Oleic acid	14.9	0.4
18:1n-7	Vaccenic acid	<0.1	0.4
18:2n-6	Linoleic acid	0.8	0.5
18:3n-3	α-linolenic acid	<0.1	0.1
18:4n-3	Stearidonic acid	0.0	0.4
20:0	Arachidic acid	<0.1	0.0
20:3n-6	Di-homogammalinolenic acid	<0.1	0.5
20:4n-6	Arachidonic acid	<0.1	1.1
20:4n-7	Eicosatetraenoic acid n-7	0.0	1.7
20:4n-3	Eicosatetraenoic acid n-3	0.0	1.0
20:5n-3	EPA	<0.1	2.5
22:4n-9	Docosatetraenoic acid	0.0	0.4
22:5n-6	Docosapentaenoic acid n-6	0.0	16.4
22:5n-3	Docosapentaenoic acid n-3	0.2	0.4
22:6n-3	Docosahexaenoic acid	41.5	40.3
Chemical characteristics			
	Free fatty acid (%)	<0.4	<0.25
	Peroxide value (mEq/kg)	<5	<5
	Nonsaponifiables (%)	<3.5	<4.5
Elemental composition (ppm)			
	Arsenic	<0.5	<0.5
	Copper	<0.1	<0.1
	Iron	<0.5	<0.5
	Lead	<0.2	<0.2
	Mercury	<0.2	<0.2
	Phosphorous	<10	<0.2

*From *Crypthecodinium cohnii*.
†From *Schizochytrium sp*.

CLINICAL TRIALS

Plasma lipids and lipoproteins

Early clinical trials evaluated the TG-lowering effects of algal-DHA in healthy individuals (Table 2). More recent studies have included efficacy and safety trials in individuals with HTG or with persistent HTG while being treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).

Table 2. Clinical studies of TG levels with algal-DHA.

Study Design	Population n*	Diet/Dose (g/d) Duration	Baseline TG (mg/dL)	Mean Change (%)		
				TG	LDL-C	HDL-C
Normal TG						
Conquer and Holub[21]	Healthy	DHA 1.62	85	-17†	-7	+17†
RCT: DB Parallel	Vegetarians 24	Placebo 0 6 wk	72	+14†	+9†	+7†
Geppert et al[22]	Healthy	DHA¶ 0.94	96	-23†§	+11†§	+7†§
RCT: DB, Parallel	Vegetarians 106	Placebo 0 8 wk	95	0	-1	-1
Wu et al[23]	Healthy	DHA‡ 2.14	124	-18	-3	+6
RCT: SB, Parallel	Vegetarians 25	Placebo 0 6 wk	134	+3	+4	+4
Agren et al[24]	Healthy 55	Fish Diet	120	-15†§	+9	0§
RCT: SB, Control		EPA 0.38				
		DHA 0.67	107	-19†§	+10†	-8
		Fish Oil				
		EPA 1.33				
		DHA 0.95				
		DHA 1.68	104	-17†§	-3	+7§
		Control 0 15 wk	116	+8	-3	-17
Nelson et al[25,27]	Healthy 6	Diet DHA <0.05	109	-12	-1	-9
Ferretti et al[26]		DHA 6.0 12 wk	73	-26†	-1	+9†
RCT: SB, Control						
Conquer and Holub[28]	Healthy 19	DHA 0.75	125	-9	-9	+5
Parallel		DHA 1.5	92	-6	+3	-5
		Placebo 0 6 wk	90	+23	-9	+2
Stark and Holub[29]	Healthy 32	DHA 2.8	143	-20†§	+9	+8†
RCT: DB, Crossover		Placebo 0 4 wk	143	-3	+3	+3†
Theobald et al[30,31]	Healthy 38	DHA 0.7	91	-2	+10†	+5
RCT: DB Crossover		Placebo 0 12 wk	94	+12	+3	+1
Sanders et al[32]	Healthy 79	DHA‡ 1.5	96	-14†	+7†	+7†
RCT: DB, Parallel		Placebo 0 4 wk	82	-2	-3	+2
Elevated TG						
Davidson et al[33]	Combined	DHA 1.25	250	-21†	+9	+6†
RCT: DB, Parallel	Hyperlipidemia 27	DHA 2.50	296	-18†	+14†	+6†
		Placebo 0 6 wk	236	+4	-2	+6
Engler et al[10,34]	Familial	DHA 1.2	120	-5	+8	+5
RCT: DB, Crossover	Hyperlipidemia 20	Placebo 0 6 wk	120	-3	+3	+7
Kelley et al[1,35]	Elevated TG 34	DHA 3.0	247	-24†	+15†	+7
RCT: DB, Parallel		Placebo 0 12 wk	257	-8	0	+3
Schwellenbach et al[36]	Persistent HTG	Fish Oil	292	-18†	+9	0
RCT: DB, Parallel	with Statins 116	EPA 0.252				
		DHA 1.0				
		DHA‡ 1.0 8 wk	283	-22†	+8	+6†
Keller et al[3]	Persistent HTG	DHA 2.0	268	-19†	0	+5†
RCT: DB, Parallel	with Statins 40	Placebo 0 6 wk	325	+3†	-9†	-2†

ALT = alanine transminase; DB = double-blind; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL-C = high-density lipoprotein cholesterol; HTG = hypertriglyceridemia; LDL-C = low-density lipoprotein cholesterol; RCT = randomized controlled trial; SB = single-blind; TG = triglyceride.

Except for the studies conducted by Geppert et al[22] and by Wu et al[23], Martek Biosciences Corporation provided algal-DHA to investigators upon request.

*Number of patients considered in the statistical analyses.

†Statistically significant from baseline values ($P \leq 0.05$).

§Statistically significant from control ($P \leq 0.05$).

‡Used *Schizochytrium sp* oil; all other studies used *Crypthecodinium cohnii* oil.

¶Used *Ulkenia sp.* oil which is equivalent to *Schizochytrium sp* oil.

Three clinical trials evaluated effects of algal-DHA supplementation on serum lipids, lipoproteins, and risk factors for heart disease in vegetarian subjects.[21–23] Vegan/vegetarian diets are typically devoid of or deficient in LC-PUFA, allowing evaluation of the independent effects of replenishment and/or supplementation of DHA. Although the precursor of DHA, α-linolenic acid is the major omega-3 fatty acid in the vegan diet, the efficiency of conversion of this fatty acid to DHA is low.[21] The studies indicated that among vegan subjects with relatively low TG levels at baseline (0.96–1.40 mmol/L), daily supplementation ranging from 0.94 to 2.14 g/d reduced TG levels by 17%–23% and increased high-density lipoprotein cholesterol (HDL-C) by 6%–17%. Two of 3 studies showed a modest decrease in the level of low-density lipoprotein cholesterol (LDL-C).[21,23] The level of LDL-C increased in vegans who had low TG levels at baseline and who received the lowest dose of algal-DHA.[22]

DHA supplementation reduced levels of TG in all 6 studies that considered healthy (nonvegetarian) individuals by approximately 2%–26%.[24–32] The largest decrease occurred in subjects with the highest baseline TG level (1.61 mmol/L, 143 mg/dL) or who received the largest dose of algal-DHA (6 g/d). In all but one study,[28] the level of HDL-C increased by 5%–9% but the change in LDL-C was inconsistent and not statistically significant.

Agren et al[24] compared supplementation with 1.68 g/d of algal-DHA with fish oil (1.33 g/d EPA + 0.95 g/d DHA) or a diet that included 4 servings of fish per week (0.38 g/d EPA + 0.67 g/d DHA). Relatively large, significant decreases in the level of TG (15%–19%) were observed in all test groups, but algal-DHA supplementation modestly reduced the level of LDL-C (3%) and significantly increased the level of HDL-C (7%).

In 3 other studies, subjects with initially low HDL-C, with combined hyperlipidemia or with childhood familial hyperlipidemia (high cholesterol), were evaluated. In all 3 studies, the level of TG decreased and the level of HDL-C increased.[10,33–36] Although the level of LDL-C increased by as much as 15%, the LDL-C rise associated with the LC-PUFA–mediated TG reduction was attributable to a shift in lipoprotein particle size from the small, atherogenic to the larger, more buoyant and less atherogenic particle size.[1,3,34,35,37–39]

There was a reported significant increase in the number of large, buoyant LDL_1 and HDL_2 particles and an accompanying decrease in the number of small, dense LDL_3 particles.[10,34] In combination, these changes resulted in a significant decline in the percentage of cholesterol that is carried by small, dense particles. A greater number of small, dense atherogenic LDL particles has been associated with an increased risk of cardiovascular events.[40] This risk may reflect an increased susceptibility of the small LDL particles to oxidation and a tendency to infiltrate the arterial wall which may cause foam cell formation and inflammation.[41,42] Mesa et al[43] reported that DHA alone from fish oil decreases the susceptibility of LDL to oxidation and may inhibit an early event linked to the progression of atherosclerosis to the same degree as reported for EPA.

A slightly different serum lipid profile was observed in the 2 studies that considered subjects with persistent HTG while being treated with statins.[3,36] Levels of TG decreased by up to 22% and HDL-C increased by 5%–6%, demonstrating an additive benefit with statins. LDL-C was unchanged in one study in which 2 g/d was administered[3] whereas LDL-C increased by 8% in the other that used 1 g/d.[36] Schwellenbach et al[36] compared the effects of DHA alone with those from fish oil and reported similar reductions in TG levels, but the algal-DHA significantly increased HDL-C by 6% whereas the level of HDL-C in the fish oil group was unchanged. Notably, a significant reduction in the level of total cholesterol was observed only in those studies whose subjects received both algal-DHA or DHA/EPA and statins (data not shown).

ANALYSIS OF TG REDUCTION FROM ALGAL-DHA SUPPLEMENTATION

Using data from 15 of 16 studies considered in the present study, linear regression analysis (SigmaPlot from Systat Software, Inc, Chicago, IL) was used to determine the effect that different doses of algal-DHA had on the percent change from baseline of TG levels (Fig. 1) and the effect that baseline TG levels had on the absolute change of TG levels (Fig. 2) when algal-DHA was administered. The study by Wheaton et al[44] was not used because it did not provide baseline data for TG levels. Algal-DHA supplementation significantly reduced fasting TG levels in a dose-dependent fashion, regardless of the type of algal oil used or level of baseline TG. It seems that supplementation of 1–2 g/d of algal-DHA, with or without concomitant statin therapy, effectively lowered TG level by 15%–20%. The absolute decrease (mg/dL) in the level of TG in subjects with HTG was markedly greater than in that observed in subjects with normal levels of TG.

BLOOD PRESSURE, HEART RATE, AND OTHER RISK FACTORS FOR CARDIOVASCULAR DISEASE

There is an unequivocal evidence that LC-PUFA offer a modest reduction in blood pressure, particularly in

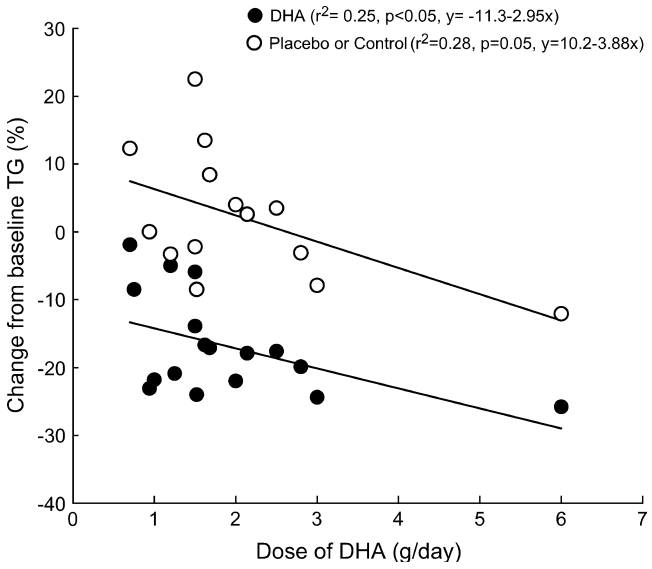

FIGURE 1. Regression analysis of percent change from baseline in TG levels vs. dose of algal-DHA.

hypertensive individuals. Mori et al[45] showed that DHA from fish oil, but not EPA, relative to placebo significantly lowered 24-hour ambulatory systolic and diastolic blood pressure and heart rate in overweight, mildly hyperlipidemic men. Two studies considered here reported that algal-DHA reduced systolic and diastolic blood pressure and heart rate (Table 3). Kelley et al[1] reported that among men with HTG, supplementation with 3 g/d of algal-DHA for 45 days significantly reduced heart rate by 8.3% and systolic

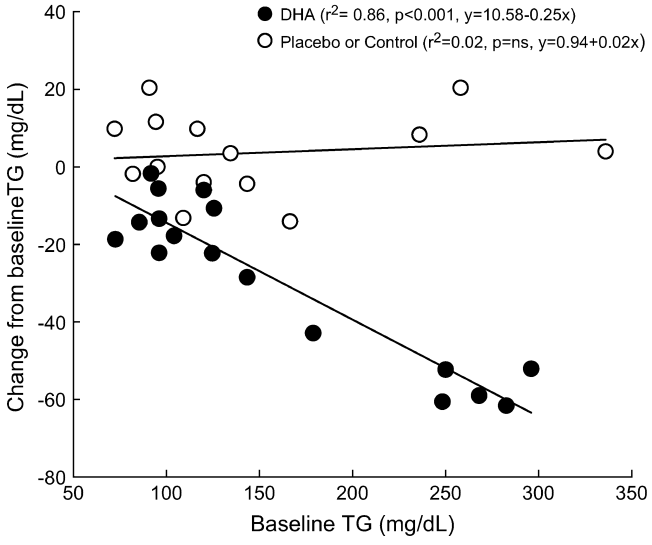

FIGURE 2. Regression analysis of absolute change from baseline in TG levels vs. baseline TG levels.

and diastolic blood pressure by 5.6% and 4.0%, respectively, compared with measurements taken at baseline. Heart rate fell by 9% and diastolic blood pressure by 19% among statin-treated cardiac patients who were administered 2 g/d of algal-DHA for 6 weeks.[3] Stark and Holub[29] reported that treatment with 2.8 g/d of algal-DHA for 4 weeks was associated with a 7% decline in heart rate but not blood pressure among postmenopausal women receiving and not receiving hormone replacement therapy.

The study by Engler et al[10] in 9- to 19-year-old children with familial hypercholesterolemia or the phenotype of familial combined hyperlipidemia demonstrated that 1.2 g/d of algal-DHA for 6 weeks improved endothelium-dependent flow-mediated dilation of the brachial artery compared with baseline and placebo; flow-mediated dilation of the brachial artery function was similar to that observed in normal levels in healthy children. It seems that young hyperlipidemic children show attenuated endothelial function as a consequence of reduced nitric oxide bioavailability.[46] If large, buoyant LDL particles enriched with DHA are more resistant to oxidation, then there may be increased nitric oxide bioavailability by increasing its production or decreasing its degradation in the endothelium.[34] The vasorelaxant effect of DHA may also increase nitric oxide synthesis or release.[10] By increasing nitric oxide bioavailability, DHA may have the potential to delay the early onset of coronary heart disease in hyperlipidemic children.[10]

The effects of a fish-enriched diet or dietary supplements of fish oil or algal-DHA on platelet aggregation and homeostatic factors were studied in healthy men.[24,47] The results indicated that a fish diet and fish oil, but not algal-DHA, inhibited in vitro platelet aggregation, but hemostatic factors were not affected by the n-3 fatty acid supplementation. Sanders et al[32] also reported no significant differences between the algal-DHA group and placebo in serum C-reactive protein, plasma VII antigen, activated FVII, fibrinogen, von Willebrand factor, plasminogen activator inhibitor-1, and markers for muscle damage and cardiac muscle damage (creatine kinase and troponin-I activities). Supplements of 1.62 g/d of algal-DHA in healthy vegetarians also failed to reduce collagen- and adenosine diphosphate–induced aggregation or collagen-stimulated thromboxane A_2 release.[21] Compared with baseline values, higher doses of algal-DHA (6 g/d) administered to healthy men for 90 days reduced urinary thromboxane B_2 excretion.[26] However, the prothrombin time, activated thromboplastin time, and the antithrombin-III levels before and after supplementation with 6 g/d of algal-DHA were not significantly different.[27] Additionally, the in vivo bleeding times did

Table 3. Effects of algal-DHA on biomarkers and/or other risk factors for cardiovascular disease.

Study	Population	Effect(s)
Normal TG		
Conquer and Holub[21]	Healthy vegetarians	Collagen-induced platelet aggregation, collagen-induced thromboxane A_2, serum viscosity, fibrinogen, and factor VIIc levels were not significantly altered.
Geppert et al[22]	Healthy vegetarians	No effect on BP or HR.
Agren et al[24,47]	Healthy	Reduced Apo B levels in the VLDL fraction. No statistically significant effect on platelet aggregation.
Nelson et al[25,27]; Ferretti et al[26]	Healthy	Apo-A1, apo B, and Lp(a) showed very little change after the high-DHA diet. No changes in blood coagulation, platelet function, or thrombotic tendencies.
Conquer and Holub[28]	Healthy	No effect on Lp(a), BP, or HR.
Stark and Holub[29]	Normal	DHA reduced heart rate by 5 beats/min; systolic and diastolic BP and MAP decreased, but statistical significance was considered a main effect of time rather than supplementation status.
Theobald et al[30,31]	Normal	The cholesterol:Apo B ratio was greater after DHA treatment, which may suggest that the LDL particle size was increased. DHA lowered diastolic BP; HR tended to be 2.1 beats/min lower after DHA.
Sanders et al[32]	Healthy	No effect on creatinine kinase and troponin-I activities.
Elevated TG		
Davidson et al[33]	Combined hyperlipidemia	Increase in non–HDL-C only observed at the higher dose of algal-DHA (2.5 g/d).
Engler et al[10,34]	Familial hyperlipidemia	Increased large, buoyant LDL_1 by 91% and HDL_2 by 14% compared with placebo. Small dense LDL_3 decreased by 48% compared with placebo. FMD increased significantly after DHA.
Kelley et al[1,35]	HTG	DHA reduced heart rate and systolic and diastolic blood pressure. DHA did not affect Apo B but reduced the number of small LDL particle size and increased the number of large particles. DHA decreased RLP-C and increased RBC n-3 index.
Schwellenbach et al[36]	Persistent HTG while treated with statins	Decreased non–HDL-C level in both groups.
Keller et al[3]	Persistent HTG while treated with statins	Decrease in small LDL particles and increase in large LDL particles. DHA reduced heart rate and decreased diastolic blood pressure and non–HDL-C levels.
Low HDL		
Maki et al[37]	Low HDL $\leq$44 mg/dL (men) and $\leq$54 mg/dL (women) but $\geq$35 mg/dL	Reduction in small dense $LDL_3 + LDL_4$ particles and increase in number of larger, less dense $LDL_1 + LDL_2$ particles.

BP, blood pressure; DHA, doscosahexaenoic acid; FMD, flow-mediated dilation of the brachial artery; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; Lp(a), lipoprotein(a); MAP, mean arterial pressure; RBC, red blood cell; RLP-C, plasma remnant–like particle cholesterol; VLDL, very low density lipoprotein.

not show any significant difference during and after algal-DHA supplementation.[27]

Kelley et al[35] considered 2 novel risk factors for cardiovascular disease: plasma remnant–like particle cholesterol and the red blood cell (n-3) index (sum of DHA and EPA as a percent of total fatty acid content) in men with HTG. Remnant-like particles that are produced from very low density lipoproteins are the major atherogenic lipoproteins that can be taken up by macrophages to produce foam cells without oxidative modification.[35,48] Algal-DHA supplementation of 3 g/d for 45 days decreased fasting plasma remnant–like particle cholesterol by 36% and increased the red blood cell (n-3) index by 109%.[35] Continued supplementation between days 45 and 91 further increased the red blood cell (n-3) index (162%) compared with baseline values.

The Third Adult Treatment Panel of the National Cholesterol Education Program identified elevated

LDL-C as the primary target of lipid-lowering therapy.[49] A new secondary target of therapy was also introduced, namely, non–high-density lipoprotein cholesterol (non–HDL-C) in patients with elevated TG levels (≥200 mg/dL).[49,50] Non–HDL-C was added as a secondary target of therapy to account for the atherogenic properties associated with remnant lipoproteins in patients with HTG.[49,50] Davidson et al[33] reported a significant increase in non–HDL-C (+5.7%) from baseline at the higher dose of algal-DHA (2.5 g/d), but not at the lower dose (1.25 g/d), in subjects with combined hyperlipidemia. However, Schwellenbach et al[36] reported a significant decrease in non–HDL-C compared with placebo when subjects with HTG were taking statins and either 1 g/d of algal-DHA or 1.25 g/d of fish oil (−4.8% and −3.7%, respectively).

Apolipoprotein B (Apo B) is a potential marker for atherogenic lipoproteins.[49] It has been proposed that Apo B may serve as an alternative to LDL-C as a risk factor, but the preponderance of evidence in favor of Apo B has not been developed sufficiently to justify replacing LDL-C as a primary risk factor.[49] In subjects with normal levels of TG, LDL-C is highly correlated with Apo B but the level of Apo B is much higher in subjects with HTG.[49] In the 4 studies that considered the level of Apo B, Agren et al[24] reported that Apo B levels decreased only in the very low density lipoprotein fraction among subjects in the fish diet and algal-DHA groups. Both Nelson et al[25] and Kelley et al[1] indicated that algal-DHA treatment did not affect levels of Apo B. Theobald et al[30] reported a significant increase in the level of Apo B in the algal-DHA group. However, the LDL-C:apo B ratio was greater, suggesting a shift toward the larger less atherogenic LDL particle size.

There is a significant association between level of lipoprotein(a) (Lp(a)) and risk of cardiovascular disease.[51,52] However, there is no evidence from clinical trials that supports a benefit from lowering Lp(a) levels with different therapies.[49] Only nicotinic acid therapy reduces Lp(a) levels, but only moderately.[53] Two studies reported data for Lp(a) levels in healthy subjects who received algal-DHA treatment.[25,28] Both studies indicated that algal-DHA supplementation did not affect levels of Lp(a). However, Nelson et al[25] reported that Lp(a) levels rose significantly in the control group.

SAFETY AND TOLERABILITY OF ALGAL-DHA

The safety of algal-DHA is well established. The Food and Drug Administration has affirmed that DHA and/or EPA at intakes of up to 3 g/d are "Generally Recognized as Safe."[54] Both DHASCO and DHASCO-S fall under these guidelines and are considered Generally Recognized as Safe.

In clinical trials, algal-DHA is found to be well tolerated. Adverse events are uncommon and limited to mild gastrointestinal complaints such as eructation or occasional taste perversion. Schwellenbach et al[36] compared the safety and tolerability of DHA and fish oil. A significantly greater proportion of subjects in the fish oil group reported fishy taste as a problem.

An ongoing long-term study of X-linked retinitis pigmentosa in 44 young men (mean age = 16 years) has reported 4-year safety data in subjects who received either 400 mg/d of algal-DHA or placebo.[44] All adverse events were minor and equally distributed between the DHA and placebo groups. Long-term algal-DHA supplementation did not compromise plasma antioxidant capacity, platelet aggregation, liver function enzyme activity, or plasma lipoprotein content.

CONCLUSIONS

Clinical trials with algal-DHA as a TG oil have demonstrated a marked reduction in serum TG levels (up to 26%) in normal individuals and in those with HTG or combined hyperlipidemia. It seems that supplementation of 1–2 g/d of algal-DHA with concomitant statin therapy not only lowers TG level by an additional 19%–22% but also raises HDL-C and lowers non–HDL-C, demonstrating an important additive effect. Algal-DHA has also been shown to be safe and well tolerated. The study that compared algal-DHA with fish oil reported that algal-DHA seems to be less likely to cause complaints associated with a fishy taste.

Algal-DHA also seems to be consistent in increasing LDL particle size, a finding that may represent an additional antiatherogenic effect. Algal-DHA seems to be effective in modestly reducing blood pressure and heart rate. The effects may be related to improvements in endothelial relaxation and attenuated vascular constriction. Mori and Woodman[20] noted that EPA is not as effective as DHA with respect to blood pressure reduction. At doses <3 g/d, algal-DHA did not compromise bleeding time or platelet aggregation.

Further studies are needed to evaluate the efficacy and safety of algal-DHA for treating subjects with very high levels of TG (>5.64 mmol/L, 500 mg/dL). Although it is clear that effectiveness of TG reduction is both dose dependent and related to initial TG level, further studies are needed to establish the minimum dose of algal-DHA needed for effectiveness, especially in populations with very high TG levels. Notably, this

review shows that the benefits accomplished using fish oil in subjects with HTG may also be attainable with a vegetarian source of algal-DHA as a TG oil.

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