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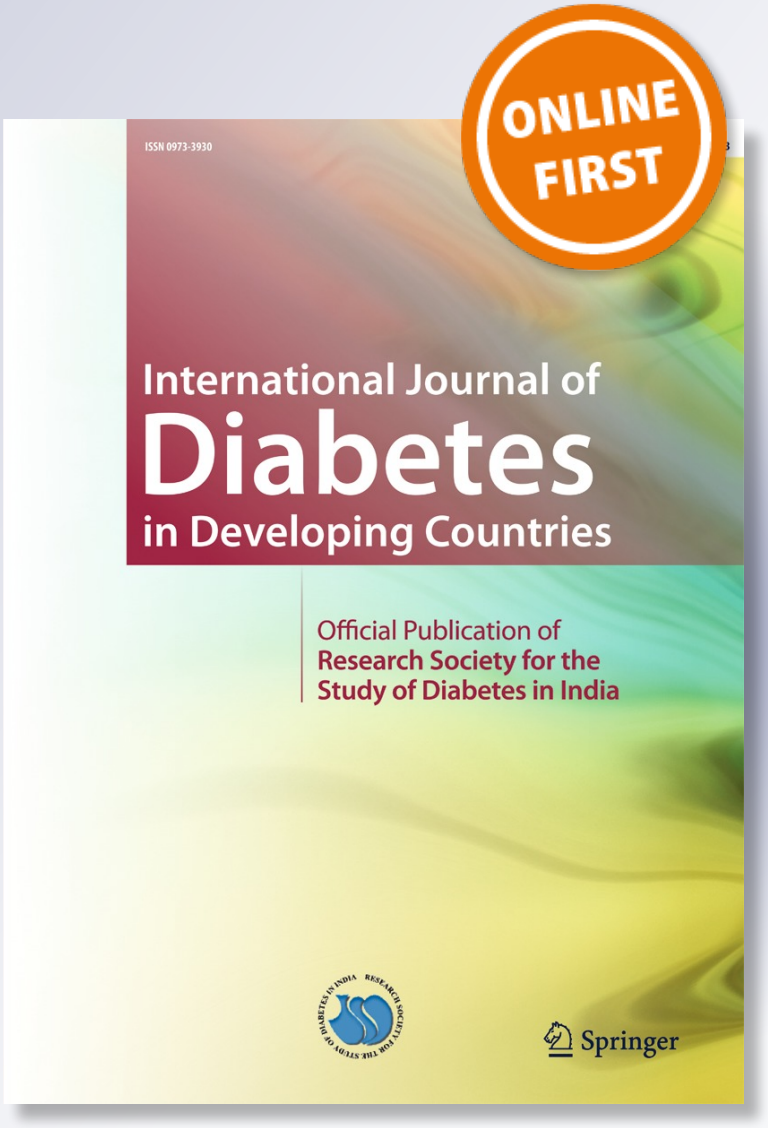

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REVIEW ARTICLE

High DHA dosage from algae oil improves postprandial hypertriglyceridemia and is safe for type-2 diabetics

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Abstract Postprandial refers to diet induced changes in plasma concentrations of sugars, amino acids and fats between 0 and 6 h following a meal. This review details the fat transport through lipoprotein particles and triglyceride fractions in the postprandial plasma. The long-chain omega-3 fatty acid docosahexaenoic acid (DHA) is more active in postprandial plasma and is more abundantly incorporated into the surface phospholipid fraction of lipoproteins. A survey of controlled clinical trials in the literature demonstrates that 1,000 mg to 2,000 mg DHA daily is effective to treat hypertriglyceridemia (HTG), mixed dyslipidemia and most effectively controls elevated postprandial triglycerides (TG). TG is a marker for total fat in circulation. Omega-3 fatty acids lower fasting and postprandial TG, an activity first discovered in 1971 in Greenlandic Inuits. Low TG and high DHA were coincident with the absence of type 2 diabetes. It is now known that DHA is the major structural and functional omega-3 component of lipoproteins in human plasma. DHA is the omega-3 to most substantially increase by mass in the phospholipid fraction of very low-density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). DHA is most effective at raising HDL levels and improves the omega-3 index in red blood cells (RBC). DHA intake also correlates with greater than 25 % reductions of fasting TG and greater than 40 % reductions in postprandial TG. Postprandial HTG is common in the type 2 diabetes; therefore, we considered the safety of DHA from *Schizochytrium sp.* algae oil and the evidence for risk reduction of coronary vascular disease (CVD) and type 2 diabetes. Recent clinical trials suggest high DHA intake from Chromista algae controls plasma TG, but does not appear to control glucocentric markers or cholesterol levels. DHA directly affects postprandial TG transport, but has little effect on insulin function and insulin resistance. Applications for use in South Asian diabetics are considered. 1,200 mg algae DHA daily over 3 months is an optimized program for direct control of postprandial HTG and is safe for type 2 diabetics.

Keywords Triglycerides · Diabetes · DHA · Vegetarian · Omega-3 fatty acids

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S. D. Doughman (✉)
Source-Omega, LLC, 11312 US 15-501 North, Suite 107-122, Chapel Hill, NC 27517, USA
e-mail: scott@source-omega.com

A. S. Ryan
Martek Biosciences Corporation, Columbia, MD 21045, USA

S. Krupanidhi
Department of Biotechnology, Vignan University, Vadlamudi 522213, India

C. B. Sanjeevi
Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden

V. Mohan
Madras Diabetes Research Foundation and Dr Mohan's Diabetes Specialties Centre, Chennai, India

Introduction

Algae oils are considered a plant source for the omega-3 (n-3) fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). However, algae are from distinct Kingdoms of Life separate from true plants and animals. The Kingdom Chromista (classified in 1981)

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contains only non-toxic species, including strains with or without pigments. The non-pigment heterotrophic single-celled algae *Schizochytrium sp.* is the only strain of algae oil covered in this review. The *Schizochytrium sp.* algae omega-6 fatty acid (n-6) docosapentaenoic acid (DPAn-6) is an important bioactive lipid component, along with some EPA. DHA is the major component. High DHA algae oils could be used for improved postprandial control in a diabetic and in the general population.

Few certified oil sources contain high levels of the bioactive lipids DHA and EPA. First, DHA is a significant structural fatty acid of emerging research (biologic) importance, abundant in Chromista algae oils. Second, EPA is a potent anti-inflammatory molecule that activates cell signaling, abundant in many fish oils. Third, the precursor to long-chain omega-3 fatty acids is known as alpha-linolenic acid (ALA). A few true plants, such as flax and certain greens and nuts contain high ALA levels. In the body, another long-chain omega-6 (n-6) fatty acid is arachidonic acid (ARA), traditionally referred to in adults, as a pro-inflammatory ligand that is competed with by EPA ligand signaling. The EPA omega-3/ARA omega-6 ratio is a common reference marker to screen for cellular pro-inflammatory potential. The total ratio of omega-3 to omega-6 fatty acids is often used as a monitor of the balance of fats [1].

Even before algae oils became commercially available, the historical omega-3 data suggested high DHA intake with food controlled chylomicron levels. The term pre-beta-lipoprotein is currently called a chylomicron, an apoB48 intestinal originating lipoprotein, not a liver originating aboB100 lipoprotein. The original Greenlandic Inuit omega-3 studies from 1971 showed pre-beta-lipoprotein concentrations inversely correlated with DHA consumption at >5 g/d [2]. These data revealed dietary postprandial benefits from a high DHA diet helped reduce circulating pre-hepatic dietary blood fat concentrations and diet induced risk of type 2 diabetes [2]. Heart health was a substantial benefit interpreted from the original Inuit data. Since type 2 diabetes risk reduction is also linked to the omega-3 Inuit studies, it is proposed that high DHA doses from any source may provide the activity linked to type 2 diabetes prevention.

DHA is more abundant than EPA in the arctic food chain [3]. These are examples of specific natural high-fat and high-omega-3 DHA dietary backgrounds. In contrast, a high carbohydrate diet can increase TG levels as much or more than a high fat diet [4, 5]. This could be a concern for urban South Asian populations consuming low omega-3 DHA levels.

Algae oil and fish oil ratios of DHA to EPA start at different places in comparison to the human body. What human plasma and RBC data independently point out is that directional metabolism of omega-3 fatty acids ensues towards a high DHA ratio in plasma and cells. Dosing studies of DHA show effectiveness for rapidly saturating n-3 levels in RBC membranes [6]. DHA metabolism occurs through retroconversion via single step beta-oxidation reactions. The 22 carbon DHA fatty acid chain (C:22) is a template the body uses to produce other C:22, C:20, and C:18 omega-3 fatty acid forms as needed in balanced amounts [6]. Optimized dosages of DHA from algae oils rapidly incorporate into serum fractions, cells and tissues that are inherently 3 to 30 fold higher in DHA composition vs. EPA [6–9]. The plasma and RBC data suggests excess dietary EPA is metabolized 'uphill' via catabolic synthesis in the liver to DHA with energy requirements in the process. Whereas excess DHA undergoes retroconversion to EPA 'downhill' through oxidative metabolism with energy release (Fig. 1).

DHA in postprandial lipidology

Most of the algal "DHA-only" literature is not, in fact, just DHA (35 %–45 %) (wt/wt). In human studies, the influence of *Schizochytrium sp.* algae DHA had also contained the strain's lesser known component DPAn-6 (7 %–15 %), and a little EPA (1 %–3 %). DHA and DPAn-6 together improve cardiovascular risk factors in healthy men and women [10, 11]. Recent meta-analysis of human clinical studies showed that DHA algae oil reduces plasma TG and increases HDL-cholesterol and LDL-cholesterol in persons without coronary heart disease, as distinct from CVD [10]. The effect of DHA algae oil on CVD risk factors had been evaluated by double-blind randomized placebo-controlled parallel-design trial of 39 men and 40 women [11]. Subjects received 4 g oil/d for 4 weeks. The active treatment provided 1.5 g DHA, 0.6 g DPAn-6, and a trace of 0.03 g EPA. Active treatment increased plasma concentrations of ARA, docosatetraenoic acid (adrenic acid), DPAn-6 and DHA by 21, 11 11 and 88 mg/L, respectively, and increased the proportions of DPAn-6 and DHA in erythrocyte phospholipids by 78 % and 27 % [11]. Adrenic acid is an intermediate lipid between ARA and DPAn-6 synthesis. The safety of increased long-chain fatty acid accumulation in plasma and RBCs from algae oil was demonstrated.

DHA and DPAn-6 have twenty two carbon chain lengths, a docosa-chain. DHA and DPAn-6 are also the terminal lipids in their respective synthetic fatty acid pathways [12]. DHA and DPAn-6 are the longest and most unsaturated and most abundant pre-docosanoid fatty acids in the human body and brain. These fatty acids are substrates for docosanoid signaling pathways, but these same lipids are best known for their physiological activities and are non-pharmaceutical and non-toxic. They are cell building blocks and accretive plasma membrane and lipoprotein phospholipids. However, DHA and DPAn-6 are not well characterized in lipoprotein biochemistry. DHA

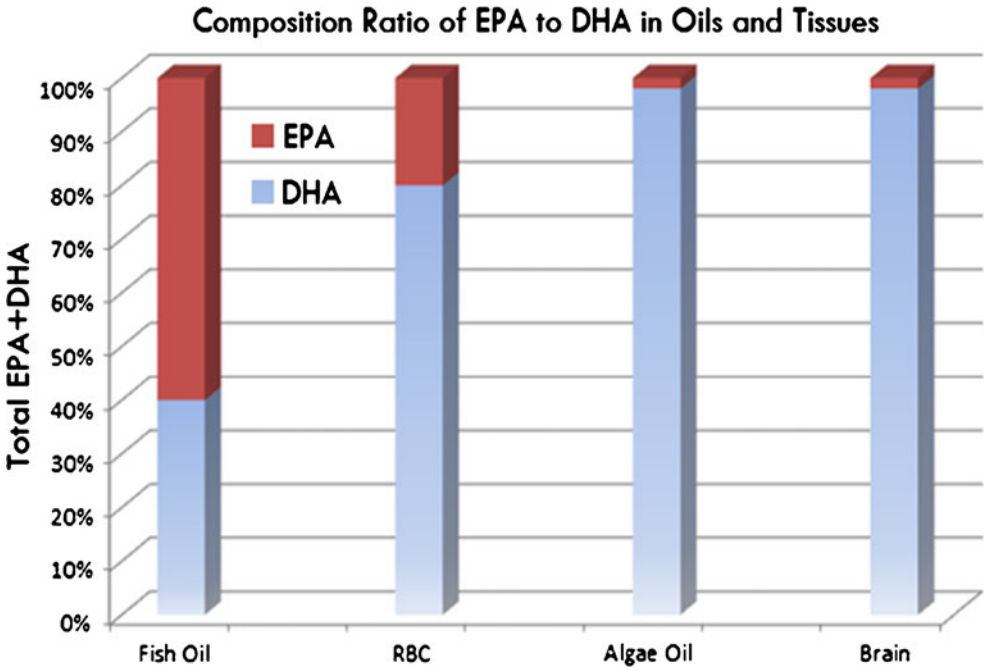

Fig. 1 Figure 1 depicts tissue blood and brain omega-3 composition ratios vs. omega-3 oil composition ratios comparing only DHA + EPA

and DPAn-6 are mainly localized to phospholipids on the inner side of the plasma membrane in cells, or on the outer phospholipid monolayer of lipoprotein particles [13]. DHA and DPAn-6 influence membrane fluidity, membrane curvatures and particle sizes. A top down lipid biochemistry model is proposed wherein *Schizochytrium sp.* algae provide preformed ratios of DHA plus DPAn-6 fatty acids within a physiological range (6:1 to 3:1) [12].

The importance of HDL control for type 2 diabetes and CVD prevention is under-defined. HDL-cholesterol increases more with DHA-alone vs. EPA-alone [10], which supports the observation that HDL-cholesterol increased from DHA treatment [14]. Whereas HDL-cholesterol is considered "good" and LDL-cholesterol is considered "bad", further analysis is needed to define the role of LDL-cholesterol in diabetes and CVD. DHA lowers TG and improves LDL particle size and density, regardless of whether the total LDL-cholesterol was changed or not [15].

Algae DHA also affects mean size and concentrations together for VLDL, LDL and HDL lipoprotein fractions, improving these markers in fasting and postprandial plasma [16]. Lipoprotein diameter redistribution is observed with either DHA or EPA. In addition, DHA and EPA intake facilitates chylomicron clearance and lipoprotein B100 particle clearance in the postprandial state [17]. A high fat diet is prone to elevated VLDL and LDL levels with low HDL concentrations. Dietary DHA intervention does not adversely affect postprandial lipase activities when improvements are observed in fasting and postprandial TG [18]. For patients with mixed hyperlipidemia, common with diabetes, statins have become the drug of choice, but reductions in lipoproteins by one statin was mainly on liver lipoprotein B100 particles, with failure of the statin to control chylomicrons with atherogenic potentials in the postprandial state [19]. Only positive benefits from DHA on postprandial particles were found when DHA was added to a standard treatment with a statin in young populations [20]. LDL size and HDL particle levels may be considered protective effects of DHA supplementation.

The effects of DHA algae oil supplementation (3 g/day) for 90 days on markers of insulin resistance were evaluated in HTG men (with hypertriglyceridemia) [21]. Although DHA supplementation increased fasting glucose by 4.7 %, DHA decreased circulating concentrations of several lipocentric markers of insulin resistance, including non-esterified fatty acids (13 %), and small dense low-density lipoprotein particles (22 %) [21]. Lipocentric markers of insulin resistance were more responsive to DHA supplementation than glucocentric markers.

The most significant DHA treatment effect is direct postprandial lipid control. The data shows that DHA most often yields greater overall plasma lipid control compared to EPA. Hansen et al., [22] observed that DHA ethyl-ester treatments impact postprandial TG with stronger effect than EPA ethyl-esters. After the intervention period, the peak response decreased postprandial TG by 26 % with EPA (P=0.04) and up to 41 % (P=0.02) at 6 h with DHA [22]. For total area under the curve postprandial TG reductions were greater for DHA, suppressed by 49 % with 4,000 mg DHA-ester (90 % pure) after 5 weeks, and only 19 % with 4,000 mg EPA-ester (95 % pure) after 5 weeks, respectively [22]. The basis of the DHA effect on the postprandial state is apparently dependent upon the biophysical properties of DHA fatty acid length plus unsaturation [22, 23].

DHA and lipoprotein composition

How does DHA traffic through the postprandial plasma? Differential DHA metabolism occurs early during the transport of dietary fat, at the point of entering the lipoprotein pool from the liver. Of key significance is the entry of dietary fat into the VLDL pool. DHA is over-incorporated into this pool compared with EPA and palmitic acid [13]. This topic of omega-3 metabolism is often overlooked and is possibly the central point of normalization of DHA and EPA ratios in the body. VLDLs retain much higher concentrations of DHA vs. EPA. Consequently, differential size redistribution of lipoproteins and selective partitioning of DHA in the early postprandial period could be principally determined by DHA/EPA ratios in the liver.

The role of DHA in VLDL biology merits further investigation. DHA becomes the majority omega-3 in the VLDL fraction regardless of whether DHA only or EPA only is consumed in the diet [13]. Still, this is a whole particle lipoprotein characterization. More specifically, the marked elevation of DHA in the phospholipid pool means that DHA is over-incorporated into the VLDL surface phospholipid pool, a lipoprotein fraction under-deposited into adipose cells and thus the non-esterified fatty acid pool [13]. DHA is an important structure-function component of lipoproteins. We propose excess EPA in the diet is synthesized by the liver into a high ratio of DHA to EPA. The data shows that even LDL remnant particles maintain high DHA concentrations [13].

DHA and heart health

DHA intake has long been inversely predictive of heart disease [25]. A few studies have considered the significance of DHA as the major human omega-3 form. Conquer and Holub [26] published a 1996 double-blind randomized placebo controlled study on algae DHA in human subjects. They reported that after 90 days, blood omega-3 parameters were consistent with humans taking high dosages of fish oil, despite prolonged high level intake of only algae DHA [26]. These results indicated that a steady state had been reached in RBCs after 3 months. The algae DHA study showed RBC increases in both DHA and EPA, through accretion of DHA and retroconversion of DHA into EPA [26]. Algae DHA dosages were 1,620 mg DHA daily for only 42 days, which more than doubled total omega-3 phospholipid levels in RBC. Also, DHA to EPA ratios in RBCs increased from 5.7 to 6.7 during treatment, having started with nearly 6 fold greater DHA levels. Retroconversion of DHA to EPA in RBCs was 12.0 %. ARA levels in RBC phospholipids decreased moderately in the DHA group and EPA increased, improving the EPA/ARA ratio. No changes were found in the total and LDL cholesterol levels with DHA supplementation in this study [26]. LDL-cholesterol/HDL-cholesterol ratio and serum triglyceride concentrations did decrease over time.

The combination of results from 16 studies also show high-dose DHA from algae lowers all HTG by over 25 % after 3 months with at least 1,000 mg to 2,000 mg DHA daily [27]. In studies of HTG men aged 39–66 years who received no algal-DHA for 8 days and then received either 3 g DHA or olive oil for 90 days, fasting levels of plasma remnant-like particle cholesterol (RLP-C) decreased by 45 % and the RBC omega-3 index increased by 109 % [24]. Decreased atherogenic RLP-C levels and an increased omega-3 index may improve cardiovascular health.

Along with important lifestyle changes, including dietary changes and weight loss, the American Heart Association (AHA) recommends a daily intake of 500–1,000 mg of n-3 FA for individuals with borderline high TG (150–199 mg/dL), 1,000–2,000 mg for individuals with high TG (200–499 mg/dL), and 2,000–4,000 mg for individuals with very high TG (≥500 mg/dL) [28]. Optimal TG levels are considered to be 100–150 mg/dL or lower. The American Heart Association recommends that individuals with documented CVD take at least 1,000 mg daily of DHA plus EPA [29]. There are no specific recommendations for how much of each, only total intake combined. Since *Schizochytrium sp.* algae oil has mainly DHA with some DPAn-6 and EPA, DHA-rich treatments with algae oil DHA contained little or no EPA yet resulted in reduced risk of sudden death, systemic inflammation, long-term atherosclerosis and ischemic heart disease, endothelial and vascular function, modestly lower blood pressure and heart rate, also in normal and mildly hypertensive individuals, plus DHA may contribute to the maintenance of grafts after coronary artery bypass surgery [15, 16, 30–37]. In the Framingham Study, further omega-3 statistical correlations of intake show improved morbidity and mortality, whereas statin intervention alone had not provided such long-term statistical improvements [30, 38–40].

The FDA has approved one omega-3 prescription (Lovaza™) for the treatment of very high HTG (above 500 mg/dl). The prescriptive ingredients include doses of DHA at 1,600 mg plus EPA at 2,200 mg as ethyl esters [41]. With ethyl esters, about 10 % of the drug is a moiety that digests into ethanol plus about 90 % omega-3 free fatty acids. Fish oil and algae oil in their native non-prescription forms are both good for the treatment of mixed dyslipidemia and moderate HTG between 200 mg/dl and 500 mg/dl and are effective for the general population. The FDA does not presently provide guidance for the use of over the counter omega-3 oils for very high triglycerides. The FDA does provide heart health guidance for over the counter omega-3 sources of fish oils and DHA algae oils. The guidance is as an adjunct to diet for CVD prevention at dosages up to 2,000 mg omega-3 fatty acids daily from supplements. However, standard fish oil

supplement sources provide lower concentrations of DHA (12 %) per gram of oil than algae oil (40 %). About 1,200 mg DHA delivers more than 1,000 mg bioavailable DHA intake per day, based on 90 % bioavailability compared to corn oil controls [42]. Algae DHA given at 1,200 mg DHA per day is suitable to provide an optimal omega-3 level and lowers HTG in 90 days [10, 16, 42].

Diabetes onset and CVD

The associated risks of a high carbohydrate diet include insulin resistance and metabolic dyslipidemia, particularly with additional high sugar consumption [43]. Evidence that added sugar can induce insulin resistance indicates a possible dietary cause for over-secretion of apoB48-contianing chylomicrons and apoB100-containing VLDL with HTG, i.e. a diet induced dyslipidemia [44].

Further studies in the area of treatment could be considered to eliminate significant statin induced risk of new onset type 2 diabetes. The data shows that for every person taking a high vs. moderate statin dose there is up to a 28 % greater risk of type-2 diabetes onset due to high statin therapy [45]. However, three-fold the numbers of individual cardiovascular events were prevented in the same study group vs. the number of new onset diabetes cases caused by high-dose statin treatment [45].

For diabetes prevention, an over-simplified LDL-cholesterol model may be referenced to statin drugs and their broad prescription. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy in meta-analysis reveals data from 5 statin trials that intensive-dose statin therapy caused increased risk of new-onset diabetes compared with a moderate-dose statin therapy [45]. Although evidence for statin mitigation of heart disease death and non-fatal heart attack (infarction) was conclusive, the evidence for prevention of CVD deaths by a statin was not conclusive [46]. Cholesterol reduction alone from intensive statin therapy reduces the risk of non-fatal events and may have a role in reducing mortality [46]; however, the LDL-cholesterol model does not support LDL-cholesterol as the sole cause of CVD.

In contrast, algal DHA reductions in CVD risk are conclusive (10, 11). Assessment is needed to gauge the protective power of algae DHA in the context of new onset diabetes. Algae DHA could become considered as a non-pharmaceutical substitute for initial statin therapy in young type 2 diabetes patients. For persons with type 2 diabetes, the risk of moderate to high dose statin treatment is not known. Family history of diabetes and lifestyle could also become important factors when considering a statin therapy.

Prevention of new onset diabetes may be studied in South Asian populations. Introduction of glycated hemoglobin (A1c) screening is a referenced method for detecting early onset diabetes in India, making it essential to study how to use the A1c screen to affect the prevalence of diabetes in different ethnic groups [47]. In Asian Indians, use of A1c criteria would result in markedly higher prevalence rates of diabetes and identify a different set of individuals with milder glucose intolerance at lower serum triglyceride levels [47]. Furthermore, there is a rapid increase in young-age groups of type 2 diabetes onset and with higher cardiovascular risk, particularly in the young poor and moderate income groups in urban India [48]. Younger occurrences have been increasingly observed elsewhere and could have a serious economic impact on lower income groups [48]. Implied local causes could be linked to local dietary lifestyle, not just in countries such as India. EPA and DHA have both shared and mutually complementary benefits, so based on current evidences, increasing consumption of either would be advantageous compared to little or no consumption at all [49].

Diet and intervention

Can intervention demonstrate improvements in South Asian populations? The epidemiology of type 2 diabetes in India was previously discussed [50]. Estimating that 2 billion people traditionally consume a LFHC diet worldwide, modern lifestyle changes and urbanization are tipping the scales towards diabetes at worldwide rates doubling every 30 years. India alone has over 300 million people with HTG and about 70 million people with diagnosable type 2 diabetes, a largely vegetarian weight-stable population [47]. The calculated number of affected people in India is 62.4 million [51]; however, the study looked at numbers with the potential use of the hemoglobin A1c marker to screen for the early onset of diabetes. These estimates take the total number to as high as 70 million [51]. These data show transition to urban lifestyles in certain populations can result in observable 2 to 3 fold diabetes onset affliction rates and the data point to increased onset in new urban diabetic populations occurs at younger ages [4, 51]. These groups include the so called “pre-statin” ages. Younger groups may benefit from dietary intervention via a defined and consistent medical food program. These types of new onset patterns are likely occurring worldwide at different rates in different locations.

Does DHA play a role in diabetes prevention? Background data from fish oil studies assessed by standard omega-3 fatty acid meta-analysis looked at incident type 2 diabetes mitigation; however, the data has limited statistical power. Independent study effects with high collinearity may not prove to be conclusive in final analysis and more studies could be needed [52]. The overall pooled findings did not

support direct adverse events or substantial benefit as a result of fish EPA plus DHA consumption towards the development nor the prevention of type 2 diabetes. The study also suggested that ALA may be associated with modestly lower risk of diabetes; however, biologic heterogeneity may have influenced the pooled data [52]. Specific study of at-risk groups is needed. Controlled studies are needed vs. retrospective analyses and these deserve further investigation.

Plasma lipid studies for preventing HTG have been more consistent. Jiménez-Gómez et al. [53] published a multicenter, parallel, randomized, controlled trial conducted within the LIPGENE study. The significant result showed long-term 12 week ingestion of 1,240 mg omega-3 s DHA+EPA from fish oil fully prevented diet-induced postprandial HTG in a LFHC group [53]. These data help substantiate a safe treatment and dose for protecting against a LFHC diet. The LIPGENE data are consistent with several controlled algae DHA trials previously reported in humans. The data imply independent treatment of the lipid panel by DHA algae oil as a program separated from direct influence on the glucose panel.

Study of DHA algae oil intervention in sub-populations is consistent in vegetarians. One safety study showed application of algae oil of about 2,000 mg DHA over 42 days in postmenopausal vegetarian women significantly lowered plasma TG [54]. Also, prolonged intake of DHA algae oil was found bioequivalent when supplementing vs. when eating fish with meals [55]. Another controlled human trial used algae DHA oil at just 940 mg DHA daily for 2 months [56]. DHA treatment produces an optimal omega-3 status in healthy vegetarians [57]. Like vegetarian, a LFHC diet with a vegetarian background may provide an opportunity for defining specific local controls for developing diabetes trials.

Insufficient vs. sufficient dietary DHA status is now clinically linked to several metabolic conditions as a possible co-cause or co-treatment, respectively [58]. Focus of doctors on omega-3 intake could be increasing, as particular emphasis has recently been placed on measurable improvements in treating elevated TG and cholesterol levels in Indian adults [59–66]. At the same time there are cautions regarding the negative pro-inflammatory properties associated with high dietary omega-6 fatty acid intake plus low omega-3 intake in the Indian diet [67]. Additional nutritional study of DHA and DPAn-6 will further define the postprandial transport of dietary omega-3 and non-omega-3 fatty acid cycles in physiology [68–70].

In conclusion, algal oil DHA bioavailability from *Schizochytrium sp.* demonstrates dose-dependent improvements in levels of chylomicrons, HDL and TG due to increased levels of DHA in the postprandial state for plasma lipid control. *Schizochytrium sp.* algae oils are safe also at high DHA dosage levels compared to body weight. Algae DHA supplementation improved plasma lipid markers, not glucose markers of insulin sensitivity in HTG men. The intake of *Schizochytrium sp.* DHA at high doses is associated with a reduced risk of CVD. Just DHA intake without EPA provides similar benefits with short-term and long-term utility. HTG is increasingly prevalent worldwide due to the spread of modern-style diets and weight gain with low physical activity. A low omega-3 index is correlated with HTG, countered by algae oil DHA treatment. The knowledge of cause and effect of all fatty acids in the diet will improve the human condition and the public health.

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