The Role of Omega-3 Fatty Acids in AMD And DED

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Abstract: Previous studies had been conducted the effects of omega-3 fatty acids on humans regarding. The previous studies showed practical effects of omega-3 on eye health but failed to address dry eye decease (DED) and age-related macular degeneration (AMD). DED is a dry eye disease which is a tear film and multifactorial ocular disease, while AMD affects the retina section of the macula. The positive impact of omega-3 PUFA on treating patient's DED and AMD was confirmed. At the same time, it was also found that omega-3 showed a positive effect in regulating an individual's nervous system, immunological system, and vascular activity. Survey which distributed in New Zealand and Australia's optometrists via professional organizations collected a result that, 80% of the optometrists asserted that seafood or fish was a practical prescription for omega-3 in dealing with DED and AMD, and approximately 95% of the optometrists suggested non-fish seafood or fish seafood as a good food source. The survey suggested that omega-3 supplements need to indicate particular patient recommendations such as brand, frequency, and dosage. The DED intake frequency and the clinical guidance of the omega-3 foods were identical to AMD frequency. In conclusion, this article argues that omega-3 fatty acids are adequate for the eye and therapeutic effect on additional inflammatory ailments.

1. Introduction

The effects of omega-3s on human health have been found to be numerous. These include beneficial effects on eye health. At present, dry eye and Age-related macular degeneration (AMD are the main diseases affecting the eye health. AMD is a disease that affects the Macula of retina area. The disease is multifactorial and complex. It is common in the elderly population, affecting the quality of life. In severe cases, there is a risk of blindness. AMD is the most common cause of blindness in the developed countries [1]. Dry Eye decease (DED) is a multifactorial ocular surface and tear film disease. It is a common disease associated with aging and modern lifestyles. Symptoms of DED include eye pain, visual impairment, and ocular surface damage, which affect people's quality of life [2].

Docosahexaenoic acid (DHA) in Omega-3 makes up 50 to 60 percent of the total fatty acid content in the rod outer segments of photoreceptors (ROSs). Continuous renewal of the membrane of ROSs depends on dietary intake of DHA or DHA precursors, and lack of DHA intake may predispose a person to AMD. chronic inflammation, oxidative stress, vasogenic processes are the main pathogenesis of AMD, and the effects provided by Omega-3 polyunsaturated fatty acids (PUFA) can reduce the occurrence of these mechanisms [3]. An eye Case-control study showed a negative association between exudative AMD and fish oil consumption [4]. A US study of AMD twins found a negative association between dietary Omega-3 PUFA intake and AMD [5].

Inflammation is the main pathogenesis of DED and plays an important role in its development [1]. An experimental study based on animal models has found that daily OMEGA-3 PUFA supplements have the potential to have a significant effect on the treatment of DED [6]. An experimental DED mouse model was used to observe the effect of hyaluronic acid mixture with artificial tear and Omega-

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3 PUFA. The results showed that Omega-3 PUFA supplementation was more effective in the treatment of inflammation and clinical symptoms of DED [7].

This article provides an overview of AMD and DED concepts, incidence, and pathological mechanisms. The second section of the article describe the concept of omega-3, chemical structure, current applications and negative effects. And collates the current clinical application data of omega-3. This article also collates the optometrists' attitudes for omega-3 in the prevention or treatment of AMD and DED. Based on the current situation, the effect of omega-3 on AMD and DED is evaluated and prospected.

2. AMD and DED

2.1 AMD

Age-related macular degeneration (AMD), a disease that commonly affects the elderly population, is a complex disease that affects the macula (the central area of the retina). The disease is multifactorial and complex. Often caused by a combination of genetic and environmental risk factors, it can lead to progressive retinal degeneration and progressive vision loss. The disease accounts for about 9% of all cases of blindness. AMD is the most universal cause of blindness in developed countries and affects about 200 million people worldwide in 2020, including 10 million people with late AMD. Its incidence and prevalence continue to rise because of population aging [8, 9].

AMD is a degenerative illness that destroys the cells and photoreceptors of the retina, resulting in central vision loss or partial vision loss and legal blindness. Major risk factors for AMD include age, genetic susceptibility, and nicotine intake. AMD is usually divided into early, intermediate, and late stages. Early AMD is usually asymptomatic and does not cause visual impairment. It is characterized by large drusen and pigment abnormalities in the macula. Patients with late AMD often have distorted vision or central visual field defects. There are two main forms of late AMD: dry or nonexudative (about 85-90%) and wet or exudative (a minority). Dry AMD is characterized by a slow progressive loss of macular Retinal pigment epithelium, photoreceptor cells, and choroidal capillary. It progresses more slowly and may eventually result in halos or blind spots in the central part of the field of vision that block part of the vision (Central Scotoma). The influence of wet AMD on vision is mainly due to the development of choroidal neovascularization (CNV) in macular region. These newly formed blood vessels tear violently, causing macular hemorrhage with secondary scarring. Pathologic neovascularization may reflect an attempt by the damaged retinal area to repair itself, with abnormal blood vessels or Retinal pigment epithelium leaking or tearing, resulting in rapid deterioration of vision. It progresses rapidly and is the main cause of severe visual loss. Nevertheless, geographic atrophy (the final stage of advanced dry AMD) can also lead to severe vision loss [10-13].

The pathophysiology of AMD is multifaceted and complex. Genetic predisposition, age-related disruption of normal retinal homeostasis, decreased lipid metabolism, immunological activation and progression to chronic inflammation, oxidative stress, vasogenic processes and ECM dysfunction are some of the causes. All these mechanisms have the potential to cause the disease. Although significant progress has been made in recent years, the exact stochastic relationship between the characteristics of the disease is still unknown [13].

2.2 DED

Dry eye disease (DED) is a multifactorial ocular surface and tear film illness that can cause ocular pain, vision impairment, and ocular surface damage. It is very common in elderly patients and in postmenopausal and post-menopausal women. DED could be acute or chronic. Dryness, discomfort, a foreign body sensation, itching, burning, photophobia, and impaired vision are the most common symptoms. The osmotic pressure of tear film normally increases because of the instability generated by DED, resulting in ocular surface irritation and structural damage.

According to the cause, DED can be divided into two categories: aqueous-deficient DED and evaporative DED. Sjögren's syndrome and non-Sjögren's syndrome are two types of aqueous-deficient DED. Aqueous-deficient DED in Sjögren's syndrome is linked to autoimmune illnesses, while non-

Sjögren's syndrome aqueous-deficient DED is thought to be caused by a lack of tear production. Evaporative DED is an increase in evaporation of the tear film, usually because of Meibomian gland dysfunction [2].

The prevalence of DED is about 5% to 50% worldwide, with or without symptoms. The prevalence of DED in Asians was higher than in Caucasians and increased linearly with age, but relatively high rates were reported in young subjects and school-age children. The prevalence is higher in women than in men and is usually significant with age [14].

Risk factors for DED include individual risk factors such as the elderly, women, Asians, and contact lens users. Environmental risk factors such as low humidity, wind, eye overuse and second-hand smoke exposure. Some clinical conditions may also increase the risk of developing DED, such as Rheumatoid Arthritis, sarcoidosis, Sjögren's syndrome, diabetes, rosacea, hepatitis C infection, allergies, Parkinson's disease. Risk factors for DED are also associated with low androgen levels, low omega-3 intake, use of some medications, and eye surgery or injury [15].

The pathogenesis of DED includes inflammation, oxidative stress, apoptosis, sex hormone imbalance and so on. Inflammation is a crucial factor in the development of DED. Because of the disease's long-term character, it's likely that immune system dysregulation results in a persistent inflammatory cycle accompanied by changes in innate and adaptive immunological responses [1].

3. Omega-3

Omega-3 is a sort of essential nutrients which is included by the parent fatty acid ALA. It is one kind of polyunsaturated fatty acids (PUFAs) with multiple cis-double bonds, which all have the third and third methyl-terminus of the fatty acid. Between the four carbon atoms, there is at least one double bond [16]. Figure 1 is about the structural formula(left) and simplified structural formula(right) of Omega3. OMEGA-3 is a long chain composed of more than 18 carbon atoms, of which it has 3-6 double bonds, and the third carbon atom at the methyl end is the first unsaturated bond of its molecule, hence the name OMEGA-3. Figure 2 is about the isomers of Omega3. Different isomers including DHA, EPA, SDA, ALA, DPA play different roles in human body.

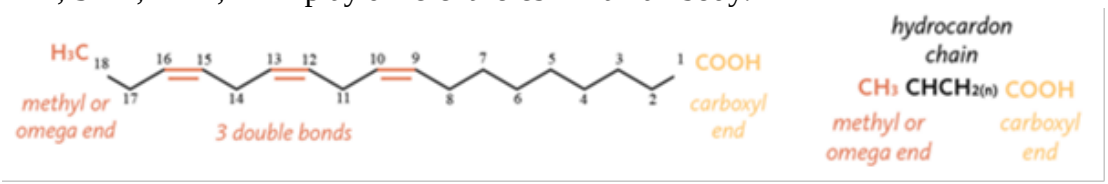

Figure 1. Structural formula (left) and simplified structural formula (right) of omega3 lpi.oregonstate.edu

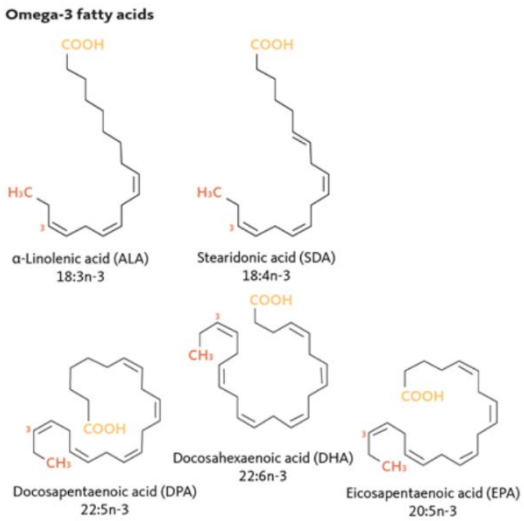

Figure 2. Configurational isomerism of omega3 lpi.oregonstate.edu

3.1 Supplements

Flaxseed oil can be used as an ALA supplement. Omega-3 have been found in natural fish oils as triglycerides. Typically, One of the three fats is omega-3. Therefore, approximately 70% of the fatty acids in fish oil are other types than omega-3 [17]. EPA and DHA are ethyl esters which is a concentrated source of a long-chain omega-3 fatty acids. EPA and DHA are both contained in krill oil which can be considered as the source of these lengthy chain PUFAs [18].

One rich source to have EPA and DHA is cod liver oil. However, some of those cod liver oil formulations may have an overabundance of pre-formed vitamin A and vitamin D [19]. DHA supplementation may also originate from algal and fungal sources. Since DHA can be converted into EPA and DPA in the body, DHA supplements are an alternate to fish oil supplements.

It is important in understanding product labels to determine the levels of DHA that a particular supplement provides due to varying levels of DHA in the formulations. Splitting an individual's two to three smaller daily doses during the day can minimize the potential for gastro-intestinal side effects to ensure more efficient absorption of omega-3 fatty acids at mealtimes.

3.2 Application

(1) Supplements During Pregnancy

Supplementation with omega-3 PUFA did not lead to a reduction in the incidence of gestational diabetes and preeclampsia. Based on findings from randomized controlled trials during pregnancy [20], women who have low omega-3 fatty acid intake may cause prolonged pregnancy.

In 2016, a meta-analysis of tests revealed that supplementation with the use of omega-3 PUFAs during pregnancy reduced the overall incidence of premature delivery, increase in gestational age and birth weight had no impact on perinatal mortality risk and the low Apgar score 1 minute after birth [21].

After the analysis about dose-response, DHA supplementation of at least 600 mg per day during pregnancy was found to reduce the risk of premature birth and underweight during birth [22].

(2) Baby Supplement

The critical period for DHA to accumulate in the brain and retina is the final quarter in the first six months of pregnancy. Breast milk is a combination of saturated fatty acids (46%), monounsaturated fatty acids (41%), omega-6 fatty acids (12%) and omega-3 fatty acids (1.3%) [23]. Though human milk includes small amounts of DHA, the solitary omega-3 fatty acid was ALA, found in traditional infant formula until 2001. While infants may synthesize DHA by ingesting ALA, they are often unable to synthesize enough DHA to prevent a decrease in DHA cell levels.

Therefore, the addition of quantitative DHA to infant formula is recommended for bringing plasmatic and cellular DHA levels in infants fed formula to breastfed infants.

(3) Prevent Cardiovascular Diseases

Hypertriglyceridemia is one of the risk factors to fall in cardiovascular disease [24]. Many monitored clinical trials have shown the increased intake of EPA and DHA produces significant reductions in serous levels of triglycerides [25]. EPA and DHA's reducing triglyceride effects increase with increasing dose [26]. The clinical significance of serum levels of triglycerides was shown at a dose of 2 grams per day of EPA and DHA [27]. Long-chain omega-3 PUFA may reduce levels of triglycerides that do not affect total cholesterol [25]. Notably, the mechanism which long-chain omega-3 PUFA supplementation reduces CHD death is unlikely that these were triglycerides, since the doses used in the studies were often too small [28]. Several cell culture studies suggest that long-chain omega-3 PUFA can reduce the excitability of cardiomyocytes by modulation of the conductance of the ion channel, compatible with the animal models have shown anti-arrhythmic effects.

In recommendations on omega-3 PUFA and cardiovascular illnesses, the American Heart Association says long-chain omega-3 PUFA supplementation can assist, reduce heart dysfunction in patients [28].

3.3 Negative Effects

Prolonged bleeding time due to high intake of omega-3 fatty acids such as EPA and DHA have been well studied and can contribute to omega-3 fatty acids' heart-protective properties Greenland Eskimo with exceptionally high EPA and DHA diets had longer bleeding times and a higher risk of hemorrhagic strokes. The issue whether prolonged bleeding is only caused by the high intakes of EPA and DHA is currently unknown [16]. The United States FDA has ruled that consuming omega-3 long-chain fatty acids is beneficial which is typically less than 3 grams a day regarded as safe and can be included in the diet. Existing evidence suggests that intake of not more than 3 grams per day is not likely to cause clinically meaningful effects hemorrhage [27]. Although no tolerable maximum intake of omega-3 fatty acids has been established by the US Institute of Medicine, EPA and DHA supplementation is recommended with caution, especially among those who present an increased risk of excessive bleeding [16, 19].

While inhibiting inflammatory reactions caused by increased intake of omega-3 fatty acids may be beneficial to patients with inflammatory or auto-immune conditions, anti-inflammatory omega-3 fatty acid concentrations may impair the immune system's ability to destroy pathogens. It is unclear that whether these findings can be interpreted as an indication of an impaired immune response in the body, the considering supply should be taken caution to exercise with omega-3 fatty acids by persons who have a weakened immune system.

4. Attitudes and Recommendations of Optometrists on the Use of Omega-3 in AMD and DED

Previous studies examined optometrists' attitudes toward omega-3 on eye disease. Meanwhile understanding of its hidden risks and advantage. Diet plays an important role lifestyle factor affecting eye disease. The reason of omega-3 fatty acids is called "essential" fatty acids is that they cannot be synthesized in the body and must be obtained from the diet [29].

There was a web-survey made by asking optometrists in Australia and New Zealand between one month in 2019(June-July) [30]. Ninety-eight percent of those who asked their patients about the daily food did not utilize any statistical techniques to evaluate eating patterns, according to the 91 percent of responders who did so. Three responders mentioned a food frequency questionnaire. Optometrists say they ask patients about nutritional supplement intake more frequently than about their diet. About a third of optometrists always or almost always (32 percent) provided general or specialized dietary advice to patients, and half of the optometrists occasionally (52 percent) did so [30].

The majority of responders (79%) indicated they advise their treatments to take omega-3 in supplements or diet to help their eye health [30]. The rest said they would not suggest omega-3 to their treatments. But no one ever advised their patients that omega-3 fatty acids were bad for them according to some respondents. Nearly 50% respondents said that they didn't provide any omega-3 fatty acid recommendations, and they didn't know enough these fatty acids to make a suggestion. In the survey, thirteen respondents thought the available study evidence was insufficient to support requests for eye health from omega-3 fatty acids, and three indicated they were being conscious of published evidence showing omega-3 were not good for eye curing. Four people indicated that they would suggest omega-3 fatty acids, but now they don't. One of the reasons given was that they didn't notice any clinical improvement in their patients. However, new evidence has persuaded them otherwise. They said other forms of treatment (e.g., light therapy for intense pulsed DED) would be preferred over dietary therapies. According to the Maturity level Eye Disease Studies with AMD, 20 percent of the 44 responders who were not likely to recommendations about omega-3 fatty acids advocated for other formulations for their patients.

Figure 3 A depicts optometrists' self-reported practices regarding human omega-3 intake, either through diet or supplementation, as an essential aspect of AMD patient care [30]. Almost everyone (more than 90 percent) suggested seafood as a food source. Nearly 80% of optometrists who prescribed fish or seafood did so with a specific frequency in mind, usually 2 to 4 times per 7 days (Figure 3C). Sixty percent of optometrists who suggested rich contained omega-3 food more likely choose nuts and

seeds, and the rest recommended green food and fruits. Participants of this survey recommended omega-3 supplements expressed more detailed information about their choices. Figure 3D creates a "cheat sheet" to make a visual picture of the complimentary replies received from 60 percent of total practitioners. About one-third of people who be tested provided detailed doses in their recommendations, range from 250mg to 5000 mg every day. 10 % of respondents said they have no specific recommendations about the specific brand of omega-3 supplements, and the rest said on specific supplement product and dosage recommendations, they would urge customers to consult a pharmacist or GP.

Figure 4A depicts optometrists' self-reported behaviors when recommending omega-3 fatty acids as part of DED therapy [30]. A higher percentage of responders said omega-3 fatty acids intake pills or from sources of food were advised to control DED (68%) according to the respondents. Omega-3 fatty acids were regarded as acceptable for evaporative and mixed DED etiologies by almost all (>99 percent) respondents who offered this recommendation (Figure 4B). Severe DED and moderate patients are less likely than those with moderate or severe DED to obtain omega-3 fatty acid recommendations. Clinical recommendations for daily intake of omega-3 and DED is similar to AMD, according to self-reported clinical recommendations (Figure 4D). Almost all (97 percent) optometrists advised patients to raise their consumption of omega-3 fatty acid-rich meals to improve DED recommended seafood sources (Figure 4E). Nuts and seeds were recommended by more than half of the respondents (60 percent), while a third claimed omega-3 fatty acids could be obtained by eating vegetables or fruits. Oral omega-3 supplementation was advised by seventy eight percent of optometrists to treat DED (Figure 4F). Omega-3 fatty acids with a long chain from marine sources (40 percent of optometrists), plant sources also provide short-chain omega-3, and a combination of long-chain and short-chain omega-3 fatty acids are the most generally advised types (29 percent of all optometrists). Figure 4G depicts a "word cloud" from one-third practitioners who gave DED-specific omega-3 supplementation recommendations. Thera Tears and Lacritec were the two most popular commercial brands in text size, with 17 percent and 15% of respondents, respectively, recommending them. Out and out, respectively Around one-third of responders offered precise dosage recommendations for omega-3s in DED, ranging from 250 mg to 6000 mg per day, while 10 percent encouraged their patients to consult to the supplement package instructions or their pharmacist's advice [30].

Optometrists' attitudes towards the application of omega-3 fatty acids in the treatment of AMD and DED, as well as their experience gained in specific practice, have important reference significance for the application of omega-3. However, more relevant research is needed to further confirm the application effect of omega-3.

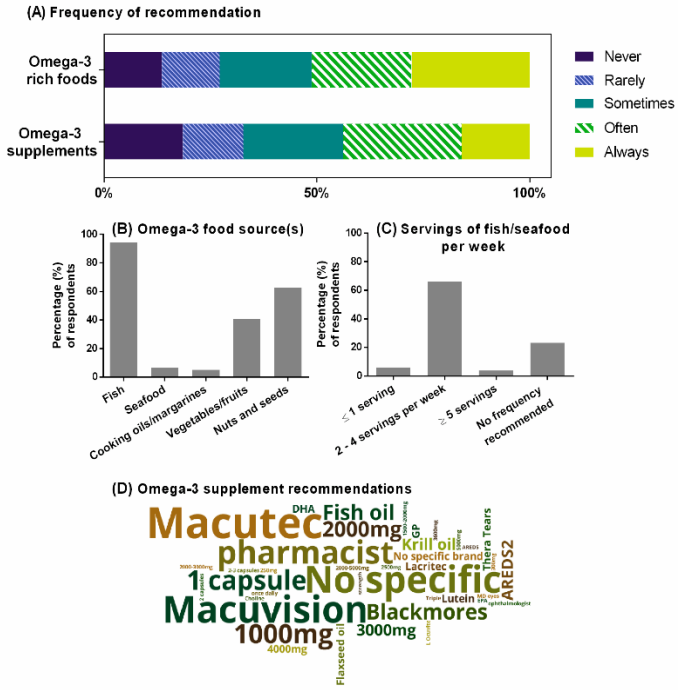

Figure 3. Self-reported clinical practices of optometrists in relation to omega-3 fatty acid intake as part of AMD therapy. (A) The frequency of recommending; (B) omega-3 food sources recommended by the testers; (C) perfect frequency for patients to consume omega-3 foods; (D) word-cloud of suggestions for Omega-3 supplementation [30].

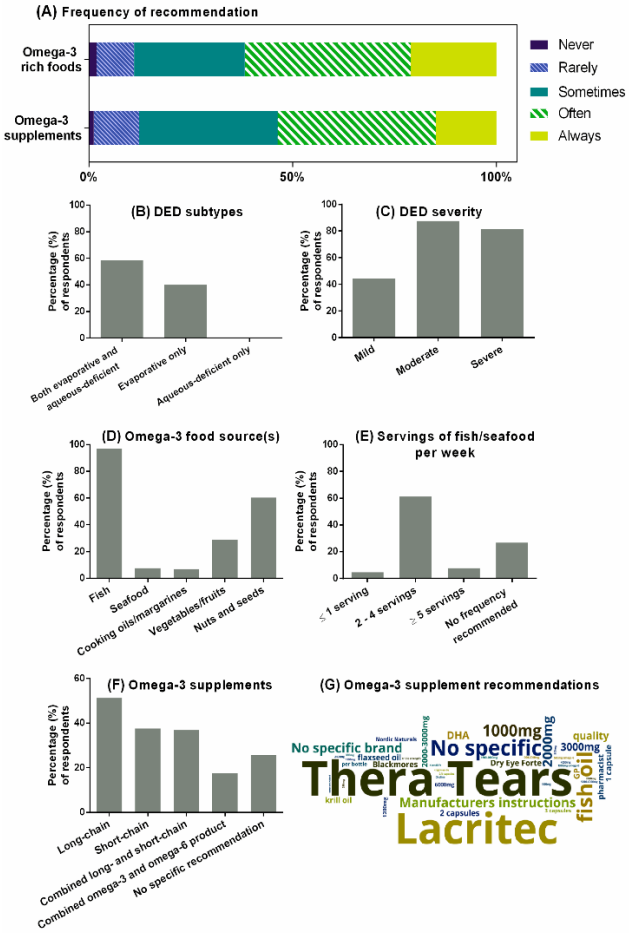

Figure 4. Self-reported clinical practices of optometrists in relation to omega-3 fatty acids for DED management [30].

5. Conclusion

The clinical application of omega-3 in AMD and DED by analyzing optometrists' attitudes towards omega-3 was demonstrated in this article. The dietary advice to patients by optometrists was compared, most of whom advised patients to increase their consumption of foods high in omega-3 fatty acids for the treatment of DED. It was discovered that consuming a diet high in omega-3 fatty acids through food or supplements is good for the eyes. The ratio of omega-6 to omega-3 fatty acids in a person's diet has a positive impact on controlling vascular activity, moderating immunological and nervous system function, and changing the balance of lipid-derived mediators throughout the body. In the future, increasing the intake of omega-3 in the diet will be one of the adjuvant treatments for DED and AMD. Through the continuous in-depth research of omega-3, its therapeutic effect on more inflammatory diseases will be discovered.

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