Review

Omega-3 Fatty Acids, Smoking and Vision Loss from Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is the leading cause of vision loss in the developed world. Despite its prevalence no cure exists for atrophic dry AMD, which is the most common form of this disease. Several lifestyle modifications including the absence or cessation of smoking have been identified as preventive to AMD development. More recently, research has indicated that a diet high in omega-3 fatty acids may be beneficial in the prevention of AMD. This review critically analyzes the literature concerning the effects of both smoking abstinence and omega-3 fatty acid intake on the prevention of AMD. Taken together, this research indicates that increased consumption of omega-3 fatty acids (e.g. fish twice or more per week) halves the risk of both early and late AMD while smoking doubles the risk of AMD.

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among individuals over the age of 55 in developed countries,[1,2] and is estimated to directly affect 1 million Canadians.[3] This disease exists in an atrophic form ("dry" AMD) and an exudative form ("wet" AMD).[4] Atrophic AMD is characterized ophthalmologically by accumulation of lipid deposits (drusen) in Bruch's membrane, the innermost layer of the choroid, and by geographic atrophy (GA) within the macula of the retina, which represent areas of retinal pigment epithelium degeneration. Approximately 10 to 20% of atrophic AMD progresses to the more serious exudative AMD, which is characterized by the presence of choroidal neovascularization (CNV). Although the etiology of AMD is unknown, environmental exposures (e.g. smoking), nutritional factors (e.g. antioxidants), and vascular pathology (e.g. atherosclerosis and hypertension) have all been linked to the development of this disease. Prevention of these risk factors is currently the only therapeutic strategy for atrophic AMD.

Rationale for Lifestyle Modification of Risk Factors

Currently, the prevalence of AMD is rising dramatically largely due to increased life expectancy within the population, and that the largest portion of this population is entering old age. The Canadian National Institute of Blindness (CNIB) has estimated that health care costs of vision loss are approximately 7.9 billion dollars annually, and that much of this expense is due to AMD.[3,5] In addition to the economic and social concerns, AMD is both physically debilitating and psychologically traumatic for patients and their families. Often, individuals afflicted with this disease lose significant independence and require assistance with activities such as walking down the street or reading their bills. Currently there is no cure; however, the CNIB and AMD Alliance International both advocate for modification of risk factors to prevent AMD.[5] These modifiable risk factors include smoking, a diet low in antioxidants and minerals, excessive sunlight exposure, and excessive weight as indicated by a high BMI.[6] Recent studies have indicated that high Omega-3 intake may prevent the development of AMD.[7-9]

Several articles have extensively reviewed the effects of vitamin supplementation for the prevention of AMD.[10,11] The purpose of this review is to critically appraise the association of a diet high in omega-3s, versus smoking (an accepted risk factor), to the risk of AMD development. This appraisal will attempt to determine whether or not high omega-3 fatty acid intake is effective at preventing AMD and if so how effective this lifestyle modification is compared with smoking cessation, an accepted modifiable risk factor for prevention of AMD.

Selection of Relevant Articles and Background Readings

To investigate the effectiveness of these modifiable risk factors to the prevention of AMD, articles which linked omega-3 fattty acids and AMD were searched for in Pubmed/Medline using the following MeSH terms: "((“Macular Degeneration”[Majr] OR (“Macular Degeneration/diet therapy”[Majr] OR “Macular Degeneration/prevention and control”[Majr]))) AND (“Fatty Acids, Omega-3”[Majr] OR “Fatty Acids, Omega-3/therapeutic use”[Majr])”. The search was limited to only include “Human”, “English”, “Clinical trial”, “Meta-analysis”, “Randomized Controlled Trial” or “Review”. This search yielded 12 papers. Of these studies, all news reports which were based on the other articles were ignored. Three of the remaining papers (a meta-analysis and systematic review, a systematic review, and a prospective cohort study) discussed all other studies identified by the search, so a critical analysis of the literature was limited to these 3 papers.

To investigate the relationship between smoking and AMD I performed the following search: “((“Macular Degeneration”[Majr] OR (“Macular Degeneration/diet therapy”[Majr] OR “Macular Degeneration/prevention and control”[Majr]))) AND (“Smoking”[Majr] OR (“Smoking/adverse effects”[Majr] OR “Smoking/drug therapy”[Majr] OR “Smoking/prevention and control”[Majr] OR “Smoking/therapeutic use”[Majr] OR “Smoking/therapy”[Majr]))” with limits for “Humans”, “English”, “Clinical trial”, “Meta-analysis”, “Randomized Controlled Trial” or “Review” articles. This search yielded 9 papers of which 4 manuscripts (one meta-analysis, one systematic review, and two cross-sectional studies) discussed all of the other articles identified by my MeSH search.

In addition, the three terms (“smoking”, “omega-3 fatty acids”, and “macular degeneration”) were evaluated together with the following search: “(“Macular Degeneration”[Mesh] AND “Smoking”[Mesh]) AND “Fatty Acids, Omega-3”[Mesh]” with no limits imposed on this search. Three articles were identified, one of which was in German. The remaining two papers were in English but had been identified from the previous searches.

Google was used to investigate and define terms as well as the pathogenesis of AMD. Robbins and Coltran’s Pathologic Basis of Disease 7th ed. was also used to understand the pathogenesis of AMD. The CNIB website was used to identify facts concerning the effect of AMD on population health.

The Effectiveness of Omega-3 Fatty Acids for Prevention of AMD

Omega-3 fatty acids are essential unsaturated fatty acids that exist in three forms; alphalinolenic acid (ALA; a short-chain omega-3 fatty acid), DHA, and eicosapentaenoic acid (EPA) (both long-chain omega-3 fatty acids). Since they exist in high concentrations in fish, investigation of omega-3 fatty acid intake is inferred in all studies from dietary questionnaires, with particular emphasis on fish intake.

Numerous studies indicate that diets high in omega-3 fatty acids may prevent development of AMD. The strongest evidence comes from a recent meta-analysis and systematic review that screened 2754 abstracts and identified 9 papers which met their inclusion criteria (3 prospective cohort studies, 3 case-control studies and 3 cross sectional studies).[7] The meta-analysis reported that all of these studies controlled for both smoking and age except for two of the cross-sectional studies which did not control for smoking. Comparison was made between “Dietary Omega-3” intake with “Early AMD” or “Late AMD”, and between “Fish” intake with “Early AMD” or “Late AMD”. Comparison between highest and lowest omega-3 fatty acid intake yielded odds ratios (OR) for early AMD of 1.49 (95% confidence interval [CI], 1.15-1.94) for ALA, 0.77 (95% CI, 0.59-1.01) for EPA, and 0.70 (95% CI, 0.52-0.93) for DHA; and for later AMD, of 0.62 (95% CI, 0.48-0.82).” OR from fish intake compared with early AMD was 0.76 (95% CI, 0.64-0.90) and for late AMD was 0.67 (95% CI, 0.53-0.85). Taken together this paper demonstrated convincingly that a diet rich in omega-3 fatty acids (especially long-chain omega-3 fatty acids such as DHA and EPA), whether in fish or other foods, was associated with a decreased risk of development of early and late AMD. Specifically, the authors concluded that consuming food rich in omega-3 fatty acids (such as fish) two or more times per week reduced the risk of development of both early and late AMD.

A systematic review that was conducted two years earlier (in 2006) analyzed 2 cohort studies, 2 case-control studies, and 2 single population-based cross-sectional studies and yielded very similar results[9] to that of the meta-analysis by Chong and colleagues (2008). Of these 6 papers, only one of the case-control papers and one of the population-based cross-sectional studies was not covered in the meta-analysis. The case-control study had a sample size of eleven and only evaluated patients with exudative AMD.[12] Interestingly, this study found that DHA levels were significantly higher in the blood of individuals with AMD,[12] a finding contrary to what would be expected from other studies. No biological

role was identified for this finding; however, a low sample size (n = 11) may have contributed to these results. The systematic review by Hodge and colleagues (2006) rated the quality of each of the 6 studies examined, with the case-control study by Ouchi et al (2002) given a grade of 0 out of 10. The second paper that was not covered by Chong and colleagues' meta-analysis (2008) was a population-based cross-sectional study that found a non-significant trend for a protective role of a high seafood diet for AMD.[13] The paper determined that low fish intake protected against late AMD (OR: 0.23, 95% CI: 0.08–0.63), but both no and high fish intake yielded no protection. Furthermore, the paper determined that no significant inverse association existed between fish intake and early AMD based on both univariate and multivariate analysis which demonstrates that a dose-dependant relationship does not exist for fish intake and later AMD. This population-based cross-sectional study[13] and the case-control study[12] were both likely excluded from the meta-analysis by Chong and colleagues[7] because the meta-analysis only considered studies in which the participants did not already have AMD. Despite overwhelming evidence from the present research that omega-3 intake is associated with reduced incidence of AMD, both Hodge and colleagues (2006) and Chong and colleagues (2008) concluded that there is "insufficient evidence to promote clinical recommendations for increased dietary intake of omega-3 fatty acids for the prevention of AMD". The authors base their conclusions on the inherent limitations in the design of the research studies conducted to date, as well as the limited number of studies (see "Limitations" section for further details).

Since publication of the meta-analysis,[7] a prospective cohort study performed by the age related eye disease study (AREDS) group has been published.[8] Most of the participants in the study were over the age of 70 and dietary omega-3 intake was determined from a questionnaire containing numerous questions concerning the type and amount of fish intake as well as other foods. Age and smoking were both controlled for. The purpose of the study was to evaluate the effect of omega-3 fatty acids on preventing progression of AMD to either GA (atrophic AMD) or CNV (exudative AMD) in participants with bilateral drusen at enrolment. Individuals who reported the highest DHA intake were 50% less likely to develop GA (OR: 0.51; 95% CI: 0.26-1.00), while those with the highest intake of EPA alone and intake of EPA with DHA together were both 60% less likely to develop GA (OR: 0.41; 95% CI: 0.21- 0.78, and OR: 0.41; 95% CI: 0.21-0.80 respectively). Individuals who reported the most frequent tuna intake were found to be 50% less likely to develop exudative AMD (OR: 0.48; 95% CI: 0.24-0.95). The authors report that this is the only paper to their knowledge which investigated differences between atrophic ("dry") AMD and exudative ("wet") AMD as outcomes. Based on their findings the authors concluded that individuals with the highest intake of omega-3 fatty acids (specifically DHA and EPA) had at least a 50% decrease in the likelihood of progression of early AMD to GA or CNV.

Taken together these studies indicate that a diet high in omega-3 fatty acids (particularly DHA and EPA) is likely to reduce the risk of development of AMD and may decrease the risk of progression from early to later, more serious forms of AMD by at least 50%.

The Risk of AMD Development from Smoking

Smoking is a well known risk factor for many chronic diseases, especially cardiovascular disease and many malignancies.[4] Several biological mechanisms have been proposed for how smoking may affect AMD including increased oxidative stress, alterations in choroidal blood flow, reduction of macular pigment, increased inflammation and/or interactions with specific genes known to cause genetic forms of AMD.[1,14]

Several studies have provided evidence linking smoking to the development of AMD. A meta-analysis published in 2008 investigated this relationship in five prospective cohort and eight case-control studies.[15] The cohort studies determined that continued smoking was associated with an increased risk of development of AMD (RR: 1.61, 95% CI: 1.01–2.57), that this risk was stronger in current smokers (RR: 2.06, 95% CI: 1.12–3.77) compared with individuals who had quit (RR: 1.40, 95% CI: 0.96–2.06), and that this increased risk was associated with both increased GA (RR: 2.79, 95% CI: 1.47–5.28) and CNV (RR: 1.48, 95% CI: 0.92–2.37). The case-control studies yielded the same findings. Smoking increased the risk of development of AMD (OR: 1.76, 95% CI: 1.56–1.99), the risk was greater in individuals who continued to smoke (OR: 2.38, 95% CI: 1.74–3.26) compared with those who had quit (OR: 1.66, 95% CI: 1.35–2.04) (all relative to non-smokers), and smoking increased the risk of development of both GA (RR: 1.71, 95% CI: 1.23–2.39) and CNV (RR: 1.96, 95% CI: 1.69–2.27). The authors concluded that smoking clearly increases the risk of AMD development; however, since the risk is much lower in past smokers than current smokers, smoking cessation may reduce the risk of AMD development and therefore should be promoted. Neither the age of onset of AMD nor the stage of AMD (early vs late) were examined in this article. Therefore, the temporal

relationship between smoking and AMD development is unclear.

A systematic review published before Cong and colleagues' meta-analysis (2008) found similar results. The review analyzed 17 studies and found that of these, 13 identified a statistically significant relationship between smoking and development of AMD (RR/OR 1.06–4.96 for smokers vs non-smokers).[16] A dose response, as measured by pack-years, was determined in seven of eight studies. As well, the one study that investigated the age of onset of development of AMD determined that smokers had an age of onset 10 years earlier than non-smokers (mean ages of 67 and 77 years, respectively).[17] Eleven of the studies investigated the risk of AMD development in individuals who quit smoking compared with current smokers and found that smoking cessation reduced the risk of AMD development but still increased AMD risk above that of individuals who had never smoked.[16] Based on these studies the authors of the systematic review concluded that there is strong evidence to suggest a causal relationship between smoking and development of AMD.

Other studies have also provided similar results. A cross-sectional study termed the EUREYE Study evaluated 4750 individuals in Britain over the age of 65.[18] This research determined that current smokers had a significant risk of development of CNV (OR: 2.6; 95% CI: 1.4–4.8) or GA (OR: 4.8; 95% CI: 2.1–11.1) whereas the OR of individuals who had quit was 1.7. The authors reported that the "attributable fraction for AMD due to smoking was 27% (95% CI: 19%–33%)." Furthermore, the authors reported that individuals who had quit smoking 20 years or more prior to the study had no increased risk of development of AMD compared with non-smokers.

Finally, a recent study investigated visual impairment in 28,000 individuals over the age of 75, compared with individuals with normal vision.[19] The study determined that current smokers were twice as likely to develop AMD compared with non-smokers (OR: 2.15, 95% CI: 1.42-3.26), and that this risk was lower in individuals who had quit smoking compared with current smokers (OR: 1.13, CI: 0.86-1.47), but was higher compared with non-smokers. The authors concluded that smoking doubles the risk of development of AMD.

Taken together, numerous studies assessing the risk of AMD development in smokers indicate that current smoking more than doubles the risk of AMD, and that quitting smoking reduces the risk but not as much as never smoking.

Limitations

Several limitations exist within the research studies analyzed within this paper. Randomized controlled trials (RCTs) are widely accepted as the gold standard of evidence based medicine. While such studies for smoking would clearly be unethical, RCTs investigating the effect of omega-3 fatty acids on the development of AMD are ethically feasible; however, no such experiments have been conducted to date. Several additional limitations were also identified by the articles that were reviewed concerning omega-3's role in AMD risk reduction.[7-9] One concern is that observational studies (case-control and cross-sectional) are limited by the possibility of both recall bias and by the inability to infer temporal associations between AMD and omega-3 fatty acid intake. In addition, the authors of the meta-analysis[7] identified that significant publication bias existed based on their funnel plot, which they attributed to the inclusion of only 9 articles. This result raises the concern that studies may have been conducted which determined that omega-3 fatty acid intake had no effect on prevention of AMD; however, these studies may not have been accepted for publication due to their negative findings. The funnel plot was not significant in the article by Hodge and colleagues (2006) and therefore no publication bias existed in this systematic review. Another concern is that individuals who consume diets high in omega-3 fatty acids likely have a better overall diet compared with individuals who have a diet poor in these lipids. Chong and colleagues (2008) identified that these individuals may consume more foods that are higher in antioxidants[10,20] and more foods which have a lower glycemic index,[21] two diet modifications associated with a lower risk of AMD. These diet differences may not have been controlled for in the observational studies. In addition, healthy diets may also reflect healthier lifestyles (exercise, decreased BMI, etc.), which also may not have been adequately controlled between groups.

In studies that investigated the association between smoking and AMD, several limitations merit consideration. Smoking is well known to be associated with many other health risks such as a poor diet and excessive alcohol intake. Specifically within the systematic review by Thornton and colleagues (2005), it was identified that of the 17 studies examined, only two controlled for vitamin and alcohol intake. In addition, all smoking habits were self-reported within each of the studies. Therefore, individual bias could have existed which may have resulted in either over-reporting or

under-reporting of smoking frequency and duration by individuals.

Summary

Consumption of a diet high in omega-3 fatty acids, largely from fish, is associated with reduction to the risk of AMD, while smoking increases the risk of both early and late AMD. Specifically, consumption of fish twice or more per week compared with intake less than once per month may halve the risk of both early and late AMD. The majority of the studies investigating the risk of AMD development from smoking indicate that smoking likely doubles the risk of AMD, and that while past smokers are still at higher risk compared with individuals who have never smoked, the risk of AMD is significantly reduced compared with individuals who continue to smoke. Also of interest, individuals who quit smoking more than 20 years ago may have the same risk of development of AMD as individuals who never smoked. No studies compared the associated risk of AMD development from omega-3 fatty acid intake in smokers versus non-smokers. Therefore, the association between these risks is unknown (e.g. additive, synergistic, or no association). Future studies should investigate the association between omega-3 fatty acid intake and the development of AMD using RCTs as a study design.

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Abbreviations

ALA = Alphalinolenic acid
AMD = Age-related macular degeneration
CI = Confidence interval
CNIB = Canadian National Institute of Blindness
CNV = Choroidal neovascularization
DHA = Docosahexaenoic acid
EPA = Eicosapentaenoic acid
GA = Geographic atrophy
OR = Odds ratio
RCT = Randomized controlled trials
RR = Relative risk

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