

Delaying adverse health consequences of aging: the role of omega 3 fatty acids on inflammation and resoleomics

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ABSTRACT

Successful aging may be defined as the separation of the natural aging process from the development of chronic diseases in later life. There is strong indication that reduction of inflammation is a hallmark of successful aging. There are suggestions from the literature that high-dose fish oil may be a useful dietary intervention in the reduction of inflammation. This review will summarize that data. The primary problem for its widespread utilization may not be the safety of high-dose fish oil, but increasing the production of finished products for a global population.

BACKGROUND

A great percentage of current health care expenses arise from treating chronic diseases that occur late in life. Delaying those health consequences of aging should represent a more cost-effective approach to future health care than trying to treat existing chronic disease after it develops.

Although aging is inevitable, the development of chronic disease is not¹. Equally, importantly is that premature mortality is related to the number of chronic diseases that a person has by age 65. More than 70% of individuals in the United States² have at least two chronic conditions by the time they reach age 65. The more chronic diseases you have, the more likely your premature mortality.

There is a growing understanding that most chronic diseases are related to increased inflammation. In particular, the most rapidly growing chronic conditions are metabolic diseases (such as diabetes) and neurological diseases (such as Alzheimer's). Furthermore, Alzheimer's disease has

a strong linkage to increased insulin resistance³, which itself is ultimately caused by increased inflammation^{4,5}.

Rather than spending massive research dollars on "moonshots" to reverse these chronic conditions, it may be more fruitful to investigate those populations those have successful aging and applying that knowledge to delay the time before such chronic disease conditions appear⁶.

Populations that have demonstrated successful agers should have a combination of both longer lifespans and, more importantly, greater health spans defined as longevity minus years of disability. From such populations, it may be possible to obtain molecular insights as to how to reduce inflammation during the aging process. Centenarians with reliable birth and health records would represent such a population. Furthermore, genetic surveys indicate that hormonal and metabolic systems of centenarians are similar to younger populations in terms of inflammatory and nutrient-sensing pathways^{7,8}.

Studying the extensive population of Japanese centenarians (age 100-105) and super centenarians (ages 105 years and greater) indicate that suppression of inflammatory markers of the innate immune system appears to correlate best with not only increased survival, but also improved physical and cognitive health⁹. These results are in line with animal models that indicate chronic activation of the innate immune system is sufficient to accelerate the aging rate and premature mortality¹⁰. This suggests that increased pro-inflammatory markers may be a primary driver of the aging process¹¹.

WHAT IS INFLAMMATION?

To understand how inflammation can be reduced, one needs to go deeper into the innate immune system. Although primitive, the innate immune inflammatory response has two distinct complex

phases. These are the initiation and resolution of the inflammatory response. Each is an active process, yet each phase interacts with each other.

The initiation of inflammation comes from the activation of the gene transcription factor nuclear factor kappa-B (NF- κ B). Once NF- κ B is activated, it moves to the DNA to cause the specific transcription of pro-inflammatory enzymes such as COX-2 that facilitate the formation of pro-inflammatory eicosanoids derived from arachidonic acid (AA). In addition, NF- κ B also induces the generation of pro-inflammatory cytokines such as IL-1, IL-6, and TNF. It is the combination of the pro-inflammatory eicosanoids and pro-inflammatory cytokines that drive the initiation of the inflammatory response.

This type of low-level cellular inflammation sets in motion a cascade of events leading to the accumulation of neutrophils into the target area of inflammation. These neutrophils have a wide variety of mechanisms that give rise to significant collateral cellular damage in the process of destroying microbial invaders or trying to repair cellular damage caused by physical injury.

However, this initial inflammatory response does not simply burn out like a burning log. It will continue unless there is a corresponding resolution response to stop the migration of neutrophils into the target area, enhance the clearance of cellular debris, and initiate the regeneration of the damaged tissue¹².

This resolution process is mediated by a unique group of hormones known as resolvins¹³. Resolvins are derived from long-chain omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Without adequate levels of EPA and DHA in the blood or in the target tissue, the resolution of inflammation is attenuated. This lack of sufficient resolution leads to long-term tissue damage that is often characterized by fibrosis.

From a pro-longevity viewpoint, the resolution of inflammation extends the functional life of the organism. This is because resolvins accelerate the regeneration process of new tissue formation. At the molecular level, pro-resolution may be the foundation for an improved health span for any organism. Thus the use of the term “pro-resolution medicine” is a more scientifically justifiable terminology as opposed to “anti-aging medicine”.

To optimize the reduction of the overall inflammatory response, one requires better clinical markers of both the upstream and downstream markers

of the inflammatory process. Traditional downstream markers of the intensity of the initiation of inflammation have included the measurement of pro-inflammatory cytokines. However, these cytokines have a relatively short half-life and are rarely found in high concentrations in the blood. Therefore, measurement of C-reactive protein (CRP) is often used as a surrogate marker because it has a longer lifetime in the blood than pro-inflammatory cytokines. CRP is formed in the liver as a consequence of increased IL-6 levels. On the other hand, downstream markers of resolution (i.e. resolvins) are incredibly difficult to study because they work at exceptionally low levels and self-destruct quickly upon synthesis.

From a pro-longevity standpoint, however, the development of upstream markers indicating the current balance of initiation and resolution precursors of inflammation may be more useful as these markers can be optimized to maintain them in appropriate ranges consistent with the resolution of inflammation. One of the most widely used upstream markers of the balance of initiation and resolution of inflammation is the AA/EPA ratio in the blood^{14,15}. Since the levels of DHA are always greater than EPA because of metabolism, the level of EPA in the blood becomes a good surrogate marker of both EPA and DHA levels¹⁶. This is important from a methodological standpoint, as the measurement of the summation of EPA and DHA and then its comparison to AA is highly instrument-dependent whereas the AA/EPA ratio is not nearly as much. Furthermore, since AA and EPA share a strong spatial similarity in three dimensions unlike DHA, they both compete for the same COX-2 enzymes that are generated by activation of NF- κ B. Thus the AA/EPA ratio also provides a marker for the attenuation of the initial phase of initiation as well as the acceleration of the resolution phase.

The AA/EPA ratio in the Japanese population^{17,18} is approximately 1.5 to 3. This can be compared to the average American¹⁹ whose AA/EPA ratio is 18. The importance of the AA/EPA ratio in correlating with mortality from heart disease can be shown in Table 1 using worldwide data to show levels of omega-3 fatty acids and cardiovascular mortality¹⁸.

Several items are apparent from Table 1. First, there was very little difference in lipid levels of the two cohorts, although a far greater percentage of the Japanese were smokers. Therefore these lipid

Table 1. Comparison of CHD parameters in Japanese and Americans relative to national cardiovascular mortality rates.

CHD Parameter	Japanese	Americans
Total Cholesterol (mg/dl)	218	213
LDL Cholesterol (mg/dl)	132	135
Smokers	49%	8%
AA/EPA ratio	2.6	11
CHD Mortality (per 100,000)	46.2	160

and lifestyle factors cannot explain the greater than 70% reduction in CHD mortality between the two countries. However, the greater than 75% reduction of the AA/EPA ratio in the Japanese compared to the Americans correlates well with the differences in the CHD mortality differences between the two countries. It should be noted that CHD mortality remains the number one cause of death in the United States.

Perhaps the Japanese are simply genetically protected against heart disease? That possibility was dismissed with one of the largest cardiovascular trials ever done, the JELIS study¹⁷. This particular trial had 18,000 Japanese patients all taking statins. In essence, statins were the placebo. Half these subjects took a large daily dose of EPA (1.8 grams per day), and the other half an equivalent amount of olive oil. The average AA/EPA ratio of both groups at the start of the study was 1.6. At the end of 3 1/2 years the Japanese taking both statins and extra EPA had decreased their AA/EPA ratio to 0.8 and had 20% fewer cardiovascular events than the Japanese taking statins and olive oil and whose AA/EPA ratio remained constant at 1.6. This would suggest that a further lowering of the AA/EPA ratio results in even greater cardiovascular protection in the Japanese.

Another indicator that lowering the AA/EPA ratio has substantial health benefits comes from animal studies using the genetically engineered fat-1 mice. This animal model has been genetically modified to convert omega-6 fatty acids into omega-3 fatty acids so that the AA/EPA ratio in these animals is approximately 1. These genetically modified animals appear to be significantly resistant to developing chronic diseases associated with inflammation, such as insulin resistance, diabetes, inflammatory injuries, and Alzheimer's²⁰⁻²⁵.

Therefore the question becomes how much EPA and DHA fatty acids does one require to increase

the resolution of inflammation? A wide variety of animal studies has indicated that a dose of 100-200 mg EPA and DHA/kg body weight per day will have significant anti-inflammatory benefits. This would translate to 7 to 14 grams of EPA and DHA per day for 70 kg person. Although such levels of 7 to 14 grams per day might seem excessive, they are similar to the estimated intake by Paleolithic individuals 15,000 years ago²⁶. It is also known from dose response studies in women with a high risk of breast cancer, that 7.5 grams of EPA and DHA per day for six months had no adverse effects²⁷. At the highest dose of EPA and DHA used in that study (7.5 grams per day), the AA/EPA ratio was only reduced to 1.2.

It was demonstrated more than 25 years ago, that daily consumption of 5 grams of EPA and DHA in healthy subjects would reduce their AA/EPA ratio from 23 to 2.5 in six weeks time²⁸. In addition, the levels of TNF, IL-1, and IL-6 were also significantly reduced in these subjects. It should be pointed out these are the same inflammatory cytokines whose reduction was related to successful aging in the Japanese centenarians⁹. However, once the supplementation stopped, both the AA/EPA ratio and the levels of pro-inflammatory cytokines returned to their original levels within 20 weeks. Other studies have demonstrated that providing 2.5 grams of EPA and DHA per day to patients with a variety chronic diseases and all having AA/EPA ratios greater than 15, that the AA/EPA ratio was reduced to less than 3 within a few weeks²⁹.

IS THE AMOUNT OF EPA AND DHA IN THE WORLD TODAY SUFFICIENT?

It is suggested that the successful reduction of inflammation in the Japanese may be a consequence of their high intake of EPA and DHA per day. This is reinforced by the fact that the Okinawans have an even greater number of centenarians per 100,000 population compared to the mainland of Japan³⁰. This is also reflected in that their AA/EPA ratio is even lower than mainland Japanese³⁰. The average daily intake of EPA and DHA in Japan is estimated to be 1.3 grams per day³¹. This can be compared to the average North American intake of only 125 mg of EPA and DHA per day³². Therefore, increasing the consumption of EPA and DHA may have the potential to significantly improve the quality of life for an aging population.

However, does there exist enough EPA and

DHA in the world for widespread supplementation? A recent publication indicated that consumption of the total worldwide marine stocks of fish oil would only be enough for 6% of the world's population to reach the same levels of EPA and DHA as found in the Japanese population¹⁶.

The reduction of inflammation to increase longevity using all available fish oil may be a difficult task. Alternative approaches might include the use of plant-based sources (such as flax, purslane, chia, etc.). However, this is unlikely since the omega-3 fatty acids in those plant sources consist of alpha linolenic acid (ALA), which is slowly and inefficiently (1-5% conversion rate) transformed into EPA and DHA. Algae sources are possible since fish oil ultimately comes from the accumulation of plankton by the fish. However, this requires considerable expense in terms of developing algae mutants rich in both EPA and DHA as well the increased cost of production and purification compared to the current refining of crude fish oil. Transgenic plant sources rich in EPA and DHA are still experimental³³. One feasible dietary alternative is a drastic reduction of the intake of omega-6 fatty acids as they compete for the same enzymes required to convert ALA into EPA and DHA in addition to being the molecular building blocks for pro-inflammatory eicosanoids. Their reduction in the diet to less than 2% of total calories increases the production of EPA and DHA from ALA³⁴. However, vegetable oils rich in omega-6 fatty acids are now the least expensive source of calories on the planet. Currently, omega-6 fatty acids represent about 8% of the total calories of the American diet. Therefore from an economic standpoint this dietary alternative is also unlikely to be employed.

SUMMARY

It is clear that the economic benefits of delaying chronic disease are more favorable than treating it after it has developed. There is also strong evidence that increased inflammation (or the corresponding lack of resolution) is the primary driver for inflammatory diseases especially those driving the increase in metabolic (i.e. diabetes) or neurological (i.e. Alzheimer's) conditions that are the fastest growing chronic diseases on a worldwide basis. Furthermore, both diabetes and Alzheimer's are strongly related to increased insulin resistance³. In addition, there is a suggestion from animal models that the neuroinflammation associated with

Alzheimer's may be a consequence of the lack of resolution³⁵. However, any increase in intensity of the resolution phase of inflammation will require increased levels in EPA and DHA in the diet to provide the necessary substrates for the increased production of resolvins.

There are numerous anti-inflammatory drugs that can reduce the initiation of inflammation. However, those same drugs also inhibit the resolution phase of inflammation³⁶. Ironically, standard anti-inflammatory drugs also function as anti-resolution drugs. This may explain why anti-inflammatory drugs have significant side effects upon long-term usage.

Reducing insulin is another potential pathway to explore. The primary drug used to treat insulin resistance is metformin. In animal studies, the chronic use of low-dose metformin generated a longer life³⁷. Unfortunately, higher doses of chronic metformin supplementation were found to be toxic³⁷. Nonetheless, a long-term clinical trial using metformin to retard aging is planned. However, it is also known that insulin resistance is strongly associated with increased levels of TNF³⁸. It was shown more than 25 years ago²⁸ that high-dose fish oil could significantly reduce the levels of TNF and the levels used in that study have not been shown to have any adverse effects.

Finally, there is the question of telomeres. It is known that the shortening of the length of telomeres is strongly associated with the aging process. In addition, it has been demonstrated by Elizabeth Blackburn³⁹ (one of the winners of the Nobel Prize winner in 2009 for her discoveries of the importance of telomeres) that a good diet, increased exercise, and stress reduction can increase the length of telomeres. However, the Japanese centenarian study⁹ indicated that telomere length was not associated with successful aging as compared to the reduction of inflammatory markers. It is of note that there is the suggestion that telomere length can be increased in dose-dependent fashion using fish oil. The highest dose used in that study was 2.5 grams of EPA and DHA per day⁴⁰.

CONCLUSIONS

The use high-dose fish oil is a dietary intervention that currently exists that may increase the likelihood of successful aging. The scientific evidence of high-dose fish oil to reduce the levels of inflammatory cytokines and pro-inflammatory eicosanoids

is robust. High-dose fish oil is also fundamental to increase the generation of resolvins necessary to drive the resolution phase of inflammation. The ability of the high-dose fish oil to decrease insulin resistance by decreasing TNF is strongly suggested from the literature. Finally, there is suggestive data that high-dose fish oil can increase telomere length. The primary problem for its widespread utilization is not the safety of high-dose fish oil, but increasing the production of finished materials for a global population to have a greater opportunity to achieve natural aging with the least amount of accompanying chronic disease. This may also be a good definition of successful aging.

FINANCIAL DISCLOSURES

Dr. Sears is also the President of Zone Labs, a medical food company.

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