Anti-Inflammatory Medicine: Dietary Modulation of Eicosanoids
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1.0 Defining Anti-Inflammatory Medicine

For the past 70 years, medicine has done an excellent job treating acute infectious disease because this type of disease can often be traced to a single cause, such as bacteria, a virus, etc. However, the major problem confronting 21st-century medicine is the treatment of chronic disease. Since chronic disease is multi-factorial in nature, current medical practice tends to treat the symptoms, not the underlying cause. Treating only the symptoms is essentially micro-managing a chronic disease. Instead, the focus of health care should be on macro-managing wellness, which can be accomplished by achieving a single, broad physiological goal:

Decreasing inflammation

The most efficient way of decreasing inflammation is the modulation of a group of hormones known as eicosanoids. Decreasing inflammation requires the increased production of “good” anti-inflammatory eicosanoids, while simultaneously decreasing the production of pro-inflammatory “bad” eicosanoids. This is because “good” eicosanoids are powerful anti-inflammatory agents, whereas “bad” eicosanoids are powerful pro-inflammatory agents (1-4). There are many drugs (aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, and corticosteroids) that can reduce the levels of “bad” eicosanoids, but they unfortunately also reduce the levels of the “good” eicosanoids. This is why the more powerful the eicosanoid-suppressing drug (such as a corticosteroid), the greater the side effects, especially with long-term chronic use.

Often overlooked by modern medicine is that diet is also a potentially powerful modulator of eicosanoid synthesis since all eicosanoids must ultimately be derived from the dietary intake of essential fatty acids (1-4). The most effective long-term way to induce the body to make more “good” eicosanoids and fewer “bad” eicosanoids is by following an anti-inflammatory diet. This is the foundation of anti-inflammatory medicine.

Such an anti-inflammatory diet should concern the appropriate balance of essential fatty acid precursors required to produce eicosanoids coupled with consistent insulin control (1-4).

The modulation of eicosanoids using an anti-inflammatory diet enables patients to begin to macro-manage their wellness instead of the chronic use of drugs to micro-manage disease symptoms. It should be emphasized that an anti-inflammatory diet is not meant to replace drugs. Its goal is to make drugs work better at lower concentrations, hence fewer side effects. However, to do so effectively, patients need to treat the diet with the same respect that they would for any prescription drug. This means taking food at the right dose and at the right time. Finally, there should be clinical markers that can be monitored by the physician that determine the patient’s success in modulating their inflammatory status.

2.0 What is Inflammation?

Understanding inflammation still remains one of the most complex areas in medicine. Too little of an inflammatory response, and the body is unable to repel microbial invasions or heal injuries. Too much of an inflammatory response, and the immune system begins attacking the body’s own organs eventually leading to chronic disease.

2.1 Types of inflammation

There are two types of inflammation. The first is classical inflammation which is associated with pain. This is why a patient goes to a physician. The pain itself is not the disease, but it is the damage caused by the chronic disease that generates constant pain signals. A far moreidious type of inflammation is silent inflammation. Silent inflammation is below the perception of pain. As a consequence, the patient does nothing to stop this type of inflammation. But after years, if not decades, of silent inflammation there is enough accumulated organ damage that pain associated with classical inflammation finally manifests. It should be pointed out that silent inflammation is not a disease any more than free radicals are. However, its presence signifies an increased inflammatory potential at the cellular level that indicates the patient is no longer well.

2.2 Mediators of inflammation

Both types of inflammation (classical and silent) are ultimately mediated by eicosanoids. This hormonal system is intricately balanced to consist of both pro-inflammatory eicosanoids that drive the inflammatory process, as well as equally powerful anti-inflammatory eicosanoids that reverse the inflammatory process. When operating at peak efficiency, the checks and balances of these eicosanoids can turn the inflammatory process on and off with remarkable precision. But if the levels of pro-inflammatory eicosanoids increase too much, or of anti-inflammatory eicosanoids are reduced too much, then the inflammatory response will be indefinitely turned on at a low level resulting in constant inflammatory attack at the cellular level that remains below the perception of pain. This is the definition of silent inflammation.

The mode of action of virtually all anti-inflammatory drugs is to reduce the levels of pro-inflammatory eicosanoids. Although there are no drugs that can increase the levels of anti-inflammatory eicosanoids, this can be accomplished by an anti-inflammatory diet rich in omega-3 fatty acids.

2.3 Clinical markers of inflammation

Although reduction of inflammation has been the key focus of medicine, there are surprisingly few clinical markers to quantify its intensity. The most obvious non-invasive marker is pain. Most commonly a marker of pro-inflammatory eicosanoids. Blood markers of classical inflammation are also relatively crude. These include increased white cell counts, exceptionally high levels of C-reactive protein (CRP), and increased red cell sedimentation rates. Recently very low levels of CRP have been advanced as a marker of inflammation (5-8), but because of its rapid increase with acute infection, the use of this marker as an indicator of chronic low-level inflammation remains controversial (9).

Silent inflammation, on the other hand, can be considered the precursor to classical inflammation and is best measured...
Another marker of wellness is fasting insulin, which is a marker of insulin resistance. It is known that fasting insulin levels greater than 10 uU/ml have far greater predictive value for the development of heart disease than elevated levels of LDL cholesterol (15,16).

The final marker of wellness is the TG/HDL ratio. This is a marker of metabolic syndrome that precedes type 2 diabetes by some 8-10 years. The TG/HDL ratio also indicates the relative size of the LDL particles (17-20). A low ratio is indicative of primarily large, non-atherogenic LDL particles, whereas a high TG/HDL ratio indicates a larger population of small, dense pro-atherogenic LDL particles. Prospective studies indicate that a low TG/HDL ratio is highly correlated with a reduction in the development of cardiovascular disease (20).

Elevated levels in these clinical markers are not an indication that chronic disease exists yet, however, it does indicate that the inflammatory potential of the patient has significantly increased. This means the potential of increased inflammation at the cellular level has also been significantly increased. Although the patient not yet ill enough to be considered to have a chronic disease, the patient can no longer be considered to be well.

The therapeutic goal of anti-inflammatory medicine is to move the patient back toward a state of wellness. That can only be achieved by decreasing the levels of silent inflammation that can be determined by the clinical markers of wellness.

### 3.0 Dietary influences on eicosanoids

A pro-inflammatory diet will increase silent inflammation, whereas an anti-inflammatory diet will decrease it. Understanding how diet can influence inflammation requires keeping back in evolutionary time when the immune system, nutrient storage, and diet were inextricably coupled.

Eicosanoids are hormones that are derived from long-chain fatty acids. Each fatty acid has a specific position on the body and their role is determined by the type of fatty acid. For example, pro-inflammatory eicosanoids, whereas those derived from DGLA are anti-inflammatory eicosanoids.

Eicosanoids are classified as either omega-6 or omega-3 fatty acid. For example, arachidonic acid (AA) and dihomo gamma linolenic acid (DGLA), and the other omega-3 fatty acid eicosapentaenoic acid (EPA), which is the building block of pro-inflammatory eicosanoids, and the other omega-6 fatty acid eicosanoids are classified as either omega-6 or omega-3 fatty acid.

Eicosanoids are hormones that are derived from long-chain fatty acids. As the first hormones, they not only allowed biological actions generated by different eicosanoids. The positioning of the double bonds determines the three-dimensional structure in space and thus the stereochemistry of the eicosanoids derived from them. The eight essential fatty acids are classified as either omega-6 or omega-3 fatty acid. As the first hormones, they not only allowed biological actions generated by different eicosanoids.

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Eicosanoids include a broad number of subgroups, including the following:

- Prostaglandins
- Thromboxanes
- Leukotrienes
- Hydroxylated essential fatty acids
- Endocannabinoids
- Lipoxins
- Resolvins

### Table 1. Clinical Markers of Wellness

<table>
<thead>
<tr>
<th>Test</th>
<th>Chronic disease is developing</th>
<th>Poor: Head on a path to chronic disease</th>
<th>Good: Head on the path to wellness</th>
<th>Ideal: State of wellness</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA/EPA ratio</td>
<td>15 or greater</td>
<td>10</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Fasting Insulin (uU/ml)</td>
<td>15 or greater</td>
<td>13</td>
<td>10</td>
<td>Less than 5</td>
</tr>
<tr>
<td>Triglycerides/HDL</td>
<td>4 or greater</td>
<td>3</td>
<td>2</td>
<td>Less than 1</td>
</tr>
</tbody>
</table>

### 3.3 Essential fatty acids and eicosanoids

Essential fatty acids are fats that the body cannot synthesize, and therefore must be part of the diet. Essential fatty acids are classified as either omega-6 or omega-3 depending on the position of the double bonds in the fatty acid molecule.

The positioning of the double bonds determines the three-dimensional structure in space and thus the stereochemistry of the eicosanoids derived from them. Of the eight essential fatty acids, only three can be synthesized into eicosanoids. Two of these are the omega-6 essential fatty acids, arachidonic acid (AA) and linoleic acid (DGLA), and the other essential fatty acid is eicosapentaenoic acid (EPA), which is an omega-3 fatty acid.

Eicosanoids derived from AA are generally powerful pro-inflammatory eicosanoids, whereas those derived from DGLA are powerful anti-inflammatory eicosanoids.
from EPA are virtually neutral in their inflammatory actions. EPA can play an important role in modulating the balance of DGLA and AA, and thus the balance of pro- and anti-inflammatory eicosanoids derived from them. The key step in this metabolism of eicosanoid precursors is ultimately controlled by one particular enzyme (delta-5 desaturase), which converts DGLA into AA; the precursor of the “bad” eicosanoids. The activity of this enzyme is profoundly affected by two dietary components: (a) the levels of insulin and (b) the levels of EPA. Both can be altered by the diet. Insulin activates the delta-5 desaturase enzyme to convert DGLA into AA (23,24), whereas EPA inhibits the same enzyme thus decreasing the levels of AA and in the process increasing DGLA (1-4, 25,26). The end result is an increase in DGLA levels and a decrease in AA levels leading to a balance of “good” to “bad” eicosanoids. This is shown in Figure 1.

Figure 1. Dietary Influences on the Metabolism of Omega-6 Fatty Acids.

Linoleic Acid

**Delta 6 Desaturase**
Inhibited by Trans Fatty Acids and DHA

**Lignan**
Dihydro gamma linolenic acid (DGLA)

**Delta 5 Desaturase**
Inhibited by Cholesterol, EPA
Activated by insulin

Arachidonic Acid (AA)

**“Good” eicosanoids**

**“Bad” eicosanoids**

There is no drug that can alter the balance of DGLA to AA, but appropriate dietary intervention with an anti-inflammatory diet can do so very effectively.

**3.4 Drugs that alter eicosanoids**

Although many physicians may not be familiar with eicosanoids, the pharmaceutical industry is, as most of the standard anti-inflammatory drugs used today alter eicosanoid levels. These drugs have a common mode of action; they inhibit enzymes that synthesizes pro-inflammatory eicosanoids. However, they have a very limited potential to alter the balance of “good” and “bad” eicosanoids because they also inhibit the formation of “good” eicosanoids. All drugs attempt to reduce the production of pro-inflammatory eicosanoids by going “downstream” to hopefully inhibit a specific enzyme instrumental in synthesizing eicosanoids. For example, the promise of COX-2 inhibitors was significantly reduced because these drugs inhibited the formation of “good” eicosanoids as well as the “bad” eicosanoids.

A far more promising approach for eicosanoid modulation is to go “upstream” to modify the balance of the essential fatty acid precursors of eicosanoids at each meal (1-4, 27) with the primary balance of the essential fatty acid precursors thus enabling the manipulation of “good” and “bad” eicosanoids with elegance and precision. This can only be achieved by an anti-inflammatory diet.

**4.0 What is the Zone?**

In 1997, Dr. Craig Head created the concept of maintaining drugs within a therapeutic zone is well known to physicians. Below that therapeutic zone, the drug is ineffective, and above that therapeutic zone, the drug is toxic. The same concept can be applied to the hormones generated by the food you eat. There are two hormonal systems that are controlled by the diet. These are eicosanoids and insulin (1-4). The balance of the dietary intake of essential fatty acids is a primary factor for eicosanoid synthesis, and the balance of protein-to-carbohydrate at every meal that controls insulin secretion. Moreover, there is a great deal of interaction between these two hormone systems.

Maintaining these two hormone systems within a therapeutic zone is possible through the consistent application of an anti-inflammatory diet that is described below.

**4.1 What is an anti-inflammatory diet?**

The simple definition of an anti-inflammatory diet is that prevents the excess production of AA thereby reducing the inflammatory substrate for the generation of eicosanoids. To achieve that goal, an anti-inflammatory diet is based upon consistent insulin control coupled with supplementation with high doses of fish oil rich in EPA in order to further modulate the synthesis of AA as described earlier (1-4).

Insulin control is achieved by balancing the protein-to-carbohydrate ratio at each meal close to the primary source of dietary fat coming from non-inflammatory monounsaturated fats. This component of an anti-inflammatory diet can be described as a moderate-carbohydrate, moderate protein, and moderate-fat diet that has approximately one gram of fat for every two grams of protein and three grams of carbohydrates. There are several important functions of insulin that aid in reducing the overall inflammatory load of a patient. These include the inhibition of toll-like receptors (such as TLR-4) that are activated by saturated fatty acids as well as inhibiting the activation of nuclear factor kappaB that is the transcription element that causes the expression of various pro-inflammatory proteins, such as the COX-2 enzymes and inflammatory cytokines (31-33). Omega-3 fatty acids can also activate other genetic transcription elements (PPAR alpha and PPAR gamma) that are important in controlling lipid metabolism and insulin sensitivity (34-36). In addition, omega-3 fatty acids can inhibit calcium channels thereby decreasing the influx of calcium into a cell that can also activate an inflammatory response (37). Finally these same omega-3 fatty acids can alter membrane fluidity enhancing the binding of hormones to their receptors.

With such a wide variety of biological actions, it is not surprising that clinical studies have indicated significant benefits can be achieved when this diet is implemented with adequate levels of these omega-3 fatty acids.

**6.0 Eicosanoids and Heart Disease**

Heart disease remains the number-one killer of Americans. The primary drug used for primary and secondary prevention of heart disease is still aspirin, even though it has no effect on cholesterol levels. Aspirin, however, does have a significant impact on eicosanoids by decreasing the production of those eicosanoids that promote inflammation, vasoconstriction, and platelet aggregation (39).

The role of cholesterol as a factor in the development of heart disease is constantly changing. At first, patients were told that only bad to worry about their total cholesterol levels. However, further research found that wasn’t such a strong predictor of future heart disease. Next came the realization that is both “good” and “bad” cholesterol. The “good” cholesterol is found in the high-density lipoprotein (HDL) particles, and the “bad” cholesterol is in the low-density lipoprotein (LDL) particles. This launched a war against “bad” cholesterol.

In more recent years, researchers have found that there are two types of LDL particles. One type consists of large, fluffy LDL particles that appear not to promote atherosclerosis or the development of plaques on the arteries. The other type consists of small dense LDL particles that are strongly associated with an increased the risk of heart disease. It appears that the balance of good “bad” cholesterol (large fluffy LDL particles) and bad “bad” cholesterol (small dense LDL) may be a determining factor in the development of heart disease. Prospective studies strongly indicate the more bad “bad” cholesterol you have, the more you are to have a heart attack while having a high level of the good “bad” cholesterol isn’t likely to have any adverse health effects (20,40).

How can you tell which type of LDL particle your patient has? All you have to do is determine the triglycerides to HDL cholesterol ratio. If the TG/HDL ratio is less than 2, the patient will have predominantly large fluffy LDL particles that are not going to cause much harm. If the ratio is greater than 4, the patient will have primarily small dense LDL particles that can accelerate the development of plaques on the arteries. None of their total cholesterol levels (41, 42). The connection between the TG/HDL ratio and heart disease was confirmed by studies from Harvard Medical School (43). This research found that the higher your TG/HDL ratio the more likely you would have a heart attack. How much more likely? In that study, those with the highest TG/HDL ratios had 16 times greater risk compared to those with the lowest ratio.

The importance of the TG/HDL ratio can be seen from the recently published results of the on-going Copenhagen Male Study that studied the effect this ratio has on the long-term development of heart disease (28). Researchers tracked healthy

7
patients who had either a low TG/HDL ratio (less than 1.7) or a high TG/HDL ratio (greater than 6). Patients with the low TG/HDL ratio who smoked, didn’t exercise, had hypertension and elevated levels of LDL cholesterol, had a much lower risk of developing heart disease than those who had a far better lifestyle and metabolic profile, but a higher TG/HDL ratio. This indicates that lowering the TG/HDL ratio has a far greater impact on whether the patient develops heart disease than by improving lifestyle factors or reducing hypertension and total LDL levels. The TG/HDL ratio is an indirect marker of both the patient’s dietary insulin control and fish oil consumption. The definitive proof of fish oil benefits was demonstrated in the GISSI trial in which heart disease patients who supplemented their diets with 0.9 grams of EPA and DHA per day for a four-year period had a 45-percent reduction in their risk of having a sudden fatal heart attack or sudden death than those in their risk of cardiovascular mortality, and a 10-percent reduction in overall mortality compared to either a placebo or Vitamin E (14). These results are equal, if not superior, to the results of statin therapy in secondary prevention trials.

Results of the GISSI Study

Overall mortality -10%
Cardiovascular mortality -20%
Sudden death -45%

Another powerful statement on the role of anti-inflammatory diet in prevention of heart disease comes from the Lyon Diet Heart Study (45, 46). In this study, heart attack survivors were split into two groups with one group put on a diet that followed the traditional Heart Association recommendations and the second group put on a diet similar to the previously described anti-inflammatory diet (rich in fruits, vegetables, and fish but containing very low amounts of omega-6 fatty acids). Although, both groups had the same cholesterol levels and same triglycerides at the end of four years, there was, a more than 70 percent reduction in both fatal and non-fatal heart attack in anti-inflammatory diet group compared to the control diet group. More important, the group following the anti-inflammatory diet experienced no sudden deaths (a primary cause of cardiovascular mortality) during the four years of the study. The only clinical difference between the two groups was that the Heart Association diet group lost weight, whereas the group on an anti-inflammatory diet maintained their weight. These results correlate with those from other clinical studies. A 0 percent reduction in their risk of sudden death (a primary cause of cardiovascular mortality) during the four years of the study. The only clinical difference between the two groups was that the Heart Association diet group lost weight, whereas the group on an anti-inflammatory diet maintained their weight. These results correlate with those from other clinical studies.

7.0 Eicosanoids and Neurological Disease

There is growing body of research that indicates high levels of omega-3 fatty acids can have significant benefits in the treatment of a variety of neurological disorders. It has been demonstrated that depression (48, 49) can be reduced with high-dose fish oil supplementation, as well as the disability caused by multiple sclerosis (50). For example, a decrease in the AA/EPA ratio from 6 to 1.5 in multiple sclerosis patients was associated with a 90-percent reduction in acute attacks and a 25-percent reduction in annual exacerbations after two years (50). Other studies have indicated that an elevated AA/EPA ratio is strongly associated with the severity of depression (51, 52). Recent studies have showed that children with ADHD who had high AA/EPA ratios, and when those AA/EPA ratios are lowered to the level found in the Japanese population, then significant behavioral improvements were observed (53).

8.0 Eicosanoids and Cancer

There is growing realization that cancer has a very strong inflammatory component. Therefore, it is likely that high-dose omega-3 fatty acids (EPA and DHA) could have a significant benefit for cancer patients. Published data indicates that cachexia can be reduced by high-dose fish oil (54). Furthermore, it is known that aspirin and non-steroidal anti-inflammatory drugs reduce the risk of a variety of cancers (55-57). This may be due to the fact that metatarsis are highly correlated with the over-production of a certain group "bad" eicosanoids consisting of hydroxylated essential fatty acids derived from AA (58).

9.0 Eicosanoids and Inflammatory Conditions

The primary drugs used for treating inflammatory conditions remain those that reduce the levels of pro-inflammatory eicosanoids. Clinical studies have indicated that rheumatoid arthritis (59), Crohn’s disease (60), inflammatory bowel disease (61), IgA nephropathy (62), and filariomyalgia (63) all respond positively to high-dose fish oil. This is probably due not only to the reduced production of pro-inflammatory eicosanoids, but also to the reduction in the secretion of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-6).

10.0 Eicosanoids and Obesity

The association of obesity with type 2 diabetes and cardiovascular heart disease is a consequence of the ability of the adipose tissue to be a significant site of inflammation (65-67), and this inflammation has been shown to be reduced by dietary omega-3 fatty acids (68) in animal studies. It has been demonstrated at Harvard Medical School using iso-caloic diets that the ratio of protein to carbohydrate found in an anti-inflammatory diet gave superior reductions of elevated markers of inflammation and also contributed to the weight loss based on the USDA Food Pyramid (29). Likewise it has been shown that an anti-inflammatory diet generates reduction in silent inflammation, whereas an iso-caloric Atkins diet significantly increases silent inflammation (30).

However, the only way to lose excess body fat permanently is to decrease caloric intake. This means reducing hunger. Recent research has demonstrated that another eicosanoid system operating in the brain may be responsible for the increased appetite that leads to obesity. AA-derived hormones known as endocannabinoids are powerful stimulators of hunger (69). It has been shown that an experimental drug that blocks the binding of endocannabinoids to their receptors may represent a preferred method of improving outcomes in obesity and the neurological side effects of these drugs have stopped their application in human. However, it has been shown in animal studies that fish oil can reduce endocannabinoid levels in the brain (71, 72).

11.0 Eicosanoids and Type 2 Diabetes

Currently an estimated 16 million people are affected with type 2 diabetes. This devastating disease a patient at a 2 to 4 times greater risk of dying from heart disease and also increases the likelihood of kidney failure, blindness, impotence, amputation, and neuropathy (73). Obviously a key to treating type 2 diabetes is the reversal of insulin resistance. Numerous studies indicate that insulin resistance is strongly associated with increased inflammation (74-76). It has been shown that when following an anti-inflammatory diet, insulin resistance can be reversed in three days. Not surprising, the combination of statins and fish oil is virtually identical to the newest dietary recommendations from the Joslin Diabetes Research Center at Harvard Medical School for treating type 2 diabetes (28).

12.0 Dietary Strategies for Optimization of Eicosanoids

Not everyone is genetically the same. This is why the essential fatty acid component of an anti-inflammatory diet can be further optimized to meet the needs of the individual patient. The recent JELIS study has also confirmed the benefits in cardiovascular outcome by lowering the AA/EPA ratio (13). In this study, more than 18,000 Japanese patients were put on statin therapy for elevated half of those patients received 1.8 grams per day of EPA, and the other half a placebo consisting of olive oil. Those receiving the extra EPA had their AA/EPA ratio reduced by 20 percent. At the end of the study, those patients supplemented with EPA had a 20-percent reduction in total cardiovascular events compared to those who were on the placebo. Thus a 20-percent reduction in cardiovascular events correlated with a 50-percent decrease in the AA/EPA ratio, whereas those on the placebo had no reduction in their AA/EPA ratio during the course of the study.

The reason that EPA could have such a profound impact comes from the fact that the statins are the only drugs known to significantly reduce triglyceride levels. Statins are highly associated with increased inflammation and silent inflammation. This may be the reason why the combination of statins and high-dose fish oil rich in EPA may represent a preferred method of improving outcomes in cardiovascular patients as demonstrated by the JELIS study (13).

12.1 Levels of EPA and DHA required

The first line of optimization is determining the level of omega-3 supplementation required for the patient. The goal of anti-inflammatory medicine is reaching an AA/EPA ratio of approximately 1.5, which is similar to that found in the Japanese population. The higher the starting AA/EPA ratio in the patient group the greater the levels of EPA and DHA that are required to reach this clinical goal. The most precise clinical determination of the supplementation required would be analysis of the TG/EPA ratio at 1.5 has little to do with the age, weight, sex of the patient, but has more to do with the initial levels of silent inflammation and where that inflammation is located. Based on those results, a diet rich in a wide variety of healthy fats, here are some suggested guidelines:

<table>
<thead>
<tr>
<th>Condition</th>
<th>EPA and DHA Required (Grams/Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight, no chronic disease</td>
<td>2.5 g</td>
</tr>
<tr>
<td>Overweight, Type 2 Diabetes, Cardiovascular Disease</td>
<td>5</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>7.5</td>
</tr>
<tr>
<td>Neurological Conditions</td>
<td>10</td>
</tr>
</tbody>
</table>

These recommended levels of EPA and DHA supplementation are based upon the United States Department of Agriculture dietary intake as described earlier. If the patient’s diet is rich in high-glycemic carbohydrates (that stimulate insulin) or rich in omega-6 fatty acids, then the recommended levels of EPA and DHA for these two dietary factors may require even higher levels of EPA and DHA to reduce the AA/EPA ratio to the desired level of 1.5.

12.2 Fish Oil Purity

The amounts EPA and DHA required to reduce the AA/EPA ratio to 1.5 often requires significant amounts of fish oil. Thus the potency and purity of the fish oil used should be of the highest standards. The physician and the patient often have no way of knowing this information. Fortunately a free resource exists that solves this problem. The International Fish Oil Standards (www.ifosprogram.com) is an independent testing program that uses the most sensitive testing equipment program available to analyze commercial fish oil products. On its free Web site, the potency and purity of fish oil products are listed from a large number of companies. Because fish oil quantity can vary greater from lot to lot, it is suggested that a patient make sure that every lot of fish oil they use is listed on that site, not just one lot potentially several years ago.

12.3 Problems with Fish Oil

The first question the physician often asks is “can a patient take too much fish oil?” The answer is potentially yes because if the AA/EPA ratio is reduced too much, the patient may not be...
Inflammation Research Foundation

known as resolvins (79-81). Resolvins are derived from both an entirely new class of powerful anti-inflammatory eicosanoids demonstrate very low-dose aspirin (0-40 mg/day) can generate now greater than ever. This is due to recent discoveries that Aspirin remains the most widely used drug in the world inflammatory eicosanoid production.

medicine, the patient needs to decrease silent inflammation the AA/DGLA ratio as well as a decrease in silent inflammation increasing of DGLA production without the likelihood of the toasted sesame oil concentrate in a fish oil product allows the specific of these are polyphenols derived from toasted sesame oil. The toasting of the sesame seeds prior to extraction causes the AA/EPA ratio achieved by the subjects in the active group of the AA/EPA ratio. 1. Kagawa Y, Nishizawa M, Suzuki M, Miyatake T, Hamamoto H, Kita T, Kirakatake A, Nakaya N, Sakata T, Shimada K, and Shirato K. “Effects of eicosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): a randomised open-label, blinded endpoint analysis.” Lancet 369:1090-1098 (2007)

12.4 Aspirin

Aspirin remains the most widely used drug in the world today, yet its ability to impact anti-inflammatory medicine is now greater than ever. This is due to recent discoveries that demonstrate very low-dose aspirin (20-40 mg/day) can generate an entirely new class of powerful anti-inflammatory eicosanoids known as resolvins (79-81). Resolvins are derived from both EPA and DHA. At higher doses of aspirin, this effect on making these new anti-inflammatory eicosanoids is entirely abolished (82). Hence low-dose aspirin and high-dose fish oil can be combined to even further enhance the ultimate goals of anti-inflammatory medicine: A longer and better life.

12.3 Conclusions

The treatment of chronic disease depends upon modulating inflammation that is ultimately controlled by eicosanoids. Anti-inflammatory medicine is defined as the use of nutritional interventions to achieve a better balance of the precursors of anti-inflammatory to pro-inflammatory eicosanoids. The success of this strategy can be measured clinically by the decrease of both the AA/EPA ratio (the marker of silent inflammation) as well as the AA/DGLA ratio (the marker of anti-inflammation). Successful application of this dietary EPA are inhibitors of the enzyme (delta-6 desaturase), which is necessary to produce gamma linolenic acid (GLA), which is the immediate precursor of DGLA. As a result, the potential inflammation-modulating benefits of omega-3 supplementation can never be fully achieved with fish oils alone.

The seemingly simple solution to this problem (adding more GLA to fish oil) turns out not to be the solution. This is because added GLA is rapidly metabolized into DGLA (which is good), but this increased DGLA becomes a substrate for the delta-5 desaturase enzyme that converts it into excess AA. This is known as the “spillover effect” (1). Although the patient initially feels a significant improvement with additional GLA supplementation compared to fish oil alone, often times within a few months, the benefits will have eroded as the increased DGLA is being converted into increased AA. In certain cases, all the anti-inflammatory benefits of fish oil can be totally reversed.

The solution to this problem lies with addition of other natural inhibitors of the delta-5-desaturase enzyme. The most specific of these are polyphenols derived from toasted sesame oil. The toasting of the sesame seeds prior to extraction causes the breakdown of certain polyphenols to form sesamin, which is a powerful inhibitor of the delta-5 desaturase enzyme (78).

Combining low levels of GLA with the appropriate amount of toasted sesame oil concentrate in a fish oil product allows the increasing of DGLA production without the likelihood of the newly formed DGLA “spilling over” into increased AA. The success of this overall strategy can be measured by a decrease in the AA/DGLA ratio as well as a decrease in silent inflammation as measured by the decrease in the AA/EPA ratio.

Thus to obtain the full benefits of anti-inflammatory medicine, the patient needs to decrease silent inflammation while simultaneously increasing the capacity for increased anti-inflammatory eicosanoid production.

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Anti-Inflammatory Medicine: Dietary Modulation of Eicosanoids

"Let food be your medicine, and let medicine be your food." -Regan Books. New York, NY (2005)

References


Inflammation Research Foundation

Anti-Inflammatory Medicine: Dietary Modulation of Eicosanoids


Glossary

**Alpha Linolenic Acid (ALA)**

This is the 20-carbon length long-chain omega-6 fatty acid that is the immediate precursor of many eicosanoids that increase inflammation. Egg yolks, fatty red meat, and organ meats are rich sources of arachidonic acid.

**Anti-inflammatory medicine**

The use of nutritional interventions to increase anti-inflammatory eicosanoids while simultaneously decreasing the production of pro-inflammatory eicosanoids.

**Arachidonic Acid (AA)**

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**A/DGLA Ratio**

This is the marker of the balance of the precursors of pro-inflammatory to anti-inflammatory eicosanoids. The higher the AA/DGLA ratio, the less anti-inflammatory eicosanoids will be produced.

**AA/EPA Ratio**

The ratio is determined from levels of long-chain omega-6 and omega-3 fatty acids in the plasma phospholipids. The AA/EPA ratio provides a precise measurement of the balance of eicosanoid precursors in a patient. The higher the AA/EPA ratio, the greater the levels of silent inflammation.

**Dihomo Gamma Linolenic Acid (DGLA)**

This is the essential fatty acid precursor of arachidonic acid. The eicosanoids derived from DGLA have powerful anti-inflammatory properties, which are opposed to pro-inflammatory properties of eicosanoids derived from arachidonic acid (AA). Adequate inhibition of the delta-5 desaturase will increase the levels of DGLA relative to AA in individual cells.

**Docosahexaenoic Acid (DHA)**

This is the omega-3 fatty acid that critical for brain function. DHA is ultimately derived from EPA. DHA is found in high concentrations in neural tissues.

**Eicosapentaenoic Acid (EPA)**

This is the 20-carbon length long-chain omega-3 fatty acid that that inhibits the formation of arachidonic acid (AA). Fish oils are the richest source of EPA.

**Essential Fatty Acids**

These are fatty acids that the body can produce and must be part of the diet. There are two classes of essential fatty acids: omega-3 and omega-6. These differ by the positions of the double bonds within the fatty acids. This positioning determines their three-dimensional structure in space, and hence the type of eicosanoids that can be made from them.

**Gamma Linolenic Acid (GLA)**

This is the immediate metabolic product of linoleic acid. This fatty acid is found in certain foods (such as oatmeal), edible oils (such as borage oil) and also found in human breast milk. GLA is rapidly metabolized into DGLA and potentially into AA depending on the activity of the delta-5 desaturase enzyme.

**Insulin**

Insulin in secreted by the beta cells of the pancreas to lower blood sugar levels. The carbohydrate content of a meal primarily stimulates insulin secretion. It is essentially a storage hormone that drives macronutrients (carbohydrates, protein, and fat) into cells for immediate use or long-term storage. High levels of insulin activate the delta-5 desaturase enzyme thus increasing AA levels.

**Linoleic Acid**

This short-chain omega-6 fatty acid that can be converted into arachidonic acid by way of intermediates such as gamma linolenic acid (GLA) and dihomo gamma linolenic acid (DGLA). Linoleic acid is the most common dietary form of all essential fatty acids.

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A new class of anti-inflammatory eicosanoids derived from EPA and DHA that is induced by conformational changes in the cyclooxygenase (COX) enzyme induced by low dose aspirin.

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The Inflammation Research Foundation is a non-profit 501(c) corporation whose mission includes physician education on the potential of anti-inflammatory medicine and sponsoring of clinical trials using anti-inflammatory medicine in the treatment of a variety of chronic disease conditions.

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