Anti-Inflammatory Medicine: Dietary Modulation of Eicosanoids
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 balance 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 that 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 generating constant pain signal. A far more insidious 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 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 intrinsically 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. A closer look at the other observations of classical inflammation (fever, redness, and swelling) are all mediated by 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...
Defining Wellness

It's not enough to assume that if patients are not sick, then they must be well. There are really three distinct stages of chronic disease as shown below:

1. Sub-chronic disease
2. Chronic Disease
3. Wellness

The opposite of chronic disease is wellness. However as wellness erodes, the end result will eventually be chronic disease. The second stage of the disease process is the development of sub-chronic disease. With sub-chronic disease, both the physician and patients know they are not well, but they aren't sick enough to be considered truly ill. This stage of sub-chronic disease is mediated by increased silent inflammation. The final stage is the actual manifestation of some type of chronic disease. Only then does the medical establishment throw its full armament at patients to hopefully drive them back into a state of wellness, and this can only be accomplished with the reduction of inflammatory response in the body. The primary hormones that represent key inflammatory mediators of the innate immune system are eicosanoids.

Defining Wellness

Chronic Disease

Chronic disease can be viewed as an excess of "bad" eicosanoids. The AA/EPA ratio in the blood is a reliable marker of the ratio of the same essential fatty acids in every cell in the body. There is no drug that can reduce the AA/EPA ratio, however it can be significantly reduced by an anti-inflammatory diet and/ or the concept of silent inflammation in a patient. The ideal AA/EPA ratio is approximately 1.5. This is the AA/EPA ratio found in the blood. This is the gold standard for determining the extent of silent inflammation at the cellular level. The AA/EPA ratio indicates a larger population of small, dense pro-atherogenic LDL particles. Prospective studies indicate that a low AA/EPA 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 there is a sub-chronic disease state 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.

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 inflammatory mediators is key to controlling the development of inflammatory mediators required to orchestrate an attack against microbial invaders. Today the interaction of the innate immune and eicosanoids still govern the intricate balancing of inflammatory responses in humans. Eicosanoids are considered "super-hormones" capable of modulating the immune system either by turning on the inflammatory response ("bad" eicosanoids) or turning off the inflammatory response ("good" eicosanoids) depending on which type of an eicosanoid a cell produces. Unlike typical hormones that are produced by a particular gland, every cell in your body is capable of producing eicosanoids. In essence, you have about 100 trillion eicosanoids in the body. The goal of anti-inflammatory medicine is to maintain an appropriate balance of "good" and "bad" eicosanoids by controlling the levels of their molecular building blocks in the membranes of each cell in the body. The terms "good" and "bad" eicosanoids are simply operational terms, terms that describe very powerful but opposite physiological actions generated by different eicosanoids. The patient needs a balance of "good" and "bad" eicosanoids to maintain wellness. This is no different than discussing "good" and "bad" cholesterol. If a patient had no "bad" cholesterol, he or she would die. What is required is an appropriate balance between "good" and "bad" cholesterol to help reduce the risk of heart disease. You can think of eicosanoids in the same way, but realize that they're vastly more powerful in their impact on the patient's overall wellness as shown below.

3.1 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 acids can be synthesized into eicosanoids. Two of these are the omega-6 essential fatty acids, arachidonic acid (AA) and linoleic acid (DGLA). The other essential fatty acid is eicosapentaenoic acid (EPA), an omega-3 fatty acid. The eicosanoids derived from AA are generally powerful pro-inflammatory eicosanoids, whereas those derived from DGLA are powerful anti-inflammatory eicosanoids. Although those derived from EPA are generally powerful anti-inflammatory eicosanoids.
Anti-Inflammatory Medicine: Dietary Modulation of 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 leading to a balance of "good" to "bad" eicosanoids. This is shown in Figure 1.

4.0 What Is The Zone?

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 one that prevents the excess production of AA thereby reducing the production of pro-inflammatory eicosanoids for the generation of "bad" eicosanoids. To achieve that goal, an anti-inflammatory diet is based upon consistent insulin control coupled with supplementation with high-flax 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 that is dependent on 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. These fat ratios represent several important biomarkers that help to modify the synthesis of AA as well as enable the synthesis of the omega-3 fatty acids. This diet is the "good" anti-inflammatory diet and the "bad" anti-inflammatory diet is that which has a high omega-6 fatty acid content.

AA/EPA ratio

Fasting insulin

TG/HDL ratio

1.5 to 3

5 to 10

1 to 2

These are also the same three clinical tests that define wellness. Although the AA/EPA ratio is the most sensitive marker of silent inflammation, TG/HDL ratio can be a very inexpensive initial screen for the potential presence of silent inflammation in a patient.

5.0 Other Physiological Benefits Of Omega-3 Fatty Acids

Although the effects of omega-3 fatty acids, such as EPA and docosahexaenoic acid (DHA), have their primary benefits in reducing inflammation by inhibiting the formation of AA-derived eicosanoids, these fatty acids also have many other important functions 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 decrease 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 seen even when this therapy 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 prevent inflammation, vasorelaxation, and platelet aggregation (38). The role of cholesterol as a factor in the development of heart disease is constantly changing. At first, patients were told that they only had to worry about their total cholesterol levels. However, further research found that this wasn't such a strong predictor of future heart disease. Next came the realization that both "good" and "bad" cholesterol are present in the blood. These are found in the high-density lipoprotein (HDL) particles, and the "bad" cholesterol is found in the low-density lipoprotein (LDL) particles. These also represent the newest dietary recommendations from the Joslin Diabetes Research Center at Harvard Medical School (4). This research found that the TG/HDL ratio and heart disease was confirmed by studies from Harvard Medical School (4). This research found that the higher your TG/HDL ratio the more likely you would 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 atherosclerotic plaques—regardless 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 (4). 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

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

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 one of the most standard anti-inflammatory drugs used today alter eicosanoid levels. These drugs have a common mode of action; they inhibit enzymes that synthesize 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 "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. This is done by modifying the 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. 

4.3 Who gets an inflammatory disease?

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 arteriosclerosis 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" and "bad" cholesterol is not so much the issue as the type of cholesterol you have. If your patient is 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).
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 plays 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’s 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 and a 25-percent reduction in their risk of cardiovascular mortality, and a 10-percent reduction in overall mortality compared to either a placebo or Vitamin E (44). 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 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 follows the Mediterranean diet (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 and a 25-percent reduction in their risk of cardiovascular mortality, and a 10-percent reduction in overall mortality compared to either a placebo or Vitamin E (44). These results are equal, if not superior, to the results of statin therapy in secondary prevention trials.

7.0 Eicosanoids and Neurological Disease

There is a 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 overall disability 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 shown that children with 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 nonsteroidal anti-inflammatory drugs have been used for many years to treat the incidence of various cancers (55-57). This may be due to the fact that metastasis 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 fibromyalgia (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 (64).

10.0 Eicosanoids and Obesity

The association of obesity with type 2 diabetes and cardiovascular heart disease is a consequence of the ability to 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-colic diets that the ratio of protein to carbohydrate found in an anti-inflammatory diet gave superior reductions of elevated markers of inflammation in the isocaloric diet 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 calorie 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.

11.0 Eicosanoids and Type 2 Diabetes

Currently an estimated 16 million people are affected with type 2 diabetes. This devastating disease pun 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 (77). Not surprisingly, an anti-inflammatory diet is virtually identical to 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.

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 reached at 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 the greater the levels of EPA and DHA that may be required to reach this clinical goal. The most precise clinical determination of the supplementation required would be analysis of the FA composition of the liver, muscle, or certain organs. In the various clinical studies conducted by the Inflammation Research Foundation, the amount of EPA and DHA required to reduce the AA/EPA ratio to 1.5 has little to do with the age, weight, or sex of the patient, but has more to do with the initial levels of silent inflammation and where that inflammation is located. Based on an analysis of the data from a wide in a wide variety of patients, 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</td>
<td>5</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>7.5</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>10</td>
</tr>
</tbody>
</table>

These recommended levels of EPA and DHA supplementation is based upon the fact that fish oil therapy can be prescribed as described earlier. The patient’s diet is rich in high-glycemic carbohydrates (that stimulate insulin) or rich in omega-6 fatty acids then the recommended level of fish oil supplementation requires a reduction in current fish oil supplementation. In animal studies that fish oil can reduce endocannabinoid levels in the brain (71,72).

12.2 Fish Oil Purify

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 potencies and purities of fish oil products are listed from a large number of companies. Because fish oil quantity can vary greatly 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 produced 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
able to mount an adequate inflammatory response to microbial
invasions. This is why blood testing is useful especially in high
dose applications. As long as the AA/EPA ratio remains above 1.5, then such problems will not occur.
Consuming up to 5 grams per day of EPA and DHA reduces the AA/EPA ratio to approximately 6. This level of the AA/EPA ratio achieved by the subjects in the active group of the Lyon Diet Heart Study (45).
Although EPA and DHA are powerful nutritional supplements to reduce the levels of silent inflammation as measured by the AA/EPA ratio, the same fatty acids also have the ability to reduce the levels of DGLA. This means a corresponding reduction in the production of powerful anti-
inflammatory eicosanoids derived from DGLA. This is because DGLA (and to a lesser extent EPA) are inhibitors of the enzyme
(delta-5 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 oils) 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, 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 seed oil. The toasting of the seeds prior to extraction causes the breakdown of certain polyphenols to form sesamol, 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.

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 (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.

13.0 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-inflammatory). Successful application of this dietary strategy is the concept of evidence-based wellness with the patient and the physician working together as a team to move the patient back to a state of wellness.

In the final analysis, anti-inflammatory medicine is a return of the foundation of modern medicine when Hippocrates said, “Let food be your medicine, and let medicine be your food.” That statement has never made more sense than when applied to dietary modulation of eicosanoids.

14.0 References

10

Inflammation Research Foundation

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Glossary

**Alpha Linolenic Acid (ALA)**

This is the short-chain omega-3 fatty acid commonly found in the diet. Common sources include flaxseed and soy oils.

**Arachidonic Acid (AA)**

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.

**AA/DGLA Ratio**

This is the ratio 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 these 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 is the immediate precursor of many eicosanoids that increase inflammation. Egg yolks, fatty red meat, and organ meats are rich sources of arachidonic acid.

**Eicosapentaenoic Acid (EPA)**

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

**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 soybean 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 is 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, proteins, and fats) 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.

**Resolvins**

A new class of anti-inflammatory eicosanoids derived from EPA and DHA that is induced by conformational shift in the cyclooxygenase (COX) enzyme induced by low dose aspirin
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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Anti-Inflammatory Medicine: Anti-Inflammatory Diets

Inflammation Research Foundation
Introduction

Although the development of obesity and type 2 diabetes have become worldwide epidemics, current medical interventions appear powerless to stop them (1). Even more discouraging is the fact that there is no consensus that defines the molecular causes of these conditions. Traditional thinking maintains that obesity and type 2 diabetes stem from a lack of willpower, and that if the individual would only “eat less and exercise more,” these epidemics would soon diminish. This review presents an alternative position suggesting that in those with a genetic predisposition, obesity and type 2 diabetes arise from low-level chronic inflammation induced by diet. This alternative viewpoint presents obesity and diabetes as metabolic disorders caused by inflammation and spread by mechanisms that have many similarities to cancer.

Types of Inflammation

There are two distinct types of inflammation. The first is an acute and intense pro-inflammatory response causing significant pain. This is considered classical inflammation. More recently recognized is chronic low-level inflammation that is below the threshold of pain. This is what I term “silent inflammation” (2-4). Since there is no pain associated with this type of inflammation, nothing is done to stop it and thus it can linger for years, if not decades, while causing continuing organ damage. If there is enough organ damage, then chronic disease finally appears. This not only includes obesity and type 2 diabetes, but also many other chronic disease conditions (2-4).

Markers of Silent Inflammation

It is very difficult to discuss this new concept of silent inflammation if you can’t measure it, especially since there is no pain associated with it. It is only recently that new clinical markers of silent inflammation have emerged. The first of these clinical markers is high-sensitivity C-reactive protein (hs-CRP). It is not a very selective marker since simple infections can raise it dramatically, and it is not a very specific marker of the inflammatory process (5-7). A much more selective marker of silent inflammation is the ratio of two key fatty acids in the blood. The first is the omega-6 fatty acid, arachidonic acid (AA), which is the precursor to pro-inflammatory eicosanoids. The other fatty acid is the omega-3 fatty acid, eicosapentaenoic acid (EPA), which generates anti-inflammatory eicosanoids. The higher the AA/EPA ratio in the blood of an individual, the greater the level of silent inflammation in various organs (2-4).

Since silent inflammation can now be measured, it is found to be strongly associated with virtually every chronic disease condition, but for the purpose of this review, I will discuss its implications in the development of obesity and diabetes.

Diet-induced Silent Inflammation

There has not been one particular dietary change in the past 25 years that has increased the levels of silent inflammation. However, there has been a convergence of three distinct dietary changes that I term, “The Perfect Nutritional Storm” (4). These dietary factors include:

- Increased consumption of refined, high glycemic-load carbohydrates
- Increased consumption of refined vegetable oils rich in omega-6 fatty acids
- Decreased consumption of long-chain omega-3 fatty acids

The first of these dietary changes is the increased consumption of refined high glycemic-load carbohydrates. The glycemic load of a particular carbohydrate is defined as the amount that is consumed at a meal multiplied by its rate of entry as glucose into the bloodstream (i.e. glycemic index). These high glycemic-load carbohydrates are not only the major components in virtually all processed foods, but also in bread products and pasta. As the cost of refined carbohydrate production has decreased in the past 25 years, the availability of products made from these ingredients has dramatically increased (8). Increased consumption of finished food products with a high glycemic load results in the increased secretion of the insulin necessary to lower the resulting post-prandial rise in blood glucose (9,10).

Increased insulin production alone is not sufficient to explain the rapid increase in silent inflammation. This requires the presence of another recent dietary component: The increased consumption of refined vegetable oils rich in omega-6 fatty acids. The coupling of an increase in insulin production with an increase in omega-6 fatty acid consumption results in the increase of AA, especially in those who are genetically predisposed (11). Since refined high-glycemic carbohydrates and refined vegetables are now the cheapest source of calories (12-14), it not surprising that the combination of these two dietary trends has increased the production of AA thus leading...
to an epidemic increase in silent inflammation. This can be understood by illustrating the metabolic pathway of linoleic acid conversion to AA as shown below in Figure 1.

**Figure 1.**
**Metabolism of Omega-6 Fatty Acids**

Linoleic acid

\[ \text{Delta 6 Desaturase (Activated by Insulin)} \]

Gamma linolenic acid (GLA)

\[ \text{Delta 5 Desaturase (Activated by Insulin)} \]

Arachidonic Acid (AA)

\[ \text{Inhibited by EPA} \]

The two rate-limiting steps in this metabolic cascade of linoleic acid to arachidonic acid are the enzymes delta-6 and delta-5 desaturase. These enzymes insert cis double bonds into unique positions in the omega-6 fatty acid molecule. Normally, these conversion steps are very slow, thus limiting the production of AA. However, insulin is a strong activator of each of these enzymes (15-18). This means that a high glycemic-load diet coupled with the increased intake of vegetable oils rich in linoleic acid will lead to increased production of AA and a corresponding increase in silent inflammation.

Finally, there is the role of the omega-3 fatty acid EPA in this metabolic cascade and its effect on silent inflammation. In high enough concentrations, EPA can inhibit the activity of the delta-6 desaturase enzyme thus reducing AA formation by acting as a feedback inhibitor. Furthermore, increased EPA content in the membrane phospholipids decreases the release of AA that is necessary to make pro-inflammatory eicosanoids. In this regard, increased consumption of EPA dilutes out existing AA, thus decreasing the production of pro-inflammatory eicosanoids. Finally, EPA is the molecular building block for powerful anti-inflammatory eicosanoids known as resolvins (19-22).

Unfortunately, the consumption of long-chain omega-3 fatty acids, such as EPA, has dramatically decreased over the past century (23). With the decrease in EPA intake coupled with the increase of refined carbohydrates and vegetable oils, the dietary stage has been set for a dramatic increase in silent inflammation.

**Obesity Induced by Silent Inflammation**

The body has a unique way of initially dealing with elevated AA levels that would otherwise increase silent inflammation. This is through the generation of healthy new fat cells. Derivatives of AA can stimulate the stem cells in the adipose tissue to create new fat cells (24, 25) for the purpose of storing any excess AA, and thus preventing it from circulating in the blood. In fact, the definition of a healthy fat cell is one that can increase the storage of triglycerides. By doing this, the adipose tissue if composed of healthy fat cells, becomes analogous to a toxic waste dump that sequesters any increased production of AA. This is clearly illustrated in children in which the greater the BMI, the higher the levels of AA in the adipose tissue (26).

There is also the problem of inherent insulin resistance that is often observed in genetically predisposed individuals. Early studies by Reaven demonstrated that insulin response to a defined intake of carbohydrates in healthy, normal weight individuals could be broken into four distinct quartiles (27). This would suggest that the lowest quartile of normal, healthy individuals could tolerate higher levels of carbohydrate consumption without a significant increase in their insulin secretion. However, it also suggests that perhaps 75% (the three highest insulin-secreting quartiles) of the U.S. adult population would have a more difficult time with increased carbohydrate consumption, with those in the highest quartile being the first to feel the effects of increased carbohydrate consumption. Since more than 66% of the U.S. adult population is currently overweight or obese (28), this may indicate the most insulin-sensitive three quartiles of the general population may already be affected by the Perfect Nutritional Storm.
The Fat Trap

Genetically predisposed individuals have a “fat trap” that can be activated by increased insulin levels (4). Incoming calories that are not immediately used are converted into fat by the liver for long-term storage in the adipose tissue. If a genetically predisposed individual has a high insulin response to carbohydrates, then the increased insulin will accelerate that storage by driving glucose into the fat cells for conversion into glycerol. Simultaneously, elevated insulin will also increase the levels of fatty acid binding proteins in the fat cell that facilitate the transfer of free fatty acids into the fat cell (29-32). The combination of the two factors will increase the deposit rates of triglycerides in the adipose tissue. However, the same elevated insulin will inhibit the hormone-sensitive lipase required to release the stored fat for conversion into ATP by the peripheral tissues (33-35). Circulating fat can be considered high-octane fuel compared to carbohydrates for ATP synthesis since far more ATP can be produced from a gram of fat compared to a gram of carbohydrate.

In essence, the individual with an active fat trap is constantly starved for ATP production. Since a typical cell can only store about 10 seconds worth of ATP, the lack of a constant supply of stored fat released from the adipose tissue to continually replace ATP forces the individual to either eat more (to get more fat into the bloodstream to make ATP) or exercise less (to conserve their existing ATP levels). In other words, they become a glutton or a sloth. These observations associated with obesity are not the cause of obesity, but the results of the metabolic consequences of elevated insulin levels on fat cell metabolism (4, 36).

This also explains the poor success of genetically predisposed individuals adherence to the long-term protocol of simply eating less and exercising more. If they eat less, there will be less available raw material to make ATP. If their fat trap is still operating, then the only alternative for the body is to begin to cannibalize its own muscle and organs to supply the necessary raw materials for continued ATP production. They will initially lose weight, but not nearly the amount of body fat that would be predicted. The same is true for exercising more. If the fat trap is still active, increased exercise will consume existing ATP stores at a faster rate, again forcing the body to cannibalize muscle mass and organs for the raw materials necessary to maintain ATP levels. This is exactly what happens in genetically bred obese mice that are forced to eat less and exercise more (37). With increased exercise and calorie restriction there is weight loss. However, upon autopsy their fat stores are still robust, but there is significant wasting of muscle mass and organs. There is no reason to believe the same phenomenon is not happening to human subjects. In addition, with calorie restriction comes an increase in the hunger hormone ghrelin (38,39). So in addition to cannibalizing tissue, the genetically predisposed individual with an active fat trap has even greater hunger when eating less. Under these conditions, willpower alone will be insufficient to continue such adverse metabolic consequences for an extended period of time.

The Life and Death of a Fat Cell

The definition of a healthy fat cell is one that can easily expand to sequester incoming fats and in particular AA, and depending on the genetic predisposition of an individual, also governs the release of stored fat for ATP production.

The problem begins when AA levels become too great in a particular fat cell. The fat cell response to insulin signaling becomes compromised due to internal inflammation. This interrupts the flow of glucose into the fat cell to provide the necessary glycerol for fatty acid storage. As a result, the fat cell has a more difficult time sequestering newly formed AA as well as other fatty acids. At the same time, insulin inhibition of the hormone sensitive lipase becomes compromised because of the same disruption in insulin signaling. These are the hallmarks of insulin resistance in the fat cell that arise far earlier than insulin resistance in muscle cells (40,41). As a result, not only do greater amounts of AA remain in circulation to be taken up by other cells potentially leading to insulin resistance in the muscle cells (causing increased hyperinsulinemia), but also the compromised fat cell is releasing greater amounts of previously sequestered AA from fat cells into the circulation (42).

As the levels of AA further increase beyond a critical threshold barrier in any one particular fat cell, cell death can take place. The necrosis of that particular fat cell causes a migration of macrophages into the adipose tissue (43-45). This increase in macrophage accumulation in the adipose tissue is clearly seen in both animal models of obesity as well as in humans. These newly recruited macrophages cause the secretion of additional inflammatory mediators, such as IL-6 and TNF, which increase inflammation within the adipose tissue (46-58). The amount of macrophage accumulation can be significantly reduced upon supplementation with high-dose fish oil rich in EPA to reduce inflammation in the adipose tissue (59, 60).
With inflamed adipose tissue, IL-6 derived from the macrophages can exit into the circulatory system to cause an increase in CRP formation in the liver. Likewise TNF generated by the same macrophages cause further insulin resistance in the surrounding fat cells, thus decreasing their ability to sequester newly formed AA as well as causing the release of more stored AA into the circulatory system. In many ways, the staging area for insulin resistance in other organs (muscles, liver, and eventually the pancreas) can be considered to start in the adipose tissue.

**Lipotoxicity: Understanding Obesity as a Cancer**

As long as the adipose tissue is composed of healthy fat cells, any increased production of dietary-induced AA can be safely handled by their continued expansion. It is only when normal fat cell metabolism becomes compromised by increased AA accumulation that lipotoxicity can occur (59, 60).

This is why obesity and cancer share many similarities. They are both characterized by increased inflammation (as marked by increased macrophage concentration), seemingly uncontrolled growth, as well as metastasis to distant sites. The excess fat mass in an individual who is actively sequestering AA from the circulation represents a benign tumor because it does not compromise physiological function. This explains why approximately one-third of obese individuals are actually quite healthy (63). These individuals are known as the metabolically healthy obese (64) and appear to have higher levels of the adipose-derived hormone adiponectin (65).

However, the accelerated release of stored AA from the fat mass into the circulation is similar to the metastatic spread of a tumor, only now it is silent inflammation that is spreading. This metastasis of silent inflammation is characterized by lipotoxicity, which is the enhanced deposition of lipid droplets in organs (muscle, liver, and pancreas) that are not designed for lipid storage. If this accumulation of lipid droplets is also enriched in AA, then the development of type 2 diabetes will be accelerated.

One of the first indications that lipotoxicity is taking place is the appearance of metabolic syndrome. Metabolic syndrome can be considered to be pre-diabetes. It is characterized by a combination of clinical markers, such as a high TG/HDL ratio, increasing abdominal fat, and hyperinsulinemia. Recent data indicate that there is a strong correlation between metabolic syndrome and levels of AA in the adipose tissue (40).

Left untreated, metabolic syndrome will usually result in the development of type 2 diabetes within 8-10 years. During this time period, the insulin resistance of the individual is continually increasing. This will cause even more AA formation if consumption of omega-6 fatty acids remains high. Since the fat cells are now compromised in their ability to sequester this increased AA production, it remains in the blood to be picked up by other organs.

The final development of type 2 diabetes only occurs when the lipotoxicity has now metastasized to the pancreas causing a decreased output of insulin (66). With insulin secretion decreased, there is a rapid rise of blood sugar levels. The development of type 2 diabetes indicates that the metastasis of silent inflammation from the adipose tissue to the pancreas is now complete.

Ironically, even extreme lipotoxicity can be reversed by the creation of new healthy fat cells. This has been demonstrated in transgenic obese, diabetic mice that were treated to over-express adiponectin, an adipocyte-derived hormone that reduces insulin resistance (67). It is hypothesized that this increased production of adiponectin activates PPAR gamma, which causes the proliferation of adipose stem cells to produce new healthy adipocytes. These transgenic obese mice become even more obese, but there is normalization of blood glucose and lipid levels (67). This is similar to the elevated levels of adiponectin found in metabolically healthy obese individuals (65). One mechanism might be that the new healthy fat cells in the adipose tissue can now sequester circulating AA more effectively to allow the dissipation of the lipid droplets in the muscle cells and beta cells of the pancreas. Essentially, this represents a reverse flow of the lipotoxic lipid droplets in other organs back to the adipose tissue.

**Treatments for Obesity and Diabetes**

For long-term success in treating obesity and type 2 diabetes, there is no drug intervention that surpasses gastric bypass surgery in efficacy (68, 69). This is especially true of Roux-en-Y gastric bypass surgery (70, 71). This surgery not only causes calorie restriction, but also causes a significant increase in post-prandial PYY secretion that is able to maintain satiety with reduced calorie intake (70, 71).

More disturbing is the recent ACCORD study, which demonstrated that tighter glycemic control in type 2 diabetes appears to result in increased mortality (72). Yet interestingly, there have been reports that use of high-dose anti-inflammatory drugs appear to successfully treat
diabetes, and by inference obesity (50). The first of these reports appeared in 1876 (73), and they continued to appear several times in the first half of the 20th century (74, 75). The reduction in elevated blood sugar was almost immediate. Unfortunately, the treatment of both obesity and diabetes is life-long therapy and the doses of these anti-inflammatory drugs required to observe therapeutic benefits could not be maintained for a lifetime without adverse side effects. However, these reports do indicate that an appropriate anti-inflammatory diet might be constructed that could have similar benefits. That type of intervention could be maintained for a lifetime.

Anti-Inflammatory Diets

The principal components of a proposed anti-inflammatory diet should be a low glycemic-load diet, low in omega-6 fatty acids and rich in EPA.

The macronutrient composition of such a diet would provide about 150 grams of carbohydrate per day. The majority of carbohydrates should be coming from low glycemic-load sources that would significantly lower the production of insulin. This can be achieved by consuming approximately 10 servings of non-starchy vegetables and limited amounts of fruits (because of their higher fructose content) per day with a relatively rigid (but not total) exclusion of high glycemic-load carbohydrates such as bread, pasta, rice and potatoes.

The total dietary allotment of only 150 grams of carbohydrate (600 calories) may initially appear difficult to achieve considering the abundance of carbohydrates in the food chain. Yet if one-third of those carbohydrates (200 calories) came from Mediterranean vegetables, the individual would have difficulty consuming even this lowered carbohydrate level because of the caloric volume of the Mediterranean vegetables. Compliance with such recommendations can be significantly enhanced when patients are counseled by telephone to facilitate a replacement of their current carbohydrates with more Mediterranean vegetables and fruits (76).

An example of the amounts of different Mediterranean vegetables that provide 50 calories per day is shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Mediterranean Vegetables</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the vegetables listed below are in 50-calorie increments. The cooked vegetables are steamed and drained. This information is solely based on the calorie content of the vegetables and does not include oils, dressings, or other condiments added during the cooking process. The canned vegetables are not in oil.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAW VEGETABLES</th>
<th>Amount for 50 Calories</th>
<th># of Cups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broccoli (176g)</td>
<td>2 cups chopped</td>
<td>2</td>
</tr>
<tr>
<td>Cucumber (402g)</td>
<td>2 medium or 3 cups chopped</td>
<td>3</td>
</tr>
<tr>
<td>Fennel bulb (161g)</td>
<td>2 cups sliced</td>
<td>2</td>
</tr>
<tr>
<td>Red/Green Peppers (186g)</td>
<td>1 ½ medium or 2 cups sliced</td>
<td>2</td>
</tr>
<tr>
<td>Mushrooms (194g)</td>
<td>1 ½ cup pieces</td>
<td>1 ½</td>
</tr>
<tr>
<td>Onion (133g)</td>
<td>1 medium or ¼ cup chopped</td>
<td>¾</td>
</tr>
<tr>
<td>Tomatoes (246g)</td>
<td>2 medium or 2 cups chopped</td>
<td>2</td>
</tr>
<tr>
<td>Spinach (214g)</td>
<td>7 cups chopped</td>
<td>3 ½</td>
</tr>
<tr>
<td>Snow Peas (126g)</td>
<td>2 cups whole</td>
<td>2</td>
</tr>
<tr>
<td>Zucchini (353g)</td>
<td>3 ¼ cups sliced</td>
<td>3 ¾</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COOKED VEGETABLES</th>
<th>Amount for 50 Calories</th>
<th># of Cups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparagus (203g)</td>
<td>1 ¼ cup or 14 spears</td>
<td>1 ¼</td>
</tr>
<tr>
<td>Artichoke (120g)</td>
<td>1 medium</td>
<td>1</td>
</tr>
<tr>
<td>Broccoli (184g)</td>
<td>1 cup chopped</td>
<td>1</td>
</tr>
<tr>
<td>Eggplant (177g)</td>
<td>1 ¾ cups cubed</td>
<td>1 ¾</td>
</tr>
<tr>
<td>Green Beans (44g)</td>
<td>1 cup</td>
<td>1</td>
</tr>
<tr>
<td>Kale (180g)</td>
<td>1 ½ cup chopped</td>
<td>1 ½</td>
</tr>
<tr>
<td>Mushrooms (186g)</td>
<td>1 ¼ cup pieces</td>
<td>1 ¼</td>
</tr>
<tr>
<td>Onion (114g)</td>
<td>½ cup chopped</td>
<td>½</td>
</tr>
<tr>
<td>Red/Green Peppers (270g)</td>
<td>2 cups pieces</td>
<td>2</td>
</tr>
<tr>
<td>Snow Peas (120g)</td>
<td>¾ cup edible peas</td>
<td>¾</td>
</tr>
<tr>
<td>Spinach (220g)</td>
<td>1 ¼ cup</td>
<td>1 ¼</td>
</tr>
<tr>
<td>Sun-dried Tomato (18g)</td>
<td>½ cup</td>
<td>½</td>
</tr>
<tr>
<td>Swiss Chard (250g)</td>
<td>1 ½ cup chopped</td>
<td>1 ½</td>
</tr>
<tr>
<td>Tomato (217g)</td>
<td>1 ½ cup diced</td>
<td>1 ½</td>
</tr>
<tr>
<td>Zucchini (310g)</td>
<td>1 ¾ cup sliced</td>
<td>1 ¾</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CANNED VEGETABLES</th>
<th>Amount for 50 Calories</th>
<th># of Cups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artichoke Hearts (210g)</td>
<td>5 pieces</td>
<td>¾</td>
</tr>
<tr>
<td>Capers (225g)</td>
<td>1 ½ cups</td>
<td>1 ½</td>
</tr>
<tr>
<td>Roasted Red Peppers (280g)</td>
<td>2 cups</td>
<td>2</td>
</tr>
</tbody>
</table>

The current recommendation of the USDA is for the consumption of at least 2 ½ cups of vegetables per day. To meet the goal of consuming 200 calories per day of Mediterranean vegetables, an individual would have to consume at least four combinations of the listed carbohydrate sources (each listed at 50 calories), which greatly exceeds the recommended USDA amounts of daily
vegetable consumption. Yet that still leaves another 400 calories (100 g) for the consumption of fruits, and limited amounts of higher glycemic-load carbohydrates so that the patient is not totally deprived of those carbohydrates hence ensuring greater long-term compliance.

The protein requirements would be approximately 100 grams of protein per day coming from low-fat sources, such as fish and chicken or vegetarian protein sources, such as tofu or imitation soybean meat products. The higher levels of protein are required to help stimulate the release of the satiety hormone PYY from the gut (77).

Finally, the fat content would be approximately 50 grams per day. The composition of the fat in an anti-inflammatory diet should be low in both omega-6 and saturated fatty acids. The omega-6 fatty acids provide the building blocks for increased AA formation and the resulting elevation of silent inflammation that drives new fat cell proliferation. Saturated fatty acids are likewise kept to low amounts since they can activate NF-kappa B via the TLR4 receptors to cause increased cellular inflammation (78-82). Thus, the bulk of the dietary fatty acids should consist of monounsaturated fats, which have virtually no effect on inflammation. These monounsaturated fats should also be supplemented by at least 5 grams of long-chain omega-3 fatty acids per day. This level of long-chain omega-3 fatty acids would increase the secretion of adiponectin by the fat cells (83-85). Increased adiponectin production can have significant benefits for reducing insulin resistance in peripheral tissues (86).

From a macronutrient standpoint, such an anti-inflammatory diet could be considered a 1-2-3 diet, meaning for every one gram of fat consumed, the individual would consume two grams of protein, and three grams of carbohydrate. This 1-2-3 ratio stabilizes postprandial insulin levels, thus relieving the inhibition of the hormone-sensitive lipase in the fat cells. As a result, the release of stored fat for ATP production is enhanced. This 1-2-3 ratio of macronutrients has been examined in various studies compared to the current macronutrient recommendations of the USDA, American Heart Association, and the American Diabetic Association under isocaloric conditions. In each of these studies, the 1-2-3 ratio has been shown to be superior in reducing hunger (87,88), reducing insulin and stabilizing blood lipid levels (89-93), reducing blood glucose levels (94,95), increasing weight loss in those patients characterized by a high initial insulin secretion to carbohydrates (96,97), and reducing silent inflammation (98). The macronutrient composition of the proposed anti-inflammatory diet is very similar to that recently proposed by the Joslin Diabetes Research Center at Harvard Medical School for the treatment of obesity and type 2 diabetes (99), which is virtually identical to dietary recommendations that were made more than a decade ago (100).

Such a macronutrient composition also represents a calorie-restricted diet providing approximately 1,450 calories per day. It has been demonstrated that this level of caloric restriction is required to maintain long-term weight loss (101). Furthermore, Markovic et al has demonstrated that caloric restriction at 1,200 calories per day can reverse insulin resistance in type 2 diabetics within four days, well before any fat loss had occurred (102). One potential mechanism of this rapid effect of caloric restriction on insulin resistance may lie in the reduction of the NF-kappa B activation in hypothalamic neurons (103).

Maintaining such a calorie-restricted diet, however, depends on controlling hunger primarily by increasing satiety. This is why an anti-inflammatory diet requires higher levels of protein (approximately 30% of total calories) to help stimulate the release of the satiety hormone PYY from the gut. It has been shown that increasing PYY levels significantly decreases hunger (104,105). Furthermore, it has been shown that decreased post-prandial PYY secretion may be the first indication of future development of type 2 diabetes well before the appearance of increased weight or increased insulin resistance (106,107).

There are additional benefits of the proposed anti-inflammatory diet. The first is a significant increase in the consumption of polyphenols (found in vegetables and fruits), which are known to have anti-inflammatory benefits (via the inhibition of NF-kappa B) as well as activation of AMP kinase to increase the production of ATP (108-110). Once AMP kinase is activated, then a number of other metabolic processes that are important in blood sugar and blood lipid control are also set into motion (111,112). Activation of AMP kinase is also the primary mechanism of action for one of the most widely used diabetic drugs (113). Another benefit of the proposed anti-inflammatory diet is a decrease in the levels of endocannabinoids (derived from AA) in the brain, which play a significant role in hunger development (114).

In many ways, such an anti-inflammatory diet could be considered similar to the Mediterranean diet with the following adjustments. The levels of high-glycemic carbohydrates such as, bread, rice and pasta, are significantly reduced, replaced by much higher levels of low-glycemic, non-starchy vegetables and fruits rich in polyphenols. The primary sources of protein would remain...
fish and chicken, and the primary fat would still be olive oil that is low in omega-6 fatty acids. One could consider the proposed anti-inflammatory diet to be the evolution of the Mediterranean diet with a far greater reduction in silent inflammation.

Since the classic Mediterranean diet is associated with a reduction in the ratio of omega-6 to omega-3 balance in the blood (115) as well as a decreased incidence of obesity, diabetes and mortality (116-119), it might be reasonable to conclude that the proposed anti-inflammatory diet would have an equal, if not greater, effect in preventing the development of chronic disease and mortality.

**Dietary Reality**

Dietary recommendations are one thing, dietary reality is often another. In fact, it is often said that it is easier to change one's religion than to change one's diet. The proposed anti-inflammatory diet, therefore becomes difficult to implement since it requires a dramatic reduction in the consumption of bread, pasta, rice, and other high-glycemic carbohydrates that individuals are accustomed to consuming.

The solution to this formidable problem requires manufacturing a new generation of baked products that not only reduces insulin secretion, but also increases the release of PYY. To accomplish this requires an understanding of molecular baking.

**Molecular Baking**

Molecular baking represents a fusion of material science technology and food technology. In essence, it treats proteins, carbohydrates, and fats as polymers that can be reorganized into different structures that look and taste like traditional bread, pasta, and rice products. The key to this technology lies in the development of extensible dough. This revolutionary new dough consists of protein, fat, and carbohydrate in a 1-2-3 ratio that can be baked as a traditional dough, but now imparts a unique variety of hormonal properties. The first is the reduction of insulin levels. By reducing the glycemic load flours through the replacement of carbohydrates with protein, the glycemic load of the final product is dramatically reduced thereby reducing insulin secretion. Such products represent low-glycemic versions of the foods that most individuals desire to eat. Now rather than restricting them from the diet because of their adverse impact on insulin secretion, their inclusion in an anti-inflammatory diet provides far greater dietary compliance for the individual since they are eating the foods they are accustomed to.

More importantly, the process used to make extensible dough for molecular baking also provides a mechanism to increase PYY secretion. Normally protein and carbohydrate are prepared separately, or if combined, they are kept at low temperatures to prevent extensive cross-linking due to increased temperatures encountered during the baking process. With extensible dough, this problem is circumvented as the interaction between protein and carbohydrates is controlled at the molecular level in the dough mixing process. As a result, when baked, the amount of cross-linking is minimized to prevent the rapid breakdown and absorption of the protein before it reaches the L-cells in the distal portion of the ileum. This is important as it is the L-cells in the lower portion of the gut that release PYY, which goes directly to the brain to induce satiety. This is exactly the mechanism for Roux-en-Y gastric bypass surgery. Much of the small intestine is bypassed, and the limited amount of protein that can be absorbed (due to the reduction of the stomach size) is delivered in high amounts directly to the L-cells. This is why the first thing that the gastric bypass patient experiences after surgery is an almost immediate lack of hunger, often for the first time in their lives. Products made using extensible dough can deliver many of the same hormonal benefits as gastric bypass surgery. This is because more of the dietary protein is delivered to the L-cells since the rate of digestion and absorption of protein in the upper section of the gut has been reduced due to the controlled cross-linking of the protein and carbohydrate during the baking process.

With the advent of molecular baking, it becomes much easier for the individual to maintain an anti-inflammatory diet since breads and pasta become an integral part of their dietary success to increase satiety. It should be kept in mind that the 1-2-3 macronutrient balance is still necessary to control insulin as this is critical for the relaxation of the fat trap, thus allowing more stored fat to be released into the circulation for increased ATP production. Keep in mind without the use of bread and pasta products made with the new extensible dough technology, the stimulation of PYY secretion will still be compromised regardless of how well the 1-2-3 macronutrient balance is maintained by the individual.

Pilot studies we have conducted indicate that approximately 1,000 calories per day of extensible dough products delivered in three meals and two snacks are sufficient to maintain high levels of satiety. This allows for another 500 calories per day for additional low-glycemic
carbohydrates, such as non-starchy vegetables and limited amounts of fruits that are rich in polyphenols. However, it must be remembered that it is the increased PYY secretion that makes it possible to maintain a calorie-restricted dietary program indefinitely.

**Summary**

Obesity and type 2 diabetes are inflammatory conditions that should be successfully treated by anti-inflammatory interventions. One such intervention is the long-term use of a proposed anti-inflammatory diet that delivers the benefits of calorie-restriction and hormonal modulation that currently can only be achieved with gastric bypass surgery. This is especially true if that anti-inflammatory diet makes extensive use of products produced by molecular baking.

**References**


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