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Anti-inflammatory Diets

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Chronic disease is driven by inflammation. This article will provide an overview on how the balance of macronutrients and omega-6 and omega-3 fatty acids in the diet can alter the expression of inflammatory genes. In particular, how the balance of the protein to glycemic load of a meal can alter the generation of insulin and glucagon and the how the balance of omega-6 and omega-3 fatty acids can effect eicosanoid formation. Clinical results on the reduction of inflammation following anti-inflammatory diets are discussed as well as the molecular targets of anti-inflammatory nutrition.

To overcome silent inflammation requires an anti-inflammatory diet (with omega-3s and polyphenols, in particular those of Maqui). The most important aspect of such an anti-inflammatory diet is the stabilization of insulin and reduced intake of omega-6 fatty acids.

The ultimate treatment lies in reestablishing hormonal and genetic balance to generate satiety instead of constant hunger. Anti-inflammatory nutrition, balanced 40:30:30 with caloric restriction, should be considered as a form of gene silencing technology, in particular the silencing of the genes involved in the generation of silent inflammation. To this anti-inflammatory diet foundation supplemental omega-3 fatty acids at the level of 2–3 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per day should be added. Finally, a diet rich in colorful, nonstarchy vegetables would contribute adequate amounts of polyphenols to help not only to inhibit nuclear factor (NF)-κB (primary molecular target of inflammation) but also activate AMP kinase.

Understanding the impact of an anti-inflammatory diet on silent inflammation can elevate the diet from simply a source of calories to being on the cutting edge of gene-silencing technology.

Inflammation is a 2-edged sword. It allows us to defend ourselves against microbial invasion and allows our injuries to heal. Yet, on the other hand, if the inflammatory response is not sufficiency attenuated, inflammation can attack our organs, leading to earlier development of chronic diseases [1]. Maintaining inflammation in a zone that is not too low but not high is one of the key factors for successful pregnancy as well as successful aging due to the reduction in earlier onset of chronic disease. However, diet, in addition to microbial invasion or physical injuries, can activate our inflammatory responses.

Diets can be either pro-inflammatory or anti-inflammatory depending on the hormonal responses they generate. This is because these hormonal responses as well as specific nutrients in the diet are intimately connected with the most primitive part of our inflammatory responses: the innate immune system. This part of our immune system has been evolutionarily conserved for hundreds of millions of year and can be considered our first line of defense in the generation of inflammation. What is important is that the innate immune system is under considerable dietary control.

INFLAMMATION AT THE MOLECULAR LEVEL

The central hub of the innate immune system is the gene transcription factor nuclear factor kappaB (NF-κB). This is the master switch that turns on the expression of inflammatory gene products (cyclo-oxygenase-2, tumor necrosis factor-α, interleukin [IL]-1β, IL-6, etc.) that amplify the initial inflammatory signals to nearby cells [2].

There are a number of dietary factors that can activate NF-κB. These factors include oxidative stress from excess calories

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and hormones derived from arachidonic acid [3,4]. Additional dietary factors include saturated fatty acids, advanced glycosylated end products (AGE), and inflammatory cytokines from nearby cells all acting through specific receptors at the cell surface can also activate NF-κB [5].

However, inflammation is not like a burning log whose fire eventually dies out. The inflammatory response consists of 2 distinct phases [5]. The first phase is the initiation of the inflammatory response. The second phase is the resolution of the inflammatory response. The resolution phase is controlled by a unique groups of hormones (resolvins, protectins, and maresins) derived from omega-3 fatty acids [6]. As long the initiation and resolution phases of inflammation are balanced, homeostasis can occur. On the other hand, if the initiation phase is too strong or the resolution phase is too weak, the end result is chronic low-level cellular inflammation. It is this chronic cellular inflammation below the perception of pain that is the driving force in the development of obesity, metabolic syndrome, and diabetes [7].

MEASURING CELLULAR INFLAMMATION

Because cellular inflammation is below the perception of pain, measuring it has posed a challenge. The earliest marker of cellular inflammation was high-sensitivity C-reactive protein (hs-CRP) [8]. This protein is synthesized in the liver in response to elevated levels of IL-6 in the blood [9]. Unlike inflammatory cytokines that either have short half-lives or only enter the blood in very low concentrations [10], hs-CRP is relatively long-lived protein in the blood and therefore is more easily measured [11]. The major clinical drawback of hs-CRP is that even slight bacterial infections can rapidly elevate its levels and, consequently, it is not very reliable marker [12]. Furthermore, it is a downstream marker of cellular inflammation as opposed to an early warning of the buildup of chronic cellular inflammation.

Inflammatory cytokines expressed by the activation of NF-κB (such as tumor necrosis factor, IL-1β, and IL-6) are better potential markers of cellular inflammation, yet their levels in the blood are very low and they are have very short half-lives, making their use as analytical markers of cellular inflammation less feasible [9,10].

Perhaps the best upstream marker of cellular inflammation is the ratio of 2 fatty acids in the blood, the omega-6 fatty acid arachidonic acid (AA) and the omega-3 fatty acids eicosapentaenoic acid (EPA). AA is the building block of pro-inflammatory eicosanoids that stimulate inflammation. On the other hand, EPA is not only a competitive inhibitor of AA for the enzymes necessary for the production of inflammatory eicosanoids but also the building block for very powerful proresolution mediators such as resolvin E1 (RvE1) and resolvin E2 (RvE2). Thus, the AA:EPA ratio in the blood provides detailed insight into the balance of inflammation and resolution in every cell in the body. Furthermore, unlike hs-CRP, the AA:EPA ratio is stable and reliable and often becomes elevated years ahead of the elevation of hs-CRP [13].

DEFINITIONS OF CHRONIC CONDITIONS THAT CAN BE TREATED BY ANTI-INFLAMMATORY NUTRITION

Although virtually every chronic disease can be connected with increasing cellular inflammation, the 3 that are most germane to pregnancy are obesity, metabolic syndrome, and diabetes.

Obesity

Obesity can be defined as excess fat accumulation. Obesity presents little obstacle in becoming pregnant. However, it is when that excess fat becomes inflamed that obesity presents a problem during pregnancy [14]. Under normal conditions, adipose tissue operates like a typical bank: taking in energy from the diet and storing it in fat cells and then releasing that energy throughout the day. Normally, this process works very well unless disrupted by increased cellular inflammation [5,13]. As a result, the subject is constantly fatigued. At the same time, cellular inflammation disturbs the intricate satiety mechanisms in the hypothalamus, leading to increased hunger.

Metabolic Syndrome

Metabolic syndrome can be considered the first stage of the metastasis of cellular inflammation from the adipose tissue to other organs, in particular the liver and the muscles. Metabolic syndrome is not a defined condition but a cluster of associated clinical markers such as elevated waist measurement, high triglycerides, low high-density lipoprotein (HDL) cholesterol, and hyperinsulinemia. All of these symptoms can be linked to insulin resistance [15]. Metabolic syndrome can be considered prediabetes because if left untreated the conversion rate to type 2 diabetes is 5% to 10% per year [16].

Diabetes

Type 2 diabetes occurs with the destruction of beta cells in the pancreas, leading to the inability to secrete sufficient amounts of insulin to control blood sugar levels. With this comes a rapid increase in blood glucose levels with a potential corresponding increase in AGE that can bind to receptors known as RAGE, which also activate NF-κB [17].

The hydroxylated fatty acid 12-HETE, which is derived from arachidonic acid, appears to be a major player in the destruction of beta cells in the pancreas [18].

BUILDING AN ANTI-INFLAMMATORY DIET

Because obesity, metabolic syndrome, and diabetes all ultimately arise from diet-induced inflammation, the logical approach to minimize the impact of these inflammation-related conditions is to follow an anti-inflammatory diet. Before I describe the practical aspects of such an anti-inflammatory diet, I first describe how various macronutrients in any diet can be either pro-inflammatory or anti-inflammatory [19].

Macronutrients and Inflammation

Omega-6 fatty acids are the basic building blocks for a wide variety of pro-inflammatory eicosanoids. However, the real molecular foundation for pro-inflammatory eicosanoids is arachidonic acid, whereas the vast bulk of dietary omega-6 fatty consist of linoleic acid. The metabolic conversion of linoleic acid into arachidonic acid goes through several steps as shown in Fig. 1.

The enzymes delta-6 and delta-5 desaturase are rate-limiting enzymes that normally control the flux of linoleic acid into arachidonic acid. Both of these enzymes are under hormonal and dietary control [20]. The hormone insulin (controlled by the amount of carbohydrate at a meal) activates these enzymes, whereas the hormone glucagon (controlled by the amount of protein at meal) inhibits their activity. The amount of insulin released in a meal depends on the glycemic load of the carbohydrates consumed. Refined carbohydrates such found in bread, pasta, and processed foods are rapidly broken down to glucose. The more rapidly the glucose enters the bloodstream, the more rapidly insulin is released from the pancreas to remove excess glucose from the bloodstream. On the other hand, carbohydrates such as fruits and vegetables have a much lower glycemic load in a meal, meaning that they have a more limited impact (especially nonstarchy vegetables) on the rise of blood glucose levels. As a result, insulin secretion is significantly reduced, and this reduces the potential activation of delta-6 and delta-5 desaturases.

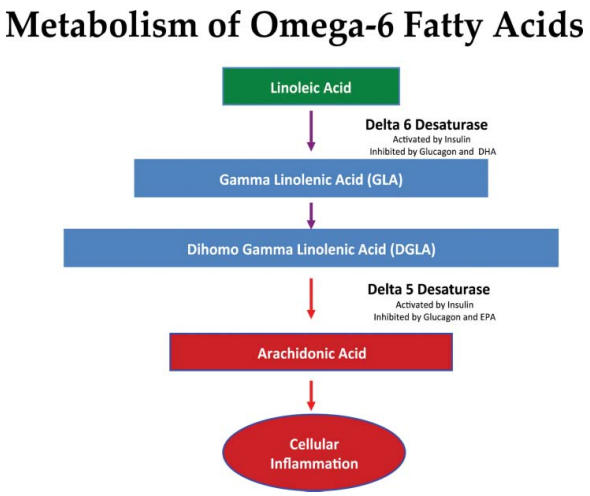

Fig. 1. Metabolism of omega-6 fatty acids.

Long-chain omega-3 fatty acids such as EPA and docosahexaenoic acid (DHA) are weak feedback inhibitors of these rate-limiting delta-6 and delta-5 desaturase enzymes necessary for the production of arachidonic acid. Therefore, as the levels of linoleic acid increase without a corresponding rise in omega-3 fatty acids, there is constant pressure to generate more arachidonic acid. When high levels of insulin (generated by a high-glycemic-load diet) are coupled with high levels of linoleic acid from the diet, the conversion of excess linoleic acid into arachidonic acid is considerably increased. This is especially true if the levels of EPA and DHA are low. With the increased levels of arachidonic acid in cells, the likelihood of producing more pro-inflammatory eicosanoids is significantly enhanced.

The role of saturated fats in the generation of inflammation is more indirect compared to omega-6 fatty acids. Toll-like receptor 4 interacts with the saturated fatty acid component of lipopolysaccharide. Saturated fats can also activate toll-like receptor 4, thus activating NF-κB although at a lower intensity than lipopolysaccharide itself [21,22].

Whereas omega-6 and saturated fats are pro-inflammatory, omega-3 has anti-inflammatory effects. As mentioned above, omega-3 fatty acids are weak inhibitors of the rate-limiting enzymes required for the generation of AA. They also compete with AA for the enzymes required to generate eicosanoids. However, the 3-dimensional structures of EPA and DHA are quite different, therefore imparting different effects. In particular, EPA and AA are very similar in 3-dimensional structure, thus making EPA a better competitive inhibitor of the cyclooxygenase enzyme required to convert AA into eicosanoids, especially into prostaglandins and thromboxanes, than DHA. As a result, the higher the level of EPA in the cell membrane relative to AA, the less likely it is that pro-inflammatory eicosanoids can be synthesized.

However, the real anti-inflammatory power of omega-3 fatty acids lies in their ability to function as substrates a wide range of proresolution mediators that include resolvins, protectins, and maresins [5,6]. These proresolution mediators are the key to reducing the levels of chronic cellular inflammation to bring any initial pro-inflammatory response back to homeostasis.

Monounsaturated fats such as oleic acid are virtually neutral in terms of eicosanoid actions. As a result, monounsaturated fats should be considered to be non-inflammatory.

Finally, there is the role of polyphenols in inflammation [23,24]. Polyphenols are the chemicals that give fruits and vegetables their color. At high enough levels, they have anti-inflammatory actions by activating the gene transcription factor PPAR-γ that inhibits the activation of NF-κB [23].

Putting It All Together

With the above short background on the hormonal effects of nutrients, it is now possible to put together the outlines of an anti-inflammatory diet.

A major problem in nutrition is that if one macronutrient nutrient goes up, then another must come down. This also means that the hormonal responses caused by a particular macronutrient nutrient will also rise and fall accordingly. The challenge is to find the right macronutrient combination to maintain the appropriate synergy of hormonal responses consistent with the continuous control of cellular inflammation.

Finding the appropriate balance of macronutrients follows a bell-shaped curve based on the protein-to–glycemic load ratio as shown in Fig. 2.

If dietary carbohydrate content in the diet is too high, this will generate excess insulin production. If this is coupled with high levels of omega-6 fatty acids, this can lead to increased cellular inflammation. At the other extreme, when the carbohydrate content is too low, this can generate ketosis with a corresponding rise in cortisol [25]. Between these 2 hormonal extreme exists a zone in which insulin levels are stabilized and blood sugar levels are stabilized, resulting in greater satiety and less fatigue.

Another important question that has to be addressed is the level of calories required for an anti-inflammatory diet to be successful. This is important because it has been shown that the consumption of excess calories also creates inflammation in the hypothalamus, leading to increased appetite [26].

HISTORY OF ANTI-INFLAMMATORY DIETS

The first anti-inflammatory diet was proposed in the book *The Zone*, published 20 years ago [19]. The central focus of this anti-inflammatory diet was one that was based on the bell-shaped curve of protein to glycemic load described in Fig. 2. In addition, there was a strong emphasis on reducing the levels of omega-6 and saturated fats with most of the fats in the diet coming from non-inflammatory monounsaturated fats.

The midpoint of the protein to glycemic load for this anti-inflammatory diet had a slight excess of carbohydrates to low-fat protein. When the overall fat content was factored in, the overall composition of the anti-inflammatory diet would be approximately 40% low-glycemic-load carbohydrates, 30% low-fat protein, and 30% fat high in monounsaturated fats and low in omega-6 and saturated fatty acids. However, this proposed anti-inflammatory diet was also a calorie-restricted one to prevent the inflammatory effect of excess calories. Thus, the absolute levels of the various macronutrients of the proposed anti-inflammatory diet are shown in Table 1 at various total caloric intakes. The usual recommendation for females would be 1200 calories per day and for males it would be 1500 calories per day.

It can be seen from Table 1 that at these caloric levels, the absolute levels of protein are adequate, the absolute levels of low-glycemic-load carbohydrates are moderate (although the volume on the plate would be significant), and the absolute levels of fats would be considered low. The macronutrient compo-

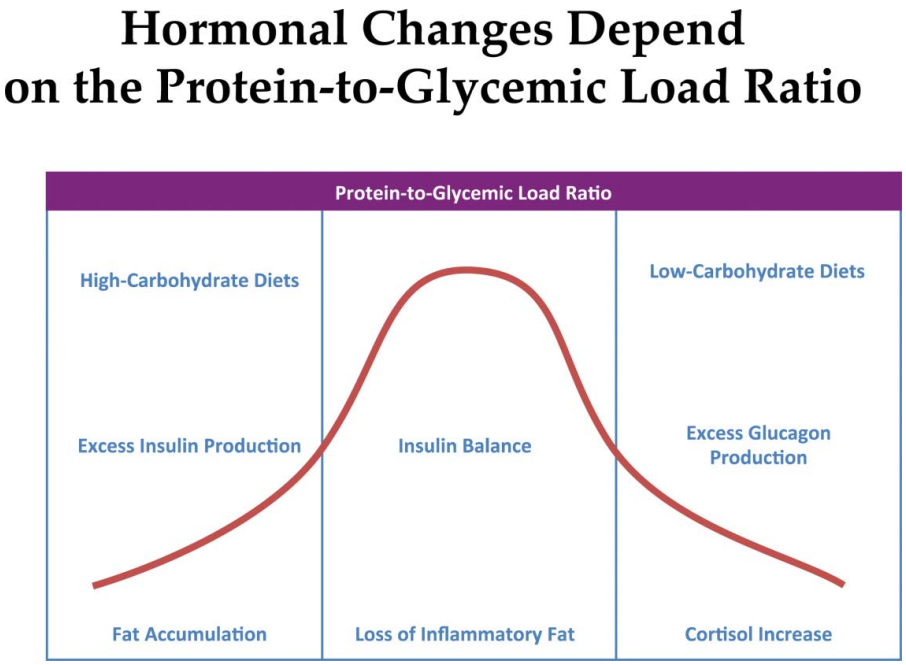

Fig. 2. Hormonal changes as a consequence of changing macronutrient composition and glycemic loads.

Table 1. Absolute Macronutrients at Various Calorie Levels

Macronutrient	1,200 calories/day	1,500 calories/day
Carbohydrate	120 g/day	150 g/day
Protein	90 g/day	112 g/day
Fat	40 g/day	50 g/day

sition on a gram basis is 1 g of fat (primarily monounsaturated fats) for every 2 g of low-fat protein and 3 g of low-glycemic-load carbohydrates (primarily nonstarchy vegetables and fruits).

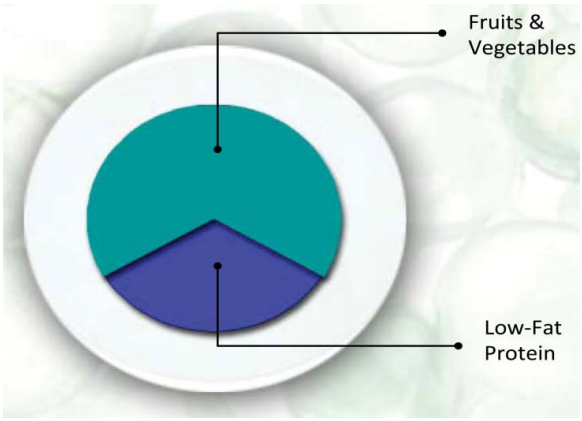

Fig. 3. Composition of a typical anti-inflammatory meal.

CLINICAL SUPPORT FOR AN ANTI-INFLAMMATORY DIET

The first clinical trial to support such a macronutrient ratio in treating diabetics was reported in 1998 [27]. In this study, it was demonstrated that insulin resistance was significantly reduced within 4 days and before any weight loss. Carefully controlled clinical trials at Harvard Medical School in 1999 gave further support to the rapid hormonal changes and improvement in satiety using such the same macronutrient ratio in overweight children [28]. Researchers at Harvard Medical School confirmed these findings in satiety in 2000 in overweight adults [29]. More recent studies at Harvard Medical School have demonstrated that this macronutrient ratio is superior in reducing inflammation compared to iso-caloric high-carbohydrate diets, even though the weight loss is identical [30].

In 2007, the Joslin Diabetes Center at Harvard Medical School announced their new dietary guidelines for treating obesity, metabolic syndrome, and diabetes [31]. These guidelines in terms of macronutrient composition and calorie content were virtually identical to those proposed more than a decade earlier [19]. Subsequent studies and other publications from the Joslin Diabetes Research Foundation has supported this anti-inflammatory diet concept [32,33].

Numerous other clinical studies of this anti-inflammatory diet having 40% of calories as carbohydrates, 30% of calories as protein, and 30% of calories as fat have demonstrated superior weight loss, improved insulin levels, increased fat loss, increased satiety, and, most important, reduced cellular inflammation [34–39].

From a visual standpoint, the composition of the plate for each meal is shown in Fig. 3.

At every meal, the plate should be divided into 3 equal sections. One section should contain low-fat protein approximately the size and thickness of the palm of the hand. Appropriate protein choices would be chicken, fish, or protein-rich vegetarian sources. The other two thirds of the plate should be filled with colorful carbohydrates (primarily nonstarchy vegetables and limited amounts of fruits). This will simultaneously maintain a low glycemic load and provide adequate levels of polyphenols. Finally, the ideal added fat would be a dash of extravirgin olive oil (approximately 5 ml). The hormonal success of this dietary balance will be indicated by the lack of hunger and maintenance of mental acuity for the next 5 hours.

CLINICAL MARKERS OF INFLAMMATORY RISK AND THEIR IDEAL RANGES

There are 3 clinical markers that are important to achieve for an anti-inflammatory diet to be considered successful. Each of these markers relates to a different component of the inflammatory response and all 3 markers should be within appropriate ranges to ensure that cellular inflammation is being managed.

AA:EPA Ratio

The first of these markers is the AA:EPA ratio. As discussed earlier, this is the first clinical marker that cellular inflammation is beginning to increase. The ideal ratio should be between 1.5 and 3. The average AA:EPA ratio in the Japanese population is 1.5 [40], whereas it is 18 in the average American population [41]. If the AA:EPA is less than 1, then the potential for bleeding increases, although there is a significant reduction in cardiovascular events compared to the use of statins [42]. As long as the AA:EPA ratio remains above 1.2, there is no indication of any increased bleeding [43].

Triglycerides : HDL Ratio

The triglycerides: HDL ratio is a surrogate marker for insulin resistance in the liver and the beginning of the development

of metabolic syndrome [44,45]. The ideal ratio should be less than 1 (using mg/dl) or less than 0.4 (using mmol/ml).

HbA1c

Glycosylated hemoglobin is a marker of long-term blood glucose control and is an indicator that type 2 diabetes is developing. It is generally accepted that HbA1c levels of greater 6.5% are indicative of diabetes and increasing mortality [46]. However, the optimal level of HbA1c should be 5% because lower levels are also associated with increased mortality [47]. These optimal ranges are shown in Table 2.

All 3 clinical parameters must be with in their optimal ranges to ensure that cellular inflammation is being controlled. If not, either a more strict anti-inflammatory diet should be employed or the addition of additional anti-inflammatory supplements should be considered.

POTENTIAL USE FOR ANTI-INFLAMMATORY SUPPLEMENTS

Often even a strict anti-inflammatory diet sometimes will not be sufficient to reach the desired ranges of the clinical markers described above. Under these circumstances, there are 2 additional anti-inflammatory supplements to consider.

Omega-3 Fatty Acids

The most important of these anti-inflammatory supplements is highly refined omega-3 fatty acids, which will help reduce the AA:EPA ratio and thus increase the proresolution potential of the diet. The definition of a highly refined omega-3 fatty acid product would be one that has very low polychlorinated biphenyl levels (5 ppb or lower). This is because all fish and the fish oils derived from them contain polychlorinated biphenyls, which are known endocrine disruptors [48,49].

A suggested serving would be about 2.5 g of supplemental EPA and DHA per day. However, the ideal dosage will be determined by titrating the blood levels of the mother to an appropriate AA:EPA ratio between 1.5 and 3. Adequate levels of these omega-3 fatty acids are critical not only for the proper neurological development of the fetus but also in reducing existing cellular inflammation in the mother.

Polyphenol Extracts

Table 2. Optimal Ranges for an Anti-inflammatory Diet

Clinical Marker	Optimal Range
AA/EPA ratio	1.5-3
TG/HDL ratio	<1 (mg/dl) or <0.4 (mmoles/ml)
HbA1c	5%

As mentioned earlier, fruits and vegetables contain polyphenols. At high enough concentrations, polyphenol extracts can activate AMP kinase via interaction with the SIRT-1 gene [5,23]. AMP kinase can be considered the central molecular switch that controls metabolism, including blood glucose control. Supplementation with purified polyphenol extracts can further increase AMP kinase activity. An appropriate dose would be 500–1000 mg of polyphenols per day.

SUMMARY

Anti-inflammatory diets are ultimately based on new breakthroughs in molecular biology that support the ability of such a dietary strategy to reduce inflammation, increase resolution, and alter gene expression. The more quickly such diets are implemented in high-risk populations, the less the likelihood of development of long-term negative metabolic consequences that are the foundation of many chronic diseases.

REFERENCES

1. Serhan CN, Ward PA, Gilroy DW, Samir S: "Fundamentals of Inflammation." Cambridge, UK: Cambridge University Press, 2010.
2. Baker RG, Hayden MS, Ghosh S: NF-κB, inflammation, and metabolic disease. Cell Metab 13:11–22, 2011.
3. monMariotto S, Suzuki Y, Persichini T, Colasanti M, Suzuki H, Cantoni O: Cross-talk between NO and arachidonic acid in inflammation. Curr Med Chem 14:1940–1944, 2007.
4. Calder PC: Dietary modification of inflammation with lipids. Proc Nutr Soc 61:345–358, 2002.
5. Sears B: "The Mediterranean Zone." New York: Random House, 2014.
6. Spite M, Claria J, Serhan CN: Resolvins, specialized proresolving lipid mediators, and their potential roles in metabolic diseases. Cell Metab 19:21–36, 2014.
7. Sears B: "The Anti-Inflammation Zone." New York: Regan Books, 2005.
8. Ndumele CE, Pradhan AD, Ridker PM: Interrelationships between inflammation, C-reactive protein, and insulin resistance. J Cardiometab Syndr 1:190–196, 2006.
9. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H: Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 17:4–12, 2006.
10. Mather SJ, Chianelli M: Radiolabelled cytokines. Q J Nucl Med 40:290–300, 1996.
11. Rifai N, Ridker PM: Inflammatory markers and coronary heart disease. Curr Opin Lipidol 13:383–389, 2002.
12. Tall AR: C-reactive protein reassessed. N Engl J Med 350: 1450–1452, 2004.
13. Sears B: "Toxic Fat." Knoxville, TN: Thomas Nelson, 2008.
14. Lionetti L, Mollica MP, Lombardi A, Cavaliere G, Gifuni G, Barletta A: From chronic overnutrition to insulin resistance: the role

of fat-storing capacity and inflammation. Nutr Metab Cardiovasc Dis 19:146–152, 2009.
15. Hotamisligil GS: Inflammation and metabolic disorders. Nature 444:860–867, 2006.
16. De Fina LF, Vega GL, Leonard D, Grundy SM: Fasting glucose, obesity, and metabolic syndrome as predictors of type 2 diabetes: the Cooper Center Longitudinal Study. J Investig Med 60: 1164–1168, 2012.
17. Bierhaus A, Stern DM, Nawroth PP: RAGE in inflammation: a new therapeutic target? Curr Opin Investig Drugs 7:985–991, 2006.
18. Wei D, Li J, Shen M, Jia W, Chen N, Chen T, Su D: Cellular production of n-3 PUFAs and reduction of n-6-to-n-3 ratios in the pancreatic beta-cells and islets enhance insulin secretion and confer protection against cytokine-induced cell death. Diabetes 59:471–478, 2010.
19. Sears B: "The Zone." NewYork: Regan Books, 1995.
20. Brenner RR: Nutritional and hormonal factors influencing desaturation of essential fatty acids. Prog Lipid Res 20:41–47, 1981.
21. Huang S, Rutkowsky JM, Snodgrass RG, Ono-Moore KD, Schneider DA, Newman JW: Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. J Lipid Res 53:2002–2013, 2012.
22. Lee JY, Plakidas A, Lee WH, Heikkinen A, Chanmugam P, Bray G: Differential modulation of toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. J Lipid Res 44:479–486, 2003.
23. Scapagnini G, Vasto S, Sonya V, Abraham NG, Nader AG, Caruso C: Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. Mol Neurobiol 44:192–201, 2011.
24. Rahman I, Biswas SK, Kirkham PA: Regulation of inflammation and redox signaling by dietary polyphenols. Biochem Pharmacol 72:1439–1452, 2006.
25. Ebbeling CB, Swain JF, Feldman HA, Wong WW, Hachey DL, Garcia-Lago E: Effects of dietary composition on energy expenditure during weight-loss maintenance. JAMA 307:2627–2634, 2012.
26. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D: Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 135:61–73, 2008.
27. Markovic TP, Campbell LV, Balasubramanian S, Jenkins AB, Fleury AC, Simons LA: Beneficial effect on average lipid levels from energy restriction and fat loss in obese individuals with or without type 2 diabetes. Diabetes Care 21:695–700, 1998.
28. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB: High glycemic index foods, overeating, and obesity. Pediatrics 103:E26, 1999.
29. Agus MS, Swain JF, Larson CL, Eckert EA, Ludwig DS: Dietary composition and physiologic adaptations to energy restriction. Am J Clin Nutr 71:901–907, 2000.
30. Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS: Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. JAMA 292:2482–2490, 2004.
31. Joslin Diabetes Research Center: 2007. Clinical Nutrition Guideline for Overweight and Obese Adults with Type 2 Diabetes, Prediabetes or Those at High Risk for Developing Type 2 Diabetes. Accessed at: http://www.joslin.org/docs/Nutrition_Guideline_Graded.pdfEPICandDiabetes
32. Hamdy O, Carver C: The Why WAIT program: improving clinical outcomes through weight management in type 2 diabetes. Curr Diab Rep 8:413–420, 2008.
33. Hamdy O, Colberg SR: "The Diabetes Breakthough." Don Mills, ON, Canada: Harlequin, 2014.
34. Layman DK, Boileau RA, Erickson DJ, Painter JE, Shiue H, Sather C, Christou DD: A reduced ratio of dietary carbohydrate to protein improves body composition and blood lipid profiles during weight loss in adult women. J Nutr 133:411–417, 2003.
35. Layman DK, Shiue H, Sather C, Erickson DJ, Baum J: Increased dietary protein modifies glucose and insulin homeostasis in adult women during weight loss. J Nutr 133:405–410, 2003.
36. Johnston CS, Tjonn SL, Swan PD, White A, Hutchins H, Sears B: Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets. Am J Clin Nutr 83:1055–1061, 2006.
37. Gannon MC, Nuttall FQ: Control of blood glucose in type 2 diabetes without weight loss by modification of diet composition. Nutr Metab 3:16, 2006.
38. Lasker DA, Evans EM, Layman DK: Moderate carbohydrate, moderate protein weight loss diet reduces cardiovascular disease risk compared to high carbohydrate, low protein diet in obese adults: a randomized clinical trial. Nutr Metab 5:30, 2008.
39. Layman DK, Evans EM, Erickson D, Seyler J, Weber J, Bagshaw D: A moderate-protein diet produces sustained weight loss and long-term changes in body composition and blood lipids in obese adults. J Nutr 139:514–521, 2009.
40. Ohnishi H, Saito Y: Eicosapentaenoic acid (EPA) reduces cardiovascular events: relationship with the EPA/arachidonic acid ratio. J Atheroscler Thromb 20:861–877, 2013.
41. Harris WS, Pottala JV, Varvel SA, Borowski JJ, Ward JN, McConnell JP: Erythrocyte omega-3 fatty acids increase and linoleic acid decreases with age: observations from 160,000 patients. Prostaglandins Leukot Essent Fatty Acids 88:257–263, 2013.
42. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y: Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 369:1090–1098, 2007.
43. Yee LD, Lester JL, Cole RM, Richardson JR, Hsu JC, Li Y: Omega-3 fatty acid supplements in women at high risk of breast cancer have dose-dependent effects on breast adipose tissue fatty acid composition. Am J Clin Nutr 91:1185–1194, 2010.
44. McLaughlin T, Reaven G, Abbasi F, Lamendola C, Saad M, Waters D: Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? Am J Cardiol 96:399–404, 2005.
45. Salazar MR, Carbajal HA, Espeche WG, Leiva Sisnieguez CE, March CE, Balbin E: Comparison of the abilities of the plasma triglyceride/high-density lipoprotein cholesterol ratio and the metabolic syndrome to identify insulin resistance. Diab Vasc Dis Res 10:346–352, 2013.

46. Levitan EB, Liu S, Stampfer MJ, Cook NR, Rexrode KM, Ridker PM: HbA1c measured in stored erythrocytes and mortality rate among middle-aged and older women. Diabetologia 51:267–275, 2008.
47. Carson AP, Fox CS, McGuire DK, Levitan EB, Laclaustra M, Mann DM: Low hemoglobin A1c and risk of all-cause mortality among U.S. adults without diabetes. Circ Cardiovasc Qual Outcomes 3:661–667, 2010.
48. Ashley JT, Ward JS, Schafer MW, Stapleton HM, Velinsky DJ: Evaluating daily exposure to polychlorinated biphenyls and polybrominated diphenyl ethers in fish oil supplements. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 8:1177–1185, 2010.
49. Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA: Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environ Health Perspect 116:761–768, 2008.