The Use of Anti-Inflammatory Nutrition To Slow The Aging Process

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President
Inflammation Research Foundation
Anti-Aging Is Best Defined As Slowing The Development Of Chronic Disease
Chronic Disease Burden Kills

- 70% of 65-yr olds have at least two chronic diseases

- Most chronic diseases have common metabolic origins

- The more chronic diseases you have the faster you die

Fontana et al Nature 511:405 (2014)
All Chronic Diseases Lead Back To Inflammation
THE SECRET KILLER

- The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER'S and other diseases
- What you can do to fight it
Chronic Diseases Associated With Excess Inflammation

- Obesity
- Metabolic Syndrome
- Type 2 Diabetes
- Heart Disease
- Cancer
- Neurological
  - Alzheimer’s, Depression, ADHD, Parkinson’s
- Auto-immune
  - Type 1 Diabetes, RA, Multiple Sclerosis
- Asthma
- Allergies
- Other inflammatory conditions ("itis")
What Is Inflammation?

- Ancient Greeks
  - Internal Fire
- Ancient Romans
  - Heat
  - Pain
  - Swelling
  - Redness
What Is Inflammation?

- Complex orchestration of pro-inflammatory and anti-inflammatory events
- Usually associated with pain
- Mediated by eicosanoids
- Treated by drugs that alter eicosanoids
  - Aspirin
  - NSAID’s
  - COX-2 inhibitors
  - Steroids
But You Need A Zone

- Too little of an inflammatory response
  - Sitting target for microbes
  - Injuries never heal

- Too much of an inflammatory response
  - The body attacks itself
Events That Turn On Inflammatory Responses

- Microbial invasion
- Injuries
- Diet
Overview Of Anti-Inflammatory Nutrition
The Science Of The Zone

- Improved hormonal control
- Resolution of inflammation
- Control of gene expression
Unique Roles For Each Dietary Intervention

- **Zone Diet**
  - Improved hormonal balance
  - Reduction of inflammation
  - Increase in satiety

- **Omega-3 Fatty Acids**
  - Acceleration of the resolution of inflammation

- **Polyphenols**
  - Activation of anti-oxidant, anti-inflammatory, and anti-aging genes
Benefits Of Being In The Zone

- Reduce the likelihood of chronic disease
- Slow the rate of aging
- Defines the evidence-based wellness
Clinical Markers of the Zone

- **AA/EPA ratio**
  - Marker of cellular inflammation
  - Maintain between 1.5 and 3

- **TG/HDL ratio**
  - Marker of insulin resistance in the liver
  - $<0.4$ (mmol/l) or $<1$ (mg/dl)

- **HbA₁C**
  - Marker of long-term glycemic control
  - 5%
Phases Of Inflammation

Initiating Event

Pro-inflammatory Initiation Response
Cellular Destruction

Anti-Inflammatory Resolution Response
Cellular Rejuvenation
What Is Cellular Inflammation?

- Mismatch between the initiation and resolution of inflammation
- Chronic activation of innate immune system
- Inflammation below the perception of pain
Innate Immune System Made Simple

Toll-Like Receptors (TLR) and AGE Receptors (RAGE)

NF-κB

DNA

Inflammatory Enzymes (COX-2) and Cytokines (IL-1, IL-6, TNF)

Cytokine Receptors

AA

PPARγ
Dietary Controls on NF-κB Activity

Omega-6 Fatty Acids, Saturated Fatty Acids, Excess Carbs, and Excess Calories

Zone Diet, Omega-3 Fatty Acids, and Polyphenols
What Causes Cellular Inflammation?
The Perfect Nutritional Storm

- Increased Omega-6 Consumption
- Increased Refined Carbohydrate Consumption
- Decreased Omega-3 Consumption
- Decreased Polyphenol Consumption
How It Happens

Omega-6 Fatty Acids

Activated by Insulin
Inhibited by Omega-3 Fats

Arachidonic Acid

Cellular Inflammation
Three Stages Of Disease

- Wellness
- Cellular Inflammation
- Chronic Disease
The Zone Diet:

Improved Hormonal Control
Food As A Drug

Food

Macronutrients
(Carbohydrates, Proteins, Fat)

Hormonal Response
(Insulin, Glucagon, Eicosanoids)
Eicosanoids Are Controlled By Dietary Fat And Insulin.

Dietary Fat

Essential Fatty Acids

Glucagon

“Good” Eicosanoids

Insulin

“Bad” Eicosanoids
The Zone Diet is Based Upon On Hormonal Control

- **High-Carbohydrate Diets**
  - Excess Dietary Glucose
  - Fat Accumulation
- **Zone**
  - Insulin Balance
  - Reduction of Cellular Inflammation
- **Ketogenic Diets**
  - Deficient Dietary Glucose
  - Cortisol Increase

Protein-to-Glycemic Load Ratio
Zone Diet Recommendations (1995)

- 40% low-glycemic load carbs
- 30% low-fat protein
- 30% monounsaturated fat, but low in omega-6 and saturated fats
- 1,200 to 1,500 calories per day
Dietary Guidelines From The Joslin Diabetes Research Center At Harvard (2007)

- 40% low glycemic load carbs
- 20-30% low-fat protein
- 30-40% monounsaturated fat
- 1,200 to 1,500 calories per day
Per Cent Calories On A 40-30-30 Dietary Balance Can Be Deceiving

<table>
<thead>
<tr>
<th>Macronutrient</th>
<th>1,200 calories/day</th>
<th>1,500 calories/day</th>
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<tbody>
<tr>
<td>Carbohydrate</td>
<td>120 g/day</td>
<td>150 g/day</td>
</tr>
<tr>
<td>Protein</td>
<td>90 g/day</td>
<td>112 g/day</td>
</tr>
<tr>
<td>Fat</td>
<td>40 g/day</td>
<td>50 g/day</td>
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</tbody>
</table>
Zone Diet Induces Rapid Changes in Hormonal Responses

Serum Insulin (change)

Plasma Glucagon (change)

High Carbohydrate, High Glycemic Load Meal

High Carbohydrate, Lower Glycemic Load Meal

Zone Meal

The Zone Diet Reduces Cellular Inflammation

How Difficult Is To Follow The Zone Diet?
Start With:

Low-Fat Protein
Balance With:

- Colorful Carbohydrates
- Low-Fat Protein
Finally Add Fat!

<table>
<thead>
<tr>
<th>Good Choices</th>
<th>Bad Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ High in Monounsaturated Fats</td>
<td>▪ High in Omega-6 and Saturated Fats</td>
</tr>
</tbody>
</table>
Vegetables
Fruits
Monounsaturated Fat
Low-fat Protein
Grains and Starches
(Use in Moderation)
The Zone Diet Is The Evolution Of The Mediterranean Diet

- It’s Mediterranean ingredients with the Zone blueprint for hormonal balance

- The more white you put on the plate, the more inflammation you create
The Zone Diet Paradox:

Calorie Restriction Without Hunger Or Fatigue
What 1,200 Calories Per Day Represents On The Zone Diet

- **Carbohydrates (120 grams)**
  - 8 servings (500 g) of cooked vegetables
  - 2 servings (200 g) of fresh fruit
  - 1 serving each of lentils (100 g) and oatmeal (100 g)
  - Provides >40 grams of total fiber

- **Protein (90 grams)**
  - Low-fat protein sources

- **Fat (40 grams)**
  - 2 tablespoons of extra virgin olive oil
The Zone Diet Is A Blueprint, Not A Philosophy

- **Vegan Zone**
  - No animal protein, no dairy or egg protein
- **Lacto-ovo Vegetarian Zone**
  - No animal protein
- **Paleo Zone**
  - No legumes, no dairy protein
- **Omnivore Zone**
  - No restrictions on protein sources
Anti-Inflammatory Supplements To The Zone Diet:

*Omega-3 Fatty Acids*

*and*

*Polyphenols*
Omega-3 Fatty Acids: The Resolution of Inflammation
Inflammation Does Not Burn Out On Its Own
What Happens When Inflammation Is Not Resolved?

- Acute Inflammation → Resolution
- Acute Inflammation → Chronic Cellular Inflammation
- Chronic Cellular Inflammation → Fibrosis
Chronic Diseases Characterized By Fibrosis

- Heart disease
- Kidney disease
- Lung disease
- Liver disease
Resolvins: Hormones of Rejuvenation

A

EPA

5-lipoxygenase → 5-HpEPE → 5S-HEPE

5-lipoxygenase → 18R-HEPE

P450

B

DHA

5-lipoxygenase → 7S-HpDHA → 7S-HDHA

15-lipoxygenase → 17S-HpDHA → 17S-HDHA

5-lipoxygenase → 7S-hydroperoxy, 17S-HDHA

7S(8)-epoxy, 17S-HDHA

RvE1

RvD1
### AA/EPA Ratio Indicates Extent of Cellular Inflammation

<table>
<thead>
<tr>
<th>AA/EPA</th>
<th>Comments</th>
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<tbody>
<tr>
<td>&lt; 1</td>
<td>Potential bleeding increase</td>
</tr>
<tr>
<td>1-3</td>
<td>Ideal for resolution of inflammation</td>
</tr>
<tr>
<td>3-6</td>
<td>Good</td>
</tr>
<tr>
<td>6-10</td>
<td>Beginning to move out of range</td>
</tr>
<tr>
<td>10-15</td>
<td>Cellular inflammation beginning to rise</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>Cellular inflammation is systemic</td>
</tr>
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</table>
How Many Omega-3 Fatty Acids Do You Need For Resolution?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Daily Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain Wellness</td>
<td>2.5 g/day</td>
</tr>
<tr>
<td>Treat Obesity, Diabetes, and CHD</td>
<td>5 g/day</td>
</tr>
<tr>
<td>Treat Chronic Pain</td>
<td>7.5 g/day</td>
</tr>
<tr>
<td>Treat Neurological Disease</td>
<td>&gt;10 g/day</td>
</tr>
</tbody>
</table>
Polyphenols:

The Color of the Zone
Polyphenols

- Provide plants with color
- Little known before 1995
- 8,000 known polyphenols
Polyphenols Modify Gene Transcription

- Anti-oxidants
  - Activation of Nrf2

- Anti-inflammatory
  - Inhibition of NF-κB

- Anti-aging
  - Activation of SIRT-1
How Many Polyphenols Do You Need?

<table>
<thead>
<tr>
<th>Function</th>
<th>Daily Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce oxidation</td>
<td>0.5 g/day</td>
</tr>
<tr>
<td>Reduce cellular inflammation</td>
<td>1 g/day</td>
</tr>
<tr>
<td>Reduce the rate of aging</td>
<td>1.5 g/day</td>
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</tbody>
</table>
Problems with Polyphenols

• Low concentration
  – 0.2% in fruits
  – 0.1% in vegetables

• Poor absorption
  – 2-20%

• Limited lifetime in the blood
  – Half life is about 2 hours
## Polyphenol Concentrations

<table>
<thead>
<tr>
<th>Polyphenol Source</th>
<th>Polyphenol content (g)/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyphenol extracts</td>
<td>40-50</td>
</tr>
<tr>
<td>Cocoa powder</td>
<td>5</td>
</tr>
<tr>
<td>Blueberries</td>
<td>0.5</td>
</tr>
<tr>
<td>Red wine</td>
<td>0.09</td>
</tr>
<tr>
<td>Spinach</td>
<td>0.07</td>
</tr>
<tr>
<td>Extra virgin olive oil</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Polyphenol Anti-Aging Actions

- Activation of AMP kinase
- Master switch for metabolism
- Mechanism of calorie restriction
AMP Kinase: The Enzyme of Life

Calorie Restriction  SIRT1  AMP Kinase

Polyphenols
Actions of AMP Kinase

Target proteins and processes activated by AMPK activation are shown in green, and those inhibited by AMPK activation are shown in red.
Reaching The Zone

- **Zone Diet**
  - Promotes hormonal balance
  - Reduces insulin resistance
  - Increases satiety

- **Omega-3 fatty acids**
  - Decreases initiation of cellular inflammation
  - Increases resolution at therapeutic levels

- **Polyphenols**
  - Anti-oxidant at low levels
  - Anti-inflammatory at moderate levels
  - Activates AMP kinase at therapeutic levels
The Gut and Aging
Our Bacterial “Organ”

- More complex than we thought
- Diet can determine overall microbe composition
- Composition can change within five days with dietary changes
- Can be source of chronic inflammation via TLR activation
Our Inner Skin That Allows Us To Live Longer

- Interface at a gigantic immunological load
  - Barbarians at the gate
  - Most dense ecological system in the world
- Mucus
  - First line of defense
- Epithelial cells
  - Primary barrier with tight junctions
- Immune cells
  - 70% of body’s immune cells are in the gut
  - Final line of defense against microbial invasion
Dietary Controls On Gut Permeability

- High-fat diets,
- Alcohol, Drugs,
- Antibiotics, and Stress

- Omega-3 Fatty Acids,
- Polyphenols,
- and Prebiotics
3 Ps of Gut Health

- Probiotics
  - Flowers

- Prebiotics
  - Fertilizer

- Polyphenols
  - Landscaper
Probiotics

- Target practice for the gut immune system
- Most come from strains in fermented foods
- Do not establish themselves in the gut
- Have limited viability
Prebiotics

- Fermentable fiber
- Provide energy for the microbes
- Promote probiotic bacteria growth
- Anaerobic fermentation of fiber into short chain fatty acids (SCFA)
  - Nutrition for microbes
  - Prevent degradation of mucus layer
  - Improve gut permeability
  - Reduce inflammation
Polyphenols

- How plants protect themselves
- Promote good microbe growth
- Inhibit pathogens
Role of Anti-Inflammatory Nutrition In Gut Health

- **Zone Diet**
  - Low-fat and calorie-restricted diet
  - Rich in fermentable fiber
  - Low in saturated and omega-6 fatty acids

- **Omega-3 fatty acids**
  - Improve gut barrier
  - Reduce inflammation

- **Polyphenols**
  - Landscapers of the microbiota
A New Powerful Message

- Diet can **turn on** inflammatory genes
- Diet can **turn off** inflammatory genes
Anti-Inflammatory Nutrition
As Gene Therapy

Polyphenols

Omega-3 Fatty Acids

Zone Diet

INFLAMMATORY GENES
Why Anti-Inflammatory Nutrition Is Important

- Cellular Inflammation
- Obesity
- Diabetes
- Alzheimer’s
Anti-Inflammatory Nutrition As 21st Century Medicine

- Reduction of cellular inflammation
- Hormonal and genetic control
- Diet will be the primary drug
- High-dose fish oil and high-dose polyphenols will be key supplements
- Return to Hippocrates
  - “Let food be your medicine and let medicine be your food”