Anti-Inflammatory Diets for the Prevention of Chronic Disease

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Objectives

• Define inflammation
• Describe how inflammation relates to chronic diseases.
• Identify role of macronutrients (carbohydrates, fat, protein) in either promoting or suppressing inflammation.
• Identify role of micronutrients (vitamins, minerals, bioactive food components) in either promoting or suppressing inflammation.
Inflammation

• **Definition:** a protective tissue response to injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissues.

• **Acute inflammation:** usually of sudden onset, marked by the classical signs, in which vascular and exudative processes predominate.
  - Classical signs: pain, heat, redness, swelling, and loss of function

• **Chronic inflammation:** may have a rapid or slow onset but is characterized primarily by its persistence and lack of clear resolution; it occurs when the tissues are unable to overcome the effects of the injuring agent.
Chronic diseases

Key Molecular Regulators:
- Prostaglandins
- Leukotrienes
- Cytokines

Cardinal signs of Inflammation:
- Calor (heat)
- Rubor (redness)
- Tumor (swelling)
- Dolor (pain)
- Loss of function

Resolution

Apoptosis
Phagocytosis
Cytokine/chemokine scavenging
Lymphatic drainage

Self-Limited

Acute Inflammation

Abscess Formation

Wound Healing Scarring

Chronic Inflammation

Adapted from: Serhan CN, AJP October 2010, Vol. 177, No. 4:1576-1591
Chronic Inflammation

- Neurodegenerative diseases
  - Alzheimer's
  - Parkinson's
- Cardiovascular diseases
  - Cardiomyopathy
  - Atherosclerosis
  - Stroke
- Musculoskeletal disorders
  - Osteoarthritis
  - Osteoporosis
  - Sarcopenia
- Metabolic disorders
  - Type 2 diabetes
  - Fatty liver disease
  - Sleep apnea
- Cancer
  - Gastric
  - Liver
  - Lung
  - Gall bladder
  - Colon
  - Rectal
  - Pancreatic
  - Prostate
  - Breast
Overweight and Obesity
Inflammation and Chronic Disease Promotion

- 70% Americans are overweight (BMI≥25) or obese (BMI≥30)
- World Health Organization predicts by 2030
  - 45% ↑ Cancer deaths
  - 34% ↑ Arthritis
  - >50% ↑ Type 2 diabetes (7th leading cause of death)
  - 50% ↑ NAFLD
  - 100% ↑ Dementia

Cancer Hallmarks

Alosco ML, Obesity (Silver Spring). 2013 Apr 27.
Hanahan and Weinberg, Cell (2011) 5:646-74
Systemic IR and inflammation

Obesity

Skeletal muscle

Adipose tissue

Liver

Steatosis
Kupffer cell activation
↑Cytokine production
ER stress

FFA uptake
↑extramyocellular adipose
Macrophage activation/recruitment

Adipocyte hypertrophy
Macrophage recruitment
Macrophage polarity switch
↑cytokine production (adipokines)
↑lipolysis
ER stress

Systemic IR and inflammation

Levels of human “networks”

Energy accumulation

→ Fat growth

→ Adipose response

→ Inflammation↑

→ Angiogenesis or vessel dilation↑
→ Adipose tissue remodeling

→ Energy Expenditure↑ Food intake↓
→ Attenuate energy accumulation

→ Insulin resistance↑
→ Hyperglycemia
→ Glucose disposal through urine

¡VIDA!
Macronutrients

- Carbohydrates (4 Cal/g)
  - 50-60% caloric intake
- Protein (4 Cal/g)
  - 1-2 g/kg body weight
- Fat (9 Cal/g)
  - <30% caloric intake
Carbohydrates

- **Good Carbs (complex carbohydrates):**
  - Starches: whole wheat pasta, rice, cereals, potatoes, corn, peas, legumes (pinto beans)
  - Fruits
  - Vegetables
  - Dairy Products (milk & yogurt)

- **Bad Carbs (anything processed):**
  - candy, chips, cookies, ice cream, etc.
Benefits of Complex Carbohydrates

- Fuel Source – 4 calories/gram
- Need glucose for your brain!
- Metabolic products: energy, CO₂, H₂O
- ↓ inflammation
- ↓ insulin resistance
- ↓ fasting glucose
- ↓ BMI
- Whole grain intake:
  - 20-40% ↓ risk in CAD
  - 20-30% ↓ in diabetes
  - 20-30% ↓ total mortality
- Other micronutrients present in complex carbohydrate sources
Simple Carbohydrates Lead to Inflammation

Refined Carbohydrates $\rightarrow$ Loss of fiber, vitamins, minerals, phytonutrients & essential fatty acids

Result $\rightarrow$ rapid swings in blood glucose & insulin; $\uparrow$ hunger and serum fatty acid levels

Acute hyperglycemia $\rightarrow$ Impaired endothelial function
$\rightarrow$ NF-$\kappa$B transcription activated
$\rightarrow$ $\uparrow$ free radicals & inflammatory cytokines

J Xu and M-H Zou, Circulation. 2009;120:1266-1286
Protein

- Fuel source – 4 calories/gram
- 2 g/kg body weight lean protein diets associated with:
  - ↓ body fat %
  - ↓ blood pressure
  - ↓ serum lipid levels
  - ↓ fasting glucose levels
  - ↑ glycemic control
  - ↓ risk for CAD, CHF, MI, and Stroke

- Plant proteins:
  - Legumes
  - Soy protein
  - Whole grains
  - Nuts

- Animal proteins:
  - Meat, chicken or fish
  - Eggs
  - Cheese
  - Milk
Fat

- Saturated: lard, butter, cheese, animal proteins
- Trans-fatty acids: Processed foods
- Monounsaturated: olive oil, olives, avocados & most nuts
- Polyunsaturated (Ω-6 and Ω-3)

- Essential: we can’t produce
  - Linoleic Acid (Ω-6): nuts, vegetable oils
  - Linolenic Acid (Ω-3): vegetable oils, cold-water fish, soybeans, flaxseeds, canola oil & walnuts
- Non-Essential: endogenous
  - Arachidonic Acid (Ω-6): chicken, beef, pork
  - DHA (Ω-3): fish
Benefits-Healthy Fat Consumption

• Fuel Source – 9 calories/gram
• Monounsaturated (oleic acid) and polyunsaturated (Ω-3 and Ω-6) fatty acids
  • ↓ Rates of CAD
  • ↓ Blood pressure
  • ↓ T-chol & LDL-C
• Ω-3
  • Anti-inflammatory
  • ↓ Anti-cancer effects (BC, CRC)
  • ↓ RA & IBD
  • ↓ neurodegenerative disorders
• Ω-6:Ω-3 ratio ≤5:1 = beneficial effects
  Western diet 15:1 = chronic inflammation

Impact of “Unhealthy” Fat

- Saturated Fats:
  - ↑ T-cholesterol, LDL-C, glucose, triglyceride, inflammatory markers;
  - ↓ insulin sensitivity

- Monounaturated Trans-Fats:
  - ↑ T-cholesterol, LDL-C, inflammatory biomarkers;
  - ↓ HDL-C levels

- Western diet 15:1 (Ω-6:Ω-3) = chronic inflammation
  - $\text{PGE}_2$
Fatty meal, stress, inflammation, mitogens

Cyclooxygenase (COX)
- COX-1
- COX-2

Lipoxygenase (LOX)
- 15-LOX
- 12-LOX
- 5-LOX

Cytochrome P450 (CYP)
- CYP2C8
- CYP2C9
- CYP2J

Prostaglandins
- PGE$_2$
- PGD$_2$

Inflammation
- Pain
- Proliferation
- Chemokine production
- VEGF synthesis
- Survival
- Migration
- Invasion
- b-FGF synthesis

Eicosanoids
- Lipoxins
  - LxA$_4$
  - LxB$_4$

Lipoxins
- Anti-Inflammation
- Allergy
- Bronchoconstriction

Leukotrienes
- LTA$_4$
- LTB$_4$
- LTC$_4$
- LTD$_4$

Prostacyclins and Thromboxanes

Epoxyeicosatrienoic acid
- 5,6-EET
- 8,9-EET
- 11,12-EET
- 14,15-EET

Decrease Inflammation
- Vasorelaxation
- Cardioprotection

sEH

Decrease Inflammation

NSAIDs

Omega-6 family

Arachidonic acid
Chronic Diseases Associated

↑Ω-6 metabolites (PGE$_2$)

- Cancer (solid tumors)
- Asthma
- Rheumatoid arthritis
- Chronic obstructive pulmonary disease (COPD)
- Cardiovascular Disease
Omega-3 (EPA/DHA)

Cyclooxygenase (COX)
- COX-1
- COX-2

Lipoxygenase (LOX)
- 15-LOX
- 12-LOX
- 5-LOX

Cytochrome P450
- CYP4A
- CYP2C8
- CYP2C9
- CYP2J

Prostaglandin
- PGE₃
- PGIl₂

Lipoxins
- 20-HEPE
- 22-HDHE

Leukotrienes
- LTB₅
- LTC₅

Thromboxanes

Anti-Inflammatory
Reduce Pain
Reduce chemokine production

Decrease Inflammation
Vasorelaxation
Cardioprotection
More potent than EET's
Improve vascular f(x)

Adapted from: C Arnold, Pharmacological Reports 2010, Vol. 62, 536-547
Micronutrients (Vitamins, minerals)
Bioactive Food Components (limonene, resveratrol, EGCG, flavonoids, etc)
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Bioactive Food Components (limonene, resveratrol, EGCG, flavonoids, etc)
Micronutrients with Antioxidant Activity

- **Vitamins:**
  - Ascorbic Acid (Vitamin C)
  - Tocopherols and Tocotrienols (α-Tocopherol: Vitamin E)
  - Carotenoids (Vitamin A)

- **Minerals:**
  - Magnesium
  - Selenium (required for other antioxidants)
  - Zinc (required for other antioxidants)

- **Other micronutrients**
  - Melatonin (hormone)
Bioactive Food Components

- 25,000 known BAFC in food supply
- Anti-inflammatory action through multiple mechanisms (ROS scavenging)

Examples of bioactive food components:
- Turmeric: Curcumin
- Chilli peppers: Capsaicin
- Ginger: [6]-Gingerol
- Green tea: Epigallocatechin-3-gallate
- Soybeans: Geristain
- Tomatoes: Lycopene
An argument for coffee: Alzheimer’s protection

- Coffee drinkers less likely to develop type 2 diabetes, stroke, depression, death from any cause, and neurodegenerative diseases, including Parkinson's and Alzheimer's
- Coffee contains polyphenols and other antioxidants
- Free radical scavenging
- Regenerated axons and dendrites
Mediterranean Diet

- Olive oil (Ω-3)
- More fish, less red meat (i.e. more Ω-3)
- Healthy grains and plant proteins
- Bread (whole wheat/whole grain)
- Abundance of fruit and vegetables
- Red wine
- Coffee!
- Caution in reductionist approach
>35,000 men

Vit E dose: (400 IU/d)

↑ in prostate in Vit E group compared to placebo ($P=0.06$)

Vit E intervention halted: 2008
>50% of individuals 60 years or older are taking supplements containing vitamin E

23% of them are taking at least 400 IU/d despite a recommended daily dietary allowance of only 22.4 IU for adult men
Vitamin E supplementation and other chronic disease?

• Modest benefit:
  • Alzheimer disease (as 1 part of a combination of oral antioxidants)
  • Age-related macular degeneration

• No benefit:
  • Prevention of cardiac events
  • Overall mortality
  • Colorectal adenomas
  • Respiratory infections in elderly individuals
  • Preeclampsia in women with type 1 diabetes
  • Prevention of cataracts or macular degeneration

Klein EA. et al JAMA, October 12, 2011—Vol 306, No. 14 1549-1559 (references within)
General Multivitamin?

- Iowa Women’s Health Study (observational cohort 38,772): ↑ risk of overall mortality with daily multivitamin in elderly women
- Physicians Health Study (N=14,641): (randomized double-blind placebo control trial) ↓ risk cancer incidence 8% Ø cancer mortality
- Risk of clinically advanced prostate cancer with 400 IU/d Vit E
- Women’s Health Initiative: Ø any cancer
- Nurses Health Study: ↓ risk colon cancer after 15 years
- Swedish Study (N=35,000 women): ↑ risk of breast cancer

Vitamins and Lifestyle (VITAL) study cohort

- 75,288 men and women
- Specifically looked at multivitamins and other supplements
- Findings
  - Multivitamins ↑ risk of breast cancer
  - Cranberry pills (Vitamin C) ↑ bladder cancer 3.44 (1.86, 6.35)
  - Zinc ↑ ovarian cancer 2.19 (1.41, 3.40)
  - Soy (multiple antioxidants) ↑ prostate cancer 1.99 (1.38, 2.87)
  - Melatonin ↑ cervical cancer 1.86 (1.19, 2.90)
  - Vitamin D ↑ thyroid cancer 1.66 (1.21, 2.28)
Final Recommendations

- Diet matters!
- Chose
  - Whole grains over white flour
  - Lean meat (especially fish)
  - Unsaturated fat
  - Variety of fruit and vegetables
- Supplements should be treated like drugs
  - Ask patients about supplement use
  - Research side-effects of supplements you might recommend
Multiple Choice Questions

1. What is the “best” fat?
   A. Saturated Fat
   B. Trans Fat
   C. Monounsaturated Fat
   D. Polyunsaturated Fat
Multiple Choice Questions

2. Inflammation causes which diseases:
   A. Obesity
   B. Diabetes
   C. Cancer
   D. None of the above
Multiple Choice Questions

3. Which is NOT a molecular regulator of inflammation?
   A. Prostaglandins
   B. Leukotrienes
   C. Cytokines
   D. Cholesterol
Multiple Choice Questions

4. If a patient asks about XX supplement for XX disease/pain/beauty concern should you:
   A. Tell them not to take it
   B. Tell them go ahead and take it
   C. Inquire about their diet to see if they are already getting adequate levels
   D. Measure blood levels
Something to Think About

Why was supplementation with the Ω-3 fatty acid, EPA a success in preventing polyps, while supplementation with Vitamin E was a failure and promoted prostate cancer?
Questions?