Inflammation…

Chronic Inflammation
And Disease

- Inflammatory response crucial for our survival. But there is a dark side.
- Biological consequences of persistent inflammation is a root cause for many diseases as varied as periodontal disease, osteoporosis, cardiovascular disease, Alzheimer's disease, depression, hypertension, type-2 diabetes, autoimmune disorders, cancer, and more.


Periodontal Disease

- Polymicrobial biofilm-associated inflammatory disease.
- Inflammatory signaling pathways lead to inflamed gingival pockets dominated by gram-negative, anaerobic, proteolytic, and motile bacteria.
- Dysregulated immune response results in prolonged inflammatory reaction and host tissue damage, acting as source of nutrients to pathogens.
- Chronic and progressive periodontal disease characterized by unresolved inflammation, fibrosis and loss of tissue structure and function.
- Despite current periodontal therapeutic approaches that target “pathogenic” species, permanent eradication of bacteria is neither possible or desirable.
Inflammation Drivers

- Result of complex interactions between genetics and environment
- Some factors include:
  - Pattern of central obesity
  - Western dietary pattern, high fructose
  - Sedentary lifestyle, lack of exercise
  - Chronic pain conditions
  - Prolonged psychosocial stress
  - Alterations in gut flora and intestinal permeability
  - Environmental exposures (smoke, toxins, endocrine disrupting chemicals)

Chronic Psychological Stress

- State of mental/emotional strain where individual perceives demands tax or exceed their adaptive capacity.

THE HPA AXIS
• Cortisol has circadian pattern, rapidly rising and peaking 30-45 minutes after awakening, then gradually declining over course of day.
• Depression associated with alterations in diurnal cortisol curve: blunted cortisol awakening response and/or inadequate decline in the evening.
• Flattening of diurnal cortisol curve is also associated with insulin resistance and type 2 diabetes mellitus.


Neuro-inflammation

• Mediated principally by reactive astrocytes and microglial cells.
• CNS threatened - microglia migrate to site and assume activated phenotype.
• Chronic neuro-inflammation linked to Alzheimer’s, anxiety, depression, and bipolar disorder. Neuro-inflammation generally precedes neurodegeneration.


Stress and Microglia

• Microglia constant surveillance mode; biosensors for stress effects on CNS.
• Mouse study: repeated unpredictable stress caused microglia in prefrontal cortex neurons to remodel neural circuits, limiting synaptic connections. All animals showed signs of anxiety and depression.
• Microglia hold “memories” of stress and have larger and more rapid response when exposed to future stressors.


Sleep and Stress

• Disruption of circadian rhythm alters gut microbiome equilibrium. Microbes and humans share circadian clock.
• Emotional and physiological stress affect gut microorganisms, impacting immune and nervous systems.
• Lactobacillus, Bifidobacterium, and Enterococcus may improve stress response.

Jegatheesan P, et al. Nutrients 2017; Mar 3(3)

• High fructose diet increases intestinal permeability.
• Bacterial endotoxin (LPS) enters bloodstream, inflammation is activated by changing insulin signaling and triggering inflammatory mediators.

Jegatheesan P, et al. Nutrients 2017; Mar 3(3)
**Review: 172 Studies to Reduce Inflammation:**

- Daily: low GL diet with minimum of 5 servings of fruits and vegetables
- Weekly: 4 portions legumes/fish, two portions white meat and one portion red meat
- Only occasional sweets optimal for reducing pro-inflammatory states associated with chronic pain.

**Glycemic Index Calculation**

GL: how rapidly a set amount of food causes blood sugar to rise

Food containing 50 g carbohydrate is given. Example below:

- 200 g of spaghetti = 50 g of carbs
- Blood samples taken every 15 minutes for first hour, then every 30 minutes, graphed and compared to 50 g of pure glucose (GI of 100)
- Retested 3 occasions and averaged with 8-10 other volunteers
- Glycemic index does not take into account serving size

**Let’s Talk Carbs**

- Provide majority calories in diet
- Body’s preferred fuel source
- Largest contributor to blood sugar control
- Human metabolomic studies show low glycemic load diet has beneficial effect on inflammation and insulin signaling

**Glycemic Load is What Really Matters**

Takes into account both GI and serving size
- GI x amount of carbohydrate (g)/100 = GL
- One teaspoon jam = 5 grams and GI 51
- GL = (51 x 5) / 100 = 2.5

Foods that slow digestion will affect GL
- Presence of fiber or fat
- Presence of acid
- Lemon or lime juice with rice; vinegar

**Dietary Fiber**

- Dietary fibers (mostly complex carbohydrates) key for healthy gut microbiota, intestinal barrier function and keeping inflammation in check
- Significant reduction in hs-CRP concentrations observed with increased fiber (30 g/d) consumption.
- Dietary fiber inversely linked to risk of death from respiratory and infectious diseases; for each 10 g/d increase in dietary fiber, mortality-relative risk from infectious and respiratory diseases decreased by 34% and 18% in men and 39% and 34% in women, respectively.
**Carbs to Fiber Ratio**

- Divide the grams of carbohydrates by 10.
- Carb to fiber ratio:
  - Higher than 10:1 is poor
  - 6:1 to 10:1 is good
  - 5:1 or less is great
- Corn flakes far left (24:1)
- Kashi GoRise cereal right (~3:1 is awesome!)

**Inflammation & Memory**

- Researchers evaluated inflammatory potential of diet in relation to mild cognitive impairment/dementia risk using DII during average follow-up of 9.7 years during Women's Health Initiative Memory Study.
- Higher inflammatory scores were significantly associated with greater cognitive decline and earlier onset of cognitive impairment.


**Anti-inflammatory diet may reduce inflammation and improve cardiovascular, metabolic, and neurologic parameters.**

**Dietary Inflammatory Index**

- Based on measuring inflammation in the body in response to specific foods (1900 studies).

**Inflammatory Food Ratings**

<table>
<thead>
<tr>
<th>FOOD</th>
<th>SERVING SIZE</th>
<th>SERVING SIZE (GRAMS)</th>
<th>IF RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGAVE NECTAR</td>
<td>1 TBSP</td>
<td>21</td>
<td>21-74</td>
</tr>
<tr>
<td>RACCAP</td>
<td>⅔ CUP</td>
<td>64</td>
<td>400</td>
</tr>
<tr>
<td>ALMOND BUTTER</td>
<td>¼ CUP</td>
<td>64</td>
<td>100</td>
</tr>
<tr>
<td>CHEESE</td>
<td>⅔ CUP</td>
<td>28.35</td>
<td>80</td>
</tr>
<tr>
<td>CHEDDAR</td>
<td>⅔ CUP</td>
<td>86</td>
<td>19</td>
</tr>
<tr>
<td>BEEF, RIBEYE</td>
<td>⅔ CUP</td>
<td>506</td>
<td>80</td>
</tr>
<tr>
<td>MUSCLE MEAT</td>
<td>⅔ CUP</td>
<td>18</td>
<td>74</td>
</tr>
<tr>
<td>SOUS D'</td>
<td>⅔ CUP</td>
<td>10%</td>
<td>40</td>
</tr>
<tr>
<td>ORGANIC, COOKED</td>
<td>⅔ CUP</td>
<td>55%</td>
<td>30</td>
</tr>
<tr>
<td>RICE, WHITE</td>
<td>⅔ CUP</td>
<td>55B</td>
<td>184</td>
</tr>
<tr>
<td>SPINACH</td>
<td>⅔ CUP</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>SALMON</td>
<td>⅔ CUP</td>
<td>85</td>
<td>65</td>
</tr>
<tr>
<td>SODA BAKED</td>
<td>⅔ CUP</td>
<td>130</td>
<td>270</td>
</tr>
<tr>
<td>TURMERIC</td>
<td>½ TSP</td>
<td>3.5</td>
<td>220</td>
</tr>
</tbody>
</table>

**Intermittent fasting elicits evolutionarily conserved, adaptive cellular responses that improve glucose regulation, increase stress resistance, and suppress inflammation.**

- 3 most widely studied regimens are alternate-day fasting, 5:2 intermittent fasting (fasting 2 days/week), and daily time-restricted feeding.
NEJM Review

• Dozens of animal and human studies reviewed to explain how fasting improves metabolism, lowering blood sugar; lessens inflammation, which improves range of issues from arthritic pain to asthma; and helps remove toxins and damaged cells, lowering risk for cancer and improving brain function.

• Data show fasting can reduce pain, stiffness, and dependency on analgesics compared to controls in RA patients.

Fish and Seafood

• Excellent source of protein high in omega 3 fatty acids. Provide vitamin D and contribute valuable nutrients: selenium, iodine, magnesium, iron and copper.

• Fish/seafood have positive effect on oral health.

• Help reduce atherosclerosis and maintain healthy blood pressure.

• Promote brain health and may help reduce the risk of depression.

• Necessary for the health of the eyes. Can help reduce dry eye syndrome.

• Crucial for health pregnancy and childhood development.

• Quells inflammation.

• Check for healthy seafood at ewg.org or Monterey Bay Aquarium.

Omega 3 Fatty Acids from Plants and Animals

- Dark green vegetables, walnut, freshly ground fish seed and other plant foods.
- Cold water fish, fish oil, fresh seaweed, clean animal foods like free range chicken, eggs, and grass-fed beef.
- ALA
- DHA
- EPA
- Intermediate Molecules
Resolution Biology

- Families of lipoxins, EPA and DHA-derived mediators (resolvins), protectin and maresins are the “brakes” for actively resolving acute inflammation.
- Take Home: resolving inflammation is “active process” partially mediated by omega 3 fatty acids.

Omega 3 and Periodontal Disease

- 30 patients with stage 3 or 4 periodontal disease treated with scaling and root planing (SRP) finished study (10 dropouts: antibiotics, COVID, etc.).
- Test group (n = 16) supplemented with 2.6 g EPA + 1.8 g DHA fish oil daily for 90 days. Control group (n = 14) received only SRP.
- Periodontal exam/salivary samples performed baseline and 3 months following initial therapy. Statistically significant reduction in bleeding on probing (BOP) and improvement of clinical attachment loss at 3 months in test group compared to control. Statistically significant higher percentage of closed pockets (probing depth ≤ 4 mm). Pro-inflammatory mediators markedly lower, anti-inflammatory IL-10 significantly higher in saliva of test vs. control group.

Omega 3 Index

- Omega-3 Index indicates % of EPA+DHA in red blood cell fatty acids.
- Should we assess omega 3 fatty acid level to optimize “anti-inflammatory” activity?
- Consider 1-2 g/day fish oil (~800-1200 mg EPA; 400-800 mg DHA.
- Note: DHA is most important during pregnancy and for young children.
Fast Facts

• Omega 3 fatty acid supplements:
  • DHA crucial during pregnancy and early childhood
  • EPA/DHA important for teens/adults/elders
  • Nordic Naturals and Carlson's reliable brands
  • 3 grams/d not linked to interaction with meds/surgery
  • Keep refrigerated after opening
  • ewg.org has lists of fish low in mercury, high in omega 3s

Magnesium

• Low magnesium intakes and serum levels associated with type 2 diabetes, metabolic syndrome, inflammation, high blood pressure, atherosclerotic vascular disease, sudden cardiac death, pain, osteoporosis, migraines, arthritis, and colon cancer.
• 50% of U.S. population consumes less than the required amount of daily magnesium.
• Deficiency associated with negative effects on calcium and vitamin D homeostasis. Magnesium required for the activation of vitamin D.
• FDA requires warning that proton pump inhibitors can cause dangerously low magnesium levels.

Magnesium and Inflammation

• Low magnesium common in chronic periodontal disease.
• Low magnesium intake associated with elevated hs-CRP (measure of inflammation in body). Adults consuming < RDA of magnesium 1.48-1.75 x more likely to have elevated hs-CRP.
• Oral magnesium supplementation decreases hs-CRP levels in healthy elders; those who are obese, and in prediabetes and diabetes.
• Hypomagnesemia may accentuate pain by unblocking NMDA receptor. Magnesium blocks NMDA receptor in spinal cord.

Magnesium Deficiency

• People with mag deficiency may have insulin resistance, menstrual cramps, leg cramps, increased pain, migraines, fatigue, anxiety and mild elevations in blood pressure.
• In more severe cases of deficiency: seizures, tingling and numbness in arms and legs, bizarre muscle movements (especially of eyes and face), personality changes, and coronary spasms can occur.
• Many medications can deplete magnesium (e.g., diuretics, PPIs, OCPs, gout medication, B2-agonists, steroids, etc.).
• Magnesium oxide, citrate, malate, glycinate and others available.
• Supplementing 300-600 mg/d (with healthy kidney function)
Definitions

- **Microbiome**—collective genomes of microorganisms in particular environment.
- **Microbiota**—community of microorganisms themselves.
- Lower diversity is marker of **dysbiosis** (microbial imbalance) and is associated with autoimmune disease, obesity, and metabolic conditions.

Valdes AM, et al. BMJ 2018;361:k2179

- Probiotics
  - Regulate/modulate immune functions, reduce risk intestinal infection.
  - Improve intestinal barrier functions, reduces endotoxemia.
  - Induce hypo-responsiveness to food antigens.
  - Improve glucose control and reduce inflammatory cytokines.
  - Inhibit tumorigenesis and may inhibit cancer progression.
  - 81 obese postmenopausal women randomized to high or low dose multi-strain probiotics or placebo for 12 weeks. Statistically significant differences in LPS, uric acid, glucose, insulin found for both doses compared to placebo.


Many dietary, lifestyle and medications can dramatically impact the microbiome and ultimately impact human health.


Patterns of Subgingival Microbial Communities

- Oral Inflammation = Systemic Inflammation
  - Severe periodontitis 6th most prevalent disease worldwide with an overall prevalence of 11.2% and around 743 million people affected.
  - Bacteria can enter bloodstream from periodontitis, untreated carious lesions.
  - Oral pathogenic bacteria including *Fusobacterium nucleatum*, *P. gingivalis*, and *A. actinomycetemcomitans* have been detected in a multitude of extra-oral tissue sites, including the lung, heart, gut, placenta, and inflamed joints.
  - *Oral Treponema* spirochetes found in brains of those with Alzheimer’s dementia and in branches of the trigeminal nerve.


- Colorectal Cancer
  - *Fusobacteria* cause excessive immune responses/tumor on cancer growth genes. Linked with colorectal cancer.
  - *Fusobacteria* have specific surface molecules assisting them to attach and invade colorectal cancer cells.
  - *F. nucleatum* associated with periodontitis, abundant in oral cavity, thought to originate there.

Esophageal Cancer

• Sixth leading cause of cancer death worldwide
• *P. gingivalis* detected in 63% of cancerous tissues, 12% adjacent tissues, and 0% of normal esophageal mucosa
• Eradication of common oral pathogen might help reduce the burden of esophageal cancer

Pancreatic Cancer and Gum Disease

• 10-year study: bacterial contents in mouthwash samples from 361 Americans who later developed pancreatic CA + 371 matched controls were analyzed.
• *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* associated with > 50% increased risk of pancreatic cancer.
• Screening tool? Prevention?


Summary of Systematic Review Analyzing the Role of Probiotics on Clinical Outcomes

Clinical Resource Tool: www.usprobioticguide.com

Turmeric (*Curcuma longa*)

• Family: Zingiberaceae (ginger family)
• Part Used: Rhizome
• Perennial plant grown in tropical areas, mostly India. Used in meat, fish and vegetable curries.
• Long history of medicinal use ~4,000 years.
• Curcuminoid pigments highly active; curcumin main curcuminoid.
Turmeric for Arthritis

- Significant anti-inflammatory activity.
- Tuft's systematic review: curcumin significantly more effective than placebo and equivalent to NSAIDs for pain relief and functional improvement.
- Results suggest curcumin and boswellia formulations could be valuable addition to OA treatment regimens by relieving symptoms while reducing safety risks.

Turmeric and Oral Health

- Turmeric/curcumin applied topically as gel or mouthwash experienced reduced grade of oral mucositis, pain, erythema intensity, and ulcerative area.
- As adjunct to mechanical means, review 5 studies show both turmeric and chlorhexidine significantly decrease plaque and gingival index.

Turmeric and Brain

- Linked to lower rates of Alzheimer's.
- Animal models: suppresses LPS induced neuroinflammation.
- Meta-analysis 6 studies: curcumin reduced depression symptoms, particularly in middle-aged patients when given at higher doses for longer periods of time.

Absorption and Safety Issues

- Turmeric/curcumin not well absorbed into bloodstream from GI tract but this may NOT matter due to impact on microbiota and intestinal barrier function.
- Turmeric/curcumin best taken 2 times per day.
- Preparations bound to phosphatidylcholine (Meriva) or piperine (2-5 mg per 500 mg curcumin) MAY offer superior absorption.
- Dose: 1000-1500 mg/d standardized extract (95% curcumin) used in most of the trials.
Ashwagandha and Stress

- Ashwagandha extract (300 mg twice daily) compared to placebo in 64 people with chronic stress.
- Serum cortisol (biological marker of stress) used to provide objective measure, as well as validated questionnaires to assess the impact of treatment on stress.
- Ashwagandha group significant reduction (P<0.001) in scores on assessment scales on day 60, as well as serum cortisol, relative to the placebo.

Ashwagandha and Sleep

- 8-week double-blind, randomized study: 250 mg or 600 mg ashwagandha extract taken in 2 divided doses significantly improved sleep quality, relative to baseline and compared to placebo.
- 10-week study 60 patients with insomnia and anxiety: 300 mg ashwagandha extract twice daily significantly improved sleep quality, sleep onset latency, and anxiety, compared to placebo.
- 12-week study 50 elderly patients (65-90 years): significant increase in sleep quality and mental alertness in morning in those taking 600 mg/d ashwagandha extract, compared to placebo.

Ashwagandha Joint Pain

- Animal models have demonstrated that ashwagandha has analgesic, anti-inflammatory and chondroprotective effects.
- 60 patients knee pain randomized to ashwagandha extract (250 mg or 125 mg Sensoril®) or placebo twice daily x 12 weeks.
- At 12 weeks, significant reduction in WOMAC and knee swelling index noted in 250 mg BID group (p<0.001) and 125 mg BID group (p<0.05).
- Pain significantly reduced in both groups (p<0.01). Group taking 250 mg BID showed earliest efficacy at 4 weeks. Well tolerated.

Ashwagandha and Weight Management?

- RDBRCT 52 subjects chronic stress given 300 mg ashwagandha extract (KSM-66®) or placebo BID for 8 weeks.
- Primary efficacy measures: Perceived Stress Scale and Food Cravings Questionnaire. Secondary measures: Oxford Happiness Questionnaire, serum cortisol, body weight, and BMI. Subjects assessed 0, 4, and 8 weeks.
- Ashwagandha group had significant improvements in primary and secondary measures, no adverse effects. *Ashwagandha root extract might help body weight management in adults under chronic stress.*
### Mindfulness Meditation
- Helps with stress perception and pain intensity, elevates mood. Quiets stream of thoughts.
- Long-time meditators have greater activation of areas responsible for sustaining attention, processing empathy, integrating emotion and cognition.
- Review of 47 trials found that meditation improves:
  - Anxiety
  - Depression
  - Pain


### Resources for Stress Reduction
- **Calm** – great app for guided meditation, bedtime stories, breathing exercises (free to $60 annual subscription).
- **Insight Timer** – ~4,000 guided meditations >1,000 teachers (self-compassion, nature, stress, podcasts). Music tracks (free to $5/mo).
- **Headspace** – meditation, videos, meditations music (free basic course, $12.99/mo, $95/year).
- **10% Happier** – performance enhancement. Busy people, stressed lives. (Free one week intro, then $100 per year).
- **Buddhify** – for the more advanced meditator. Can sort by location, activity and/or emotion. (Small monthly fee, premium is $30/yr).

---

### 73

## Move more.
- Whether it's the 7-minute workout, cycling, yoga, or taking long walks – one of surest ways to maintain heart, brain, bone and muscle health is daily exercise. **Just do it.**

## Eat food.
- Minimally processed, low glycemic load, diverse, and largely plant-based diets. Organic, local, and/or humanely raised when possible. Avoid endocrine disruptors.

## Meditate.
- Meditation widens the gap between trigger and response, allowing you to feel a greater calm and awareness. It's a game changer for almost anyone.

## Stay connected.
- Social isolation and loneliness is as dangerous as being an alcoholic or being obese. Invest in your friends and family.

## Take a multi.
- Many lack when it comes to key micronutrients. A food based multi can be insurance against the gaps. Age and gender appropriate.

## Get enough sleep.
- A good night's sleep goes a long way to maintaining health.

## Consider lab tests:
- hs-CRP, vitamin D, omega-3 index, specific micronutrients.

## Nurture spirit.
- The search for meaning and purpose is a fundamental part of being human. A richly nourished inner life is a source of strength during hard times. Look inward. Honor mystery.

---

### 75