Pain Management: Symptomatic Relief of Inflammation

Robert A. Bonakdar, MD FAAFP FACN
Director of Pain Management
Scripps Center for Integrative Medicine
@DrB_Well
Too Much or Too Little Sleep Linked to Inflammation

Can Exercise Cause Inflammation in the Body?

Just 20 minutes of exercise enough to reduce inflammation, study finds

Overview: Understand

1. Inflammation: **timing & stages** matter
2. Inflammation manifests as key **causes** of pain (and disability)
3. Inflammation has many **sources** that travels down **key pathways**
4. New upstream approaches can **modify** these pathways and **resolve** ongoing inflammation
Inflammation Has Two Stages

1. Initiation
2. Resolution

Without Resolution, Inflammation Can Become Persistent & Chronic

If the immune response is left unresolved, tissues can be negatively impacted over time.

- Fibrosis
- Scarring
- Impaired cellular Function
- Degeneration
- Hypersensitivity

Chronic Inflammation Can Lead to Chronic Diseases

**Sources**
- Inactivity
- Obesity
- Aging
- Nutrient Deficiency
  - Cellular dysfunction
  - Dysbiosis...

**Chronic Systemic Inflammation** THROUGH ACTION ON:
- Adipocytes
- Immune Cells
- Brain Cells
- Systemic and local increase in cytokine concentrations
- Immune Cells

**CAUSE**
- Insulin Resistance
- Type 2 Diabetes
- Atherosclerosis
- Alzheimer’s Disease
- Huntington’s Disease
- Parkinson’s Disease
- Cancer
- Arthritis

Top 10 Causes of Disability

1. Arthritis or rheumatism - 8.6
2. Back or spine problems - 7.6
3. Heart trouble - 3.0
4. Mental or emotional problem - 2.2
5. Lung or respiratory problem - 2.2
6. Diabetes - 2.0
7. Deafness or hearing problem - 1.9
8. Stiffness or deformity of limbs/extremities - 1.6
9. Blindness or vision problem - 1.5
10. Stroke - 1.1

Number (in millions) of 47.5 million U.S. adults with a disability

Relations of C-Reactive Protein and Obesity to the Prevalence and the Odds of Reporting Low Back Pain

- ...significant associations between... systemic inflammation (CRP) and LBP
- Specifically, those with ↑ CRP levels have nearly twice the odds of reporting LBP

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Figure 3. Assumed mode of action of RvE1 in inflammatory pain

Inflammation

- TRPV1
- TNFα
- pERK

Central terminals

Postsynaptic neurons

- Heat hyperalgesia
- NMDA-R activation
- Mechanical allodynia

Glutamate

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Mind-body therapies and control of inflammatory biology: A descriptive review

• A number of lifestyle approaches can help:
  – Exercise: resistance, aerobic or combination
  – Deep breathing
  – Meditation / MBSR
  – Yoga / Tai Chi / Chi Gong
  – Sleep optimization
  – Social Support / Connection
  – Humor…
Our intake is one of the most powerful anti-inflammatory tools
Magnesium Research 2006; 19(4): 237-43

High fructose consumption combined with low dietary magnesium intake may increase the incidence of the metabolic syndrome by inducing inflammation*
<table>
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A Program Consisting of a Phytonutrient-rich Medical Food and an Elimination Diet Ameliorated Fibromyalgia Symptoms and Promoted Toxic-element Detoxification in a Pilot Trial

1. Eliminate Allergenic foods &
   - Refined and added simple sugars
   - Artificial colorings, sweeteners;
   - Caffeinated beverages;
   - Gluten-containing grains;
   - Eggs & dairy products
   - Hi arachidonic acid foods

2.
Mindful Portion & Rate

Cutting Calories Reduces Dangerous Inflammation

Non-obese people who ate 12% less showed benefits that might protect against chronic disease.

• Faster eating (<15 min to complete meal) associated with ↑ interleukin-1β IL-6 even after accounting for caloric intake & BMI


Eating rate is associated with cardiometabolic risk factors in Korean adults Lee, K.S. et al. Nutrition, Metabolism and Cardiovascular Diseases, Volume 23, Issue 7, 635 - 641

Low Glycemic load diet increased kynurenate by $\sim40\%$ – compared with the HGL diet

Kynurenic and Quinolonic Acids Bind to NMDA Receptors

- KYNA is NMDA receptor antagonist
- QUIN is NMDA receptor agonist

High Glycemic Diet

Low Glycemic Diet

Pain

MINIREVIEW

Quinolinic acid, the inescapable neurotoxin

Gilles J. Guillemin

**Polyphenols**
(Anti-oxidant / Anti-inflammatory)

<table>
<thead>
<tr>
<th>Food</th>
<th>Health Benefits</th>
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<tr>
<td><strong>Apples</strong></td>
<td>Provide polyphenols</td>
</tr>
<tr>
<td><strong>Blackberries</strong></td>
<td>High levels of anthocyanins</td>
</tr>
<tr>
<td><strong>Black tea</strong></td>
<td>Theaflavins</td>
</tr>
<tr>
<td><strong>Blueberries</strong></td>
<td>High levels of anthocyanins</td>
</tr>
<tr>
<td><strong>Broccoli</strong></td>
<td>A range of health-giving polyphenols</td>
</tr>
<tr>
<td><strong>Cereal bran</strong></td>
<td>High in fibre and phenolic acids</td>
</tr>
<tr>
<td><strong>Cherries</strong></td>
<td>Contain antioxidant anthocyanins</td>
</tr>
<tr>
<td><strong>Cherry tomatoes</strong></td>
<td>High levels of quercatin</td>
</tr>
<tr>
<td><strong>Coffee</strong></td>
<td>Phenolic acids</td>
</tr>
<tr>
<td><strong>Cranberries</strong></td>
<td>Procyanadnin, which can prevent infections</td>
</tr>
<tr>
<td><strong>Dark chocolate</strong></td>
<td>Cocoa contains epicatechin</td>
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<tr>
<td><strong>Green tea</strong></td>
<td>Polyphenols</td>
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<tr>
<td><strong>Oranges</strong></td>
<td>Contain hesperedin, which aids a healthy heart</td>
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<tr>
<td><strong>Peaches</strong></td>
<td>Contain epicatechin and phenolic acids</td>
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<tr>
<td><strong>Plums</strong></td>
<td>Similar role to peaches</td>
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<tr>
<td><strong>Raspberries</strong></td>
<td>Contain anthocyanins</td>
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<td><strong>Red grapes</strong></td>
<td>Anthocyanins and phenolic acids</td>
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<td><strong>Red onions</strong></td>
<td>High levels of cancer-fighting quercatin</td>
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<td><strong>Spinach</strong></td>
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<tr>
<td><strong>Strawberries</strong></td>
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[www.EWG.org](http://www.EWG.org)

Polyphenols to the Rescue

Kaempferol, a dietary flavonoid, ameliorates acute inflammatory and nociceptive symptoms in gastritis, pancreatitis, and abdominal pain.

- **Kaempferol (KF) is the most abundant polyphenol in tea, fruits, vegetables, and beans**

[Reference](https://www.researchgate.net/profile/Woo_Yang2/publication/275586979_Kaempferol_a_dietary_flavonoid_ameliorates_acute_inflammatory_and_nociceptive_symptoms_in_gastritis_pancreatitis_and_abdominal_pain/links/5594c5ff08ae99aa62c5ad1c.pdf)


## Dietary Strategies for Lowering Inflammation & Pain → R’s

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SPMs

EPA and DHA are converted to SPMs that resolve inflammation. But the conversion is inefficient in the face of inflammation.

Conversion from EPA and DHA is a multi-step process that may be affected by a person’s health status.

Different SPMs work together to resolve the immune response and inflammation.

17-HDHA & 18-HEPE is reduced following fish oil supplementation in Metabolic Syndrome patients compared with healthy controls.

Figure 3. Assumed mode of action of RvE1 in inflammatory pain

Inflammation

- TRPV1
- TNFα
- Glutamate
- TNFα

RvE1↓

- pERK
- Heat hyperalgesia

Central terminals

Postsynaptic neurons

- NMDA-R
- pERK
- Mechanical allodynia
IRB-approved multi-center open case series

Study Goals:
✓ Understand the role of SPMs in clinical management of chronic inflammatory conditions
✓ Assess the impact of 6 softgels per day for 4 weeks and potential for significant difference when dose was increased to 8 softgels per day. Doses chosen considering the chronic inflammatory nature of the patient types

Patients with inflammatory conditions/symptoms (n=34)

Inflammatory condition included:
• Chronic pain
• Fibromyalgia
• Increased inflammatory markers e.g. hsCRP

Week 1
- Received 6 SPM softgels per day
- Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.

Week 4
- Received 8 SPM softgels per day
- Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.

Week 8
- Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.
Key point: Inflammatory biomarkers significantly reduced – appropriate for tracking SPM response

**hsCRP:** 43% reduction from baseline within 4 weeks and remained significantly reduced

**PGE2** was reduced by 41% at 8 wks and was shown to normalize (200-400 pg/mL) at 8 wks
SPMs and Pain:
Brief Pain Inventory (BPI) scores reduced significantly by 46% at 4 weeks and 50% at 8 weeks

At 4 and 8 weeks, there was a significant reduction in:
✓ Pain at its worst, least and average pain over last 24-hours

At 4 and 8 weeks, there was a significant reduction in interference of pain in
✓ General activity
✓ Mood
✓ Walking ability
✓ Normal work
✓ Relations with others
✓ Sleep
✓ Enjoyment of life
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An increase of 100 mg/day magnesium was associated with reductions in:

- hs-CRP
- IL-6
- TNF--R2
- sVCAM-1
Long term magnesium supplementation influences favourably the natural evolution of neuropathy in Mg-depleted type 1 diabetic patients (T1dm)

- RCT: 110 DM; Low Mag; (RBCMg < 2.3 mMol/l)
- Tx: to receive 300 mg Mg++ daily x 5 yrs
- EMG normalized only in early PNP
- HgA1c improved but not significant
- Longer DM and lower Mag predict worsen.

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<th>Neuropathy At 5 years</th>
<th>Decrease</th>
<th>No Change</th>
<th>Worsening</th>
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<tr>
<td>Magnesium</td>
<td>39%</td>
<td>49%</td>
<td>12%</td>
</tr>
<tr>
<td>Control</td>
<td>8%</td>
<td>31%</td>
<td>61%</td>
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p < 0.0001
Vitamin D Deficiency Promotes Skeletal Muscle Hypersensitivity and Sensory Hyperinnervation

Sarah E. Tague, Gwenaëlle L. Clarke, Michelle K. Winter, Kenneth E. McCarson, Douglas E. Wright, and Peter G. Smith

Departments of Molecular and Integrative Physiology, Pharmacology, Toxicology and Therapeutics, and Anatomy and Cell Biology, and Kansas Intellectual and Developmental Disabilities Research Center, University of Kansas Medical Center, Kansas City, Kansas 66160
Vitamin D & Inflammatory Cytokines

• RDBPCT of 4,000 IU Vit D₃ to patients on analgesics for chronic pain

• Those on vitamin D versus placebo noted a significantly larger decline in pain scores & rescue medications at 3 months.

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<th>PGE2 Decrease</th>
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<tr>
<td>Vit D</td>
<td>54.3%</td>
<td>39.2%</td>
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<tr>
<td>Placebo</td>
<td>16.1%</td>
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Oxidative Stress Correlates with Headache Symptoms in Fibromyalgia: Coenzyme Q₁₀ Effect on Clinical Improvement

- Coq₁₀ 300mg/day able to improve energy production & reduce pain by >50%
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Anti-inflammatory effects of bifidobacteria by inhibition of LPS-induced NF-kB activation

Christian U Riedel, Frey, K, and Blum, Stephanie

Inflamm Bowel Dis ● Volume 14, Number 11, November 2008
Hops & UC-II

Nutritional Approach for Relief of Joint Discomfort: A 12-week, Open-case Series and Illustrative Case Report

- Hops (THIAAs) 600 mg/d &
- Undenatured type 2 collagen (UC-II)
- MSQ decreased from 20.76 $\rightarrow$ 12.24 $\pm$ after 2 wk ($P < .001$).
- More than 2/3 of participants able to discontinue use of analgesics

Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

• 8 RCTs

• These RCTs provide scientific evidence that supports the efficacy of turmeric extract (about 1000 mg/day of curcumin) in the treatment of arthritis.

Daily JW, Yang M, Park S. Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis- A Systematic Review and Meta-Analysis of Randomized Clinical Trials
The Use of Ginger (Zingiber officinale) for the Treatment of Pain: A Systematic Review of Clinical Trials

• …the available data provide tentative support for the antiinflammatory role of Z. officinale constituents, which may reduce the subjective experience of pain in some conditions such as osteoarthritis.
Combinations

• Inflavonoid Intensive Care
• Ultrainflammex Powder*
  – Turmeric
  – Ginger
  – Quercetin
  – Bioflavanoids
  – Protein & Amino Acids*
Next Steps: Can we begin to use these approaches in our practice?

A protein-enriched low glycemic index diet with omega-3 polyunsaturated fatty acid supplementation exerts beneficial effects on metabolic control in type 2 diabetes.

- This diet “in a real-life clinical setting improves glycemic control and also reduces waist circumference and silent inflammation…”
Conclusions

• Chronic inflammation deserves special attention
• While there are many approaches to reducing inflammation and pain,
• OPTIMIZING OUR INTAKE is a foundationally important way to resolve chronic inflammation and pain
• An individualized approach which guides our patients towards a healing diet and evidence based supplementation is key.
Pain Management: Symptomatic Relief of Inflammation

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