~ Inflammation ~
Keep it, treat it or find its root?
An evidence based review

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Objectives and Disclosures

- Review of acute and chronic inflammation
- Discuss the role of the microbiome in inflammation
- Understand the current literature around NSAIDs for inflammation
- Review of treatment options: botanical, dietary and lifestyle factors

- Disclosures: President, Direct Osteopathic Primary Care in north Denver.
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- Sidney Dungan OMS 4 and Reese Beisser OMS 3 who contributed to this lecture.
An osteopath is only a human engineer, who should understand all the laws governing his engine and thereby master disease.

Andrew Taylor Still
Inflammation

- The process by which the immune system recognizes and removes harmful stimuli and begins the healing process.
- There are two main types of inflammation: acute and chronic.
The Problem of Pain

- Over the past 2 decades the number of American adults suffering from pain increased from 120.2 to 178 MILLION.
- That is 41% of the adult population
Pain Today – According to the NIH

- Pain
  - affects more Americans than diabetes, heart disease and cancer COMBINED.
  - is cited as the most common reason Americans access the health care system.
  - is a leading cause of disability and it is a major contributor to health care costs.
- America spends >$600 BILLION per year on the treatment of pain
- Chronic pain is the most common cause of long-term disability.
- According to the National Center for Health Statistics (2006), approximately 76.2 million, one in every four Americans, have suffered from pain that lasts longer than 24 hours and millions more suffer from acute pain.

1 in 4
Acute inflammation

- Acute inflammation may be regarded as the first line of defense against injury
- 5 cardinal signs\(^1\):
  - rubor (due to vasodilation promoted by prostaglandin, histamine, serotonin, bradykinin)
  - calor (due to increased blood flow)
  - tumor (due to increased vascular permeability, which allows leukocytes to extravasate into the extravascular space)
  - dolor (due to irritation of nerve endings by physical and chemical forces)
  - functio laesa (due to pain causing reflex guarding or spasm)
- If this well-orchestrated acute inflammatory response becomes dysregulated, it can progress to chronic inflammation\(^1^4\)
- Fibroblast dysregulation results in formation of granulomas, adhesions, contractures, keloids
- Continued secretion of cytokines and other factors, ongoing tissue destruction, and impaired homeostasis\(^1^0\)
Acute inflammation

- 3 phases:
  - **Phase I: Acute Phase**
    - Early: inflammatory response (2-4 days).
      - Insult → acute reflex vasoconstriction → vasodilation (release of chemical mediators from mast cells and platelets)
    - Late: tissue repair (2 weeks)
      - Phagocytosis by neutrophils and macrophages to remove foreign and dead tissues
      - Macrophages secrete chemokines, cytokines, and GFs (including TNF alpha and IL-6) which recruit fibroblasts (responsible for collagen synthesis), stem cells, osteoprogenitor cells (responsible for bone synthesis)\(^\text{10}\)
  - **Phase II: Tissue Formation/Regeneration (2-3 weeks)**
    - Re-epithelization, capillarization (formation of granulation tissue), fibroplasia (formation of collagen and scar tissue)
    - Macrophages switch to reparative phenotype\(^\text{3}\)
  - **Phase III: Remodeling Phase (up to 1 year; non-pathologic)**
    - Strengthening of repaired tissue (organization of collagen)
    - Restoration of tissue homeostasis
    - Reduction of fibroblasts and macrophages to pre-injury levels (exit site of injury or eliminated by apoptosis)\(^\text{3}\)
Chronic Inflammation - Prolonged inflammatory changes lasting several months to years

Causes:\n- Dysregulation of acute inflammation
- Failure to remove causative agent (virus, protozoa, fungi, toxins, foreign materials)
- Autoimmune disorders in which the body attacks healthy tissues
- Inflammatory and biomechanical inducers causing oxidative stress and mitochondrial dysfunction (free radicals, oxidized lipoproteins, homocysteine)
Chronic Inflammation - Prolonged inflammatory changes lasting several months to years

Risk factors\textsuperscript{14}:

- **Obesity**: adipocytes secrete inflammatory mediators
- **Diet**: Diet rich in \textit{saturated fat, trans-fats, or refined sugar} is associated with higher production of pro-inflammatory molecules
- **Smoking**: Causes localized inflammation and lowers production of anti-inflammatory molecules
- **Low sex hormones**: testosterone and estrogen suppress the production and secretion of pro-inflammatory markers
- **Stress**: physical and emotional stress are associated with inflammatory cytokine release
The Balance of Inflammation ~ from an Osteopathic lens

- The Wisdom of Inflammation

- Edema = bracing. This facilitates blood flow to the injury. Circulation brings macrophages and inflammatory markers.
  - Macrophages are required to recruit osteoblasts and osteoclasts
  - Our body’s clean up crew is on the way to a new injury or fracture site right away

- Our Health knows how to heal. The beautiful biochemistry of healing is more complicated and intricate than any of our modern interventions.

- Symptoms are messengers, an expression of the Health and what it needs

- How do we support Health and know when to intervene?
- How can we see symptoms in the larger context of root cause?
The "Big Bang" in Obese fat: Events initiating obesity-induced adipose tissue inflammation

- Intestinal inflammation precedes and strongly correlates with diet-induced obesity and insulin resistance
The Effect of Diet on Inflammation

- Article: The relationship between the dietary inflammatory index and prevalence of radiographic symptomatic osteoarthritis: data from the Osteoarthritis Initiative
  - N=4358 from the Osteoarthritis Initiative
  - Knee pain: clinical symptoms and Xray
  - Controlled for 11 confounders: weight and chronic disease

- Participants with the highest dietary inflammatory index score had a significantly higher level of radiographic symptomatic knee OA
Diet and Inflammation

- Anti-inflammatory foods: Think Mediterranean Diet
  - Phytochemicals and micronutrients found in vegetables and fruit
  - Fiber/Whole grains
- Pro-inflammatory: Think SAD (Standard American Diet)
  - Saturated fatty acids
  - Trans fatty acids
  - Processed food
Diet alone might not be the only culprit: obesity as a root of inflammation
Solutions to the metabolic and musculoskeletal inflammatory interface

“Although there are several candidates for dietary intervention, prebiotic fiber and probiotic supplementation targeting the microbiome (Nicolucci et al., 2017; Parnell et al., 2017), and decreased intake of dietary sugar (Te Morenga et al., 2013) are three safe, readily available, and translatable dietary interventions to protect against MSK damage due to metabolic disturbance that warrant further investigation.”
Inflammation and the microbiome

- Dysbiosis and “leaky gut” have been studied in association with increase risk for ankylosing spondylitis and spondyloarthritis
  - Subclinical gut inflammation causes larger proteins (like zonulin—a biomarker for dysbiosis) to pass through the gap junctions in the gut and become absorbed in general circulation.
  - This increases lipopolysaccharide activation and activates macrophages releasing the major players of inflammation: IL-1β, IL-4, IL-6, IL-10, TNF-α, CRP
Summary – Pain and Inflammation, there is more to the picture than meets the eye
Treatment of Inflammation
Evidence Based Medicine on anti-inflammatory medication use in acute inflammation

- **Yes to anti-inflammatory medications in acute inflammation:**
  - **Bone:**
    - Results of large 2019 study suggest that the use of ASA for DVT prophylaxis in ankle fracture patients is safe and without risk for delayed union, nonunion or malunion.\(^8\)
  - **Tendon:**
    - A 2020 study showed that administration of postoperative NSAIDs and duration of their use did not influence clinical outcomes of rotator cuff repair.\(^9\)
  - **Ligament:**
    - Research suggests that the benefit of NSAIDs in ligamentous injury may be less likely from decreasing inflammation, and more likely from limiting the pain and swelling of these injuries, increasing patients’ chances of regaining function and returning to activity sooner. Studies have demonstrated that treatment of ligamentous ankle injuries with nonselective NSAIDs results in less pain and an earlier functional recovery compared to treatment with placebo.\(^{15,13}\)
  - **Neuro:**
    - Anti-inflammatories in neuroinflammation are generally recommended, as neuroinflammation in the damaged mammalian brain triggers glial scarring that hinders axon rewiring.\(^3\)
Evidence Based Medicine on anti-inflammatory medication use in acute inflammation

- **No to anti-inflammatory medications in acute inflammation:**
  - **Bone:**
    - TNF-alpha plays a crucial role in promoting postnatal bone repair through the induction of osteoprogenitor cell recruitment or osteogenic cell activation in the context of intramembranous bone formation. In a study of TNF-alpha receptor knockout mice, both models of bone repair (marrow ablation and simple transverse fracture) demonstrated delayed bone healing in the TNF-alpha receptor deficient mice.⁶
    - Similarly, macrophage depletion in a tibial fracture model in mice resulted in smaller callus formation, less bone deposition, and more fibrotic tissue.¹⁷
    - 3 of 20 limbs from animals treated with prednisone achieved radiographic union while 13 of 16 control limbs achieved union. The radiographic density of bone in the defect as well as callus size were greater in the control limbs than in the limbs from prednisone-treated animals.¹⁸
    - There was a marked association between nonunion and the use of NSAIDs after injury (p = 0.000001) and delayed healing was noted in patients who took NSAIDs and whose fractures had united.⁷
  - **Tendon:**
    - Given that the pathophysiological process of tendinopathy is degenerative rather than primarily inflammatory, there appears to be little role for NSAIDs outside of the initial symptomatic pain relief during the first few days after injury.¹⁵
Alternatives to NSAIDs

- Acetaminophen
  - shown to be as effective as NSAIDs for pain reduction after musculoskeletal injury\(^4\)

- Topical NSAIDs
  - A systematic review of randomized controlled trials reported that topical NSAIDs significantly reduced pain and resulted in low incidences of systemic and local adverse effects.\(^{12}\)

- Immobilization, ice, compression, elevation (especially during phase I)

- Heat during phase II and III
  - Heat, resistance and proprioception exercises during phase III to encourage tissue remodeling and alignment
Treatment: Lifestyle Modification

- **Physical exercise**: human clinical trials have shown that energy expenditure through exercise lowers multiple proinflammatory molecules and cytokines independently of weight loss

- **Dietary considerations**
  - **Low-glycemic diet**: Diet with a high glycemic index is related to high risk of stroke, coronary heart disease, and type 2 diabetes mellitus. It is beneficial to limit consumption of inflammation-promoting foods like sodas, refined carbohydrates, fructose corn syrup in a diet.
  - **Reduce intake of saturated and trans fats**: Dietary saturated and synthetic trans-fats aggravate inflammation, while omega-3 polyunsaturated fats appear to be anti-inflammatory.
  - **Fruits and vegetables**: Blueberries, apples, brussels sprouts, cabbage, broccoli, and cauliflower are high in natural antioxidants, polyphenols, and other anti-inflammatory compounds.
  - **Fiber**: High intake of dietary soluble and insoluble fiber is associated with lowering levels of IL-6 and TNF-alpha.

- **Healing Dysbiosis**
Treatment: Turmeric

- **Mechanism of action**: cox-2 inhibitor (like NSAIDs)
- **Dosage** – generally >1500 mg (500 mg curcuminoids) two to three times daily for Osteoarthritis
  - ½ life is ~ 2 hours so BID-TID dosing is required
  - Take with fatty meal an/or with black pepper (bioperine or piperine) to enhance absorption of curcuminoids
  - Look for preparations of rhizome (root) and dosage in curcuminoids (active ingredient)
  - Other preparations that have been made to enhance absorption: Meriva and Theracurmin
- **Need to know**: hold for surgery as you would other NSAIDs. Turmeric has antiplatelet effects.
- **Adverse effects**: diarrhea, headache, nausea, can stimulate gallbladder contractions, can increase risk for calcium oxylate kidney stones
- For complete review of Turmeric check out Consumer Labs [https://www.consumerlab.com/](https://www.consumerlab.com/)
Treatment: Turmeric


  This 2018 review summarized updated information on the traditional uses, chemical constituents, and bioactive compounds of turmeric, to explore its antinociceptive effects in pathological pain and evaluate future therapeutic opportunities. Pathological pain was evaluated in relation to sciatic nerve injury, spinal cord injury, diabetic neuropathy, alcoholic neuropathy, opioid tolerance or opioid-induced hyperalgesia, and chemotherapy induced peripheral neuroinflammation.

- **Summary**: Curcumin plays a beneficial role in the treatment of pathological pain. The clinical studies reviewed provide compelling evidence and justification for the use of curcumin as a therapeutic treatment for pain relief. Curcumin was shown to be generally well tolerated at high doses. The bioavailability of curcumin is addressed, including the use of adjuvants such as piperine and phospholipids. The authors recommend more high-quality clinical studies be undertaken to evaluate the clinical effectiveness of curcumin in subgroups of patients suffering from pathological pain.
Treatment: CBD

- What to look for:
  - **Active ingredient:** Cannabidiol (CBD) is an active ingredient derived from the hemp plant.
    - BEST – look for a product that lists the amount of CBD per serving (not per bottle)
    - Avoid – products listing hemp oil or merely cannabinoids – these products tend to have unpredictable amounts of CBD
    - Hemp extract – may contain significant amounts of CBD (Hemp oil is unlikely to have predictable dosage of CBD)
  - **Dosing** – variable most studies with therapeutic benefit (seizure) have used 300 mg or more. Typical dosing is 30 mg daily.
    - Fat soluble – best with a fatty meal
    - Half life: 24 hours – more with fatty meals (up to 36 hours)
  - **Mechanism:** modulation of the endocannabinoid system
  - **Adverse effects:** gastrointestinal s/e at higher doses
Treatment: CBD


- **Summary:** This was a review evaluating the recent preclinical and advanced clinical trials on cannabis-based medicines, including CBD, and pain and inflammation.

- Patients with chronic Arthritic and musculoskeletal pain were reported to be the most prevalent users of CBD products. Numerous preclinical studies have shown that cannabinoid receptor agonists block pain and attenuate inflammation. The latter may be due to CBD’s ability to up-regulate cannabinoid receptor activity or increase endocannabinoid production.

- Included in the review were 79 trials that “concluded that there was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity.” Furthermore, preclinical evidence suggests that CBD protects against inflammatory intestinal inflammation and may have a use in inflammatory bowel diseases.
Treatment: Boswellia

- **Boswellia serrata** - the gum resin of Indian Frankincense tree: thought to contain boswellic acids (AKBA) that have anti-inflammatory properties.

- **Mechanism of action:** AKBA is a potent inhibitor of 5 lipoxygenase, a key enzyme in the biosynthesis of leukotrienes. Also appears to inhibit matric metalloproteinases MMP-3s that break down cartilage, collagen and connective tissue.

- **Dosage:** Typical dose of boswellia extract is 100-500 mg daily two to three times daily
  - Tips: If only boswellia resins are listed it is less likely to be as potent as boswellia extract as only 1% of the resin is AKBA while 6-40% of the extract is AKBA.
  - Take along with fatty foods to enhance absorption

- **Adverse effects:** few, some report gastrointestinal – diarrhea
Treatment: Boswellia


- **Summary**: The reviewers from Tufts Medical Center concluded that curcumin and boswellia formulations were statistically significantly more effective than placebo for pain relief and functional improvement. Curcumin had similar efficacy outcomes to NSAIDs and participants taking curcumin were significantly less likely to experience gastrointestinal adverse events. There were no significant differences between curcumin, boswellia and placebo in safety outcomes. Reviewers suggest that curcumin or boswellia formulations could be a ‘valuable treatment for relieving symptoms of knee OA, while also reducing safety risk.’ Limitations of the review included a limited number of trials and small study sizes.
Treatment: Others to consider

- **Green and black tea polyphenols:** Tea polyphenols are associated with a reduction in CRP in human clinical studies.

- **Fish Oil:** The richest source of the omega-3 fatty acids. Higher intake of omega-3 fatty acids is associated with lowering levels of TNF-alpha, CRP, and IL-6.

- **Micronutrients:** Magnesium, vitamin D, vitamin E, zinc and selenium.
  - Magnesium is listed as one of the most anti-inflammatory dietary factors, and its intake is associated with lowering of hsCRP, IL-6, and TNF-alpha activity.
  - Vitamin D exerts its anti-inflammatory activity by suppressing inflammatory mediators such as prostaglandins and nuclear factor kappa-light-chain-enhancer of activated B cells.
  - Vitamin E, zinc, and selenium act as antioxidants in the body.
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MD: Mediterranean diet; CVD: Cardiovascular disease; CDD, Chronic degenerative disease; PUFA: Polysaturated fatty acids; MTHFR: Methyltetrahydrofolate reductase; FTO: Fat mass and obesity-associated; MnSOD: Manganese superoxide dismutase; HMGCR: 3-Hydroxy-3-methylglutaryl-coa reductase gene; MCR4: Melanocortin-4 receptor; TNFα: Tumor necrosis factor-α; NFκB: Nuclear factor kappa-light-chain-enhancer of activated B cells; IL: Interleukin; GSTM: Glutathione S-transferase mu.
Treatment: Osteopathy
References