Nutrition and Pain

Food as Medicine

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Disclosures

• None
“Our food should be our medicine and our medicine should be our food”

~ Hippocrates
Nutrition & Pain: A Complicated Relationship......Involves Inflammation

• Complex interaction between food, inflammation, pain

• Many different biochemical rxn’s with positive and negative feedback regulation

• Misstep at any one of many different steps→ induce inflammatory cascade if not caught by intrinsic protective mechanisms

• Because of the complexity of the systems involved......Current literature exploring the role between diet & pain is quite heterogeneous, vast and sometimes difficult to understand!
Complex pathways....

**Hormesis** - refers to a biphasic dose response to an environmental agent characterized by low dose stim or beneficial effect & a high dose inhibitory/toxic FX

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Ex: Antioxidants such as Glutathione play a pivotal role in reducing oxidative stress

TNF-proinflammatory

But......Glutathione can possess prooxidant activity causing a hormetic effect enabling the body to bolster its endogenous antioxidant defenses

TNF- triggers anti-inflammatory cytokines
Inflammation:

• Normal defense mechanism that protects host!
• Crucial to initiate pathogen-killing and tissue – repair processes to restore tissue homeostasis
• Normally tightly-regulated to minimize collateral tissue damage
• Regulation requires the activation of feedback pathways
  • inhibition of proinflammatory mediators,
  • alterations in inflammatory mediator receptor density or release
  • recruitment/activation of regulatory cells
Inflammation - Pathological

• Dysregulation of normal control processes
  • Can have a genetic predisposition to dysregulation of proinflammatory and antiinflammatory cytokines→ chronically ill individuals; ?chronic pain pts?
  • *Dietary choices that lead to depletion of antiinflam or antioxidant precursors
  • Altered ratio: bad gut bacteria > good gut bacteria→ increased proinflam. Mediators---→ chronic systemic inflammation

• CSI- has been associated w/obesity, T2D and neurodegenerative disorders

• & PAIN

• (Amor et al., 2014; Cani et al., 2007; Minihane et al., 2015).
Inflammation - Pathological

• During inflammation, several different types of cells promote the production of pro-inflammatory mediators:
  • Including interleukin (IL)-1β, IL-6, IL-8, among others;
  • Tumor necrosis factor (TNF)-α
  • Reactive oxygen species (ROS) aka free radicals
  • Nitric oxide (NO)
  • Prostaglandins (PGs)
  • NF-KB
“All disease begins in the gut!”

-Hippocrates
Gut Microbiome and the relationship between inflammation, pain and diet: First line of defense

• Food meet the gut microbiota initially before being absorbed as bioactive products
• Therefore, any issue regarding the relationship between diet and pain is closely related to the gut flora (GM)
• Many bioactive substances that act as anti-inflammatory mediators are first introduced to our systems in the gut:
  SCFA's (ex: acetate, propionate, and butyrate) anti-inflammatory mediators produced by bacterial fermentation of dietary fiber in the GI tract
  A diet enriched in plant-derived fibers such as Psyllium can alleviate pain in irritable bowel syndrome (IBS) via the GM-released SCFAs
Gut Microbiome

• Most human bacteria fall within 4 general phyla:
  • *Actinobacteria, Firmicutes, Proteobacteria, Bacteroidetes*

• Gut Bacteria/flora
  • maintain the integrity of the gut lining
  • proper pH balance
  • Convert sugars into SCFA's
  • Synthesize many enzymes, vitamins and hormones
Gut Flora

- Average human male - 30 trillion cells w/~ 40 trillion bacteria, most of which reside in his digestive tract

- Environmental Factors-
  - DIETARY habits
  - drug treatments
  - Stress
  - Genetics
  - Age and intestinal motility
  - Stool frequency (lose ~ few trillion w/BM)

- Weizmann Institute of Science
Composition changes signal potential health problems:

• Numerous studies have reported changes in the gut flora during not only obesity, diabetes, and liver diseases but also cancer and even neurodegenerative diseases.

• Some metabolic disorders, such as obesity and diabetes, are associated with shifts in the microbiota at the phylum level (i.e., in the Firmicutes/Bacteroidetes ratio).

• Potential source/target of novel therapeutics.
Potential source of novel therapeutics? 
Fecal Microbial Transplant

• Excellent response rates (>90%) have been reported in relation to FMT for antibiotic-resistant *C. difficile* (van Nood E; Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013;368:407–415)

• Believed that FMT works by repopulating the patient’s microbiome with diverse microorganisms that competitively exclude *C. difficile*.

• Not really novel..... 340 AD- *Zhou Hou Bei Ji Fang* “A Handbook of Prescription for Emergencies” the first Chinese emergency medicine book- stated that pts dying from severe diarrhea could be cured with a swallow of a human feces suspension.
FMT

• Safe; except...... 2019- 73 yo man died after FMT
  • “The man was a participant in a clinical trial run at Massachusetts General Hospital and received fecal transplant capsules made in November with fecal material from one stool donor, according to a paper published Wednesday in the New England Journal of Medicine.”

• “In Boston scientists have offered FMT through clinical trials to people with peanut allergies and Crohn’s disease as well as to people who are obese.” STAT website

• “…….investigating the effect of fecal transplants before a stem cell transplant; the other is evaluating fecal transplants as a treatment for hepatic encephalopathy…” STAT
Leave your drugs in the chemist's pot if you can cure the patient with food.

-Hippocrates
Can diet really affect pain?

• A systematic review and meta-analysis of nutrition interventions for chronic noncancer pain- 2018

• 13 of 16 studies found sig reduction in participant reported pain

• vegan ($n = 7$); vegetarian ($n = 3$); Mediterranean diet ($n = 2$); anti-inflammatory diet ($n = 1$)

• Studies that altered the overall dietary pattern, or intake of one specific nutrient had greater reductions in pain scores than studies that prescribed a supplement or fasting diet

A systematic review and meta-analysis of nutrition interventions for chronic noncancer pain Brain, K. et al J.Hum Nutr&Diet 2018;32(2) 198-225
Diet - pain

• Systematic reviews – Looking at Fibromyalgia and RA

• Effect of specific diet interventions (vegetarian, vegan and the Mediterranean diet) on self-reported pain

• Statistically significant differences in pain scores c/w SAD

Fibromyalgia

• increased oxidative stress parameters are more strongly associated with severity of FMS. Involvement of TRPM2 and TRPV1 channels on hyperalgesia, apoptosis and oxidative stress in rat fibromyalgia model: Protective role of selenium. Sci Rep. 2017 Dec 13;7(1):17543)

Garlic

• “The effect of a garlic supplement on the pro-inflammatory adipocytokines, resistin and tumor necrosis factor-alpha, and on pain severity, in overweight or obese women with knee osteoarthritis”

• 76/80 post-menopausal overweight or obese women w/mild to moderate knee OA

• 1000 mg garlic/day for 12 weeks At week 12, resistin conc. Sig ↓ in garlic group

• Serum TNF-α levels did not change significantly within or between the two groups.

• Pain scores were significantly reduced in the garlic (P = 0.002), but not in the placebo (P = 0.674), group

• Phytomedicine. 2018 Sep 15;48:70-75.
One Link:

Most of the studies showing pain reduction were using plant-based diets!

What is in plants that allows our bodies to fight inflammation and ultimately reduce pain?
How can the food we eat influence our pain? They provide anti-inflammatory mediators

- Polyphenols/Flavonoids
- PUFA’s
- Glutathione
- NAC
- Etc
- Etc
- Etc
The Brilliance of Plants

• Plants are exposed to UV radiation daily
  • UV/UV-B exposure causes development of free radicals $\rightarrow$ inflammation

• Developed evolutionary strategy to deal with the DNA damaging effects of daily sun exposure
  • Polyphenols/Flavinoids
Proinflammatory cytokines:

• TNF-α- associated with a wide range of diseases, including infection, autoimmune disease, allergy, and tumorigenesis

• IL-1β, IL-6, IL-8, IL-12, IL-18

• Resistin- resists insulin; potential mediator of T2DM and cardiovascular disease (Ando et al., 2005; Fain et al., 2003; Oliver et al., 2006; Schwartz and Lazar, 2011)

• Adipokines are a family of hormones and cytokines with both pro- and anti-inflammatory effects that are secreted by adipose tissue.

• NF-κB (nuclear factor kappa light chain enhancer of activated B cells) is a family of highly conserved transcription factors that regulate many important cellular behaviors, immunity, inflammatory responses, cellular growth and apoptosis. NF-κB is also involved in diseases such as cancer, arthritis and asthma) activation of the NF-κB pathway has been implicated in several inflammatory states-
Polyphenols

• More than 10,000 polyphenol compounds have been identified in various plants (berries, fruits, veg, beans, nuts, spices etc)

• several sub-classes, such as the phenolic acids, flavonoids, stilbenes and lignans

• Olive oil & red wine

• The antioxidant activities have been widely studied, including scavenging of free radicals, inhibition of lipid oxidation, reduction of hydroperoxide formation
Polyphenols

• Polyphenols-modulate the gut bacteria composition & NF-kB pathway, and hence downregulate this key inflammatory cascade. (*The Int J Biochem & Cell Bio* 81 (2016) 393–402)

• Polyphenol **red wine** extract protects intestinal epithelial cells from inflammation induced by pro-inflammatory cytokines (TNF-α, IL-6 and IL-1) via, among other mechanisms the inhibition of the NF-kB pathway by suppressing cytokines-induced IkB degradation (*Nunes et al.*, 2013, 2016)
Dietary Flavonoids & Polyphenols:

- All flavonoids are polyphenols,
- Not all polyphenols are flavonoids.
- Plants produce flavonoids as a protection against parasites, oxidative injury and harsh climatic conditions.
- Several dietary flavonoids exhibit anti-oxidative, anti-inflammatory, and anti-osteoporotic activities.
- GM metabolize the flavonoids to improve bioavailability, and physiological activity of these compounds.
Flavonoids-


- The main dietary sources of flavonoids include tea, citrus fruit, citrus fruit juices, berries, red wine, apples, soy and legumes.
• The ability of flavonoids to reduce hyperalgesia involve:
  • μ- and δ-opioid receptors
  • endocannabinoid system.
• Inhibiting the inflammatory signal and modulating the cyclooxygenase (COX)-2 activity;
• Targeting the L-arginine/NO signaling (chemical way);
• Interacting with neuromodulating pathways, including the γ-aminobutyric acid (GABA) receptor signaling
Flavonoids

In a randomized, double-blind crossover trial, daily intake of 50 g of strawberries,

• Sig. reduced osteoarthritis-related knee pain by reducing the release of proinflammatory cytokines IL-6, TNF-α, and IL-1β (Schell J. Strawberries improve pain and inflammation in obese adults with radiographic evidence of knee osteoarthritis. Nutrients, 2017; 9:e949)

• Similar evidence for blueberries (Du C. Blueberries improve pain, gait performance, and inflammation in individuals with symptomatic knee osteoarthritis. Nutrients, 2019; 11: e290)

• Flavonoid Morin, present in Moraceae fruits, such as fig, breadfruit, mulberry, reduces bone cancer pain by acting on the CB2 cannabinoid receptor system

Glutathione

- Tripeptide (cysteine, glycine, and glutamic acid) found in relatively high concentrations in many bodily tissues (Pizzorno, J. Glutathione! Integr. Med. 2014, 13, 8–12)

- Low glutathione tissue levels in many chronic dz,
  - hypothesis that increasing glutathione levels can help prevent and/or mitigate the progression of these diseases

- “Tissue detoxer”- maintenance of redox balance, reduction of oxidative stress, enhancement of metabolic detoxification, and regulation of immune system function

- Chelates Heavy Metals naturally- esp. mercury

- Toxins deplete glutathione
Glutathione

• Optimizing glutathione may be strategy to improve health, decrease pain, BUT clear, causal relationships between glutathione status and disease risk remain to be clarified
• Nonetheless, human clinical research s/o nutritional interventions, incl. amino acids, vitamins, minerals, phytochemicals, and foods can have important effects on circulating glutathione which may translate to clinical benefit
• Genetic variation is a modifier of glutathione status and influences response to nutritional factors that impact glutathione levels.
N-acetylcysteine (NAC)

• NAC----→ GLUTATHIONE

• N-acetyl cysteine (NAC) is a supplement form of cysteine; Cysteine is found in most high-protein foods, such as chicken, turkey, yogurt, cheese, eggs, sunflower seeds and legumes

• Other foods high in glutathione precursors are broccoli, cauliflower, and asparagus. Vegetables with a high sulfur content yield naturally high glutathione levels.

• Research s/o may be helpful to counteract neurodegenerative & psychiatric dz

• may be neuroprotective w/prevention of dementia
NAC

• 2019 study - 90 pts over 8 weeks supplemented with NAC + pregabalin vs pregabalin + placebo

• Results: adjuvant NAC more efficacious in improving neuropathic pain assoc w/DB-PN (Heidari et al. J Pain Res.12:3147-3159. doi: 10.2147/JPR.S228255)

• Rat model of CRPS- Topical midronate-NAC produced significant anti-allodynia(J Neurochem. 2019 Dec 19:e14943)

• Oral administration of N-acetyl cysteine prevents osteoarthritis development and progression in a rat model.(Sci Rep. 2019 Dec 10;9(1):18741)
Dietary Polyunsaturated Fatty Acids (PUFAs)

Various PUFAs will provide series of different prostaglandins, which can participate in the peripheral anti-inflammatory mechanisms


Imbalance of PUFA's – contribute to proinflammatory state

• Focus- Omega 3 and Omega 6 PUFA's

• Both are concentrated in cell membrane phospholipids

• Imbalance => XS Ω6 : Deficiency of Ω3
Omega 6/Omega 3 ratio

- Anthropological and epidemiological studies indicate that human beings evolved on a diet with a ratio of omega-6 to omega-3 of ~1/1.
- Western diet ratio is ~ 15/1 to 16.7/1.
- This ratio promotes the pathogenesis of many diseases, including cardiovascular disease, cancer, osteoporosis, inflammatory and autoimmune diseases.

- Simopoulos A. Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases. Biomed Pharmacother. 2006 Nov;60(9):502-7
Omega-3

• 3 major types of Ω-3 FA's derived from food:
  • Alpha linolenic acid (LNA) (not Linoleic (LA))
  • Eicosapentaenoic (EPA)
  • Docosahexaenoic (DHA)

• Omega 3 FA -----> DHA/EPA ----->eicosanoids(R) aka: resolvins -----> resolve inflammation
  • suppress IL-1β, TNFα, IL-6

• Omega 6 -----> Linoleic acid (LA) ----->AA ----->
  Eicosanoids( prostaglandins, thromboxanes, leukotrienes, etc) ===> Inflammation
  • leads to oxidation LDL, platelet aggregation, interferes with the incorporation of EFA in cell membrane phospholipids
Gut Microbiome/PUFA

• Long-term dietary intake of Ω-3 PUFAs is considered particularly effective in modifying the human gut microbiota,
  • decreasing *Faecalibacterium*
  • increasing *Bacteroidetes* and butyrate-producing bacteria of the *Lachnospiraceae* family

*L. Costantini L. Impact of omega-3 fatty acids on the gut microbiota. Int J Mol Sci, 2017; 18: E2645*
Omega 6/Omega 3 ratio

• The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk

• A ratio of 2-3/1 suppressed inflammation in patients with rheumatoid arthritis

• Ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences (Simopoulos A. et al; Biomed Pharmacother 2002 Oct;56(8):365-79)
Omega -3

• *2017 study*: Omega-3 PUFA supplementation in pts w/neuropathic pain
  • Increased plasma DHA ($P<0.001$)
  • reduced plasma sphingosine levels ($P<0.001$)
  • Sphingosine-1-phosphate receptor 1 activation in astrocytes contributes to neuropathic pain. (Chen Z et al; *Proc Natl Acad Sci U S A.* 2019 May 21;116(21):10557-10562. doi)

• Recent study (2019) 40 pts.
  • Dietary supplementation with omega-3 PUFAs reduces neuropathic pain symptoms in Mexican-Americans with type 2 diabetes (*Duran et al; Diabetes Metab Syndr Obes.* 2019;12:109-120)
Ω3 PUFA

• Lin, N., Shi, J., Li, YM. et al. Lipids Health Dis (2016) 15: 133.
• Systematic review and meta-analysis of randomized controlled trials
  • Eight studies involving 955 participants were included; all reported on CRP levels.
  • Ω-3 PUFAs significantly reduced CRP concentration compared with control $P = 0.003$
Omega 6

• Soybean oil is currently the biggest source of omega-6 fatty acids in the US because it is really cheap and found in all sorts of processed foods

• Also found in vegetable oils:
  • corn, borage oil, sunflower, cottonseed

LA-Linoleic acid
  predominant Ω6 FA- converted to arachadonic acid

Some studies are showing conflicting results: Cochrane Database Syst Rev. 2015 Nov 16;(11):CD011094.

insufficient evidence to show an effect of increased or decreased omega 6 intake on CVD risk factors such as blood lipids and blood pressure. Very few trials were identified with a relatively small number of participants randomised.
DHA

Omega 3 FA --> DHA/EPA-->-eicosanoids(R) aka: resolvins -- ----> resolve inflammation

• DHA- very important structural component of the brain, skin, retina
• Essential for the growth and fnx dev of brain in infants
• Required for maintenance of normal brain function in adults
• Important precursor for lipid derived modulators of cell signaling, gene expression and the INFLAMMATORY process
• Found in cold water fish: salmon, tuna, herring, halbut, etc
Edible Mushrooms:

- Mushrooms are rich in anti-inflammatory components:
  - polysaccharides, phenolic and indolic compounds, mycoesteroids, fatty acids, carotenoids, vitamins, and biometals
- Good source of carbohydrates, mainly chitin that fulfills the role of dietary fiber
- They are a valuable source of proteins containing essential amino acids, (Dembitsky, Terent’ev & Levitsky 2010).
- Mushrooms are low in calories, rich in PUFAs
Anti-inflammatory properties of edible mushrooms

• Fungal **polysaccharides** have been shown to have a positive effect on human health. **Trehalose**, a **disaccharide**, imparts protective properties to cells against **protein denaturation**.

• trehalose reduces **lipid peroxidation** and **arachidonic acid** from cell membrane **phospholipids**, induced by **reactive oxygen species**.

• trehalose can inhibit pro-inflammatory proteins, namely, cyclooxygenase-2 and inducible nitric oxide synthase (iNOS)
  • COX-2 and iNOS play a key role in the alcohol-induced inflammatory brain damage during adolescence (**Pascual et al., 2007**).
Lions Mane

• Some edible fungi, such as the lion’s mane mushroom, have been used for several thousand years to treat digestive diseases

• Recently, a polysaccharide component from lion's mane was shown to have antioxidant activity in gastric epithelial cells (Wang M. et al 2017 PLoS One. 2017;12:e0181546)

• Mouse model-lions mane extract was able to kill H. pylori (at higher doses), but also inhibits H. pylori adherence to epithelial cells (at lower doses) (Wang G Int.J Med Mush, 21(1):1–11 (2019))
### Selected components from fruiting bodies of edible mushrooms & their anti-inflammatory properties:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharides:</td>
<td>repression of pro-inflammatory proteins: cyclooxygenase-2, inducible nitric oxide synthase (iNOS), IL-1; inhibition of IκB-α subunit degeneration, inhibition of nuclear transcription factor NF-κB signalling, reduction of lipid peroxidation, prevention of DNA damage; reduction of metabolites with carcinogenic character, anti-mutagenic, chemo- and radioprotective prebiotics, growth stimulation of nI bacterial intestinal flora</td>
</tr>
<tr>
<td>- trehalose,</td>
<td></td>
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<tr>
<td>- β-glucans (e.g. lentinan), - chitosans</td>
<td></td>
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<tr>
<td>Proteins</td>
<td>inhibitory activity against proliferation of tumor cells without cytotoxicity to the normal cells, immunoregulatory properties, stimulation of Th-1 lymphocytes population through induction of IL-2 and IFN-γ, inhibition of COX-2, prostaglandin E2 synthase</td>
</tr>
<tr>
<td>- lectins</td>
<td></td>
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</tbody>
</table>
Selected components: fruiting bodies of edible mushrooms & their anti-inflammatory properties: ([Muszyńska et al Food Chem 2018])

<table>
<thead>
<tr>
<th>Substance</th>
<th>MOA</th>
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</thead>
<tbody>
<tr>
<td>Phenolic compounds:</td>
<td>inhibition of free radical formation, inhibition of cyclooxygenase,</td>
</tr>
<tr>
<td>- gallic acid</td>
<td>lipoxygenases, microsomal monooxygenase, NADH oxygenase, as well as</td>
</tr>
<tr>
<td>- protocatechuic acid</td>
<td>C protein kinase, inhibition of leukocyte adhesive molecules generation, repression of IL-1β and IL-6 protein synthesis</td>
</tr>
<tr>
<td>- p-hydroxybenzoic acid</td>
<td></td>
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<tr>
<td>- p-coumaric acid</td>
<td></td>
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<tr>
<td>- cinnamic acid</td>
<td></td>
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<tr>
<td>- caffeic acid</td>
<td></td>
</tr>
<tr>
<td>Vitamins:</td>
<td>prevention of cellular membrane phospholipid peroxidation, antioxidant properties, inhibition of NF-κB signalling, repression of aminotransferases and INF-Y, repression of hsCRP protein, free radical scavengers,</td>
</tr>
<tr>
<td>- vitamins of B group</td>
<td></td>
</tr>
<tr>
<td>(thiamine, riboflavin, biotin, pyridoxine)</td>
<td></td>
</tr>
<tr>
<td>- vitamin C</td>
<td></td>
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<tr>
<td>- tocopherols</td>
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Micronutrients and pain

• It is important to correct dietary-induced overproduction of prostaglandins
  • which can be caused by a relatively high dietary Ω-6 : Ω3
  • low Selenium intake, or nutritional deficiency conditions leading to tissue glutathione depletion

• Prostaglandins
  • sensitize the C-fibers to hyperalgesia (EurPain, 2007; 11: 528-534)
Micronutrients and Pain

• Selenium deficiency is associated with pain exacerbation, particularly in cases with muscle damage and OA (Chariot P. Muscle Nerve, 2003;27: 662-668)

• Zinc - can inhibit TRPV1 and reduce neuropathic pain resulting from chemotherapy (Luo J. Zinc inhibits TRPV1 to alleviate chemotherapy-induced neuropathic Pain J Neurosci, 2018 38:474-483)
Micronutrients

• Micronutrient supplementation as a preventative strategy to control inflammatory disorders has shown promise particularly Vit. D,C,E but needs more study

In Summary:
Inflammation & Pain: the dietary link

- Chronic Inflammation can result in chronic disease and pain
- Certain foods promote inflammation
- Certain foods are considered anti-inflammatory
- The results on anti-inflammatory treatment are still limited and controversial due to little evidence and methodological heterogeneity
"If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health."

Hippocrates
Dietary supplements

• Nutritional supplements containing
  • Ω3 polyunsaturated fatty acids (PUFAs)
  • vitamin D, taurine, selenium, magnesium, zinc
  • flavonoids, zerumbone, curcumin,
  • "in addition to balanced exercise, can significantly enhance the analgesic effect of standard therapy regimens for conditions accompanied by chronic pain"
Supplementation

- Vit D - 2000-4000 IU/day
- Vit B12 - 1000ug/D sublingually
- Vit C – 2000 mg/D
- Magnesium – taken to bowel tolerance: as much as tol. daily to produce 1-2 easy-to-pass BMs
  - Overdose=diarrhea, tx=reduced daily dose Mg
- Curcumin - about 1000 mg/day
  - Best absorbed in presence of oil and small am. black pepper
Supplementation: Turmeric

• Turmeric extracts contain three primary compounds, which are commonly referred to as curcuminoids:
  • curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin.
• Curcumin-most highly studied, but.....low overall oral bioavailability due to extremely low absorption
• DMC-Chemically, DMC similar to curcumin- lacks the methoxy group bound to the benzene ring- improved chemical stability and activity c/w curcumin
• DMC-beneficial pharma actions: anti-inflammatory, neuroprotective, antihypertensive, antimalarial, antimicrobial, antifungal, and vasodilatory properties (similar to curcumin)(Hataminpour;J Cell Physiol 2019)
• Efficacy as adjunct tx arthritis(Daily. J Med Food 2016)
Supplementation: Magnesium

- Fibro pts often def. In Mg
- Supplements-may improve BP, palpitations, migraine frequency, sleep, muscle cramps
- Causes muscular relaxation
- Controls rate of nerve firing
Supplementation: Vit B12

- Needed: healthy blood cells, optimal bone density
- Deficient - cause neurologic dysfunction
- Vit B12 injections in pain pts. (not def): reduced pain scores, analgesic use (Mauro 2000 Eur Rev Med)
- 61-87 yr olds w/o cog impairment & nl. Vit B12 levels: brain size correlated w/B12 level (Vogiatzoglou 2008, Neurology)
- Sublingual route avoids need for injections and bypasses any impairment in GI tract absorption
- Supplementation- may improve pain, insomnia and fatigue
Supplementation: Vit C

- Antioxidant
- Needed for production of collagen, some hormones and neurotransmitters
- Essential for tissue repair & adaptation to stress
- Acts as a coenzyme that is needed to synthesize and use certain amino acids
- Helps increase the absorption of iron from the intestines
Supplementation: Magnesium

- Intracellular mineral (can be depleted even w/nl. Serum levels)
- Bones/muscles are reservoirs
- Used in 300+ metabolic rxn's
- Essential for optimal bone density and collagen production
- Helps regulate serum glucose levels
• Deficiencies are common in northern hemisphere (Holick 2007, N Engl J Med; Melamed 2008, Arch Inter Med)
• Deficiency assoc. W/inflammation and susceptibility to illness (Carlberg 2019, Nutrients)
• Supplementation improves m.strength in men & women (Grimaldi 2013, Med Sci Sports Exerc)
• studies concerning vitamin D are known to be rather heterogeneous, yielding contradictory results
EPIC: European Prospective Investigation Into Cancer and Nutrition 2009 Potsdam study

• Evaluated 4 lifestyle factors on health
  • Never smoking
  • BMI < 30
  • 3.5 hrs/wk physical activity
  • Diet—vegetables, fruits, whole-grain breads, low quantities of meat

• 23,000 participants
• 7.8 years
EPIC

• Pts with all 4 factors at baseline
• 78% lower risk of dev. Chronic disease specifically:
  • 93% red. Risk DM
  • 36% red. Risk Cancer
  • 81% red. risk MI
  • 50% Less chance of strokes

• Common denominator of all these chronic conditions: INFLAMMATION!
• While melatonin has been established in regulation of circadian rhythms, an independent role has been also shown for neuroprotection and specifically for anti-amyloidogenic effects.

• Neurological disease deaths have risen 36% worldwide in 25 years.

• Melatonin is a neuroregulator hormone that has free radical scavenger, strong antioxidant, anti-inflammatory, and immunosuppressive actions. These major properties of melatonin can play an important role in the pathophysiological mechanisms of neurological diseases.

Illnesses do not come upon us out of the blue. They are developed from small daily sins against Nature. When enough sins have accumulated, illnesses will suddenly appear.

- Hippocrates