Introduction to Functional Medicine
Welcome to the Sunday Session!

I. Goals
- To add to your existing knowledge
- To remind you of how much you already know
- To identify straightforward solutions to complex problems
- To broaden your vision of your clinical sphere of influence

What's the Connection?

II. Philosophy and Practice: Chiropractic and Functional Medicine
- Natural compatibility with many chiropractic approaches
- FM increases organization and reproducibility
- FM expands our perspective – greater pattern recognition
- What is the common ground between chiropractic and functional medicine perspectives?

III. Innate Recuperative Capacities Emphasized
- Both prefer to optimize the self-corrective actions of the body over introducing invasive external influences
- Conservative care
- Recognition of public health need to reduce polypharmacy and expensive/high-risk procedures
Wellness and Prevention

- Both reinforce the value and need for preventive and wellness services rather than waiting for a health crisis
- Continuing to operate past the reversal of disease until vitality is restored
- Working proactively to maintain exceptional health

Patient Centered Care

- Both emphasize patient empowerment and active participation to achieve superior outcomes
- Emphasis on listening
- Collaborative and coaching roles over authoritarian approach
- Self-care focus
- Shared responsibility for health outcomes
- Managing expectations

Bodily Interconnection

- Both recognize that the location of a cause is not always the location of its effects
- As in the neurologically mediated manifestations of subluxation/joint dysfunction or the effects of unhealthy gut bacteria on psoriasis
- Includes mind-body connection
  - Example: microbial endocrinology

Microbial Endocrinology

- Defined as a bi-directional communication between host (hormones, immune system) and our microbial flora
- Organisms in our microbiome are able to recognize human hormones and respond to changes in their concentration
  - Most studied in situations of host stress
  - Most studied in catecholamine family of hormones
  - Most studied in gut microbiome
  - Other studies sites include skin and oral cavity

- A stressed host is vulnerable, not just because of immune suppression by catecholamine hormones, but also because of:
  - Increased bacterial proliferation
  - Increased virulence
  - Elevated toxin expression
  - Increased attachment
  - Enhanced invasiveness
- When your patient is stressed, some of the gut bacteria know it - and they tell their friends!
- Additional reading: http://jpe.endocrinology-journals.org/content/225/2/R21.full.pdf

Leaky Gut

- Damaged Villi/ Poor Absorption
- Damaged Cell junctions

Wisconsin Chiropractic Association
Strategies for FM Implementation

- Intake forms
- New patient history
- Returning patient history
- Examination and patient assessment
- Treatment modalities
- Outcome markers
- Integration across the care team
- Growth of perspective and knowledge base
- Getting started in your practice

Intake Forms

- Represent an opportunity to gather information outside of your visit time
- Increases your knowledge of the patient’s status and circumstances
- Allows some detailed (laborious) and potentially uncomfortable lines of questioning to be somewhat separated from you, their doctor
- Can be viewed as a perpetual work in progress, responding to your experiences and insights in practice

Intake Forms

- Consider providing forms in advance to improve detail, recall and efficiency
- Include areas for diagnoses from previous practitioners and signs/symptoms the patient can self-report
- Provide an explanation/justification for the length of the forms
- Assess willingness/openness to participation in key areas
  - Diet
  - Physical activity
  - Supplements
  - Follow up visits
  - Psychosocial
- Assess perceived support from social network for areas above
  - Collectively or individually

Intake Forms

- Collect as much information as possible about behavioral patterns
  - Dietary
  - Activity/movement (aka exercise)
  - Social support networks
  - Nutritional supplements
  - OTC and Rx meds
  - Sleep hygiene
  - Work and financial situation
  - Sources of stress
  - Occupational, recreational, home exposures

Intake Forms

- Dietary patterns
  - Special diet
    - Self-initiated or prescribed?
  - Frequency of restaurant meals and fast food
  - Typical meal?
  - Frequency of grocery shopping and meal preparation
    - Patient’s role/level of participation?
  - Preferred foods
  - Commonly avoided foods
  - Reasons why?
  - Connection between food behavior and stress
  - Connection between food intake and health/symptoms
  - Familiarity with reading food labels

Intake Forms

- Sleep hygiene
  - Regularity of bedtime
  - Use of screens at night
  - Intensity of interior light
  - Environmental sounds
  - Intake of caffeine, alcohol, nicotine
  - Timing of physical activity
  - Timing of meals and snacks
  - Use of bed for non-sleep activity (e.g. TV, portable devices, reading, writing)
**Intake Forms**

- Toxic exposures and frequency
  - Pesticides
  - Herbicides
  - Heavy metals
  - Paint/carpet/dry cleaning (solvents and VOC)
  - Mold
  - Cigarette smoke
- Include dental Hx
  - Source of toxic exposure via mercury amalgam fillings
  - Source of systemic inflammation via deficient oral hygiene, bacteremia
  - Bacterial endocarditis ~4x more likely

**New Patient History**

- Pursue lines of questioning related to positive or borderline responses on intake forms/MSQ
- Use timeline or similar document to account for details and place them chronologically
- Organize using matrix and timeline
- Tell the patient’s story and note discrepancies, omissions, corrections to prior information
- Narrow down physical examination procedures by imbalances identified and conditions suspected
- “When is the last time you felt well?”

**Returning Patient History**

- Elicit as much detail as possible about ongoing care plans and conditions diagnosed by other practitioners
- Create opportunities for patient’s assessment of clinical status and treatment plan success to be heard
- Complex patients: consider scheduling one longer visit to fill out a timeline and retell the patient’s story
  - Especially helpful for existing patients who did not receive a functional medicine intake

**Examination**

- Take vitals each visit, or have a chiropractic assistant perform these exams
- Be aware of additional areas where physical findings can influence diagnosis or management of common chronic conditions, including signs of nutritional deficiency/insufficiency
  - Nails
  - Hair
  - Skeletal muscle
  - Skin
  - Teeth and oral cavity

**Examination – Nail Clubbing**

- Pulmonary disease
  - Including neoplasm
- Cardiovascular disease
  - Including infection
- Gastrointestinal disease
  - Including IBD, neoplasm
- Hyperthyroidism

**Examination - Koilonychia**

- Iron deficiency
  - Pt may be anemic
- Deficiency of protein-forming sulfur-containing amino acids
  - Cysteine, methionine
- General protein deficiency
- Hemochromatosis
- Diabetes mellitus
- Organic solvent exposure
- Prolonged high-altitude exposure
- Normal variant in infancy
Into to Functional Medicine
Chris Browne, DC

Examination – Beau’s Lines

- Severe systemic disruption
- Infection
- Myocardial infarction
- Peripheral vascular disease
- Uncontrolled diabetes mellitus
- Zinc deficiency
- General malnutrition
- Hypocalcemia

Examination – Terry’s Nails

- Hepatic cirrhosis
- Congestive heart failure
- Diabetes mellitus
- Chronic renal disease/transplant
- Age-related

Patient Assessment

- Matrix is useful here
  - Evidence of core clinical imbalances can help guide diagnosis and formulation of treatment plan
- Laboratory testing – will depend on what you suspect
  - Retain and use your foundation of lab interpretation
  - Add specialized tests when other sources of information are unavailable or unreliable

Treatment Modalities

- Is the body missing something it needs to heal?
  - Movement
  - Nervous system signaling
  - Nutrients and substrate
  - Emotional well-being

- Is something currently present that impedes the body’s healing capacities?
  - Removing harmful inputs to your patient’s physiology can be as powerful as anything added
  - First step in environmental medicine Tx plans

Outcome Markers

- Utilize physical examination and laboratory assessment to monitor outcomes and maintain/alter treatment plan as needed
- Most importantly: choose them and stick with them!
  - The more objective, the better
  - Clinical utility
  - Substantiate necessity & effectiveness of care plans
  - Validated instruments are helpful
    - NDI, ROQ, FSQ
- Consider including at least one for each complaint/Dx under your care

Integration Across the Care Team

- Assess your patient population:
  - Define the likely diagnostic/therapeutic categories
  - Decide which services you would like to provide
  - Which services can be appropriately delegated to staff?
- Identify candidate practitioners for referrals
  - Recommendations from your patients
  - Practitioner reviews
  - Informational/marketing materials
Integration Across the Care Team

- Develop and maintain inter-professional relationships
  - Occasional lunches
  - Service projects
  - Referrals and thank-you letters
  - Pings

- Map referrals for complex patients
  - Consider a written inventory of care types recommended, identify and provide referrals

Perspective and Knowledge

- For doctors of chiropractic, much of the clinical growth that occurs from learning functional medicine is a result of:
  - Connecting existing knowledge in new ways
  - Adding depth to previously learned topics
  - Expanding the kinds of patients and problems you treat

Getting Started

- Begin with a few (or just one or two) existing patients with chronic or complex health conditions
  - Apply core functional medicine tools
    - General framework: GO-TO-IT
    - Individual tools (e.g. MSQ, timeline, matrix)
  - Construct treatment plan based on:
    - Order of priority
    - Core clinical imbalances (“nodes” on matrix)
  - Established doctor-patient relationship helpful
  - Initiate your plan and reassess, adjusting your approach as needed until improvement is noted
  - Apply these insights to your next encounter with a similar patient or imbalance

Prospective Patients and Public Outreach

- Incorporating FM into your “elevator speech”
  - Revealing the connections between different body systems and conditions
  - Treating your symptoms as messages from the body to be interpreted rather than suppressed
  - Goal of identifying and correcting smaller imbalances before illness manifests

Mini-case Example

- 47 y/o F in NAD, WDWN, returns to your office for upper- and mid-back pain, having not been in for 4 months. Your CA reports her blood pressure to be 146/90 mm Hg, BMI = 28 kg/m².
  - Per your office policy, she brought copies of all her laboratory test results since her last visit with you
  - Reveals hypertriglyceridemia (210 mg/dL) and elevated LDL/HDL ratio
  - All other lab values WNL

Mini-case Example

- In interviewing the patient, you learn that since her PCP diagnosed her with stage 1 primary HTN she has been adhering to the DASH diet prescribed by the same practitioner for the past 3 months. It has not been successful in fully controlling her HTN, although it has improved moderately (by -8/ -6 mm Hg). The planned next step if greater improvement does not occur by her next follow-up is a prescription for hydrochlorothiazide. She would prefer to avoid this if possible.
  - Why do you ask? Can you help?
### First Steps
- Off to a good start
  - Provided a listening-intensive environment
  - Collected results of recent testing
  - Measured height, weight
  - Measured BP
  - Asked about current management plan and progress
- Collecting more data:
  - Waist circumference = 91 cm (35.8")
  - Waist-hip ratio (WHR) = .95

### Identifying the Imbalances
- This patient’s HTN is better understood as a part of ____.
- Key nodes on the FM matrix:
  - Communication (insulin resistance, adipokines)
  - Transport (HTN, cardiovascular deconditioning)

### Epidemiology of MetSyn
- Estimates vary based on different guidelines used
- >25% of US adults fit WHO/ATPIII criteria for metabolic syndrome
- 4-5% of US children and adolescents (and growing)

### Next Steps
- Significant findings:
  - Detailed diet Hx
    - Reveals 2-3 sugar-sweetened beverages per day (24-36 oz/day)
    - ~70 g added sugar per day
    - Found online description of DASH diet with 3 servings/day “sweets” listed
    - Otherwise appears mostly compliant with diet plan
  - Psychosocial Hx
    - Work situation moderately stressful, supervisor has confrontational management style
  - Activity
    - Low: 15-30 minutes per week of slow to moderate paced walking

### Significant Findings = Leverage Points
- Activity
  - Attitude and word choice important – consider motivational interviewing approach
  - Enjoyment and personal choice
  - Identifying and meeting personal goals
  - Incremental challenges to provide attainable goals
  - Celebration of achievements, large and small
  - Avoid “exercise”, “should” and instilling fear
- Goals
  - Develop habits of routine movement
  - Choose 2-3 favorite activities
  - Increase cardiovascular endurance
  - Reduce adiposity, increase muscle mass
Protecting Doctor and Patient

- Psychosocial
  - Determine if imminent risk exists
  - Mandatory reporting
  - Substance abuse
  - Refer to mental health services if uncertain of status/stability
  - Non-judgmental listening

- Mandatory reporting

Significant Findings = Leverage Points

- Psychosocial strategies for patients not at risk
- Social support networks
- Breathing pattern training
- Yoga, tai chi, dance, sports, other body movement
- Mindfulness
- Manual therapy (adjustments, soft tissue)
- Neurotransmitter support

Significant Findings = Leverage Points

- Key dietary step: reduce consumption of sugar sweetened beverages
  - Contribution to insulin resistance
  - Contribution to HTN?
    - Very likely

Implementing a Foundational Whole Food Diet - Overview

- Dietary content
  - Vast majority of food is nutrient-dense, minimally processed
  - Variety of colors, tastes and textures
  - Intentional, light consumption of favored nutrient-sparse foods
  - Avoidance of toxic foods and food-like substances

- Clinical action steps
  - Delivery to patient
    - By you, an employee/coworker, or outside practitioner
  - Follow-up and tracking

Whole Food Diet: Key Components

In summary

- A whole food diet to promote human health should include a variety of minimally processed, nutrient-dense plant foods, lean sources of protein and a balanced selection of fats.

General Recommendations

- For an average, 2000 calorie diet:
  - Legumes: 200-350 calories/day
  - 1 cup cooked kidney beans = 225 calories
  - Whole grains: 30-40 g/day carbohydrate (from these foods)
  - “Regular”-vegetables: 250-350 calories/day
  - 1 cup cooked cauliflower = 30 calories (!)
  - Starch-dominant vegetables: 100-200 calories/day
  - Fruits: 100-200 calories/day
  - Protein-dominant foods (lean): 7.8 oz/day
  - Dairy: 15-20 g/day protein (from these foods)
  - Fat-dominant foods: 20-25 g/day fat (from these foods)
  - E.g. avocado, oils, butter, coconut milk
  - Excluding nuts and seeds
  - Nuts/seeds: 15-25 g/day fat (from these foods)

Plant Food Antioxidants

- Nonvitamin dietary antioxidants
  - Carotenoids
  - ß-carotene, lycopene
  - Polyphenols
  - Flavonoids
  - Anthocyanins
  - Isoflavones
  - Phenolic acids
  - Ellagic acid/EGCG
  - Lignans
  - Many phytoestrogenic compounds
  - Stilbenes
  - Resveratrol

Plant Food Antioxidants

- Why not get antioxidants from a pill?
  - Can be helpful in select cases where higher doses are needed
  - Modulate biochemical pathways in illness
  - Enhance resistance to toxic exposures
  - Synergistic effect of combined antioxidants
  - Many phytonutrients yet to be discovered, classified, tested
  - Dose-response relationship is not linear
  - Antioxidants at low concentration can be pro-oxidants at higher concentrations
  - Vitamin C
  - Carotenoids
  - High concentrations of one antioxidant can block uptake/utilization of others

Organic Produce

- USDA definition and requirements:
  - “No prohibited substances applied [to soil] for 3 years prior to harvest”
  - List of allowed and prohibited substances available online at: http://www.ecfr.gov
  - Title 7 → Subtitle B → Chapter I → Subchapter M → Part 205 → Subpart G
  - Provides for exceptions if other options not deemed effective and if “the handler and certifying agent agree on the substance, method of application, and measures to be taken to prevent contact…”
  - Provides for exceptions due to weather damage, etc.
  - No genetic engineering (GMOs)
  - No irradiation
  - No sewage sludge exposure
  - Yearly inspection

Organic Produce

- Health and safety implications of herbicide and pesticide exposure (occupational and residential/consumer)
  - Dermatitis
  - Non-Hodgkin and follicular cell lymphoma, leukemia, multiple myeloma
  - Liver, stomach, prostate, brain, breast, ovarian, pancreatic cancers
  - Parkinson disease
  - Birth defects
  - Impaired neural development
  - Impaired fertility
  - Endocrine disruption
  - Epigenetic modification
Identifying Dietary Exposure Sources

- Environmental Working Group
  - Incorporates pesticide residue concentration data into a ranked list of produce items (greatest to least concentration)
  - Full list
  - “Dirty dozen”
    - Apples
    - Peaches
    - Nectarines
  - +9
  - “Clean fifteen”
    - Avocados
    - Sweet corn
    - Pineapples
  - +12
- Updated yearly
- Mobile app for commercial food evaluation

Fruits and Vegetables

- Health benefits
  - Nearly universally agreed upon: disease prevention
  - CVD
  - MI, CHD, stroke show largest effect sizes
  - COPD
  - Cancer (general)
  - Obesity
  - Asthma
  - Rheumatoid arthritis
  - Osteoporosis
  - Dementia
- Requires variety to achieve optimal benefit
- Synergistic interaction among phytonutrients
- Scientific understanding of individual molecules still limited, additive and synergistic effects only minimally explored
- Culinary spices and herbs included
### Fruits and Vegetables

- **Health concerns**
  - Some varieties retain high concentrations of pesticide residues
  - Fruit consumption must be limited in diabetics
  - Juice is not equivalent
    - Quantity
    - Mixed fruit and vegetable juices
    - Missing fiber component (already lacking in SAD)
  - Fiber contributes to satiety
  - Soluble fiber lowers blood cholesterol
  - Higher glycemic index
  - Commercial preparations often contain:
    - Added sugar
    - Preservatives, fungal enzymes (orange juice) – immune reactions

- **Quantity**
  - Mixed fruit and vegetable juices
  - Missing fiber component (already lacking in SAD)

- **Sulfite-containing products**
  - Dried fruits
  - Wine
  - Fruit juice
  - Molasses
  - Pickled foods
  - Dried potatoes
  - Wine vinegar

### Sulfite-Sensitive Asthmatics

- Reactions may be d/t impaired action of sulfite oxidase
- Nutritional therapeutic option – Molybdenum (Mo) supplementation
  - Adult dose: 500-1000µg/day
  - Necessary cofactor for sulfite oxidase
  - Coadministration with Cu 1-2 mg/day
  - Advisable d/t Mo complexing w/ Cu in the gut
  - Take Cu apart from Mo supplements
- General approach: public “open trial” if not acutely toxic
  - As with all products, caveat emptor

### Whole Grains

- **Health benefits**
  - Beneficial nutrient profile:
    - High fiber
    - Moderate protein
    - Prebiotic content (e.g. inulin)
    - Antioxidant phytonutrients
    - Methyl donors
  - Outcomes and effects:
    - Reduced hs-CRP levels
      - Full effect observed at 1 serving/day
    - Reduced all-cause and CVD mortality
    - Reduced risk of CVD and type II diabetes mellitus

- **Health concerns**
  - Association with celiac disease
  - Under-diagnosed autoimmune enteropathy (as high as 6:1 undiagnosed)
  - Significant population of wheat- and gluten-sensitive individuals
    - Fasano et al., estimate at up to 6%
    - 30% (276/920) of IBS patients (Rome II) demonstrated wheat sensitivity
  - Appears to be mediated by susceptibility to immune activation:
    - Reduced Treg populations
    - Increased IL2, IL4
    - Increased intraepithelial lymphocyte populations
    - Enhanced neutrophil migration
    - Gut barrier disruption
Fatty Acid Balance and Inflammation

- The fats we consume provide substrate for cell signaling molecules including eicosanoids.
- Most fat-containing foods contain higher levels of n-6 fatty acids
  - Linoleic acid – vegetable oil
  - Arachidonic acid – animal fat
- Proposed “ideal” n-6/n-3 ratios vary
  - In those with adequate fat intake, ratio is more important than dosage
  - 1:1 to 4:1 commonly cited
  - 4:1 most realistic while conferring strong benefit

Organic Meat

- USDA requirements:
  - Specifies prohibited substances in raising and feeding livestock, including:
  - Growth promoting drugs (e.g. hormones)
  - Supraphysiologic supplement dosing
  - Plastic feed pellets
  - Requires pasture tending in the same manner as organic crops
- Specifies living conditions and handling procedures including:
  - Housing conditions
  - Veterinary care
  - Cleanliness of drinking water
  - Access to exercise areas

Fish

- Health benefits:
  - High protein
  - Highly favorable n-6/n-3 fatty acid ratio
  - Reductions in risk for:
    - Cardiovascular disease
    - Prostate cancer
    - Colorectal cancer
    - Rheumatoid arthritis
  - Potential for enhanced cognitive development in children of mothers who ate fish while pregnant
  - Predicated on consumption of uncontaminated/minimally contaminated fish
Fish

- Health concerns:
  - Bioaccumulation accounts for most problems with fish toxicity
  - Mercury contamination (mostly present as MeHg) – risk of CVD, neurodegeneration, impaired neural development
  - Partially ameliorated by dietary selenium
  - Significant variation among studies and species based on meta-analysis evidence:
    - Lower content in farmed versus wild fish
    - Lowest overall concentration in: tilapia (US-NYC), butterfish (US-NYC), seabass (US-VA)
    - Highest overall concentration in: marlin (US-Gulf), shark (several varieties, US), swordfish (Bermuda, Spain)
  - Free full text available here: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556626/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556626/)

- Health concerns (cont’d):
  - PCBs (polychlorinated biphenyls), a class of organochlorine utilized in industrial coolant applications
    - Production banned in US since 1979, highly persistent
    - Exert disruptive effects on endocrine, neurological and immune systems
    - Higher content in Atlantic salmon, sardines
    - Lower concentrations in wild caught Pacific salmon

Beef

- Health benefits
  - High protein
  - Moderate to high micronutrient content:
    - Zinc, selenium, choline, phosphorus, niacin, pyridoxine, cobalamin
  - Favorable n-6/n-3 fatty acid ratio possible

- Health concerns:
  - CVD, cancer risk (esp. colorectal) and mortality
  - Recent meta-analysis evidence (2014): lowest all-cause mortality relative risk (for highest vs lowest consumption) of unprocessed red meat (RR 1.10), higher risk for processed red meat (RR 1.23), highest for total red meat (RR 1.29)
  - Exacerbation of inflammatory pathologies and imbalances
  - Excess arachidonic acid intake
  - Cooking methods
    - Charred/seared/well-done meat introduces carcinogenic and pro-inflammatory compounds
    - PAHs, HCAs
    - AGEs
  - Grass- versus grain-fed: background
    - Transition to exclusive grain feeding occurred in 1950’s
    - Cost savings
    - Decrease number of feeding days
    - Decreased acreage per cow
    - Culinary preference shift
      - Increased “marbling” (intramuscular fat)
    - Recent shift in market demand
      - Lean meat becoming more popular
      - Increased awareness regarding different raising methods
    - Concerns regarding CVD

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Beef

- Grass-versus grain-fed: quantifiable differences
  - Grass fed beef:
    - Contains less total fat
    - Contains more trans-vaccenic acid (TVA)
    - Substrate for conjugated linoleic acid synthesis
    - Anti-cancer effects in humans
    - Apparently divergent in health effects from industrially produced trans fatty acids (e.g. HDL)

- Grass-versus grain-fed: quantifiable differences (cont’d)
  - Grass fed beef:
    - Has a lower n-6/n-3 fatty acid ratio
    - Per CA Daley, et al. 2010:
      - Grass-fed: 1.44-3.2 (variation by breed)
      - Grain-fed: 3.00-13.6 (variation by breed)
    - Has a higher antioxidant content
      - Glutathione, α-tocopherol, β-carotene

  - Suggested serving size: 3-4 oz, 2 servings/day max

Chicken

- Health benefits
  - High protein
  - Moderate to high micronutrient content:
    - Niacin, pyridoxine, phosphorus, selenium
  - No apparent risk increase for colorectal cancer
  - Skinless preparations tend to demonstrate better health impacts
    - E.g. reduction of dyslipidemia, improved n-6/n-3 FA ratio

- Health concerns
  - Arsenic contamination via drugs in feed (antimicrobial, weight gain promoter, pigmentation enhancer)
  - Elevated risk of bladder and lung cancers in conventionally-raised chicken consumers
  - Not detected in vast majority of antibiotic-free chicken (1/13 positive samples), not detected in any organic chicken (0/25 positive samples)
  - In response, FDA approval withdrawn for arsenic-containing drugs in food producing animals
  - Hormones, antibiotic residues, resistant infections
  - Proactive vs reactive health choices

Acid-Base Balance

- Collateral benefit of dietary repletion with K, Mg, Ca
- Blood pH remains tightly regulated @ 7.40 ± .05
- Urine pH more variable
  - Responds to dietary inputs
  - May respond to mineral supplementation
  - Alkaline urine more conducive to concentration and elimination of toxic metabolites
  - Ionization of weak acid metabolites increased in alkaline environment
  - More ionized form → less reabsorption into the blood from renal tubule
  - Applies to fluoride, methotrexate, salicylates, phenobarbital, chlorophenoxy herbicides
  - Most studied in acute poisoning with IV NaHCO₃ administration
Our taste preferences are malleable, responding to the foods we are exposed to.

Our preferences shift and change as we seek novelty and variety.

Mindful eating can help us adapt to new foods, enjoy old favorites and reduce overconsumption.

**Helpful Materials**

- **Dietary goals overview**
  - Prioritizing goals: Include patient preference

- **Planned “cheat” foods for light/occasional consumption**
  - Choose in advance so that decision making is maximally rational

- **Recipe suggestions**
  - Focus on easy to find, inexpensive ingredients whenever possible
  - Nutrient dense foods arranged by type, color, antioxidant
  - Planned “cheat” foods for light/occasional consumption

- **Email, text, telephone between visits**
  - Choose in advance so that decision making is maximally rational
  - Test them yourself (and walk the talk)

- **References**

Autoimmune multi-system disease, joint-focused
- Inflammatory polyarthropathy
- Cutaneous nodules
- Vasculitis
- Cardiopulmonary complications
- Anemia
- Neuropathy

References

#### References

Case example: RA

- 45 y/o F in mild apparent distress, well developed but appearing slightly undernourished, presents for her initial evaluation in her office for worsening joint pain and reduced mobility related to her previously diagnosed RA (2 years before presentation). You measure her blood pressure to be 126/84 mm Hg. BMI = 17 kg/m^2.
- Per your office policy, she brought copies of all her laboratory test results from the past year
  - Elevated CRP = 43 mg/dL
  - CBC is WNL

Pertinent Findings from Intake Forms

- **Diet**
  - Frequent fast food (3x/week) and restaurant meals (5x/week)
  - Heavy reliance on prepackaged, manufactured convenience foods
- **Physical activity**
  - Minimal, no regular activity
- **Sleep hygiene**
  - Irregular bedtimes (± 1.5 hours)
  - Uses a phone or tablet to browse the internet before going to sleep most nights
- **Psychosocial**
  - Very limited support network, feels isolated
  - Indicates level of anxiety/fear for future as “severe”

Pertinent Findings from History

- In interviewing the patient, you learn that:
  - She was bottle fed (formula) throughout infancy and early childhood
  - ATM
  - Her diagnosis of RA 2 years ago occurred several months after losing her job and house
  - Stress, dietary changes, sleep changes
  - ATM
  - Her current treatment regimen consists of corticosteroids during flare-ups and NSAIDs to manage pain. She has not received nutritional advice, nor has she been counseled on activity beyond a recommendation to “keep moving when you feel able”
Identifying the Imbalances

- Does this patient have a “joint disease”? 
  - Yes and no
- Key nodes on the FM matrix: 
  - Defense and repair (autoimmunity, chronic systemic inflammation) 
  - Structural integrity (joints and periarticular tissues) 
  - Assimilation (dysbiosis, intestinal permeability, malabsorption)

The Time to Intervene was Yesterday...

- If her condition continues to deteriorate, this patient’s future Tx could involve: 
  - DMARDs 
  - Methotrexate, et al. 
  - Biologics 
  - Joint replacement surgery

Treatments: Defense/Repair and Assimilation

- For a patient with RA (or any autoimmune disease), dietary and nutritional strategies should be a first-line therapeutic consideration

Why Is This So Important?

“the mucosa is directly exposed to the external environment and taxed with antigenic loads consisting of commensal bacteria, dietary antigens, and viruses at far greater quantities on a daily basis than the systemic immune system sees in a lifetime”.


Increased epithelial permeability for antigens is a crucial primary or secondary event in the pathogenesis of several disorders


Healthy Gut

- Healthy Villi/Good Absorption 
- Healthy Cell Junctions
**Leaky Gut**

- Damaged Villi/ Poor Absorption
- Damaged Cell junctions

**What are the Triggers of Increased IP?**

- Poor Dietary Choices & nutrient insufficiencies
- Stress
- Infections/Dysbiosis
- Medications
- Systemic Disease
- Low Stomach Acid & other insufficiencies
- Toxic Exposures

**Break of Tolerance Due to Cross-Reactive Antigens**

- **TOLERANCE TO SELF**
  - self antigen
  - non-self antigen

- **AUTOIMMUNITY**
  - cross-reacting exogenous antigen

Two common emulsifiers (used to improve texture and extend shelf life in most processed foods)
- carboxymethylcellulose (CMC; a/k/a cellulose gum)
- polysorbate 80 (PS80)

**Nature** 519, 92–96(05 March 2015) doi:10.1038/nature14232

**The autoimmune process** can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier function.

**IL-1, TNF, LPS, Bacteria**

- kB
- NF-κB
- RelA
- iNOS

**Mechanisms of Disease**: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune disease

**References**


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**Distant Signs and Symptoms**

- Local reaction/localized symptoms
- Physical disruption of mucosal barrier
- Increased mucosal permeability
- Bacterial/yeast/protozoa/LPS
- Food protein translocation
- Portal and systemic overload
- Immunologically mediated reactions (and perpetuation)

**Triggers**:
- nutrient insufficiency, medication, dysbiosis, parasite, food reaction, surgery, etc.

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**Treatments: Defense/Repair and Assimilation**

- **Elimination diet**
  - Improvement in disease activity, symptom scores, long-term clinical status
- **ATM**
- Commonly involved foods
  - Corn
  - Wheat
  - Bacon/pork
  - Oranges
  - Milk
  - Oats
  - Rye
  - Egg
  - Beef
  - Coffee
- Consider nightshade family elimination for recalcitrant cases

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**Reminder: RA and Malnutrition**

- Malnutrition is more common in RA patients, due to:
  - Functional capacity losses
  - Emotional distress/psychosocial
  - Malabsorption
  - Villous atrophy noted in RA patients more frequently than general population

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**Treatments: Defense/Repair**

- **Sodium restriction – early evidence**
  - Excess sodium concentration drives TH17 cell induction via activation of p38/MAPK pathway:
    - In vitro human TH17 induction
    - In vivo murine TH17 induction and increased autoimmunity (EAE)

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**Treatments: Defense/Repair and Assimilation**

- Once dietary mediators have been identified and eliminated, implement a diet consisting of minimally processed whole foods
- Emphasize enjoyment, variety, nutrient density, ease of preparation/storage

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**Treatments: Defense/Repair and Assimilation**

- **Fasting**
  - Reduces symptoms during fasting period
  - Anti-inflammatory, removal of food antigen exposures
  - Symptoms generally return upon resumption of food intake
  - Periodic (multiple consecutive days)
    - 1-3 week fasting – greatest improvement in clinical status
  - Intermittent (alternate days/1-2x per week)
    - Alternate day fasting significantly reduces inflammatory biomarkers (TNF-α)
    - Alternate day fasting appears superior to once or twice weekly fasting
  - Fasting followed by vegetarian diet
    - Greater long term effects with clinically significant improvement in disease activity
    - Supervision may be necessary for longer fasts or comorbidities

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**Diagram**

IL-23
IL-17
ROTY/ROx
STAT3, IRF4, AHR,
BAX, NOTCH1, and Runx1

IL-21, IL-6 + TGFβ

IL-25
IL-27
IL-1β
TNFα
Sodium

IL-17A, IL-17F, IL-22,
IL-21, GM-CSF, TNFα,
IL-9, IL-10, and IFNγ

Treatments: Defense/Repair and Communication

- Advanced glycation end products (AGEs)
  - Products of nonenzymatic Maillard reaction
  - Activate RAGE leading to increased ROS generation
  - Induces NF-κB, Th1 differentiation
  - Formation of neoantigens increasing T cell mediated immune responses
  - Osteoclast activation in RA → accelerated osteoporosis

Maillard Reaction

- Protein + sugar + heat (>285°F)
- Absence of water and alkaline environment facilitate

Culinary desirability

- Produces browning
  - Fried foods
  - Toast
  - Roasted vegetables/meats
  - Roasted coffee
- Produces aromatic/flavorful compounds
  - Some of which happen to be pro-inflammatory, immune-sensitizing, and/or carcinogenic

Greatest content in:

- Grilled/roasted meat
- High-heat processed foods (fried)
- Highly processed sugar-rich foods

Treatments: Defense/Repair

- Vitamin A (preformed) – 5,000-50,000 IU/day (time limited at doses ≥ 15,000 IU/day)
  - Ineffective in monotherapy trials — let’s not use it that way
  - Promotes Treg formation
  - Suppresses Th17 differentiation

- Monitor for toxicity symptoms and signs
  - Dry skin (pruritus, cracking) and dry lips
  - Anorexia
  - Fatigue
  - Headache
  - Psychiatric disturbances
  - Osteopenia
  - Arthralgias/myalgias
  - Bone pain

- Brassica vegetables/indole-3-carbinol - 200mg bid
  - Murine model evidence of root extract efficacy in inflammatory arthritis
  - NF-κB inactivation
  - Protective action at AhR

- Garlic
  - Anti-inflammatory – reduces IL-6, IL-8, TNF-α
  - Inhibition of MMPs
Treatments: Defense/Repair and Structural Integrity

- Vitamin D - 1,000-2,000 IU/day
  - Prevents progression in murine models
  - Reduces number of dendritic cells (APCs) and B cells (decreased immunoglobulin)
  - Reduces Th17 differentiation, IL-17 and IL-22 secretion
  - Prevention of bone loss in corticosteroid therapy

- Green tea, EGCG – 400mg bid, apart from meals
  - Murine models demonstrate in vivo:
    - Decreased pro-inflammatory gene expression
    - IL-18, IL-6, IL-8, TNF-α, NF-κB reduction
    - Down-regulation of fibroblast-like synoviocyte (FLS) anti-apoptotic proteins
    - Decreased production of MMP-1,2,3

- Alpha-lipoic acid – 200-600mg bid
  - Murine models demonstrate in vivo:
    - NF-κB binding inhibition
    - Reduced IL-1ß, IL-6, TNF-α, NF-κB concentrations

- n-3 fatty acids: 3-10 g/day combined EPA+DHA
  - 2012 meta-analysis of 10 RCT studies (total n=183)
    - Significant reduction in NSAID use
    - > 3 month duration, > 2.7 g/day dose
  - Other meta-analyses have demonstrated:
    - Decreased tender joint count and AM stiffness duration
    - Reduced joint pain severity and painful joint number
  - Olive oil > 10 mL/day
    - Anti-inflammatory polyphenolic content
    - Improves murine models of arthritis
    - Clinical signs: joint edema, cartilage damage reduced
    - Biomarkers: MMP-3 and inflammatory cytokines reduced
    - May improve efficacy of n-3 fatty acid therapy

- Gamma linolenic acid (GLA) – 3-7g/day
  - Borage seed oil, evening primrose oil
  - RCT evidence generally favorable
  - Decreased pain
  - PGE1 synthesis facilitated, anti-inflammatory benefit
  - Anti-inflammatory diet
    - Weight loss, especially if obese
    - Decreased mechanical stress on damaged articular surfaces if weight bearing joints involved
    - Reduction in dysregulated, inflammatory adipokine signaling

- Curcumin – 2-3g/day in divided doses
  - Inhibits IL-18 and IL-6 expression
  - Pro-apoptotic to FLS
  - Boswellia serrata extract (~60% boswellic acids) – 1,200-3,000mg/day in divided doses
    - Must be administered with fat-containing foods for maximum bioavailability
    - Inhibits leukotriene synthesis via 5-LOX
    - Inhibits TNF-α and IL-18 expression
    - Reduces Th17 cell differentiation

Additional Treatment Considerations for This Patient

- Sleep hygiene guidance
- Low-impact exercise plan
- Referral for support group/counseling
- Breathing and visualization exercise
**Outcome Markers**

- CRP, autoantibodies
- Questionnaires
  - RAQoL
  - HAQ-DI
- Diet diary
- Frequency of physical activity

**Rheumatoid Arthritis – Prevention**

- Preventive information should be provided to all first-degree relatives
- Dietary antioxidants
  - Fruit intake
  - Cooked vegetables
- Antioxidant supplements
  - Vitamin C – highest vs lowest tertile
  - Zinc – 15 mg/day
- Vitamin D sufficiency/supplementation
  - 2012 meta-analysis suggests significant protective effect
  - Highest total exposure group = ~24% risk reduction
  - Supplementation = ~24% risk reduction

**Rheumatoid Arthritis – Risk Factors**

- Family Hx
- Females ~3:1
- High work stress
- Coffee ≥4 cups/day
  - Moderate to no association depending on study
  - Irrespective of caffeine content
- Obesity
  - Moderate to no association depending on study

**Juvenile Rheumatoid Arthritis – Treatment Modifications**

- Reduced dosage for supplements based on age and body weight
- Decreased growth/impaired nutritional status common
  - Increase protein as % of total calories
  - Ensure multivitamin use
- Low zinc status more common in JRA with ≥5 joints involved
  - Zinc picolinate – 10-30mg/day
  - Copper 2-1mg/day with long term therapy
  - Iron 2-10mg/day with long term therapy
  - Magnesium 50-200mg/day with long term therapy

**References**

Common condition, estimates vary widely (1-8% prevalence), ~7:1 female predominance
- Chronic, diffuse, multifocal pain
- Most frequently localized to muscles, joints
- Common inclusion of head, visceral, and throat pain
- Sensory hyper-responsiveness
  - Hypersalivation/allodynia
  - Paresthesia/paresthesia
  - Sensitization to light, sound, odor
- Non-sensory symptoms
  - Fatigue
  - Sleep disturbance
  - Memory impairment
  - Mood alteration

References


Pascal S. et al. Low n-3 long chain polyunsaturated fatty acid intake reduces IFN-gamma production from rheumatoid arthritis patient

References

A Deeper Look at Fibromyalgia

Fibromyalgia (FM) – Pain-related Terminology

- Pain – from IASP: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”
- Nociception – neural transmission of inputs indicative of tissue damage or direct threat (noxious stimuli)
- Hyperalgesia – increased pain perception in response to a normally milder noxious stimulus
- Allodynia – pain perception in response to a non-noxious stimulus

Fibromyalgia (FM)
Fibromyalgia - Pathophysiology

- Central (CNS) sensitization – neuroplastic alterations
  - Result: amplification of pain and other somatic/visceral sensation – widespread hyperalgesia and allodynia
  - Enhanced activity of nociceptive pathways
  - Increased nociceptive neurotransmitter secretion
    - Substance P, calcitonin gene related peptide, bradykinin, glutamate, NO, etc.
  - Nociceptive projection neurons in spinal cord convert to wide dynamic neurons
  - Accept non-nociceptive input
  - Decreased inhibitory control of nociceptive neurons
    - GABA, glycine mediated inhibition

- Contributing factors to the development of central sensitization
  - Tissue injury/irritation resulting in prolonged/intense nociceptive signaling
  - Peripheral sensitization – increased peripheral neuronal response to noxious stimuli
    - Result: regional hyperalgesia
    - Induced by prolonged, repeated, or severe tissue injury and inflammation
    - High intensity stimulation of spinal cord ascending nociceptive pathways
      - Activation of “silent” nociceptors which secrete pro-inflammatory mediators (neurogenic inflammation)
  - Psychological stress/trauma – HPA axis dysregulation
  - Genetic susceptibility
    - 1st degree relatives ~8.5x more likely to have FM
Fibromyalgia - Pathophysiology

- Mitochondrial dysfunction
  - Most studied in muscle mitochondria
  - Reduced antioxidant enzymatic activity
  - Increased ROS
  - Impaired AMPK signaling
  - Reduced tolerance to oxidative stress
  - Reduced mitochondrial autophagy and proliferation
  - Hypothesized increased permeability transition pore opening with subsequent calcium efflux into cytosol
  - Observed in platelets, potential generalizability to neurons
  - Hyperexcitability

Fibromyalgia

- Diagnosis
  - 1990 ACR criteria – includes “tender point” examination
  - Designed for clinical trials
  - No longer recommended to establish Dx
  - Tender points can be useful outcome marker
  - 2011 ACR criteria
  - Designed for epidemiological research
  - More inclusive of non-pain Sx
### Fibromyalgia – General Tx Plan

- Address central sensitization
- Therapeutic neuroscience education
- Cognitive-behavioral therapy
- Awareness practice/mindfulness-based stress reduction
- Reduction of peripheral sensitization
  - Anti-inflammatory Tx, manual therapy, exercise

- Address mitochondrial dysfunction
  - Dysbiosis correction
  - Refined carbohydrate restriction
  - Therapeutic fasting
  - Dietary antioxidant intake
  - Supplementation
  - Exercise

### Fibromyalgia – Nutritional Treatment

#### Coenzyme Q10 (CoQ10) – 200-400 mg/day
- Significant benefit vs placebo in RCTs
- Increased AMPK signaling, serotonin quantity, antioxidant enzyme expression, mitochondrial proliferation
- Decreased pain, fatigue, depression
- High dose supplements available; positive RCTs used tid dosing

#### Acetyl-L-carnitine – 500 mg tid
- 2 RCTs, both showed benefit over placebo
- Decreased pain
- Decreased depressive symptoms
- Mitochondrial nutrient
  - Antioxidant activity
  - Facilitates acetyl-CoA and lipoic acid synthesis
  - Antioxidant activity
  - Stimulates mitochondrial proliferation

#### n-3 fatty acids: 2-8 g/day combined EPA+DHA
- Anti-inflammatory
  - Directly reduces nociceptive signaling and sensitization centrally and peripherally
  - Substrate for production of resolvins
  - Counteracts central neural plasticity, anti-nociceptive
  - Reduces pain in response to inflammatory stimuli
Fibromyalgia – Nutritional Treatment

- Magnesium 300-800 mg/day
  - Limited trial data, generally unfavorable
  - Positive effect not observed under blinded/placebo-controlled conditions
  - FM patients have lower Mg status
  - Indirect effects via increased ROS and inflammation
  - IV administration
  - Trial data unfavorable
  - Anecdotal reports suggest potential superiority vs PO
  - Further suggestive of Myers cocktail superiority vs Mg alone

- 5-hydroxytryptophan (5-HTP) – 50-150 mg tid
  - 2 placebo-controlled trials, both demonstrate benefit
  - Improvements in tender point count, pain severity, fatigue, sleep, anxiety, morning stiffness
  - Side effects relatively common (24-30%)
  - Nausea
  - Sleep disturbances
  - Likely MOA – increased neurotransmitter supply (5-HT) for descending inhibitory pathways
  - Relative contraindication – coadministration with MAOI, tricyclics, SSRIs

- Melatonin – 5-15 mg at bedtime
  - RCT evidence supportive
  - Superior to amitriptyline in 1 RCT
  - “Marginal benefit” of combined melatonin and amitriptyline
  - Similar effect size to fluoxetine
  - Significant benefit with combined melatonin and fluoxetine

- 5-HTP
  - Nausea
  - Sleep disturbances

- Gluten free diet – preliminary evidence
  - Case series
    - Increased intraepithelial lymphocytes in all participants – evidence of immune response
    - Limited generalizability
    - 15/20 patients achieved complete remission of FM
    - Case control – FM + IBS
    - Significant improvement in pain and disability only in participants with increased intraepithelial lymphocytes
  - General elimination diet warranted for recalcitrant cases

- Thiamine – 600-2,000 mg/day
  - No trial data, case series (n=3) supportive
  - No adverse effects reported in high dose studies with up to 7 g/day
  - ≥ 7g/day produced nausea, indigestion, no serious effects
  - MOA uncertain

- Therapeutic fasting
  - Increased AMPK activation
  - Autophagic removal of dysfunctional mitochondria
  - Decreased ROS and inflammation

Fibromyalgia – Nutritional Treatment

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    - Significant improvement in pain and disability only in participants with increased intraepithelial lymphocytes
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Wisconsin Chiropractic Association
Fibromyalgia – Physical Activity

- Exercise
  - Anti-inflammatory – reduction in peripheral sensitization
- Aerobic exercise
  - Improvements in pain, fatigue, mood, functional capacity
  - Low to moderate intensity, 2-3x/week
- Aquatic training
  - Improvements in pain, stiffness, functional capacity
  - No superiority over land-based aerobic exercise based on meta-analyses
- Strength training
  - Limited evidence suggests inferiority to aerobic exercise, superiority to flexibility training

Fibromyalgia – Mind-Body Treatments

- Meditation/awareness practice
  - Attenuates pain-related cortical processing
  - Improves stress management/coping ability
  - Increasing effect with duration and type of meditation practice
  - Longer duration (measured in years) – improved effect
  - “Open monitoring” more effective than “focused attention”
  - Awareness-focused yoga beneficial
  - Primary reduction in unpleasantness vs intensity of pain

Awareness Practice – Group Exercise

- Focused attention
- Open monitoring

Fibromyalgia – Mind-Body Treatments

- Balneotherapy and hydrotherapy
  - Meta-analysis evidence mildly supportive
  - Pain reduction, moderately sustained up to 3 mo
  - Decreased pain with exercise
  - No impact on depressive Sx

Fibromyalgia – Mind-Body Treatments

- Cognitive behavioral therapy, pain education, psychological treatment
  - Improved physical functional status
  - More cost-effective than pharmacotherapy
  - Greater improvement in quality of life scores
  - Primary alterations in pain scores, depressive Sx, cognitive perception of pain, coping ability, sleep disturbance
  - Effective in juvenile FM

References

Osteoarthritis

- Non-classical inflammatory arthropathy affecting the articular (hyaline) cartilage, synovium and subchondral bone as well as ligaments, tendons and adjacent musculature
  - Knee
  - Hip
  - Spine
  - Hands

- Most common arthritis
  - Prevalence ~15%
  - Lifetime risk ~47% in women, ~40% in men for knee OA
  - Other sites vary in risk by sex
  - Radiographic signs significantly exceed symptomatic cases
  - Risk factors more predictive than radiographic signs
### OA – Risk Factors

- **Age > 55 years**
- **Obesity**
  - Maximal impact on knee and hip (weight bearing)
  - Knee:
    - BMI +5kg/m² = 35% increased risk
    - Association stronger in women
  - RR of 8.1 for BMI > 30kg/m²
- **Trauma**
  - Macro – frank injury
  - Micro – repetitive overuse
- **Low-antioxidant diet**

### OA – Pathophysiology

#### Chondrocyte senescence

Characterized by:
- Decreased autophagy
- Greater proportions of dysfunctional mitochondria
- Accumulation of misfolded proteins
- Decreased sensitivity to growth factors
- Increased production of pro-inflammatory mediators (intrinsic inflammatory stress)
- Increased production of ECM-degrading enzymes (MMP)

#### Subchondral bone

- Sclerosis with decreased nutrient diffusion to chondrocytes
- Elevated concentrations of pro-inflammatory mediators
- Brings inflammatory stress to deep layer of articular cartilage

#### Synovium

- Immune cell activation and infiltration
- Elevated inflammatory cytokine concentrations in OA

#### OA can be described as an inflammatory-degenerative or inflammatory-catabolic disease with primary manifestations at the joints
**OA - Pathophysiology**

- Systemic inflammation contributes to OA pathogenesis and predicts severity of clinical presentation
- Elevated serum IL-6 and IL-10 associated with higher pain and disability scores
- Elevated IL-6 and TNF-α predict increased rate of joint destruction
- Elevated CRP noted in OA patients vs healthy controls
- Elevated IL-17 noted in OA synovial tissue

**OA – Core Imbalances**

- Defense/repair: inflammation, autoimmune features
- Structural integrity: disrupted articular and periarticular structures, altered biomechanics
- Communication: dysregulated adipokine signaling

**OA – Additional Imbalance Considerations**

- Assimilation: dysbiosis, intestinal permeability increase and increased antigen exposure
- Energy: mitochondrial dysfunction, increased ROS production in chondrocyte senescence
- Mental/emotional: immune and GI impacts via microbial endocrinology, under-reported in elderly

**OA Treatment: Structural Integrity, Communication**

- Weight loss
  - In high-risk groups (overweight and obese patients), 11 lbs (5kg) of weight reduction confers 50% risk reduction for knee OA
  - Weight loss of > 5.1% body weight improves functional capacity (reduced disability scores) in knee OA Pts
  - Improvement in pain ratings also observed

**OA Treatment: Structural Integrity, Defense/Repair**

- Weight loss
  - Smaller improvements (decreased rate of cartilage volume loss) observed with 1% body weight reduction in obese patients
  - Adipokine expression detected in synovial tissue
  - Altered pattern of expression in OA patients
  - Weight reduction may beneficially impact OA independently of biomechanical effects
  - Adiponectin normalization
    - Increased adiponectin
    - Decreased leptin

**OA Treatment: Communication, Defense**

- Tomato juice: 280 mL/day (~9.5 oz/day)
  - Reduced oxidative stress
  - Reduced adiposity and associated metrics
  - Total body weight
  - Waist circumference
  - BMI
  - Shift in adipokine signaling towards anti-inflammatory profile
    - Increased adiponectin
    - Decreased MCP-1,
OA Treatment: Defense/Repair

- Dietary restrictions/elimination diet
  - Nightshades (genus Solanaceae: tomato, potato, eggplant, bell pepper, tobacco)
  - No trial data, some clinical case/ anecdotal evidence

- General elimination diet
  - Greater likelihood of detecting and removing mediating foods by not limiting categories considered
  - No trial data

- n-3 fatty acids: 2-8 g/day combined EPA+DHA
  - Reduces systemic inflammation
  - Reduces nociceptive signaling and pain in response to inflammatory stimuli
  - EGCG: 400mg bid, apart from meals
  - Murine models demonstrate in vivo:
    - Decreased pro-inflammatory gene expression
    - IL-1ß, IL-6, IL-8, TNF-α, NF-kB reduction
    - Decreased production of MMP
    - Mouse OA models further show:
      - Articular cartilage preservation
      - Reduced pain behavior/increased movement
      - Reduce pro-inflammatory and pro-nociceptive mediators in DRG

- Ginger extract: 500-1400 mg/day
  - Products should contain gingerols, shogoals and paradols
  - Ratios will vary by species, cultivation and preparation
  - Anti-inflammatory
  - Inhibits COX-2, LOX
  - Reduces pro-inflammatory prostaglandin and leukotriene synthesis
  - Inhibits TNF-a in inflammarily activated synovocytes (TNF-a/IL-β)
  - Reduces inflammatory stress on synovium
  - Caution: medication interactions - anticoagulant effect
  - Warfarin: potentiates anticoagulant effect
  - Nifedipine: synergistically inhibits platelet aggregation

- Boswellia serrata extract: 800-2000 mg/day
  - Products should contain 60%+ boswellic acids
  - Must be administered with fat-containing foods for maximum bioavailability
  - Anti-inflammatory
  - Inhibits PGE synthase-1 and catabepin G
  - Inhibits leukotriene synthesis via 5-LOX*
  - Inhibits TNF-a and IL-1ß expression
  - Reduces Th17 cell differentiation
  - Recent Cochrane review evidence (2014) indicates significant benefit
    - Mean pain reduction ~42%
    - Mean functional improvement ~25%
    - Combination with curcumin may enhance benefit
    - Superior to celecoxib in reducing pain and tenderness, increasing functional capacity (walking distance)
    - Equal to celecoxib in increasing range of motion and reducing joint crepitus

OA Treatment: Structural Integrity

- Curcumin – 1.5 - 3 g/day in divided doses
  - Reduces ROS biomarkers in OA patients
  - Reduces systemic inflammation
  - Reduces chondrocyte sensitivity to IL-1ß
  - Reduces proteoglycan catabolism, chondrocyte apoptosis

- Glucosamine sulfate – 1,500mg/day
  - Proteoglycan precursor (hydrophilic component of cartilage ground substance)
  - In vitro increase in proteoglycan synthesis, inhibition of catabolism, stimulation of repair
  - RCT data mixed but generally favorable, meta-analyses show smaller effect sizes
  - Decreased: pain, functional impairment, rate of progression (joint space narrowing)
  - Long-term treatment (6 mo-3 years) necessary to achieve clinical improvement in some patients
  - Minimal to no benefit for OA of the lumbar spine
  - 57% reduced risk of knee replacement within 5 years after Tx for 1-3 years
OA Treatment: Structural Integrity, Defense/Repair

- Chondroitin sulfate – 1,200mg/day
  - Polysaccharide component of proteoglycans
  - RCT data mixed but generally favorable, meta-analyses show smaller effect sizes
    - Decreased: pain, functional impairment, rate of progression
    - One RCT (n=300) showed complete arrest of progression (joint space decrease = 0.0 mm) vs. placebo group (joint space decrease = 0.14 mm) after 2 years
    - Increased: joint mobility scores
    - 6-12 months for peak clinical improvement
    - Independent anti-inflammatory action
    - NF-kB and COX-2 inhibition
    - MMP inhibition

- Niacinamide – 500mg 3-6 times per day
  - Single pilot RCT, n=42
    - Decreased: disease progression, anti-inflammatory medication use
    - Increased: joint mobility, AST levels (20% avg increase)
    - Unchanged: pain levels
    - More frequent dosing appears effective d/t short half-life
    - Monitor liver enzymes with doses ≥ 1,500 mg/day
    - Potential MOA – Inhibition of NO synthase
    - NO excess in chondrocytes inhibits synthesis of aggrecan, the core protein in proteoglycans

- Methylsulfonylmethane (MSM) – 1.5-6 g/day
  - Improvements noted in pain and disability scores
  - Modest effect size, uncertain clinical significance
  - No more adverse effects than placebo groups
Regular, restful sleep (1x/day, 7-9 hours; naps PRN but discouraged)
- Disturbed sleep in common (> 50%) in OA patients
- Pain disturbs sleep
- Lack of sleep increases pain
- Reduced inhibition
- Reduced tenderness threshold
- Partially mediated by inflammation
- Sleep hygiene
- Consistency is critical
- Melatonin 0.25-8 mg, 15-45 mins before bedtime
- 5-HTP 100-200 mg, 30-60 mins before bedtime
- Caution in patients taking MAOI, SSRI drugs
- Kava, Valerian, Pediculium

References


Consistency is critical
- 9

Hx


References


Consistency is critical
- 9

Hx


References


Consistency is critical
- 9

Hx


### Constructing a Diabetes Treatment Plan Using a FM Matrix/CCI-informed Approach

**Diabetes Tx Plan – Communication**
- **Goal:** Improve insulin sensitivity
- **Weight loss** – motivational interviewing techniques, thoughtful activity coaching and dietary guidance
- **Less adipose tissue = increased adiponectin secretion**
- **Avoid refined carbohydrates/sugars**
- **Reduced hyperinsulinemia and concomitant receptor downregulation**
- **Chromium 200-1000 µg/day (picolinate form most effective)**
- **Potentiates insulin receptor activation**
- **Enhances post-activation phosphorylation reactions**
- **Independent facilitation of GLUT-4 translocation to membrane**

**Diabetes Tx Plan – Detoxification/Biotransformation**
- **Toxicant Avoidance**
  - Selective consumption of food subject to biological magnification (food = primary human source of PCB exposure)
  - Fish sources/species (wild caught salmon, tilapia = lower levels)
  - Dairy (butter shows direct relationship to environmental PCB levels)
  - Animal fat
- **Aryl hydrocarbon receptor (AhR) modulators**
  - Protective ligands
    - Indole-3-carbinol (I3C) – brassica vegetables
    - Curcumin

**Diabetes Tx Plan – Detoxification/Biotransformation (cont’d)**
- **Aryl hydrocarbon receptor (AhR) modulators**
  - Pathogenic ligands
    - Polychlorinated biphenyls (PCBs)
    - Polychlorinated dibenzo-p-dioxins (PCDDs)
    - Industrial byproduct, biological magnification
    - Polychlorinated dibenzofurans (PCDFs)
    - Industrial byproduct, biological magnification
- **Curcumin**
  - Induces glutathione transferases, NADPH and quinone reductase (facilitates phase II)
### Diabetes Tx Plan – Immune/Inflammation

- Minimize systemic inflammation:
  - Weight loss
  - Less adipose tissue = decreased TNFα, IL-1β, RBP4
  - Anti-inflammatory diet
- Fatty acid therapy
  - EPA + DHA - 3-6 g/day
  - GLA - 2-4 g/day
  - Curcumin – 1-2 g/day (95% extract, +piperine)
  - (inhibits NF-κB, COX2, LOX)
- Alpha lipoic acid – 600mg/day
  - Inhibits NF-κB

### Diabetes Tx Plan – Oxidation/Reduction

- Oxidative stress decreases insulin sensitivity and results in a positive feedback loop
  - Direct inactivation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) by ROS
  - Accumulation of G3P which is shunted into ROS-generating pathways
- CoQ10 – 100-400mg/day
  - Decreased ROS production
  - Mitigation of cardiovascular complications
- Dietary antioxidants

### Diabetes Tx Plan – Assimilation/Microflora

- Decreased refined carbohydrate consumption
  - Shifts bacterial populations toward commensals, away from pathogens
  - Pathogenic bacterial inflammation in the gut lumen induces phosphorylation of IRS-1 = reduced insulin sensitivity
- Increased soluble fiber
  - Non-starchy vegetables, whole grains, legumes
- SIBO assessment/eradication if indicated
- Probiotic foods/supplementation
  - Yogurt associated with lower DM risk
  - 17% reduction with once daily consumption – Chen et al., 2014 (meta analysis, 17 cohorts, total n = 459,790)
Diabetes Tx Plan – Structural Integrity

- Chromium picolinate
- Decreased membrane cholesterol = increased fluidity
- Protein intake – 20-30% of total calories
  - 0.8g/kg/day minimum
  - Less in renal failure/impaired renal function
  - Addresses increased protein turnover in skeletal muscle
- Exercise
  - Prevents atrophic changes/wasting associated with loss of inhibition to protein catabolic pathways in skeletal muscle
  - Facilitates weight loss and improves insulin sensitivity

Diabetes Tx Plan – Care Team

- Ensure regular blood glucose monitoring occurs
- Discuss/obtain results of serum potassium and renal function monitoring to prevent hyperkalemia
  - Renal failure
  - ACE/i-K sparing diuretics
- Maintain contact with prescribing physicians to ensure that medication dosages are adjusted to prevent:
  - Hypoglycemia
  - Hypotension
  - Hypocholesterolemia

References