Bone Health, Osteoporosis and Osteoarthritis

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Functions of Bone

- Movement, support, protection
- Red and white blood cell production
- Triglyceride storage
- Mineral storage and homeostasis
- Acid/Alkaline balance
- Growth factor storage
- Phosphate metabolism
- Detoxification

What Is Bone?

- Bone matrix is a living growing tissue
- Consisting of:
  - Approx 25% collagen, the protein that provides the flexible framework
  - Approx 50% crystallized mineral salts including calcium phosphate, calcium carbonate, magnesium hydroxide, fluoride & sulphate provides the strength & hardens the framework
  - 25% water

Bone Homeostasis

- Bone health is maintained by a balanced remodeling process that ensures the continual replacement of old bone, weakened by normal microfracture, with new bone
- Involves a 2 part process of bone resorption by osteoclasts & subsequent new bone formation by osteoblasts/osteocytes

Downey PA, Siegel MI. Bone Biology and the Clinical Implications for Osteoporosis, *Physical Therapy*, 2006; **86**(1): 77-91
Bone Remodelling

- Local collections of osteocytes, osteoblasts, and osteoclasts work together to control bone formation and resorption, creating a functional unit referred to as the *basic multicellular unit* (BMU)
- Throughout life bone is constantly renewed
- Failure to reach peak bone mass or disturbances to remodeling can result in bone fragility

Downey PA, Siegel MI. Bone Biology and the Clinical Implications for Osteoporosis, *Physical Therapy*, 2006; 86(1): 77-91
Bone Remodeling

- Can be thought of as a bone bank account with deposits & withdrawals
- During childhood & the teenage years there are more deposits than withdrawals, this increases bone density, length & weight
- Deposits peak during the third decade of life
- Dependant on adequate nutrition & exercise

Downey PA, Siegel MI. Bone Biology and the Clinical Implications for Osteoporosis, *Physical Therapy*, 2006; 86(1): 77-91
Bone Remodeling

- Following the third decade of life bone withdrawals can exceed deposits
- However at every stage in life the balance between withdrawal (resorption) & deposits (formation) is affected by local & systemic signals
- The average life cycle for bone remodelling depends on the size of the bone, eg the distal femur takes about 4 months
- In adults, BMUs remodel or replace 10% of the skeleton annually

Downey PA, Siegel MI. Bone Biology and the Clinical Implications for Osteoporosis, *Physical Therapy*, 2006; 86(1): 77-91
Physiology

- Remodeling serves 3 purposes:
  - Renews bone before deterioration sets in
  - Redistributes bone matrix along lines of mechanical stress
  - To supply Ca from skeleton to maintain serum Ca
- It is also the manner in which injured bones heal

Physiology

- Bone remodeling begins with the differentiation & activation of osteoclasts
- These cells lay down an acidic environment on the bone surface allowing proteolytic enzymes to degrade the bone matrix
- Osteoclasts are activated by mechanical forces, inflammatory T cells, a number of growth factors, IL-1, IL-6, TNF-α, RANKL
- Osteoblasts then line the surface of the bone & lay down new uncalcified bone

Central Role of Estrogen

- Estrogen plays a fundamental role in bone homeostasis in both men & women
- Osteoblasts, osteocytes & osteoclasts all have estrogen receptors
- Estrogen deficiency enhances osteoclast formation & prolongs the resorption phase by reducing the apoptotic rate of osteoclasts
- Thus the balance between withdrawal & deposition is tipped in favor of withdrawal

Osteoporosis (OP) is a chronic progressive skeletal disease characterized by:

- Microarchitecture deterioration
- Low bone mass

As a result the bones become fragile with the increased risk of fracture, especially of the hip, spine & wrist

Sambrook P, Cooper C. Osteoporosis, Lancet 2006; 367(9527): 2010-2018
Symptoms

- Osteoporosis is a silent disease, as people can not feel their bones getting weaker
- Most do not know they have osteoporosis until a fracture occurs, from a major fall or from a simple action such as sneezing
- Vertebral fractures obviously can be felt & can cause pain
- Signs such as loss of height & kyphosis are associated with osteoporosis

http://www.nof.org/osteoporosis/diseasefacts.html
Types of Osteoporosis

- Type 1 or postmenopausal osteoporosis
  - The most common & related to estrogen decline/deficiency

- Type 2 or senile osteoporosis
  - Affecting males & females more than 70 years of age
  - Associated with the kidneys’ decreased ability to produce \(1,25(\text{OH})_2\text{D}_3\) the active form of vit D\(_3\)
  - Results in decreased Ca absorption, which increases parathyroid hormone & bone resorption
Types of Osteoporosis

- Type 3 or secondary osteoporosis is associated with a variety of conditions:
  - Poor nutrition
  - Heavy metal exposure: cadmium, Mercury, Lead
  - Drug use: corticosteroids, thiazolidinediones, PPIs, heparin, NSAIDS
  - Inflammatory GIT disorders
  - Chronic renal failure, RA, diabetes, cushing’s syndrome, depression
  - Cancer particularly multiple myeloma

Iqbal MM. Osteoporosis: Epidemiology, Diagnosis and Treatment. *Southern Medical Journal* 2000; 93(1): 2-18
Nutritional Risk Factors

- Caffeine
- Soda
  - Interferes with calcium/phosphorus balance
  - Phosphorus binds with calcium, leaving calcium unavailable to the body
  - Calcium is thereby drawn from bones
- Sugar
  - Decreases calcium & magnesium absorption
  - Contributes to intestinal dysbiosis

Nutritional Risk Factors

- Salt
  - Increases calcium excretion
- Nutritional deficiency
  - Protein, vegetables and fruit
  - Vitamins: D, C, K, A,
  - Minerals: Ca, P, K, Mg, Zn, Si, Mn, Fe, Cu,
  - Omega-3 fatty acids
- Alcohol consumption
  - Toxic to osteoblasts & interferes with Ca absorption

Other Risk Factors

- Female
- Petiteness
- Age
- Tobacco use
  - BMD of smokers 20-30% lower than that of non-smokers
  - Enhances estrogen metabolism
  - Increases inflammation
  - Cadmium toxicity

Other Risk Factors

- Lack of childhood exercise
- Adult sedentary lifestyle
- Multiple pregnancies & breastfeeding
  - Nutrients prioritized to baby
- Hyperthyroid
  - TH increases bone resorption
- Hyperparathyroid
  - Increases bone resorption

Other Risk Factors

- Anorexia nervosa
- Subclinical hypercortisolism and hypercortisolism
- Peripheral arterial disease
- Depression
**Herbal Treatments**

- The majority of epidemiological & clinical research on the role of natural medicines & osteoporosis treatment & prevention has focused on phytoestrogenic plant compounds.

- Epidemiological data strongly suggests that the ingestion of phytoestrogenic compounds produces a lower incidence of osteoporosis & bone fractures, as well as menopausal symptoms such as hot flashes.

Phytoestrogens

- A group of plant derived molecules that possess estrogen like activity
- Several different phytochemical classes are known to interact with estrogen receptors, the most intensely studied are:
  - Isoflavones
  - Lignans

Phytoestrogens

- Studies demonstrate that isoflavones compete strongly for estrogen receptors, however their stimulation of these receptors is much weaker than estradiol.
- In other words they are partial estrogen agonists which can function as estrogen agonists OR antagonists depending on the hormonal milieu.

Phytoestrogens

- In a high estrogen environment such as in premenopausal women, their displacement of endogenous (& exogenous) estrogens is thought to have an antiestrogenic effect.
- In contrast in lower estrogenic environments, as in post menopausal women they are thought to provide a net estrogenic effect.

Pharmacokinetics

- The bioavailability of phytoestrogens & isoflavones in particular is dependant on a number of factors
- Isoflavones are present in plants & extracts from plants as glycosides (sugar + aglycone) & are inactive in this form
- The active principles are derived from the aglycone component
- The GIT needs to hydrolyse the bond between the sugar & aglycone via intestinal glucosidase enzymes
Pharmacokinetics

- Intestinal metabolism of isoflavones to their aglycone forms is crucial for ensuring bioavailability & therapeutic activity
- The health of intestinal microflora is pivotal in the healthy metabolism of estrogenic phytochemicals
- Individual differences in intestinal microflora have been proposed as a possible reason why there is some inconsistency in the clinical effects of phytoestrogens

Gut Metabolism of Isoflavones

Gut Metabolism of Diadzin

- As seen on a previous slide, the isoflavone diadzin is reduced to the aglycone diadzein by enzymes (glucosidases) produced by the gut microflora.
- Diadzein is then subjected to further reduction as a result of the action of the gut microflora to produce equol, which is the active estrogenic compound.

Non-responders to Isoflavones

- There are large individual variances in the capacity to produce equol (up to 400 fold) & hence a therapeutic effect
- Dietary fat consumption is known to reduce this capacity\(^1\)
- Dietary supplementation with fructooligosaccharides such as inulin are known to increase the capacity to produce equol\(^2\)

Non-responders to Isoflavones

- Oral antibiotics are known to reduce equol production\(^1\)
- Numerous clinical experiences in treating women with menopausal symptoms with herbal extracts containing isoflavones have demonstrated that a gut flora protocol is beneficial in bringing about a therapeutic effect in those clients that do not respond initially
- This provides the rationale for the gut flora protocol for non-responders

Exercise

- Exercise is often recommended for increasing BMD, possibly by stimulating estrogen receptors.
- However, the increases in BMD are often small with exercise alone.
- But when exercise is combined with isoflavone therapy much larger increases in BMD have been observed.

Epimedium

- A TCM herb that tonifies the kidneys & fortifies the yang. Actions which strengthen bones
- Indicated for weak limbs
- Epimedium contains a unique flavonoid icariin, along with the isoflavones genistein and daidzein
- Many OP experimental studies have been conducted on either the herb or Icariin

Epimedium: Clinical Trial

- Epimedium-derived icariin and isoflavones demonstrated beneficial effects in late postmenopausal women, without resulting in a detectable hyperplasia effect on the endometrium
- 24-month randomized double-blind placebo-controlled clinical trial
- 100 postmenopausal women with lumbar spine BMD, with T scores of between -2 & -2.5

Epimedium: Clinical Trial

- Active group (n=50) received a daily dose of Epimedium extract containing 60 mg icariin, 15 mg diadzein and 3 mg genistein
- Placebo group (n=50)
- Both groups received 300 mg of calcium as citrate daily
- Epimedium significantly ↓ levels of deoxypyridinoline at 12 months (43% p=0.000) and 24 months (39% p=0.000), with no change in the placebo group

Zhang G, Qin L, Shi Y. *J Bone Miner Res* 2007; 22(7): 1072-1079
Epimedium: Clinical Trial

- Osteocalcin increased 5.6% (p=0.530) at 12 months and 10.7% (p=0.267) at 24 months. No change in placebo group
- Serum estradiol, no change in the Epimedium group

Zhang G, Qin L, Shi Y. *J Bone Miner Res* 2007; **22**(7): 1072-1079
Epimedium: Clinical Trial

- BMD (lumbar spine) treatment group
  - ↑ 1.0% at 12 months
  - ↑ 1.3% at 24 months
- BMD (lumbar spine) placebo group
  - ↓ 1.7% at 12 months
  - ↓ 2.4% at 24 months
- Difference b/w placebo at 12 months p = 0.044
- Difference b/w placebo 24 months p = 0.006

Zhang G, Qin L, Shi Y. *J Bone Miner Res* 2007; 22(7): 1072-1079
Epimedium: Clinical Trial

- BMD (femoral neck) treatment group
  - ↑ 1.1% at 12 months
  - ↑ 1.6% at 24 months
- BMD (femoral neck) placebo group
  - ↓ 1.4% at 12 months
  - ↓ 1.8% at 24 months
- Difference b/w placebo 12 months p = 0.061
- Difference b/w placebo 24 months p = 0.008

Zhang G, Qin L, Shi Y. *J Bone Miner Res* 2007; **22**(7): 1072-1079
Bone Complex

Epimedium herb top 12:1 extract 200 mg
from *Epimedium sagittatum* herb top 2.4 g
Containing icariin 20 mg

Red Clover herb flowering top 5:1 extract 100 mg
from *Trifolium pratense* herb flowering top 500 mg
Containing isoflavones 8 mg

Kudzu root 10:1 extract 70 mg
from *Pueraria lobata* root 700 mg
Containing puerariae isoflavones calculated as
diadzin, puerarin, daidzein 28 mg

Black Cohosh root 4:1 extract 20 mg
from *Cimicifuga racemosa* root 80 mg

Suggested Dose: These herbs 3 times daily
Bone Complex

**Indications:**
- Pre-treatment and treatment of osteopenia, (particularly in postmenopausal women)
  - In conjunction with weight-bearing exercise
  - A healthy diet containing food sources of calcium and vitamin D
- Management of osteoporosis
- Support and maintain healthy bone density
- Beneficially influence bone remodeling
OP Prevention 30-50 Years Old

- Calcifood Powder, 1 to 2 tablespoons per day
- Cataplex D, 1 tablet 3 times daily
- Garlic 5000mg, 1 tablet 2 to 3 times daily
- Bowel Flora Protocol yearly
- Exercise
Menopausal OP

- Bone Complex, 1 tablet 3 times daily
- Ostrophin, 2 tablets 3 times daily
- Calcifood Powder, 1 to 2 tablespoons per day
- Cataplex D, 1 tablet 3 times daily
- Zinc Liver Chelate, 1 tablet 3 times daily
- Whey Pro Complete
- Garlic 5000mg, 1 tablet 2 to 3 times daily
- Bowel Flora Protocol yearly
- Exercise
Synergistic Support for Fracture Healing

- Gotu Kola Complex, 3 to 4 tablets daily
- Bone Complex, 3 to 4 tablets daily
- Echinacea Premium, 1 tablet 2 times daily
- Ostrophin, 2 tablets 3 times daily
- Calcifoood Powder, 1 to 2 tablespoons daily
- Whey Pro Complete, 1 tablespoon 2 times daily
- Cataplex D, 1 tablet 3 times daily
- Cataplex C, 3 tablets 2 to 3 times per day
- Zinc Liver Chelate, 1 tablet 3 times daily
Secondary OP

- Bone Complex, 1 tablet 3 times daily
- Ostrophin, 2 tablets 3 times daily
- Calcifood Powder, 1 to 2 tablespoons per day
- Cataplex D, 1 tablet 3 times daily
- Zinc Liver Chelate, 1 tablet 3 times daily
- Whey Pro Complete
- Garlic 5000mg, 1 tablet 2 to 3 times daily
- Bowel Flora Protocol yearly
- Exercise
- Treat the cause
Bowel Flora Protocol for Non-Responders

- Gut Complex, 1 capsule twice per day
- Pre-Biotic Inulin, 1 to 1 ½ teaspoons twice per day

If required include,

- Vitanox, 2 to 3 tablets per day
- ProSynbiotic, 3 capsules per day
Pathophysiology of OA

OA results from a complex interaction of mechanical, biochemical, molecular and enzymatic feedback loops

- Articular cartilage
- Subchondral bone
- Synovial membrane
- Synovial fluid

Martel-Pelletier J, Pelletier JP. *Eklem Hastalik Cerrahisi* 2010; 21(1): 2-14
Articular Cartilage

- Articular cartilage
- Tidemark
- Calcified cartilage
- Cement line
- Subchondral bone plate
- Subarticular spongosia
Articular Cartilage

- Matrix metalloproteinases (MMPs) and aggrecanases are responsible for cartilage matrix degradation
- Aggrecan is a large aggregating proteoglycan that contains chondroitin sulfate and keratan sulfate and is important for the weight-bearing properties of cartilage
- Later cartilage mineralization (predominantly calcium pyrophosphate and phosphate) occurs and could accelerate inflammation

Synovium

- Synovitis occurs in early OA but can be subclinical
- Becomes more extensive as OA progresses, with synovial hypertrophy and hyperplasia occurring
- Increased numbers of immune cells, such as activated B cells and T lymphocytes
- Synovitis may contribute to the progression of cartilage degradation

Martel-Pelletier J, Pelletier JP. *Eklem Hastalik Cerrahisi* 2010; 21(1): 2-14
Subchondral Bone

The subchondral bone plate is in direct contact with the cartilage and could influence its degradation.

Subchondral bone alterations may precede cartilage degeneration.
Subchondral Bone

- Early microvascular damage affecting the venous circulation in subchondral bone is found in OA.
- Increasing evidence bone marrow lesions (BMLs) and bone cysts play an important role.
- BMLs are strongly associated with radiological progression of knee OA and BML enlargement predicts increased cartilage loss, and the reverse.

Martel-Pelletier J, Pelletier JP. *Eklem Hastalik Cerrahisi* 2010; **21**(1): 2-14
Subchondral Bone/Cartilage Crosstalk

- Micro-cracks at the bone/cartilage junction
- Growth factors secreted by osteoblasts but not chondrocytes have been detected in deep layers of cartilage
- Altered subchondral bone osteoblasts contribute to the degradation of overlying cartilage by leakage of biochemical factors

Inflammation in OA

- Cytokines, particularly interleukin (IL)-1β
- Tumor necrosis factor (TNF)-α
- Nitric oxide (NO) and reactive oxygen species. NO reduces the major anabolic processes and increases the catabolic processes
- Leukotrienes (LT) and prostaglandins (PG) particularly PGE₂ produced from arachidonic acid (AA) by cyclo-oxygenase (COX)-2 followed by PG synthase
Is OA a Systemic Disease?

- While the OA definition links it to mechanical stress, predisposition to such stress could be more important.
- OA is more widespread in the body than is apparent from clinical studies.
- This is consistent with other data suggesting that OA is a disease that is primarily dependent on systemic predisposition to a particular type of bone response to mechanical stress.
- Generalized OA is a strong predictor of disease progression.

1 Rogers J, Shepstone L, Dieppe P. *Arthritis Rheum* 2004; 50(2): 452-457
Advanced Glycation End Products

- A prominent feature of aging is the modification of proteins by glucose and fructose (glycation)
- Glycated proteins undergo a series of reactions to become Advanced Glycation End Products (AGE)

AGEs and OA

- Age-related accumulation of AGEs in articular cartilage causes increased stiffness of the collagen network which in turn makes the cartilage collagen network more brittle and prone to damage.
AGEs and OA

- Increased severity of OA correlates with higher cartilage AGE levels\(^1\)
- AGEs in cartilage trigger AGE receptors (RAGE) on chondrocytes and synoviocytes to increase production of cytokines and matrix degrading enzymes, which degrade and breakdown cartilage\(^2\)
- AGEs via RAGE could therefore contribute to the development and/or progression of OA\(^2\)

OA and Circulation

- OA is linked to primary cardiovascular (CV) disease
- A high prevalence of CV risk factors and vascular comorbidity have been described in OA
- Factors strongly associated include Hyperlipidemia and hypertension
- A higher risk of CV death is associated with widespread OA

OA, Circulation and Subchondral Bone

- One recent review suggested there is mounting evidence that a microvascular pathology plays a key role in the initiation and/or progression of OA.
- Disruption of microvascular blood flow in subchondral bone may reduce nutrient diffusion to articular cartilage in OA.
- Ischemia in subchondral bone due to microthrombi may produce osteocyte death, bone resorption and articular damage in OA.

Drawing the Threads Together

- Importance of subchondral bone circulation, synovial circulation and AGEs in the development and progression of OA places great emphasis on diet and lifestyle factors and treatments which support and enhance microcirculation.
- Anti-inflammatory treatments are only one part of the equation.
- Cytokine modification needs to be an important focus and will likely be disease modifying.
Treatments that support the integrity of the connective tissue cells, chondrocytes and fibroblasts, are important especially in the early stages.

Antioxidants may have a role to play as well.

Include treatments to improve blood quality.

Insulin resistance is also a factor to consider.
Key Products

- Boswellia Complex
- Glucosamine Synergy
- Saligesic
- HerbaVital
- Gotu Kola Complex
- Ginkgo Forte
- Garlic 5000mg
- Gymnema 4g
- Silymarin
- Vitanox
- St John’s Wort 1.8g
Boswellia: A Rational Therapy for OA

- Research has centered on the triterpenoids, especially the boswellic acids, which are considered to be responsible for the observed anti-inflammatory and antiarthritic activities of the resin.
- They were originally discovered to act as inhibitors of the enzyme 5-LOX *in vitro*, reducing the formation of inflammatory leukotrienes.
- However, subsequent research has identified a range of anti-inflammatory effects.
Boswellia: A 2010 review

- Inhibition of 5-LOX, but only minor activity on PGE production
- Downregulation of TNF-α by inhibition of NF-κB
- Inhibition of IL-1β production
- Inhibition of matrix metalloproteinase activity
- Inhibition of C3-convertase of the complement system
- Particularly active are 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-β-boswellic acid (AKBA)

Ammon HP. *Phytotherapy* 2010; 17(11): 862-867
Boswellia and Osteoarthritis

- After 8 weeks of treatment:
  - Pain index 2.7 → 0.26
  - Loss of movement 2.8 → 0.30
  - Swelling index 1.1 → zero
- Results were highly statistically significant and clinically relevant (p<0.001)
- Changes in the treatment parameters were large
- All patients chose to continue with the Boswellia following the completion of the trial!

Trial Design

Other outcomes:

- ↑ knee flexion
- ↑ walking distance
- Well tolerated only minor GIT adverse reactions

Improved Clinical Outcomes

- Consuming Boswellia with a high fat meal improved Boswellia bioavailability by a factor of 5
- Acetyl-11-keto-β-boswellic acid (AKBA)
  - 6.0 ng/mL for the fasted conditions
  - 28.8 ng/mL with food
- Randomized, open, single-dose study
  - 12 healthy male volunteers
  - 786 mg of Boswellia extract either with or without a standard high-fat meal

Sterk V, Buchele B, Simmet T. *Planta Med* 2004; **70**(12): 1155-1160
Boswellia Complex

Boswellia dry gum 7:1 extract  277 mg
from *Boswellia serrata* gum resin 1.9 g
containing boswellic acids 180 mg
Celery Seed fruit 6:1 extract  166.7 mg
from *Apium graveolens* fruit 1.0 g
Ginger rhizome 5:1 extract  60 mg
from *Zingiber officinale* rhizome 300 mg
Turmeric rhizome 25:1 extract  80 mg
from *Curcuma longa* rhizome 2.0 g
containing curcuminoids 70.4 mg

**Dosage:** 1 tablet 2 to 4 times per day
Osteoarthritis Core Support

Boswellia Complex
1 tablet 2 to 4 times daily
Important to be taken with meals

Glucosamine Synergy
1 capsule 3 times daily
Thank You

And special thanks to Associate Professor Kerry Bone and Rob Santich for their help and input with this seminar