Treating Osteoporosis “Naturally”: Update on Microbiome

Susan V. Bukata, MD, FAOA, FAAOS
Department Chair Orthopaedics
Professor Orthopaedics
UC San Diego

Disclosures

- Speaker’s Bureau
  - Radius
- Consulting
  - Amgen, Radius, Solarea
- Research funding
  - Hansjorg Wyss Foundation
- Board Membership
  - Orthopaedic Research Society

Objectives

- To review how the gut biome and immune system interact
- To review how the gut biome can influence bone mass
- To review comorbidities that affect gut biome composition and are known risks for low bone mass
- To explore emerging data on food and supplements that can help preserve bone mass

Treating Osteoporosis the “Natural Way”

- Common response from patients when given diagnosis
  - What can I eat?
  - Tell me the exercises to do?
  - I’ll take that calcium to fix my bones
  - Tell me what supplements to buy

Treating Osteoporosis the “Natural Way”

- Our current tools in this area are not great at fracture reduction
  - Calcium and Vitamin D important for maintaining strong bones for a lifetime
    - not shown to decrease fracture risk once normal range
  - Exercise
    - slows bone loss
    - keeps architecture in as strong a configuration as possible
  - Supplements like Vitamin C and Vitamin K2 may help with collagen crosslinks
  - We get a ton of phosphorous (thank you fertilizer)
  - Estrogen and Testosterone are technically “natural”

No diet has been shown to reduce fractures
but….
If you can eat 4Kg of blueberries a week….

WHAT????

The gut and the immune system

- Most of the cells in the human body (90%) are microbes and most are in the distal gut
- Heterogeneous microbe population
  - 10^{14} cells
  - 5000 species
  - 5 million genes (by current estimates)
- Majority are anaerobic
- Traditional stool culture only picks up living microbes
- DNA extraction from stool can pick up both living and dead microbes at the “end of the line”

Gut biome and the immune system

- What do these microbes do?
  - Improve energy and nutrient extraction from foods
  - Eliminate pathogenic bacteria
  - Stimulate tissue production
    - Proliferation and viability of intestinal epithelial cells
    - Improve barrier function of gut epithelial cells

The gut and the immune system

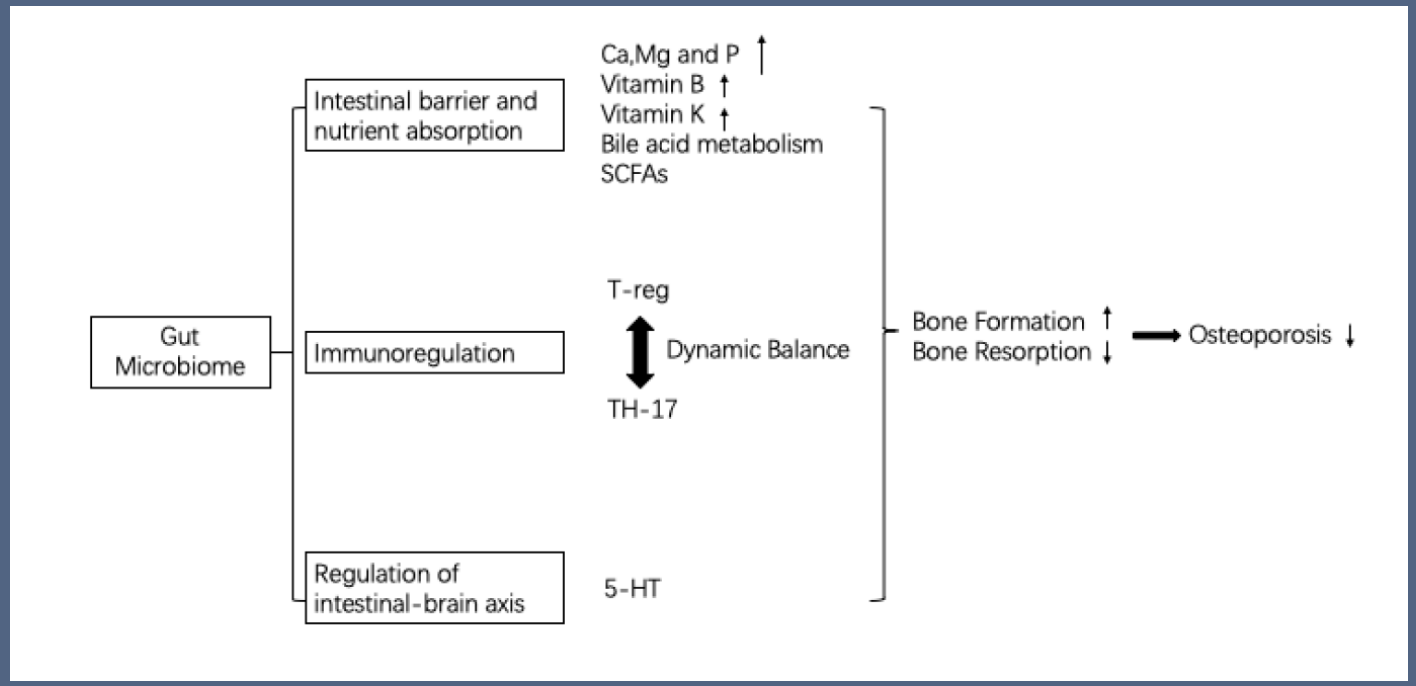
- Many things create a chronic inflammatory state in the gut
  - sex steroid deficiency
  - Western diet high in fat
  - Overuse of antibiotics
- Gut microbiota in constant communication with immune system
  - Suppress response to commensal microbes
  - Help protect host from invading pathogens (bacterial and ?viral)
  - Microbe population associated with systemic “inflammation” levels likely T cell mediated
  - Diseases like obesity, diabetes, cancer, certain antibiotics can increase that inflammation signal to the T Cells

So how does this relate to the bone?

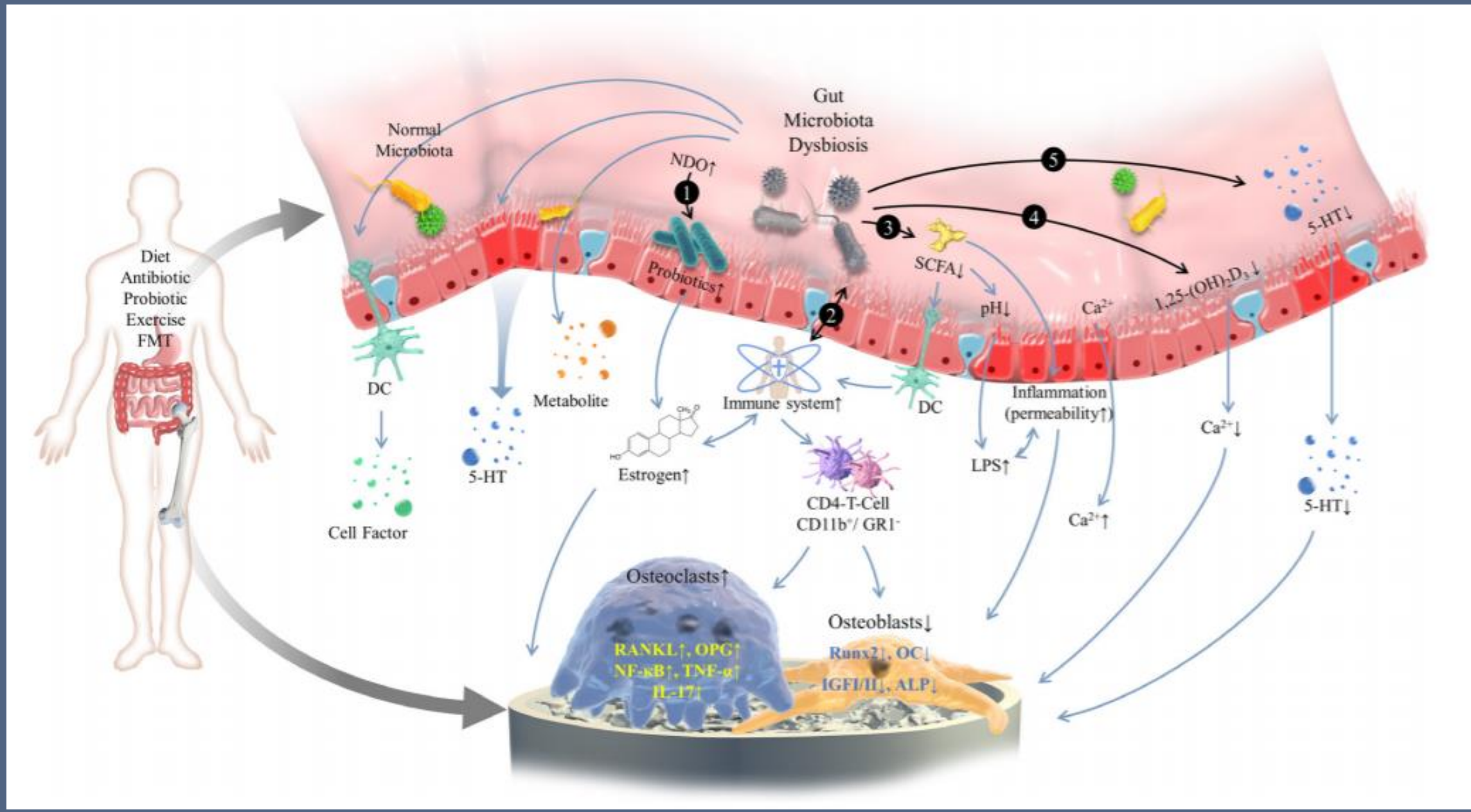
- Osteoporosis and osteoarthritis share common immune component
  - Enhanced CD 4+ cells
  - Increased production of proinflammatory and osteocyte stimulating factors
  - Dysbiosis may change immune response and alter migration monocytes and lymphocytes into tissues including bone marrow
  - Th-17 cells migrate to bone marrow and recruit osteoclast precursors
  - Osteoclasts induce production T-regulatory cells
    - Can activate TNF a producing CD 4+ cells
- short-chain fatty acids
  - generated by fermentation of complex carbohydrates by the gut microbiota
  - important regulators of both bone formation and resorption

  (Zaiss MM, et al: . *J Clin Invest* 2019; **129:** 3018–28)

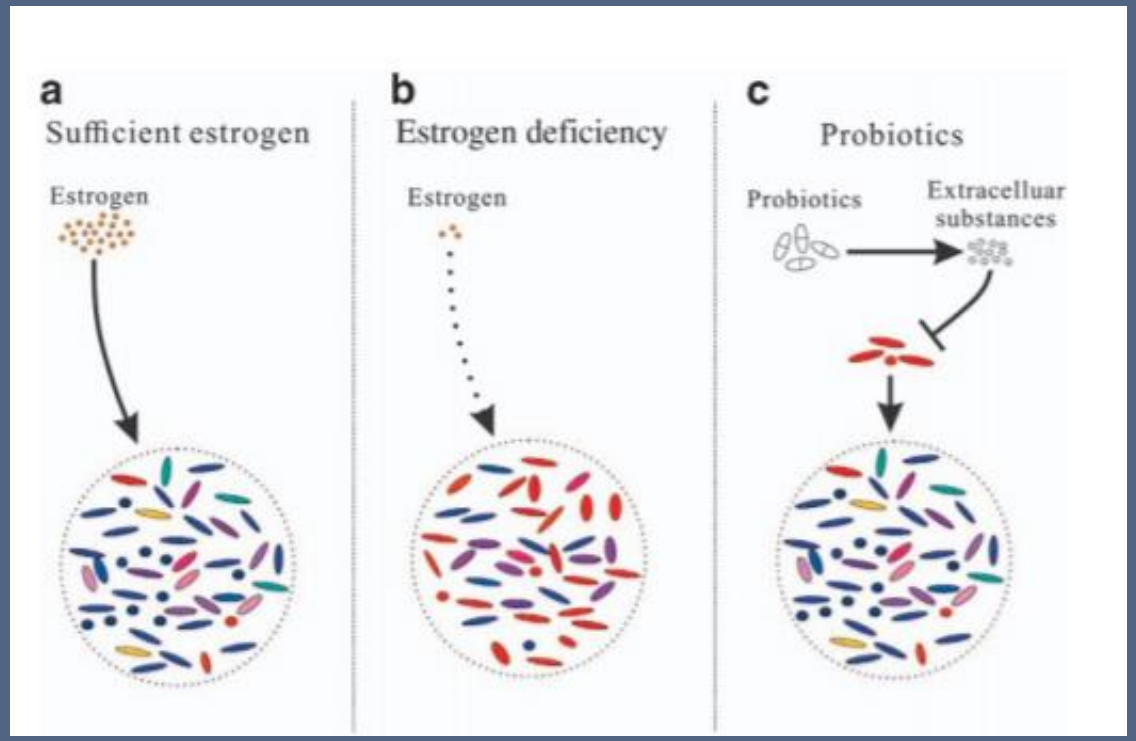
The gut, the bone and the immune system



- Role in management of nutrient absorption and balance
- Balance of immune modulated inflammation
- Some connection to brain regulatory factors that can have a direct effect on bone mass regulation

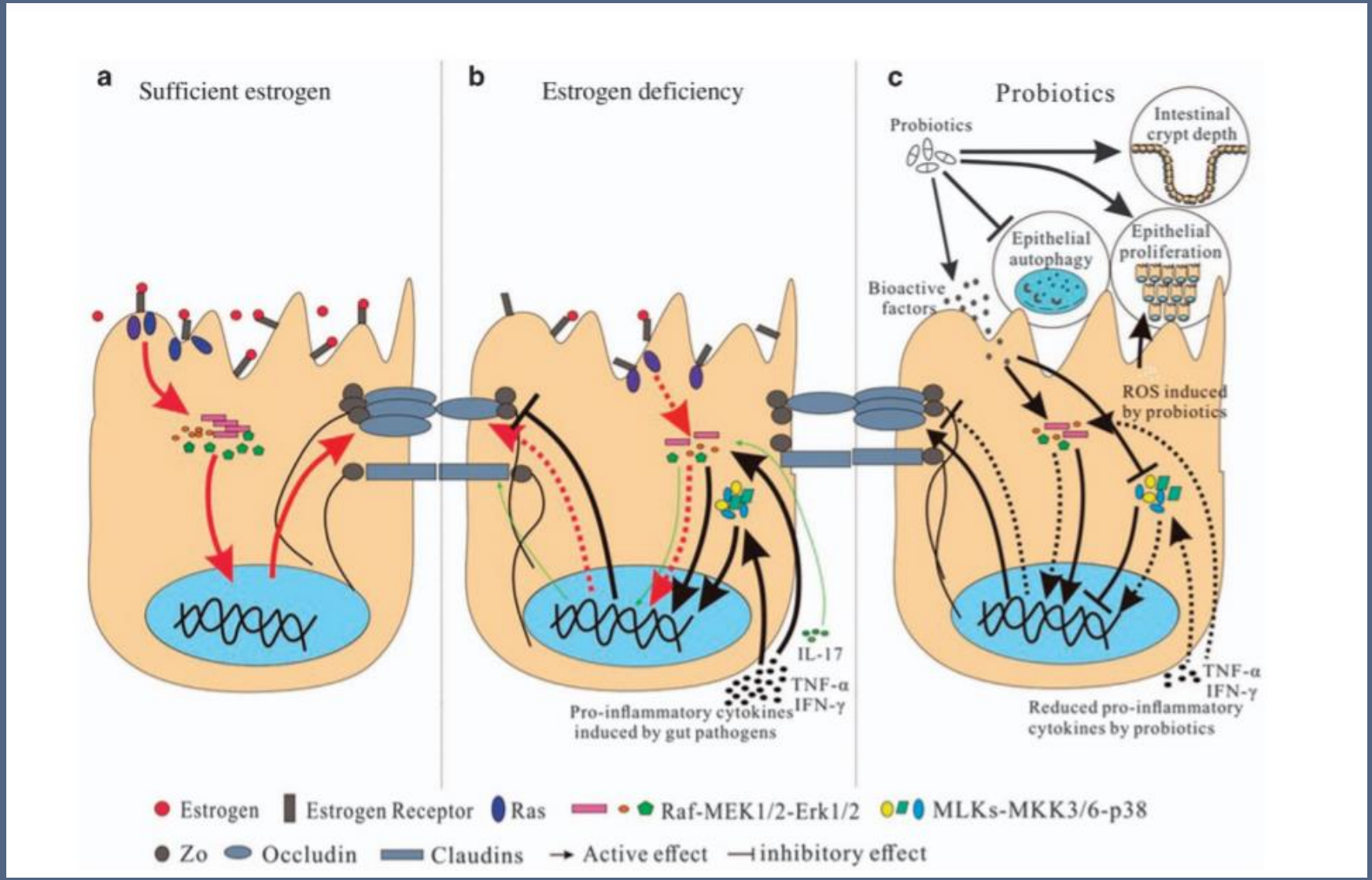

Diet
Antibiotic
Probiotic
Exercise
FMT
Normal Microbiota
Gut Microbiota Dysbiosis
NDO↑
Probiotics↑
SCFA↓
pH↓
Ca2+
1,25-(OH)2D3↓
5-HT↓
DC
Metabolite
Immune system↑
DC
Inflammation (permeability↑)
Cell Factor
5-HT
Estrogen↑
LPS↑
Ca2+↓
Ca2+↑
5-HT↓
CD4-T-Cell
CD11b+/ GR1-
Osteoclasts↑
RANKL↑, OPG↑
NF-κB↑, TNF-α↑
IL-17↑
Osteoblasts↓
Runx2↓, OC↓
IGFI/II↓, ALP↓

Rodent studies showed normalized gut biome with estrogen deficiency



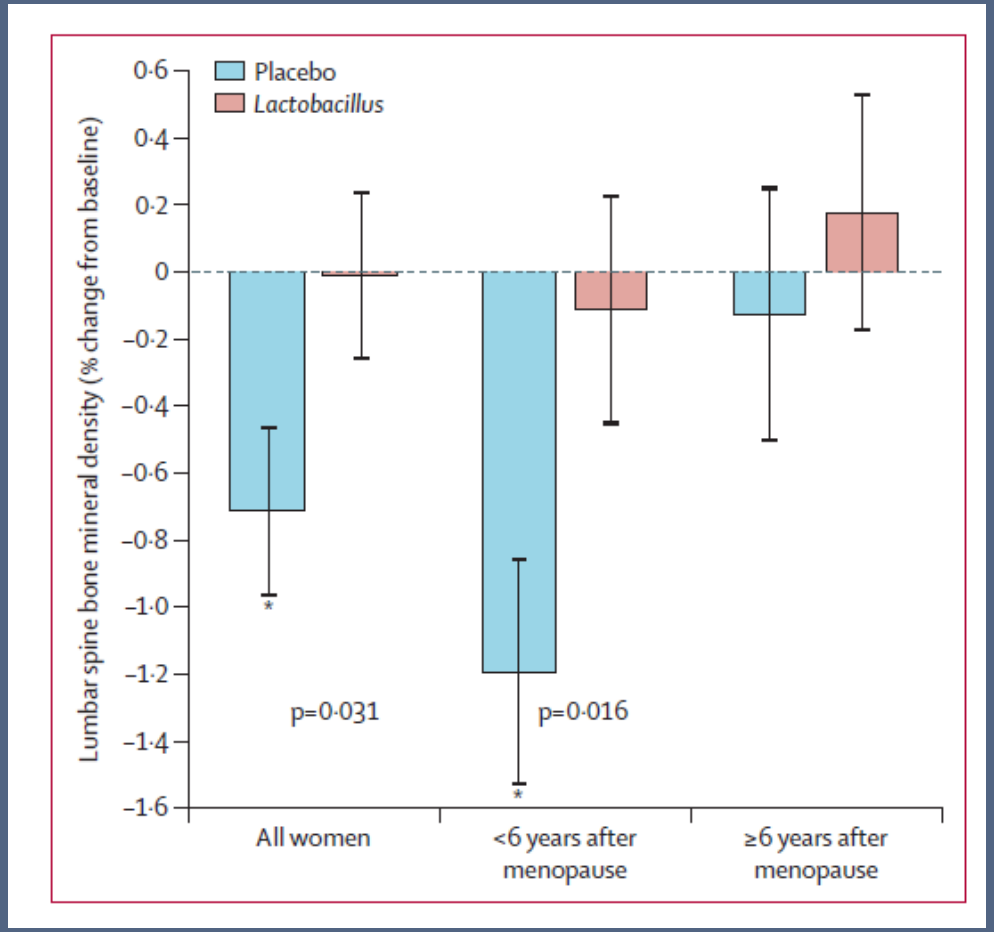
- Estrogen loss was followed by dysbiosis (changes toward more inflammatory gut bacteria)
- Probiotics helped produce some extracellular substances that blocked change
- Resulted in minimal change in gut biome despite estrogen loss
- Ovarectomized mouse model showed bone loss protection with probiotic

One could wish the story was this simple



Using probiotics to decrease bone loss in women

- **randomised, double-blind, placebo-controlled, multicenter trial in Sweden**
- **249 women treated for 12 months with 3 strains of Lactobacillus bacteria (paracasei and 2 plantarum) or placebo**
- Healthy women in the early post-menopausal phase(≥2 years and ≤12 years since the last menstruation
- ≥1 year since last HRT
- T score of more than –2.5 at the lumbar spine (L1–L4)
- body-mass index (BMI) of between 18 and 30



Jansson, et al: *Lancet Rheumatol* 2019; 1: e154–62

Using probiotics to decrease bone loss in women

- No effect on bone loss at the hip
- Well tolerated, inexpensive
- effect size on LS-BMD
  - minor magnitude compared with the effects of the first-line OP treatments
  - Interesting biggest difference if <6 yrs since menopause
  - May be helpful in the early phases of bone loss

	Within-group comparison (month 12 *vs* baseline)		Difference between groups
	Lactobacillus (n=116)	Placebo (n=118)	
Primary outcome			
LS-BMD	−0·01% (−0·50 to 0·48)	−0·72% (−1·22 to −0·22)*	0·71% (0·06 to 1·35)†
Secondary or explorative outcomes			
Total hip BMD	−1·18% (−1·54 to −0·82)*	−1·00% (−1·37 to −0·63)*	−0·18% (−0·65 to 0·29)
Trochanter BMD	−1·29% (−1·94 to −0·64)‡	−1·27% (−1·92 to −0·61)*	−0·02% (−0·87 to 0·82)
Femoral neck BMD	−1·39% (−1·84 to −0·95)*	−0·74% (−1·20 to −0·29)*	−0·65% (−1·23 to −0·07)†

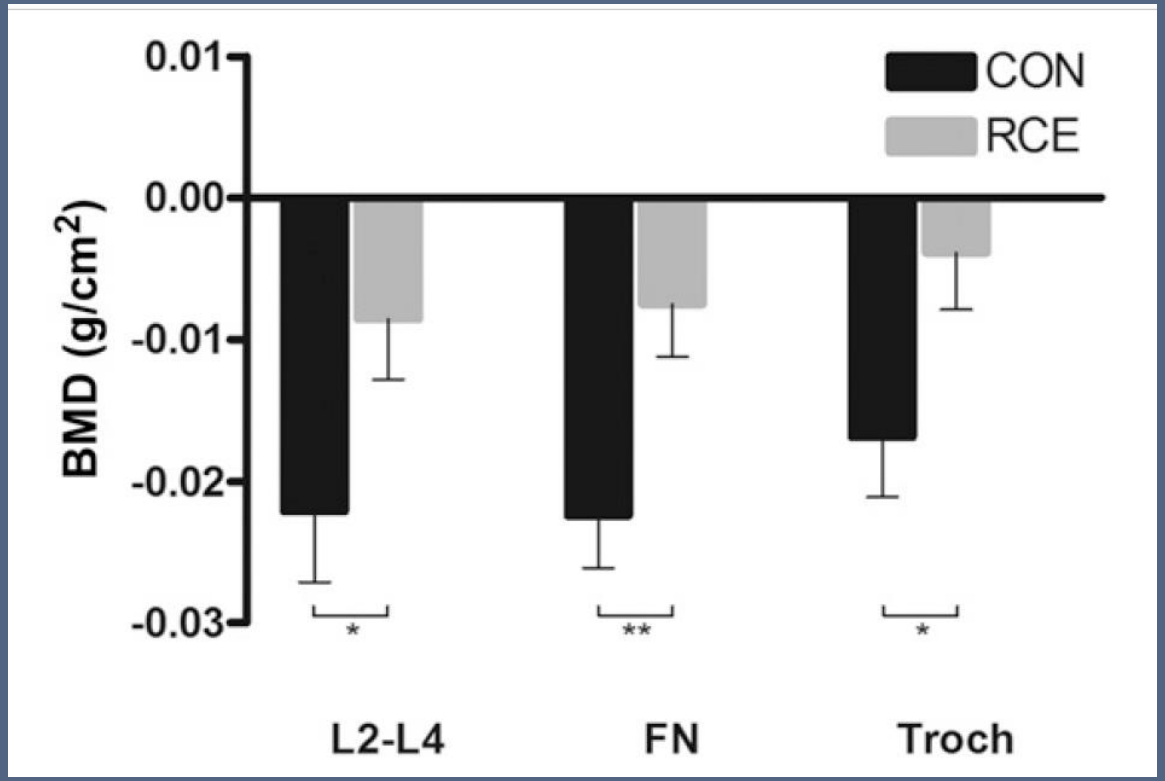
Data are least square mean (95% CI). The primary outcome was the difference between groups for relative change after 12 months in lumbar spine bone mineral density (LS-BMD). Adjustments for site, baseline age, and baseline years after menopause were done using analysis of covariance (ANCOVA) for comparisons between groups. BMD=bone mineral density. *p<0·001 for within-group comparison using Wilcoxon signed rank-sum test. †p<0·05 for between-group comparison using ANCOVA. ‡p<0·01 for within-group comparison using Wilcoxon signed rank-sum test.

Table 2: **Analyses of the relative change in the primary and secondary BMD outcomes**

Jansson, et al: *Lancet Rheumatol* 2019; 1: e154–62

Using probiotics to decrease bone loss in women

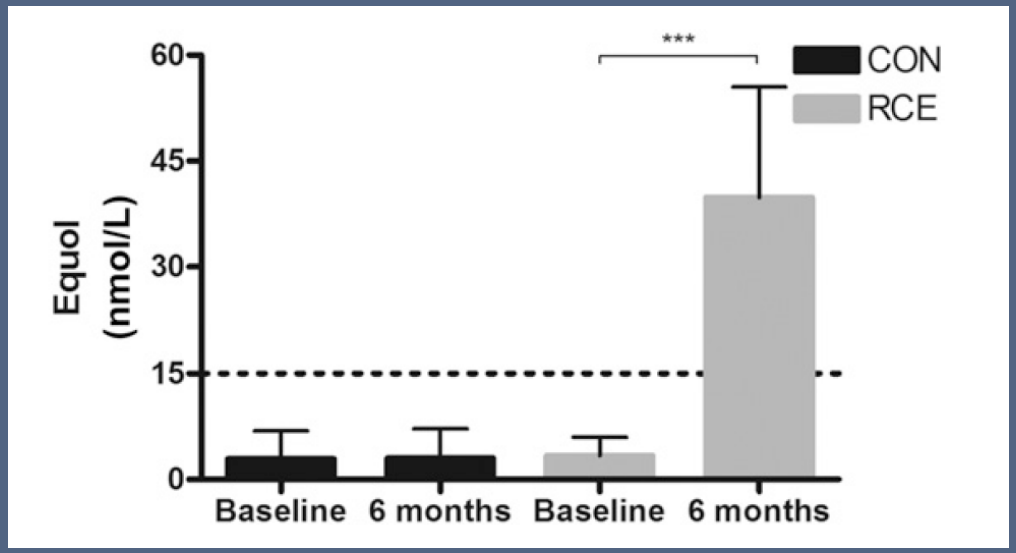
- 78 postmenopausal women
  - T score of 21 to 22.5
  - age of 60-85
  - No major breast cancer risks
- Twice daily Red clover extract (isoflavone) and probiotic or placebo for 12 months
- Bone loss decreased at lumbar spine, femoral neck and greater trochanter
- promoted a favorable estrogen metabolite profile



Lambert MNT, et al Am J Clin Nutr 2017;106:909–20.

Using probiotics to decrease bone loss in women

- Equol is nonsteroidal estrogen
  - selective estrogen receptor affinity
  - Produced in the gut from metabolism of isoflavones
- May be helpful in attenuating bone loss
- Isoflavone and probiotic mixed in study
  - Confounder to the gut biome question

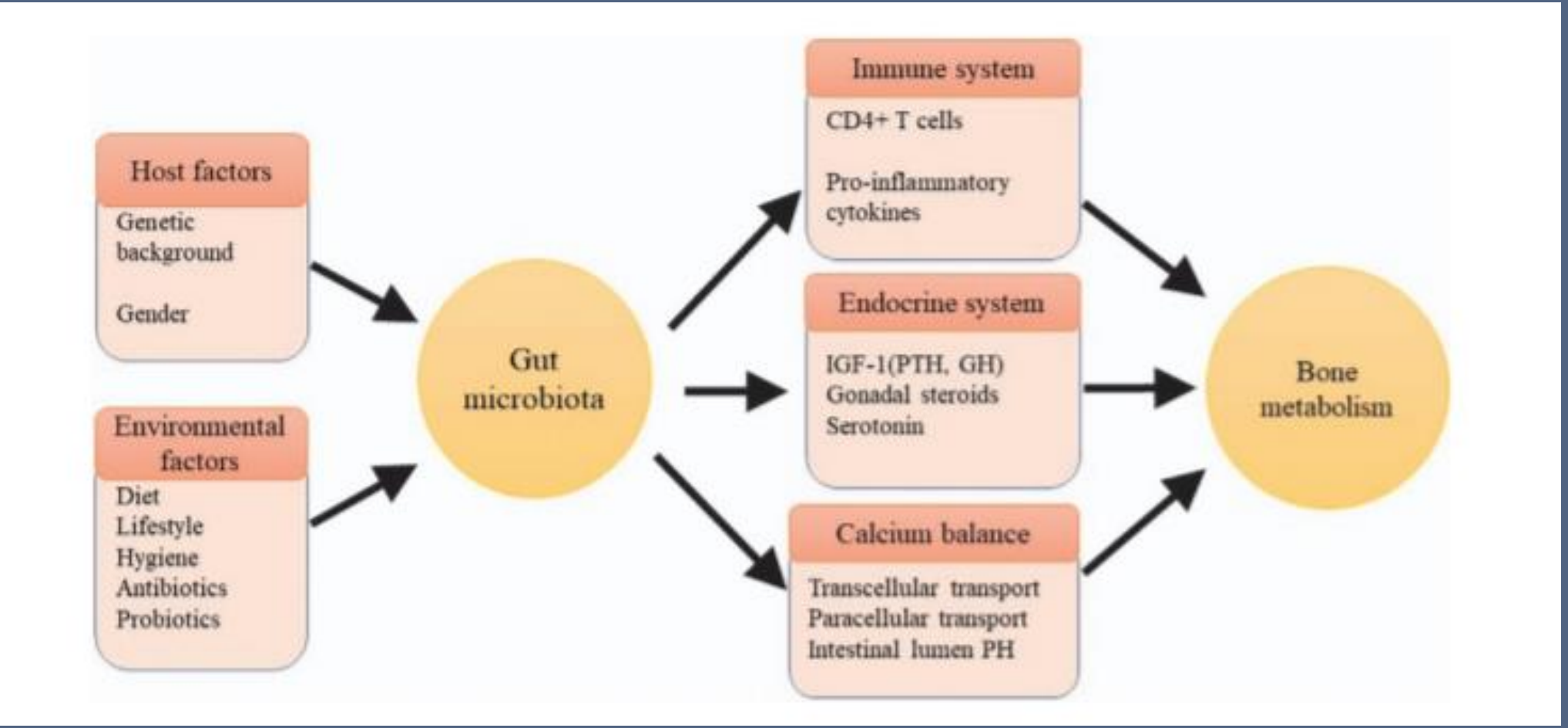


Lambert MNT, et al Am J Clin Nutr 2017;106:909–20

Gut biome and osteoporosis

- Clearly early phases of discovery
- Intriguing early results for bone mass stabilization
- No information on fracture prevention and given smaller effect, would require very large study to see
- May be a tool for bone mass maintenance, especially early in menopause
- More research needed, but interesting start
  - Inexpensive
  - Lifetime of use?
  - Better acceptance because not a traditional “drug”?

Complex balance that may be modifiable



What do I take now?

- No studies done on current commercially available supplements
- Group that did Lactobacillus plantarum study has commercially available drinks
  - Not the same mix as the study
  - Shown to help with GI inflammation
  - No direct studies yet in OP or OA

So why 4 Kg of blueberries?

- Blueberries
  - Full of prebiotic fibers that when broken down make short chain fatty acids
  - Also full of microbes that can be beneficial
- The food we eat are full of microbes
  - Many things that your Mom said were good for you are full of beneficial microbes
  - Its bacteria, yeasts, and molds which can all play a role in inflammation balance in the gut
  - More work is needed but interesting early science

Thank you

sbukata@health.ucsd.edu