The Macronutrient-Microbiome Axis: A Novel Paradigm in Osteoporosis Management

Presented By :Sayed Hossein Davoodi

Shahid Behshti University | 2025

OVERVIEW

- **Key Question:** Are macronutrients (proteins, fats, carbohydrates) merely energy sources, or are they physiological messengers for bone health?
- **Central Theme:** Discovering the dynamic interaction between the quality of dietary intake, the gut microbiome, and bone metabolism.
- **Objective:** To present a novel framework for the prevention and management of osteoporosis in the clinical setting.

Unresolved Clinical Paradoxes in Nutrition and Bone Health

- **Protein:** Anabolic necessity vs. acidogenic potential.
- **Fats:** Vitamin carriers vs. pro-inflammatory drivers.
- **Carbohydrates:** Energy substrate vs. detrimental refined forms.
- **Conclusion:** The necessity for a unifying mechanism to explain these contradictions.

How the Gut Communicates with Bone?

- **Gut Microbiota:** A metabolic organ.
- **Key Metabolites:** Short-Chain Fatty Acids (SCFAs): Butyrate, Acetate, Propionate.
- **Production:** Gut microbial fermentation of dietary fiber.
- **Final Outcome:** Regulation of the balance between osteoblasts and osteoclasts.

Microbial Metabolites and Direct Signaling

- **SCFAs** cross the intestinal barrier and directly influence bone cells (e.g., HDAC inhibition, GPR43 activation).
- **Epigenetic Regulation:** HDAC inhibition → enhanced osteoblastogenesis.
- **Receptor-Mediated Apoptosis:** GPR41/43 activation → induced osteoclast apoptosis.
- **Final Outcome:** Regulation of the balance between osteoblasts and osteoclasts.

Microbial Metabolites and Indirect Mechanisms

- **Immunomodulation:**
  - SCFAs promote T-regulatory (Treg) cell function.
  - SCFAs suppress pro-osteoclastogenic Th17 differentiation.
  - Net effect: Downregulation of RANKL signaling.
- **Barrier Function:**
  - SCFAs enhance intestinal epithelial integrity.
  - Prevent metabolic endotoxemia (LPS translocation).
  - Reducing gut permeability and preventing systemic inflammation.
- **Endocrine System:** Impacting gut-derived serotonin secretion (an inhibitor of bone formation).
- **Final Outcome:** Regulation of the balance between osteoblasts and osteoclasts.

Macronutrient Focus: Carbohydrate Quality: The Prebiotic Lever

- **Detrimental:** Refined carbohydrates, simple sugars.
  - **Outcome:** Dysbiosis, inflammation, increased resorption.
- **Beneficial:** Fermentable fibers, resistant starch.
  - **Sources:** Alliums, legumes, cooled starchy foods.
- **Outcome:** SCFA production, bone protection.

Macronutrient Focus: Dietary Fats: The Lipidomics of Bone Health

- **Pro-Inflammatory Fats (Stimulate Osteoclasts):**
  - High Omega-6 to Omega-3 ratio.
  - **Mechanism:** Precursor to PGE2 (potent RANKL stimulator).
- **Anti-Inflammatory Fats (Support Osteoblasts):**
  - Omega-3 Fatty Acids (EPA/DHA): Fatty fish, algae.
  - Oleic Acid (Omega-9): Extra Virgin Olive Oil (EVOO).
  - **Mechanism:**
    - Omega-3: Precursors to resolvins and protectins (inflammation-resolving), enhance microbial diversity.
    - EVOO: Prebiotic effect, boosts *Lactobacillus* and SCFA production.

Macronutrient Focus: Protein: Resolving the Acid-Base Dilemma

- **The Concern:** Acidogenic potential (High PRAL).
- **The Resolution:** Co-ingestion with fermentable fibers.
  - Microbial SCFA production → systemic bicarbonate generation → effective acid buffering.
- **Clinical Implication:** The net skeletal effect of protein is determined by dietary fiber intake.

Clinical Comparison: Two Different Approaches, Two Opposite Outcomes

- **Diet A: Western Diet (Bone-Depleting)**
  - Protein: High in red meat, low in fiber.
  - Fats: High in Omega-6, low in Omega-3.
  - Carbohydrates: Sugars and refined flour.
  - **Microbiome Outcome:** Dysbiosis, low SCFA production, inflammation.
  - **Bone Outcome:** Stimulated osteoclast activity, decreased Bone Mineral Density (BMD).
- **Diet B: Enhanced Mediterranean Diet (Bone-Supportive)**
  - Protein: Fish, legumes, poultry.
  - Fats: Olive oil, nuts.
  - Carbohydrates: Vegetables, fruits, whole grains.
  - **Microbiome Outcome:** High microbial diversity, high SCFA production.
  - **Bone Outcome:** Inhibited osteoclasts, supported osteoblasts.

From Theory to Practice: A Guide to Prescribing a Diet for the Gut-Bone Axis

- **Smart Protein:**
  - Combine plant-based (lentils, beans) and animal-based sources (fish, chicken).
  - Always consume alongside abundant vegetables.
- **Strategic Fats:**
  - Replace common vegetable oils with olive oil and canola oil.
  - Consume fatty fish at least twice a week.
  - Limit oils high in Omega-6.
- **Fermentable Carbohydrates:**
  - Include daily: garlic, onions, leeks.
  - Consume legumes at least 3 times per week.
  - Choose whole grains over refined ones.
  - Utilize the 'cook-and-cool' technique to increase resistant starch.

Conclusion and Future Directions:Integrating the Gut-Bone Axis into Clinical Practice

- **Paradigm Shift:** Bone health is a function of systemic metabolic and immune health, mediated by the gut.
- **Therapeutic Target:** The microbiome is a modifiable target via diet.
- **Future Perspective:** Personalized nutrition based on microbiome profiling and postbiotic therapeutics (e.g., SCFA supplements).
- **Key Messages:**
  1. SCFAs (resulting from fiber fermentation) are key protective molecules for bone.
  2. A diet rich in prebiotics is the superior strategy for strengthening this axis.

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THANK YOU

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