Gut Microbiome and Chronic Disease
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Speaker Discloser
Nothing to disclose

Objectives
• Discuss current research (within past 2 years) linking gut microbiome and connection with chronic disease.
• Describe the role of diet in modulation of microbiota and effect on disease states.

Suggested learning codes:
2080 – Microbiology, food toxicology
4040 – Disease prevention, health promotion
5160 – Cardiovascular disease
5190 – Diabetes mellitus
5220 – Gastrointestinal disorders
5370 – Weight management, obesity

Agenda
1. Overview of factors affecting gut microbiome
2. Inflammatory Bowel Disease
3. Cardiovascular Disease
4. Diabetes (type 2)
5. Obesity

Factors Affecting Gut Microbiome
• Age
• Sex
• Exposure to medications
• Diet
  • This is our silver bullet!

Gut Dysbiosis – the cornerstone
• Alterations in normal gut flora

Chronic Disease Connection
• Theorized to have a direct impact on reducing the integrity of the gut barrier OR
• Absorption of bacteria structural components and metabolites
**Inflammatory Bowel Disease**

- Current dietary treatments
- Microbial Byproducts – Short chain fatty acids
- Butyrate
  - Reduced synthesis found in patients with active and inactive CD and active UC

Lasema-Mendez et al. / Crohn's and Colitis (2018)

**IBD and the Microbiota – Mouse Model**

- Pathogen Free and Germ Free mice were placed on custom diets (over 30 different combinations) then given dextran sulfate sodium (DSS) to induce colitis
- Disease severity measured by weight change from baseline, colon length, intestinal permeability, serum inflammatory markers
- Evaluated microbial makeup of mice by fecal analysis

Llewellyn et al. / Gastroenterology (2017)

**IBD and the Microbiota – Mouse Model**

- High psyllium diets resulted in the highest levels of butyrate in the intestinal lumen and decreased disease severity
- Diets highest in protein (specifically casein) increased severity of colitis
- 6 fold difference in survival between 2 groups – high casein/low psyllium and low casein/high psyllium (4.4 days vs 26.7 days)
- Differences in inflammatory markers, histopathology and colon length, microbial diversity and makeup
- Microbiome crucial - diet had no effect in germ free mice

Llewellyn et al. / Gastroenterology (2017)

**Cardiovascular Disease**

- Several potential areas of modulation including metabolic byproducts and bacterial translocation:
  - SCFAs
    - ex vivo administration of SCFA leads to lowered blood pressure by eliciting vasodilation
    - Butyrate supplementation has been related to reduced aortic lesions
  - TMAO

Battsonn et al. / JNB (2017)

**CVD and TMAO**

- TMAO = transmethyamine N-oxide
- High levels of choline intake have been related to high levels of serum TMAO
- Choline rich foods =
  - Animal proteins (eggs, beef, pork)
  - Soy
  - Beans/legumes

Zhu et al. / Cell (2016)

**CVD and TMAO**

- Increased levels of TMAO in humans have been associated with increased risk of MI, stroke, and mortality from CVD in a variety of patients
- Higher levels of circulating TMAO are associated with increased atherosclerosis in mice
  - But not germ free mice

Battsonn et al. / JNB (2017)
TMAO and early Atherosclerosis in humans
- German study of 220 subjects (90 males, 130 females, average age 46, BMI 29.5)
  - All had family history of DM2, BMI >27 kg/m², history of glucose intolerance or DM
- Subjects got up to 10 sessions with an RD. Goal to reduce fat intake, reduce saturated fat intake, increase dietary fiber, and achieve 5% weight loss
- Anthropometrics, lab values (including TMAO), and cIMT (carotid intima-media thickness) monitored

Randrianarisoa et al. Scientific Reports (2016)

- Intervention decreased anthropometrics and metabolic parameters, though TMAO levels were unchanged overall
- cIMT also improved
- When TMAO serum levels were stratified into tertiles the group with the greatest decrease there was a significant decrease in cIMT

Randrianarisoa et al. Scientific Reports (2016)

Diabetes Mellitus – Type 2
- Gut microbes and their metabolic byproducts have relevant functions in host metabolic pathways
  - Intestinal glucogenesis
  - Insulin sensitivity
  - Lipid accumulation
  - Glucose control
- Increased gut permeability may aggravate metabolic inflammation and insulin resistance in DM2

Candela et al. British J Nutr (2016)

The Ma-Pi 2 diet and microbiome in DM2
- Human trial with 40 intervention group (ave. age = 66) and 13 healthy controls (ave. age = 32)
  - Diagnosed with DM and on treatment excluding insulin
  - 2 intervention groups – 21 to Ma-Pi 2 diet and 19 to Control diet for 21 days
- Ma-Pi 2 diet
- Control diet based on Italian consensus recommendations for DM2 diet

Candela et al. British J Nutr (2016)
The Ma-Pi 2 diet and microbiome in DM2

- Decreased blood glucose noted in both intervention groups (fasting and post-prandial)
  - Ma-Pi 2 median 126 mg/dL to 95 mg/dL (F), 127 to 100 (PP)
  - Control median 138 mg/dL to 108 mg/dL (F), 147 to 127.5 (PP)
- Decreased total cholesterol, LDL-cholesterol, TNA-α in both groups, though greater in Ma-Pi 2 diet
- No statistically significant changes in weight, BMI, waist circumference or hip circumference noted

The Ma-Pi 2 diet and microbiome in DM2

- Microbiome make-up between DM2 patients and healthy individuals was different at baseline but not after dietary intervention
- Both intervention groups had increased diversity
- Both diets increased Bacteroids, Dorea, and Faecalibacterium
- Other changes specific to amino acid, lipid and secondary metabolite metabolic pathways were also noted after diet intervention

The Ma-Pi 2 diet and microbiome in DM2

- Obese microbiota in animal experiments leads to fat accumulation with and without dietary changes
- Obesity in humans is associated with decreased microbial diversity
- Always the conundrum – does genetics/disease affect microbiome first, or does diet? And which had a greater impact?

High Fat Diet, Obesity, and the Microbiome – Mouse Model

- 54 mice (24 BL6 “obesity-prone” mice, 30 Sv129 “obesity-resistant” mice)
  - Some fed low fat diet, some fed high fat diet, some fed high fat diet + indomethacin*
  - Low fat diet = 10% energy from fat
  - High fat diet = 60% energy from fat
- Fecal samples analyzed from each group (including whole genome sequencing)
High Fat Diet, Obesity, and the Microbiome – Mouse Model

• Baseline difference – Sv129 mice had a higher gene count in their fecal analysis compared to BL6 mice
• Low gene-count associated with more obesity and inflamed phenotype in mice and humans
• Microbiome between low fat diet and high fat diet was significantly different
• High fat diet caused increased Firmicutes:Bacteriodetes ratio, decreased abundance of Bacteriodetes and increased Clostridium, Roseburia, and Lactobacillus

Xiao et al. Microbiome (2017)

High Fat Diet, Obesity, and the Microbiome – Mouse Model

• No significant difference in gut microbiome was noted between high fat diet and high fat diet + indomethacin
• There was a difference in prevalence of obesity between groups
• There was a difference in microbiome between mice strains prior to high fat diet, but this disappeared after diet induction

• Importance – demonstrates that DIET has larger impact on gut microbiome than obesity

Xiao et al. Microbiome (2017)

Summary

• IBD – promising animal models showing diet changes can impact microbiome and disease severity
• CVD – initial human studies show some benefit, but not to degree of animal studies
• DM2 – initial evidence that significant diet changes in humans can improve microbial makeup and disease burden
• Obesity – animal studies are very promising, but more research needed (especially in human subjects)

References and Further Reading

• Zhu W et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk, Cell (2016)
• Randrianarisoa E et al. Relationship of serum TMAO levels with early atherosclerosis in humans, Scientific Reports (2016)
• Candela M et al. Modulation of gut microbiota dysbiosis in type 2 diabetic patients by macrobiotic Ma-Pi 2 diet, British Journal of Nutrition (2016)
• Xiao L et al. High-fat feeding rather than obesity per se drives taxonomical and functional changes in the gut microbiota in mice, Microbiome (2017)

Further reading

• Park JS et al. The gut microbiota regulates host immune responses during Helicobacter pylori infection, Journal of Immunological (2010)
• Bonis I et al. The gut microbiota and the host immune system. Journal of Immunological (2010)