What have Gut Bugs got to do with Diabetes and Obesity?

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The Microbiota

- Bacteria in the gut (the microbiota) plays a role in obesity, obesity-related inflammation, and insulin resistance.

- Gut Microbiota – (formerly called gut flora) it is the microbial community living in our gut:
  - At least 10,000 different known species
  - Weight = 2 kg
  - 1/3 is common to most humans
  - 2/3 is unique to each individual

Gut Microbiota Worldwatch  http://www.gutmicrobiotawatch.org/gut-microbiota-info
Microbiota and Microbiome

- Are we really human?
  - We have 30 trillion human cells
  - We host 100 trillion bacterial cells
- What about the functionality of our genes?
  - Human genome codes for approximately 23,000 genes
  - Genomes for the bacteria of the gut alone encode for 3.3 million genes
- Microbiome – the aggregate genomes and genes found in the members of the microbiota.
- Metagenomics - Study of the genes of our microbiome. Focuses on characterizing the structures, functions, and dynamic operations of microbial communities that live within the human host.

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Projects to Study Association Between Microbiome and Health

• The complexity of the gut microbial community has been extensively studied in the last few years due to new technology (3.3 million genes have been catalogued)
• Human Microbiome Project – found 2 million genes
• MetaHit Consortium:
  • 77% of subjects had 800,000 genes
  • 23% had 400,000 genes
  • Lower gene counts were associated with obesity
Why is Microbiota so Important?

- DIGESTS CERTAIN FOODS
- PRODUCES SOME VITAMINS (B AND K)
- COMBATS OPPORTUNISTIC PATHOGENS – SPECIES PREVENT COLONIZATION OF PATHOGENIC BACTERIA
- IMMUNITY (A BARRIER EFFECT) – RELEASING SUBSTANCES INHIBITING GROWTH OF PATHOGENIC GERMS
- THE DEVELOPMENT OF INTESTINAL MICROVILLI

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An Important Relationship

- Mutualistic
- Ferments unused energy substrates
- Trains immunity
- Regulates gut development
- Supplies vitamins for the host
- Produces fat storing hormones
- Some species are disease producing
What shapes our Microbiota?

- Baby’s gut is sterile at birth and colonization depends on:
  - Vaginal vs. C-section
  - Breast milk vs. infant formula
- Stabilized by the age of three
- Can change as we age

What shapes our Microbiota (cont.)?

- Nutrition
- Genetics
- Antibiotic use
- Environment:
  - Microbiota has changed with international travel and transport of food
  - We share microbes with our family and pets
- Diabetes

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Examples of how Disease Caused by Bacteria has Evolved

Diseases of 150 years ago:

• Cholera
• Pneumonia
• Scarlet fever
• Diptheria
• Whooping cough
• Tuberculosis
• Smallpox

Modern Day Diseases:

• Obesity
• Diarrhea
• Diabetes
• Atherosclerosis
• Colitis
• Crohn’s Disease
• Autism
• Asthma
• Eczema
• Multiple sclerosis

Divisions/Phyla

- Firmicutes – gram positive: largest comprising 200 genera. Some friendly (Lactobacillus); some not (Strep)
- Bacteriodetes – gram negative: 20 genera
- Actinobacteria – gram positive
- Obesity is associated with:
  - Reduced diversity
  - Higher ratio of Firmicutes to Bacteriodetes
  - Depletion of Bifidobacteria
  - Higher proportion of Actinobacteria
  - Most of these changes are associated with a high fat diet

“It has been assumed that the obesity epidemic in the developed world is driven by an increasingly sedentary lifestyle and the abundance of low-cost high-calorie foods,”

“However, our results suggest that excess caloric consumption is not only a result of undisciplined eating, but that intestinal bacteria contribute to changes in appetite and metabolism.”

Andrew Gewirtz, PhD, associate professor of pathology and laboratory medicine at Emory University School of Medicine
Mechanisms Contributing to Obesity and Insulin Resistance

Dysbiosis:

- Increased energy harvest from the diet—firmicutes are better at extracting energy
- Possible regulation of eating behavior
- Chronic low-grade inflammation (endotoxemia)
- Modulation of fatty acid tissue composition
- Modulation of gut derived peptide secretion

Excessive Weight Gain during Pregnancy
linked to excess numbers of firmicutes in the Clostridium and Staph families

European Congress on Obesity study on Probiotics, Pregnancy and Obesity Reduction, 2009
Inflammation, Fat Storage, and Obesity

1. Monosaccharides and SCFA

2. HFD ↑ gut permeability

3. ↑ LPS leads to Inflammation and insulin resistance

3. ↓FIAF enhancing LPL and fat storage

4. ↓FA oxidation d/t ↓ AMPK activity

Increased fatty acid storage in adipocytes

Most of this can be restored with a healthy diet
Fatty Acid Tissue Composition

- Microbiota can enhance the storage of fatty acids in the adipocytes
- Suppresses the secretion of fasting induced adipose factor (FIAF)
- FIAF inhibits lipoprotein lipase
- High LPL contributes to fat storage and adipose tissue hypertrophy
- Slows down the activity of enzymes involved in mitochondrial fatty acid oxidation
- Healthy bacteria reverses this and restores FIAF function and normal energy metabolism
My thanks to Meghan Jardine who organized our AADE presentation in August 2014 in Florida for her contribution of a number of the slides to this point.

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Digestion and SCFAs

- Colonic Microbiota ferment material not digested in upper gut (starch, non-digestible carbs or fructans and some proteins and amino acids)
- Products of fructans metabolism are SCFAs, mainly
  - Acetate
  - Propionate
  - Butyrate

- Hua V. Lin et al, Published April 10, 2012 DOI: 10.1371/journal.pone.0035240
Human Colonic Model Study

Consumption of dietary fiber is associated with appetite suppression via elevation of plasma levels of the anorectic gut hormones Peptide YY and glucagon-like peptide-1 (GLP-1).

SCFAs act directly on human primary colonic cells to stimulate the release of the anorectic gut hormone PYY. These results offer a mechanism by which dietary fiber may suppress appetite and reduce food intake in humans.

Acetate a Different Mechanism

This study was motivated by data showing that fermentable carb weight loss in humans and rodents did not consistently show increases in anorectic hormones GLP-1 and PYY

“Acetate…acts to directly suppress appetite through central hypothalamic mechanisms involving changes in trans cellular neurotransmitter cycles [opening] up new research directions into the promotion of acetate production by colonic microbiota and therapeutic strategies for the prevention and treatment of obesity.”

Nature Communications Volume: 5, Article number: 3611 DOI:doi:10.1038/ncomms4611 Received 16 July 2013 Accepted 11 March 2014 Published 29 April 2014
Gut Microbes: A Second Brain

“Bacteria in the gut are manipulative. There is a diversity of interests represented in the microbiome, some aligned with our own dietary goals, and others not.”

Carlo Maley, PhD

Different Metabolites found in urine of “chocolate desiring” vs “chocolate indifferent”
The Microbiome-Brain Connection

- Immune cells and neurons produce and sense many of the same chemicals; but data is showing that microbes interact with the brain by producing molecules that impact behavior without altering the immune system—direct interaction with the nervous system.

- Stress changes the levels of Lactobacillus that affects the brain chemistry in both mothers and offspring.
Gut Microbes Communicate with the Brain in 3 ways

Directly through the vagal nerve, which connects the network of nerves in the gut to the brain;
Through circulating immune cells that are primed in the gut and travel to the brain;
Via metabolites produced by microbes in the gut that circulate to the brain.
Probiotics for Stress or Depression?

Bacteria that modulate the immune system and limit inflammation beneficial;
Best exposure is during childhood
Studies using heat killed bacteria are showing benefits
Building a Healthy Gut

- A virtual organ, somewhere between 300-1000 different species live in the gut
- Gut microflora fall in to three enterotypes with an association between the concentration of the microbials and the types of foods eaten
Enterotypes and Diet Influence

- Prevotella is related to plant carbs and simple sugars...diet typical of agrarian societies
- Bacteroides is associated with animal proteins, amino acids and saturated fats (SAD)
- Ruminococcus is prevalent in people who consume lots of alcohol and PUFAS
- P/B ratios assess effect of interventions on the gut microbiota
Gut Microbiome and NAFLD

- Altered gut microbiome can independently cause obesity, most important risk factor for NAFLD
- Microbial metabolites and cell components contribute to the development of hepatic steatosis and inflammation, key components of nonalcoholic steatohepatitis (NASH), the severe form of NAFLD

A Silent Epidemic

- 60% DT2 have NAFLD
- 60-80% Obese have NAFLD
- NAFLD is a leading indicator for future development of DT2 and CV disease
- 50% of livers harvested for transplant have NAFLD
- Difficult to test non-invasively, liver biopsy is gold standard test, liver ultrasound, labs, clincopathological scores...are used.
- Est. 30% of U.S. adults, 5% infants and up to 17% adolescents have NAFLD
- Lifestyle changes indicated: weight loss/calorie restriction, 1 hr vigorous activity daily, mgmt. of comorbidities

Probiotics
Pro=For Biotics=Life

Original purpose was to provide microbial lactase for milk digestion by humans
Ann Intern Med 2010; 152: 797-803

The healthy GI microbiome is diverse and may benefit from supplementation
Commonly Recommended

**If using antibiotics:** Lactobacillus rhamnosus GG and/or Saccharomyces boulardii

**IBS or Gastro issues:** Bifidobacterium infantis 35624, Bifidobacterium bifidum MIMBb75 and/or Lactobacillus plantarum 299V

**Traveling abroad:** Saccharomyces boulardii

**Bad breath, gingivitis or periodontal infections:** Lactobacillus reuteri LR-1 or LR-2 (mouthwash or lozenge) and Weisella cibaria

**Vaginal Infection, UTI:** Lactobacillus acidophilus, Lactobacillus rhamnosus GR-1, lactobacillus reuteri RC-14…Lactobacillus reuteri RC-14 and Lactobacillus rhamnosus GR-1 for yeast

Source: http://dailyburn.com/life/health/choose-best-probiotic/
Bacterial Culture in Pill or Food

- Should be high grade (USP, GMP certs)
  - Evidence Based
- Taken with food, 2 hours before or after antibiotics
- Heat and stomach acid will affect both good and bad bacteria cultures
Fecal Transplant—when a pill just won’t do

Quick, inexpensive and a 90 percent cure rate

Mayo performed 1st FMT in 2011; patient had severe refractory C. diff pseudomembranous colitis and had been bedridden for weeks. Donor was patient's brother. Patient left hospital 24 hours later.

"Patients with CDI are missing certain gut flora, usually as a result of antibiotic use," Dr. Orenstein explains. "I suspect some kind of signaling takes place between healthy bacteria and the mucosa of the gut, and without that signaling, C. difficile can take over. Restoring the missing flora seems to be the key."
Hygiene Hypothesis

“gross habits may decrease the likelihood of developing allergies”
Why Are Allergies Increasing?

The occurrence of allergic disease is skyrocketing, and some estimates are that as many as one-in-five Americans have an allergic condition.

Overwhelming evidence from various studies suggests that the "hygiene hypothesis" explains most of the allergy epidemic.

UCLA Health, 2/26/15
Foods that Harm the Gut

- Sugars, both natural and artificial
  - Fried and Processed foods
- Meat and Fish (unbalanced ratio of Omega 6)
- Non-Organic Fruits and Veggies
- NOTE…probiotics are destroyed by coffee, chlorinated water, antibiotics in food or taken orally…
A Special Condemnation of Sucralose

Duke U study in Journal of Toxicology and Env Health: Splenda significantly depresses # of good bacteria in gut
--found in soda, juices, chewing gum, yogurt, candy, toothpaste, more (over 4000 products at the time of this study)
Throw Away Artificial Sweeteners!!

…” consumption of commonly used NAS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota.

…Collectively, our results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.”

*Nature 514, 181-186 (09 Oct 2014)*
Foods that Help the Gut

Fermented foods like miso, Kombucha, sauerkraut, pickles, yogurt (non dairy!), kefir

Prebiotics (insoluble fibers, resistant starches--foods like asparagus, apples, bananas, garlic, beans, legumes, whole grains)
Kefir

Water Kefir contains more diversity than yogurt, the following is a list of the major species in active bacteria and yeasts that are generally found in water kefir:

**Bacteria**

*Species Lactobacillus*

- *L. brevis*
- *L. casei*
- *L. hilgardii*
- *L. hordei*
- *L. nagelii*

*Species Leuconostoc*

- *L. citreum*
- *L. mesenteroides*

*Species Acetobacter*

- *A. fabarum*
- *A. orientalis*

*Species Streptococcus*

- *S. lactis*

**Yeasts**

- *Hanseniaspora valbyensis*
- *Lachancea fermentati*
- *Saccharomyces cerevisiae*
- *Zygotorulaspora florentina*

The Argument for a Plant Based Diet

CONCLUSIONS A diet rich in carbohydrate and fiber, essentially based on legumes, vegetables, fruits, and whole cereals, may be particularly useful for treating diabetic patients because of its multiple effects on different cardiovascular risk factors, including postprandial lipids abnormalities.

C. De Natale, et al 2009 American Diabetes Assoc
Bacteria and a Plant Based Detox Cleanse

- American Gut Project studied a 3 day dietary cleanse effect on gut microbiota.
- Dietary cleanse involving only fruits and vegetables showed a spike in *Akkermansia*, a genus of bacteria thought to help ward off obesity and diabetes;
- Returning to SAD diet negated changes.
Fermentation and PH

When it comes to gut health and well-being of your gut microbes, nothing matters more than fermentable substrates

Jeff Leach, June 26, 2013 blog post
Human Food Project, Anthropology of Microbes
The effects of a low-fat, plant-based dietary intervention on body weight, metabolism, and insulin sensitivity

- Published 2005 in The American Journal of Medicine the study by Dr. Barnard and company looked at 64 people for 14 wks.

Conclusion

- Adoption of a low-fat, vegan diet was associated with significant weight loss in overweight postmenopausal women, despite the absence of prescribed limits on portion size or energy intake.
Gut Flora and Obesity

- Dr. Michael Greger's discussion on how one may be able to modify gut flora to facilitate weight loss

- Dr. Michael Greger has a great site called NutritionFacts.org
Food for Life Program

1. Begin a Plant Based Diet.
2. Avoid Added Vegetable Oils and Other High Fat Foods
3. Favor Foods with a Low Glycemic Index
4. Go High Fiber – at least 40 grams/day
5. All you want of the 4 food groups: whole grains, legumes, fruits, vegetables
Teaching the Lifestyle

- PCRM.org
- Hundreds of Instructors in the US trained by PCRM to provide an intro to the plant based lifestyle
Plant-Based Nutrition For Diabetes COI
Plant-Based Nutrition for Diabetes

Forum
- COI: Plant Based Nutrition for Diabetes Announcements
- COI: Plant Based Nutrition for Diabetes Discussions

Blogs
- Plant Based Nutrition for Diabetes Blog
  - Plant-Based Nutrition for Diabetes at AADE15 (Jul 30, 2014 11:18 AM)
  - Setting (Almost Unattainable) Goals (Jun 29, 2014 11:09 PM)
  - Nutrition Therapy for Adults with Diabetes (May 28, 2014 09:38 AM)
  - Are you Offering Patients the Plant-Based Nutrition Option? (Apr 29, 2014 02:01 PM)
  - It’s National Nutrition Month! (Mar 12, 2014 12:39 AM)
  - Rethinking Milk (Feb 24, 2014 09:22 AM)
  - You can Change the World with Your Voice! (Jan 21, 2014 10:44 AM)
  - Q & A on Plant-Based Diets for Diabetes (Jul 02, 2013 09:00 AM)
  - Plant-Based Diets and Diabetes Webinar Review (Jul 02, 2013 08:39 AM)
  - Plant-Based Nutrition for Diabetes COI Presence at AADE Leadership Forum 2012 (Dec 05, 2012 02:17 PM)

File Library
- COI: Plant Based Nutrition for Diabetes Files
  - ADA Type 1 Position Statement (Jul 04, 2014 01:04 PM)
  - PBN for Diabetes at TX AADE State Conference April 12th (Apr 15, 2014 11:27 AM)
  - Meat Consumption as a Risk Factor for Type 2 Diabetes (Feb 26, 2014 08:28 AM)
  - Vegetarian Diets and Blood Pressure (Feb 26, 2014 08:22 AM)
  - Plant-Based Diets for Diabetes Webinar (Jun 28, 2013 01:26 PM)
  - Plant-Based Diets for Diabetes (Jun 28, 2013 12:46 PM)
  - Nutritional Update for Physicians: Plant-Based Diets (Jun 18, 2013 11:26 AM)
  - Plant-Based Nutrition for Diabetes COI Poster for AADE12 (Nov 20, 2012 01:01 PM)
  - Low Literacy Plant-Based Foods Plate (Aug 09, 2012 02:11 PM)
  - Low Literacy Plant Based Foods Handout (Aug 09, 2012 02:09 PM)
Thank you

Q & A