Transforming Diabetes Care

Gut Bacteria and Diabetes: What We Know and What We Don’t

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Development of diabetes in humans

Genes

Environment

Behaviors
The interrelationship between organisms in the gut and the factors associated with diabetes is incredibly complex.
What we’re going to talk about

• The gut microbiome

• The role of the gut in immunity

• The role of the gut microbiome in type 1 diabetes

• The role of the gut microbiome in obesity and type 2 diabetes

• Can we affect diabetes development or progression through the microbiome?
Man as a magnificent structure...\(^1,2\)

The average human is a composite of species ... a ‘super organism’ which has:

- about 37.2 trillion human cells
- approximately 20,000 active genes
- ... but that’s not all


2) [https://www.sciencedaily.com/terms/human_genome.htm](https://www.sciencedaily.com/terms/human_genome.htm)
We function as scaffolding for numerous other organisms in a symbiotic relationship\textsuperscript{1-3}

- The cells in every person are outnumbered by bacterial cells in the gut alone by 100 to 1
- The genes in every person are outnumbered by bacterial genes by 1000 to 1
- The variety of organisms in man is more diverse than in any other naturally occurring colonization
- The bacteria in the gut collectively weigh almost 6 pounds
- The bacteria in the gut alone have a myriad of positive, neutral, and in some cases negative effects and are collectively referred to as the gut microbiome

When we think of bacteria we think of bad stuff …

Cholera, Plague, Typhoid, ‘Flesh eating bacteria’…and many more nasty things
So here’s some things we know about the bacteria in YOU
Looking at the gut in cross section...

- Cells in the intestine are exposed to bacteria and food breakdown products all the time.
- In addition, the gut is a major place where non-self antigens are recognized by interaction with the immune system which is integrated with the intestinal cells.

https://www.researchgate.net/figure/237097190_fig1-Fig-1-The-intestinal-mucus-layer-and-host-microbiota-interactions-Periodic-acid-Schiff
Polling Question

Which of the following affects the composition of the gut microbiome?

a) The country you live in
b) Cesarean section delivery
c) Breastfeeding
d) A & C
e) All the above
Jean Anthelme Brillat-Savarin
1755-1826

Brillat-Savarin is often considered as the father of low-carbohydrate diets. He considered sugar and white flour to be the cause of obesity and he suggested instead protein-rich ingredients.

“Tell me what you eat and I will tell you what you are”
Many things affect the type of bacteria in the gut at any time.
Shifts in gut bacteria:

with age and country

Yatsunenko T., et al.
Nature 2012;486:222

with different exposures

Koenig JE, et al.
OK, I got the bacteria part, but how is that related to type 1 diabetes?
Development of diabetes in humans

- Genes
- Environment
- Behaviors
Genes play an important role
The negative view of bacteria has led to changes in our cleanliness behaviors.
The Hygiene Hypothesis

• The Hygiene Hypothesis suggests that a lack of early childhood exposure to infectious agents, symbiotic microorganisms (such as gut flora, etc), viruses and parasites increases susceptibility to allergic and immune diseases by suppressing the natural development of the immune system. In particular, the lack of exposure is thought to lead to defects in the establishment of immune tolerance.

Immune system processes antigens

- Processing antigens that pass through the gut is pivotal to **immune tolerance**, **immune recognition**, and in some cases a **profound immune response** to those antigens

Cerf-Bensussan N, and Gaboriau-Routhiau V. Nature Reviews-Immunology 2010;10:735
Immune system processes

Cross section of a mouse intestine stained to show epithelial cells (in red) and immune cells (in blue and green) and their proximity at every level.

Vitamin D plays a key role...
Tight Junctions: vital to cells as structural support and to restrict passage of various compounds

Susceptibility to type 1 diabetes is both genetic and associated with a viral infection.

One proposal for the autoimmune reaction is the establishment of a persistent enteroviral infection of beta cells that may represent an initiating event leading to changes such as chemokine secretion that facilitate the infiltration of immune cells.


Artists conception of Enterovirus (cover art from Diabetologia)
Enterovirus protein (VP1) in pancreatic islet cells

Pancreas islets from a person with type 1 diabetes. [A] stained for Insulin (brown) and glucagon (red), [B] Class 1 HLA molecules and Enteroviral protein. [C] cells positive for enteroviral protein (VP1) marked by arrows.


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Polling Question

What are leverage points to enhance the role of the microbiome thus affecting the development of type 1 diabetes

a) Sterilizing the gut with antibiotics
b) Giving microorganisms orally
c) Giving Vitamin D
d) B & C
e) All the above
Some additional terms

• Probiotic- A supplement made up of one or more organisms (bacteria currently…) meant to purposefully seed these bacteria in the gut

• Prebiotic – food for your gut bacteria, not just food you eat, but often added ‘soluble fiber’ such as oligosaccharides
Is there anything we can do to the microbiome to affect type 1 diabetes?
‘Probiotics’: feeding (and changing) your inner ‘biome’ ...

- Probiotics contain cultures of so-called ‘good’ bacteria.
- Probiotics can be capsules, powders, gels and liquids [e.g. acidophilus milk]
- With over 10,000 different organisms in the gut, some are beneficial (symbionts), some may cause disease (pathobionts) and some we just plain don’t know that much about...which ones are the right ones?

Probiotics can effect the development of type 1 diabetes: the TEDDY Study

- Ongoing prospective cohort study started 2004; population was 7473 infants at high genetic risk for type 1 diabetes
- Details of infant feeding, probiotic supplementation and infant formula use monitored from birth

Uusitalo U, et al. JAMA Pediatrics 2016;170;20
Breastfeeding associated with lower chance of developing type 1 diabetes

- Two cohorts from databases in Denmark and Norway
- From over 155,000 mother and child pairs, the lack of breastfeeding was associated with a 229% increase in the likelihood of developing type 1 diabetes.

Lind-Blix NA, et al. Diabetes Care 2017;online May 9
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Do gut bacteria have a role in obesity and type 2 diabetes?
Development of diabetes in humans

- Genes
- Environment
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The ‘Leaky Gut’...

When the gut barrier deteriorates, endotoxins from various bacteria as well as other products may leak into the blood.
Mechanism for ‘leaky gut’: ... encroachment!

Microbiota encroachment is a feature of metabolic disease, particularly insulin resistance–associated dysglycemia.
Bacteria encroach on the gut wall, endotoxin and bacteria leak into the circulation.
Bacterial products, changes in adipose tissue lead to insulin resistance and ↓ insulin release

1) ↑ fat and sugar (Western) diet → ↑ bacterial release of lipopolysaccharide (LPS)
2) LPS → inflammatory cytokines into portal system
3) ↑ translocation of bacteria and LPS into visceral adipose tissue, ↑ inflammatory cytokines
4) Adipocytes release free fatty acids (FFA)
5) Reduced clearance of inflammatory mediators from visceral adipose tissue
6) ↑ LPS, FFA, and cytokines into portal circulation ↓ liver metabolism and insulin sensitivity
7) ↑ delivery of LPS, FFA, cytokines into systemic circulation negatively affect B-cell and systemic insulin sensitivity

Conrad D and Wueest S. Physiology 2014;29:304
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Can we proactively modify our gut bacterial populations?
Some things that we know affect the gut/bacteria relationship

- Meformin increases the population of *Akkermansia muciniphila* by 18 fold, enhancing the digestion and of mucin, increasing short chain fatty acids and feeding intestinal cells\(^1\)
- Some lactobacilli, and plant principles (e.g. grape extract) inhibit alpha glucosidases in the gut much like acarbose\(^2\)
- A number of prebiotics feed the microbiome increasing the population of L-cells in the gut which produce increased amounts of GLP-1\(^3\)

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More on *Akkermansia muciniphila* ...

- A mucin-feeding gram negative organism constituting 3-5% of the intestinal microbiome
- Concentrations inversely correlated with obesity and diabetes in many human studies
- Pre-biotic consumption (soluble fiber) is metabolically beneficial and increases *A. muciniphila* concentrations
- In rodent studies administration of *A. muciniphila* decreases adipose tissue inflammation
- Dietary polyphenols found in many colored fruits and vegetables (e.g. red wine, cocoa) increase amounts of *A. muciniphila* as well as increasing Lactobacilli and Bifidobacteria

1) Tilg H. and Moschen AR. Gut 2014;63:1513
Fiber: what it is and why you need it

• Some Raw Vegetables
  o Jicama
  o Jerusalem artichoke
  o Dandelion greens
  o Raw or cooked onions
• Wheat Dextrin
• Inulin
Probiotics in type 2 diabetes: effects on markers of diabetes control, inflammation and oxidative stress

Randomized, controlled, double blind study; 45 patients with T2DM studied for 6 weeks, comparing fermented milk plus *L. acidophilus* plus *B. animalis* versus plain fermented milk.

- ↓ Fructosamine
- ↓ Hemoglobin A1C
- ↓ LDL cholesterol
- ↓ Inflammatory cytokines

Randomized, controlled cross-over study; 62 patients with T2DM, 6 weeks exposure to ‘Synbiotic’ food (*L. sporogenes* plus inulin) versus control food w/o microorganisms or prebiotic.

- ↓ Serum insulin
- ↓ Fasting glucose
- ↓ C-reactive protein
- ↑ Reduced glutathione


Recent studies suggest a role of the gut microbiome in the processes of inflammation and atherosclerosis subsequent studies suggest that choline and also carnitine metabolism can result in TMAO

What we don’t know...
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