Cardiometabolic Syndrome
Chad P. Edwards, DO
None

I’m not paid by anyone except my patients…
Definition

Metabolic Syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function.

It is a risk factor for:
• Diabetes
• Fatty liver
• Several cancers
• Cardiovascular disease
Criteria

**World Health Organization (WHO):** Insulin Resistance +2 or more of

- **Waist:Hip Ratio**
  - >0.90 (men)
  - >0.85 (women)
  - Or BMI >30

- **Hypertriglyceridemia:** >150 mg/dL

- **Low HDL**
  - <35 (men)
  - <39 (women)

- **Elevated Blood Pressure:** >140/90 or use of antihypertensive

- **High Fasting Glucose:** IFG, DM, impaired glucose tolerance, insulin resistance

- **Microalbuminuria:** microalbumin/Cr ratio >30 mg/G or albumin excretion rate >20 mcg/min
Criteria

**ATP III** – 3 or more of the following

- **Waist circumference**
  - >40” (men)
  - >35” (women)

- **Hypertriglyceridemia**: >150 mg/dL

- **Low HDL**
  - <40 (men)
  - <50 (women)

- **Elevated Blood Pressure**: >135/85

- **Fasting Glucose**: >100
Why do we care?

Statistics
• 20-25% of the world’s adult population
• 3x increased risk of MI/Stroke
• 2x increased mortality from MI/Stroke
• 5x more likely to develop DM
Cause

Idiopathic?
- Insulin resistance
- Obesity
- Physical inactivity
- Aging
- Proinflammatory conditions
- Hormonal challenges
- **Gut dysbiosis**
Several hormones are involved in the pathogenesis of metabolic syndrome.
Carbohydrates $\rightarrow$ Blood Sugar $\ (70-100) \rightarrow >140 \rightarrow$ AGEs

- Glucagon
- Epinephrine
- Cortisol
- Etc.

Insulin

Fat Cells

Insulin Resistance
Leptin

- Leptos (Greek) – thin
- The “satiety hormone” – decreases hunger
- Opposite of ghrelin
- Released from adipocytes (other tissues also)
- Helps regulate fat stores (adipose)
- **Decreased with**: sleep deprivation, increased testosterone, physical exercise, short-term fasting
- **Increased with**: OSA, emotional stress, increased estrogen, dexamethasone, insulin, obesity
Adiponectin

• Secreted from adipocytes
• Plays an important role in insulin action and cardiovascular health
• May enhance beta-oxidation and suppress gluconeogenic enzymes
  • Counteracts the lipotoxic effects of obesity & T2D that leads to IR
• Enhances endothelial function and inhibits atherogenesis
• Ideally >14 mcg/mL
• Higher risk of T2D when low
70-80% of lipids liberated by adrenaline are burned as fuel


How Adrenaline and Caffeine Work to Increase Fatty Acid Oxidation

Caffeine doubles the effect
Low insulin or high glucagon increases FA oxidation
Incretins

**Glucagon-Like Peptide-1 (GLP-1)**
- Therapeutically administered subcutaneously
  - Pharmaceutical GLP-1ra resist DPP-4 catabolism
- Synthesized & secreted from enteroendocrine cells throughout small & large intestine
  - Also from the brainstem
- Increased with carbs, protein, and fats
- Also **induced with IL-6**
- Increases insulin
- Decreases glucagon
- Decreased levels seen in obese patients

**DPP-IV Inhibitors**
- Therapeutically administered orally
- Prevents catabolism of GLP-1
- Decreased in bariatric patients
Figure 1. Direct Pharmacological Actions of GLP-1R Agonists
GLP-1R agonists act directly via the GLP-1R on pancreatic islets, heart, intestine, subpopulations of immune cells, kidney, and brain.
Adipose Tissue

- Energy storage
- **Highly active endocrine organ** that coordinates hormonal, metabolic, inflammatory, and neurohumoral activities
  - Pro-inflammatory
    - IL-6, TNF-α, monocyte chemoattractant protein-1, IL-8
  - Anti-inflammatory
    - IL-1ra, IL-10, adiponectin
  - Pro-inflammatory is dominant in whole-body metabolism

- Omental fat is particularly inflammatory
  - IL-6, IL-8, TNF-a, plasminogen activator inhibitor-1
Gut Microbiota

Determined by the food we eat
Dietary intervention impact on gut microbial gene richness

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Complex gene–environment interactions are considered important in the development of obesity1. The composition of the gut microbiota can determine the efficacy of energy harvest from food2–4 and changes in dietary composition have been associated with changes in the composition of gut microbial populations5–6. The capacity to explore microbiota composition was markedly improved by the development of metagenomic approaches7,8, which have already allowed production of the first human gut microbial gene catalogue9 and stratifying individuals by their gut genomic profile into different cohort size. At a threshold of 480,000 genes, corresponding to that from the accompanying manuscript11, there were 18 (40%) low gene count (LGC) and 27 (60%) high gene count (HGC) individuals, harbouring on average 379,436 and 561,499 genes respectively, a one-third difference. A difference in diversity between lean and obese individuals was reported previously12, but the difference among the obese was not described.

We then examined the baseline phenotypes of the study population. The LGC group had significantly higher insulin resistance and fasting
Dietary intervention impact on gut microbial gene richness

- Composition of gut microbiota can determine the efficacy of energy harvest from food
- Dietary changes associated with changes in gut microbiome
- High gene diversity of microbes associated with leanness
- Diet of highly processed foods is linked to less microbe diversity
Metagenomics is an emerging field focused on characterizing the structures, functions and dynamic operations of microbial communities sampled in their native habitats without the need for culture. Here, we present findings from a 16S rRNA gene sequence- and whole community DNA shotgun sequencing-based analysis of the adult human gut microbiomes of lean and obese mono- and dizygotic twins. Our findings indicate that a core microbiome can be found at the gene level, despite large variation in community membership, and that variations from the core are associated with obesity. These findings have implications for ongoing Human Microbiome Project(s), and highlight important challenges to the field of metagenomics.

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The core gut microbiome, energy balance, and obesity

16s rRNA analysis of gut microbiome

lean and obese mono- and dizygotic twins (n=154)
The core gut microbiome, energy balance, and obesity

The gut microbiota is highly variable between individuals

Family members have more similar microbiota
The core gut microbiome, energy balance, and obesity

Little difference between mono- and dizygotic twin microbiota

Early environment is key determinate of adult gut microbiota
The core gut microbiome, energy balance, and obesity

There is an identifiable core microbiome composed of genes encoding various signaling and metabolic pathways.
The core gut microbiome, energy balance, and obesity

Obesity was associated with phylum level changes in the microbiota, reduced bacterial diversity and metabolic pathways involved in nutrient harvest.
Microbial Reprogramming Inhibits Western Diet-Associated Obesity

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Abstract

A recent epidemiological study showed that eating ‘fast food’ items such as potato chips increased likelihood of obesity, whereas eating yogurt prevented age-associated weight gain in humans. It was demonstrated previously in animal models of obesity that the immune system plays a critical role in this process. Here we examined human subjects and mouse models consuming Westernized ‘fast food’ diet, and found CD4\(^+\) T helper (Th) 17-biased immunity and changes in microbial communities and abdominal fat with obesity after eating the Western chow. In striking contrast, eating probiotic yogurt together with Western chow inhibited age-associated weight gain. We went on to test whether a bacteria found in yogurt may serve to lessen fat pathology by using purified Lactobacillus reuteri ATCC 6475 in drinking water. Surprisingly, we discovered that oral L. reuteri therapy alone was sufficient to change the pro-inflammatory immune cell profile and prevent abdominal fat pathology and age-associated weight gain in mice regardless of their baseline diet. These beneficial microbe effects were transferable into naïve recipient animals by purified CD4\(^+\) T cells alone. Specifically, bacterial effects depended upon active immune tolerance by induction of Foxp3\(^+\) regulatory T cells (Treg) and interleukin (II)-10, without significantly changing the gut microbial ecology or reducing ad libitum caloric intake. Our finding that microbial targeting restored CD4\(^+\) T cell balance and yielded significantly leaner animals regardless of their dietary ‘fast food’ indiscretions suggests population-based approaches for weight management and enhancing public health in industrialized societies.


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Microbial reprogramming inhibits western diet associated obesity

Western “fast food” diet is associated with obesity

Immune system plays a critical role
Microbial reprogramming inhibits western diet associated obesity

Oral *Lactobacillus reuteri* therapy alone was sufficient to change the pro-inflammatory immune cell profile and prevent abdominal fat pathology and weight gain regardless of their “fast food” intake.

The protective effects require induction of IL-10
Serum IL-10

- Control
- Control + *L. reuteri*
- Fast Food
- Fast Food + *L. reuteri*
Ectopic Fat in Insulin Resistance, Dyslipidemia, and Cardiometabolic Disease

Gerald I. Shulman, M.D., Ph.D., NEJM, 371;12, September 18, 2014

TYPE 2 DIABETES CURRENTLY AFFECTS MORE THAN A THIRD OF A BILLION people worldwide and is the leading cause of end-stage renal disease, non-traumatic loss of limb, and blindness in working adults, with estimated annual worldwide health care costs exceeding half a trillion dollars. Furthermore, the worldwide prevalence of type 2 diabetes is projected to increase by more than 75% during the next two decades, with the largest increases occurring in Asia and the Indian subcontinent. Although impaired beta-cell function is ultimately responsible for the progression from normoglycemia to hyperglycemia, insulin resistance precludes beta-cell dysfunction and plays a major role in the pathogenesis of type 2 diabetes. After carbohydrate ingestion, glucose is deposited primarily in muscle and the liver as glycogen, and alterations in insulin responsiveness in these organs result in fasting and postprandial hyperglycemia.

In this review, I focus on recent studies using magnetic resonance spectroscopy (MRS) that have implicated ectopic lipid accumulation in the pathogenesis of insulin resistance in muscle and the liver and have clarified the role of muscle-specific insulin resistance in promoting increased hepatic lipogenesis, nonalcoholic fatty liver disease, and atherogenic dyslipidemia. I then propose a potential link between inflammation and macrophage-induced lipolysis in the progression from ectopic lipid-induced insulin resistance to impaired glucose tolerance and type 2 diabetes.

GLUCOSE–FATTY-ACID CYCLE HYPOTHESIS OF INSULIN RESISTANCE IN MUSCLE

The association between excess lipid storage in the form of obesity and insulin resistance has long been recognized, and proton (1H) MRS studies have shown an even stronger relationship between intramyocellular lipid content and insulin resistance in muscle. However, the molecular mechanism by which fat causes insulin resistance remains unclear.

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Intracellular fat reduces beta-oxidation making weight loss more difficult.
Non-caloric artificial sweeteners (NAS) are among the most widely used food additives worldwide, regularly consumed by lean and obese individuals alike. NAS consumption is considered safe and beneficial owing to their low caloric content, yet supporting scientific data remain sparse and controversial. Here we demonstrate that consumption of commonly used NAS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota. These NAS-mediated deleterious metabolic effects are abrogated by antibiotic treatment, and are fully transferrable to germ-free mice upon faecal transplantation of microbiota configurations from NAS-consuming mice, or of microbiota anaerobically incubated in the presence of NAS. We identify NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrate similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, our results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.

Non-caloric artificial sweeteners (NAS) were introduced over a century ago as means for providing sweet taste to foods without the associated high energy content of caloric sugars. NAS consumption gained much popularity owing to their reduced costs, low caloric intake and perceived health benefits for weight reduction and normalization of blood sugar levels. For these reasons, NAS are increasingly introduced into commonly consumed foods such as diet sodas, cereals and sugar-free desserts, and are being recommended for weight loss and for individuals with diabetes or obesity. However, NAS have been associated with a number of adverse health effects. Since all three commercial NAS comprise ~5% sweetener and ~95% glucose, we used as controls mice drinking only water or water supplemented with either glucose or sucrose. Notably, at week 11, the three mouse groups that consumed water, glucose and sucrose featured comparable glucose tolerance curves, whereas all three NAS-consuming mouse groups developed marked glucose intolerance (P < 0.001, Fig. 1a, b).

As saccharin exerted the most pronounced effect, we further studied the composition and function of the intestinal microbiota across the NAS-consuming mouse groups.
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

• Non-caloric artificial sweeteners (NAS) are among the most widely used food additive in the world

• NAS drives glucose intolerance through compositional and functional changes in the gut microbiota

Nature, 2014. doi:10.1038/13793
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Metabolic changes are fully transferable from NAS treated mice to germ-free mice with fecal transplantation or from microbiota cultured with NAS demonstrate similar NAS induced-dysbiosis in humans with development of glucose intolerance

Nature, 2014. doi:10.1038/13793
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

“Our results suggest that NAS consumption in both mice and humans enhances the risk of glucose intolerance and that these adverse metabolic effects are mediated by modulation of the composition and function of the microbiota. Notably, several of the bacterial taxa that changed following NAS consumption were previously associated with type 2 diabetes in humans.”

Nature, 2014. doi:10.1038/13793
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

“Artificial sweeteners were extensively introduced into our diets with the intention of reducing caloric intake and normalizing blood glucose levels without compromising the human ‘sweet-tooth’. Together with other major shifts that occurred in human nutrition, this increase in NAS consumption coincides with the dramatic increase in the obesity and diabetes epidemics. Our findings suggest that NAS may have directly contributed to enhancing the exact epidemic that they themselves were intended to fight.”

Nature, 2014. doi:10.1038/13793
Source: Centers for Disease Control and Prevention
How does Cesarean Birth Affect Immunity, Inflammation and Autoimmunity?
Cesarean Delivery Rate, 1990-2012*

*Data for 2012 are preliminary.

Primary and Repeat Cesarean Delivery Rates Among Low-Risk Women,*
by Age, 2011

*Low risk is defined as non-breech, singleton deliveries at 37 weeks or more gestation; Data are from 36 states and the District of Columbia that implemented the 2003 revision of the birth certificate as of January 1, 2011, representing 83% of all US births.

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. 2011 Natality File. Analysis conducted by the Maternal and Child Health Bureau.
Mom Knows Best: The Universality of Maternal Microbial Transmission

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Summary

The sterile womb paradigm is an enduring premise in biology that human infants are born sterile. Recent studies suggest that infants incorporate an initial microbeome before birth and receive copious supplementation of maternal microorganisms through birth and breastfeeding. Moreover, evidence for microbial maternal transmission is increasingly widespread across animals. This collective knowledge compels a paradigm shift—one in which maternal transmission of microbes advances from a taxonomically specialized phenomenon to a universal one in animals. It also engenders fresh views on the assembly of the microbiome, its role in animal evolution, and applications to human health and disease.

Introduction

While the human microbiota comprises only 1-3% of an individual's total body mass, this small percentage represents over 100 trillion microbial cells, outnumbering human cells 10 to 1 and adding over 8 million genes to our set of 22,000 [1,2]. This complexity establishes a network of interactions between the host genome and microbiome spanning gut development [3], digestion [4,5], immune cell development [6-9], dental health [10,9], and resistance to pathogens [11,12]. Recent studies have also provided a greater understanding of how the composition of an individual's microbiota changes throughout development, especially during the first year of life [3,13]. While the general dogma is that the placental barrier keeps infants sterile throughout pregnancy, increasing evidence suggests that an infant's initial inoculum could be provided by the birth process itself [14,15] and its importance cannot be understated.

While maternal transmission of microbes in humans has attracted considerable attention in the last few years, nearly a century's worth of research is available for vertical transmission of symbionts in invertebrates [22]. Similar to gut bacteria in humans that assist nutrient intake, many invertebrates associated bacteria function as nutritional symbionts that supplement the nutrient-poor diet of their host with essential vitamins or amino acids [22,24]. Since these indispensable symbionts cannot live outside of host cells, they cannot be acquired from the environment and are faithfully transferred from mother to offspring in offspring [22,25]. Maternal transmission in invertebrates has been reviewed elsewhere [22,26,27], and Box 1 and Box 2 highlight examples of host-specific symbionts across invertebrate phyla.

By integrating previous studies in invertebrates with recent evidence for maternal microbial transmission in human and other vertebrates, we explore the question: Can a role be envisioned for this universal phenomenon in the human kingdom? As a result, a considerable new phase of study in invertebrate symbiotic transmission underway. Thus, this essay presents current evidence for maternal microbial transmission and provides new insights into its impact on microbiome assembly and evolution, with applications to human health and disease.

Internal Maternal Transmission

At the turn of the twentieth century, French pediatrician Henri Texier asserted that human infants develop within a sterile environment and acquire their initial bacterial inoculum while traveling through the maternal birth canal [28]. More than a century later, the sterile womb hypothesis remains dogma, as any bacterial presence in the uterus is assumed to be dangerous for the fetus. Indeed, studies of preterm delivery have found a strong correlation between intrauterine infections and preterm labor, especially when birth occurs less than 30 weeks into the pregnancy [29,30]. Since preterm birth is the leading cause of infant mortality worldwide [31], much attention has focused on identifying the bacterial culprits responsible for spontaneous preterm labor. Surprisingly, most of the bacteria detected in intrauterine infections are commonly found in the female genital tract [29], and risk of preterm birth is markedly increased in women diagnosed with bacterial vaginosis during pregnancy [32]. Interestingly, the vaginal microbial community varies significantly among American women of different ethnicities (Caucasian, African-American, Asian, or Hispanic), with African-American and Hispanic women more likely to harbor a microbiota traditionally associated with bacterial vaginosis (predominance of anaerobic bacteria over Lactobacillus species) [33] and a higher rate of spontaneous preterm deliveries (reviewed in [34]).

While intrauterine infection and inflammation is important in understanding the etiology of preterm birth, relatively few studies have examined the uterine microbiome of healthy, term pregnancies...
A Case-Control Investigation of Perinatal Risk Factors for Childhood IDDM in Northern Ireland and Scotland

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Objective — To identify perinatal risk factors for childhood insulin-dependent diabetes mellitus (IDDM) and determine if they differ between early-onset and late-onset disease.

Research Design and Methods — We selected 258 diabetic children in Northern Ireland and 271 diabetic children in Scotland from population-based registers. For each diabetic child, five matched control subjects were drawn from the same population. All perinatal data were recorded routinely at birth. Odds ratios (ORs) were estimated for parental age, social class, breast-feeding, deprivation measures, and other perinatal variables.

Results — Scottish data indicated an increased risk among children born to older mothers (OR = 2.43, 95% confidence interval [CI] 1.49–3.97 for mothers ≥35 years of age relative to those <25 years of age). Northern Ireland data showed no such effect. Only Northern Ireland data showed an excess risk in children of professional or managerial families (OR = 1.51, 95% CI 1.11–2.04). A small but nonsignificant reduction in risk among breast-fed children was observed only after adjustment for social class (OR = 0.76, 95% CI 0.54–1.07). Deprivation measures were associated with reductions in risk. Children delivered by cesarean section were at increased risk in both Northern Ireland (OR = 1.66, 95% CI 1.10–2.50) and Scottish (OR = 1.70, 95% CI 1.12–2.59) data. In Northern Ireland data only, children of first pregnancies were at increased risk (OR = 1.41, 95% CI 1.09–1.82).
A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland

258 IDDM from Northern Ireland, 271 from Scotland

5 matched controls for each diabetic child
A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland

Risk increase for IDDM with cesarean delivery

- Northern Ireland + 66%
- Scotland + 70%
Why Are C-Section Deliveries Linked to Childhood Type 1 Diabetes?
Kendra Vehik and Dana Dabelea

The incidence of type 1 diabetes (T1D) is increasing worldwide at an annual rate of 3.9% (1). Early life factors have been shown to be associated with increased T1D risk and perhaps involve the development of the immune system (2). Congenital section (C-section) deliveries have increased by 50% since the 1990s (3) and have paralleled the increasing trend in the incidence of T1D (4). A recent meta-analysis of 20 studies worldwide reported that C-sections, independent of maternal age, birth weight, and breastfeeding, contributed a 20% increase in the risk of T1D (4).

Altered gut microbiota, bacterial exposures during pregnancy, perinatal stress, and the hygiene hypothesis have all been proposed as possible explanations for the observed associations (4). A potential mechanism that has received recent attention suggests that the types of bacteria found on the newborn's skin may influence the development of their immune systems and their future health (5). Studies have shown that vaginal delivery exposes the baby to microbes that resemble the mother's vaginal bacteria (e.g., Lactobacillus, Prevotella, and Streptococcus); in contrast, C-section exposes the baby to microbes that resemble those found on the skin (e.g., Staphylococcus, Corynebacterium, and Propionibacterium) (5). Children born by C-section lack the benefit of protective vaginal bacteria, which may make them more susceptible to viruses, allergies, and asthma later in life (6). Such findings are contributing to the development of novel etiological hypotheses for T1D development by suggesting that the initial microbiota to which a neonate is exposed, and which may be related to the type of delivery, is important in the development of child's immune system and in modulating its response to external agents later in life.

Yet, not all high-risk children delivered via C-section develop T1D (4). In a Norwegian case-control study, a PTEN (protein tyrosine phosphatase, non-receptor type 22) polymorphism has been shown to increase T1D risk if the child was delivered vaginally (7), underscoring the importance of exploring potential interactions between perinatal exposures and susceptibility genes in the pathogenesis of T1D. Genome-wide association studies have identified IFIH1 as a helicase enzyme that produces type 1 interferon in response to viral infections, such as enteroviruses. It has been proposed that IFIH1 is activated by exposure to a virus to produce type 1 interferons, which leads to upregulation of major histocompatibility complex class I on β-cells, thus increasing autoreactive CD8+ cytotoxic T-lymphocyte recognition of β-cells (9). Liu et al. (10) analyzed 13 single nucleotide polymorphisms (SNPs) in the 450kb IFIH1 genomic region and identified four variants to be significantly associated with T1D in two large U.S. Caucasian cohorts (rs577457, rs1180676, rs211485, and rs13422767). Their analysis revealed that the major allele (C) carriers were at higher risk of T1D with the highest risk conferred to those with the homozygous genotype (GG), even after adjustment for sex, diagnosis age, and HLA-DQB1 genotypes. Additionally, they found that IFIH1 expression was significantly higher for the major allele homozygous genotypes. Carriers of the IFIH1 major allele polymorphism have a higher IFIH1 expression, which possibly controls the immune response to environmental exposures and increases the risk for T1D (10).

Bonfaccio et al. (11) proposed an interesting and novel explanation for the observed association between C-section delivery and increased T1D risk that this group and others had previously reported (Fig. 1). First, C-section delivery, a surrogate marker for early life microbiota, specifically influences progression from a preclinical disease state (autoimmunity) to T2D. Second, this progression is further enhanced in the presence of genes that modulate the immune response to environmental agents, such as the IFIH1 polymorphism. As a result, the highest risk of progression is seen in children exposed to both environmental and genetic factors associated with immune response modulation. Such findings, if replicated in other populations, offer novel avenues for prevention of T1D through interventions affecting host's immune response to environmental agents and likely targeted at children who have already developed autoimmunity.

The BABYDIAB study provides a mature cohort of children identified at birth and prospectively followed for the development of T1D. Several limitations inherent to this cohort exist and include the fact that this is not a population-based cohort but one enriched with individuals at high genetic and familial risk for autoimmunity and T1D. The high genetic risk population studied in BABYDIAB likely represents a higher susceptibility group for T1D. Further studies are needed to determine the potential role of early life microbiota in the development of T1D.

References:
Why are C-section deliveries linked to childhood Type-1 Diabetes?

Early life factors have been shown to be associated with increased T1D risk and perhaps involved in the development of the immune system.

A recent meta-analysis of 20 studies worldwide reported that C-sections, independent of maternal age, birth weight, and breastfeeding, contributed a 20% increase in the risk of T1D.

Diabetes, Vol. 61, January 2012
Immune regulation genes

First microbe exposure (delivery mode) → Modification of immune response systems

Genetic predisposition (HLADR-DQ)
Why are C-section deliveries linked to childhood Type-1 Diabetes?

Children born by C-section lack the benefit of protective vaginal bacteria. The initial microbiota to which a neonate is exposed, and which may be related to the type of delivery, is important in the development of child’s immune system and in modulating its response to external agents later in life.
In Summary

- Metabolic syndrome is a major problem increasing in incidence
- Hormones dictate metabolism
- Inflammation alters hormones and metabolism
- Gut microbiota alters inflammation and hormones
- Gut microbiota affected by gut health & nutrition
Traditional Approach

- Manage hypertension
- Manage LDL – statins
- Optimize HDL – lifestyle, Niacin
- Triglycerides – Omega-3s (Lovaza), fibrates
- Hyperglycemia – metformin, GLP-1ra, DPP-4
- Lifestyle – nutrition & exercise
A word on Statins

- Finnish study found 50% increase in T2D in people taking statins
  - Decreased insulin sensitivity 24%
  - Increased insulin secretion by 12%
- NEJM study showed 27% increase in diabetes in people taking rosvuvastatin
- “Although it is clear that statins prevent heart disease in patients at high risk or with established cardiac disease, the use of statins in patients at lower risk (for primary prevention before any cardiac events have occurred) is less certain.” Shah R, Goldfine A. Statins and risk of new-onset diabetes mellitus. Circulation. 2012;126:e282-e284.
How SHOULD we address this?

1. Aggressively target the “Healthy Trinity”
   1. Whole food nutrition, eliminate processed foods
   2. Exercise
   3. Reduce stress, Improve Rest
2. Probiotics and prebiotics
3. Whey &/or pea protein supplements
4. Nutritional supplements
5. Medications when needed to optimize health
Questions?