New Horizons in the Prevention of Type 1 and Type 2
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Trekking to Ontario – Banting and Best Museum
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  DiabetesEd
Objectives

1. Describe the role of gut Bacteria and gut hormones in type 1 and type 2 diabetes.
2. Discuss current research on the prevention and cure for type 1 diabetes.

Diabetes in America 2012

- 28 million or 8.3%
- 79 million have pre diabetes

CDC 2012

Estimated lifetime risk of developing diabetes for individuals born in U.S. in year 2000

Narayan et al, JAMA, 2003
Type 1 Rates Increasing Globally

- 23% rise in type 1 diabetes incidence from 2001-2009
- Why?
  - Autoimmune disease rates increasing over all
  - Changes in environmental exposure and gut bacteria?
  - Hygiene hypothesis
  - Obesity?

Risk Of Developing Type 1 Diabetes

- General Pop 0.3%
- Sibling 4%
- Mother 2-3%
- Father 6-8%

Type 1 Diabetes Associated with other immune conditions

- Celiac disease (gluten intolerance)
- Thyroid disease
- Addison’s Disease
- Rheumatoid arthritis
- Crohn’s
- Multiple Sclerosis
• 34% BMI 30+, 34% BMI 25-29
• We burn 100 cals less a day at work
• 1/3 of all overwt people don’t get diabetes

Obesity - other factors?

• Not only humans are gaining weight globally
• Animals are getting heavier too (and not just the domestic kind).
• Factors – sleep deprivation, AC, other?

Marmosets to macaques


Bacterial Cells Outnumber Human Cells 10 to 1
Getting to the Gut

- Gut bacteria and body weight
- Gut bacteria health influence on expression of type 1 and type 2
- Gut hormones

The Work of Gut Flora

Electron micrograph of small intestine and bacterial inhabitants in green.

Normal Gut Bacteria

- Diverse
- Collected over a life time through
  - Environmental exposure
  - Types of foods consumed
  - Breast or bottle fed?
  - Parents
  - Vaginal delivery or C-Section
- Help us
  - utilize energy
  - fight off invaders
Intestinal Health – A Balancing Act

- Major Groups
  - Firmicutes
  - Bacteroidetes
  - Plus thousands of others
  - Diversity of gut bacteria more protective

Weight and Gut Bacteria
New and Early Research

- Leaner people
  - More bacterial diversity
  - More bacteroidetes
  - Gut bacteria less efficient at converting food to calories

- Obese people
  - More firmicutes
  - Gut bacteria very efficient at calorie extraction

- Bacteria tend to run in families
  
Newsweek, July 6 2010

Fatty Foods Trigger Leaky Gut?

With diabetes, a high fat meal appears to trigger:
  - Passage of bacterial endotoxins through intestinal wall
  - Increase levels of inflammatory cytokines and triglycerides
  - Seems to be worse if eat frequent fatty meals throughout the day – increases presence of lipopolysaccharide endotoxins

Research by Alison Harte, PhD - Clinical Endocrinology News- Nov 11, 2011
H. Plyori a Gut Culprit?

- *Helicobacter pylori* infection doubled risk of DM among Latinos 60 yrs +
- Study details:
  - 1,789 Latino men, women in Sacramento Area Latino Study on Aging (SALSA)
  - During 10 yr study, 18% developed diabetes
  - 2.7 times more likely to develop diabetes if seropositive for *H. pylori* (also assoc w/ higher BMI)
  - Why? Inflammation?

Reported at Annual Meeting of Infectious Disease Society of America – Research led by Dr. Christine Y. Jeon of Columbia University - Clinical Endocrinology News- Nov 11, 2011

Type 1 Diabetes & Gut Bacteria

- Exciting research in Finland
  - 8 children with same risk of getting type 1 diabetes based on family history and HLA DQ genotype
  - In the 4 children with ATB conversion, w/in 6 months before, the levels of firmicutes decreased and bacteroidetes increased.
  - The bio diversity also decreased
  - Hope that can id kids early on and halt progression to type 1.

DIPP – Diabetes Prediction and Prevention Study

Gut Bacteria Shift Prior to Diagnosis

**Type 1 Diabetes**
- ↑ Firmicutes
- ↑ Bacteroidetes
- Less diverse
- Less stable

**No Type 1**
- ↑ Firmicutes
- ↓ Bacteroides
- Healthy Microbiome, diversity increased
Gut Hormones and Bacteria

Post Gastric Bypass
- the diversity of gut bacteria increase
  - Firmicutes
  - Bacteroidetes
- availability of gut hormones also increase

Gut Hormone Replacement in Type 1?
Liraglutide Study
- 14 type 1 pts, 24 wks received liraglutide daily w/ insulin therapy
  - Lowered wt – 68 kg to 63kg
  - Lowered A1c – 6.5 to 6.1
  - Basal insulin dropped by 48%
  - Bolus insulin lowered by 42%
  - Less glucose fluctuations

Annual meeting of Endocrine Society -8/11
Dr Anjay Varanasi investigator
Prevention to Cure of Type 1

- Determining who is at risk
- Environmental triggers
- Pharmacologic interventions to halt autoimmune destruction
- Transplantation
- Artificial Pancreas

How do we know someone has Type 1 vs Type 2

- Type 1
  - Positive antibodies
  - GAD
  - ICA
  - IAA and others
  - Younger the person is, the more quickly it develops
  - Older people take longer to develop

Autoantibodies Assoc w/ Type 1

Panel of autoantibodies –
- GAD65 - Glutamic acid decarboxylase –
- ZnT8 - Zinc Co-Transporter 8
- ICA - Islet Cell Cytoplasmic Autoantibodies
- IA-2A - Insulinoma-Associated-2 Autoantibodies
- IAA - Insulin Autoantibodies
Evidence from type 1 prevention studies suggest that measurement of islet autoantibodies identifies individuals at risk for developing type 1 diabetes.

Such testing may be appropriate in high-risk individuals … in the context of clinical research studies - see, for example, http://www2.diabetestrialnet.org

The Jonas Brothers and their mother Denise Jonas join TrialNet researchers to deliver an important message to family members of people with type 1 diabetes

TrialNet Sites
TrialNet Natural History Study

Who is eligible for screening?
- Ages 1-45 & immediate family member w/ DM
- Ages 1-20 for extended family

What is the screening test?
- Single blood test for panel of autoantibodies
- Those < 18 & Ab neg rescreened yearly

What happens if they have 1 or > Abs?
- Monitoring and on-going surveillance Genetic screen: HLA class II
- Metabolic screen: Oral glucose tolerance test

Type 1 Prevention - Stages

Primary Prevention -
- Genetic susceptibility

Secondary Prevention
- Islet Autoimmunity

Tertiary Prevention
- Expressing Type 1 Diabetes

Primary Prevention of Type 1

Strategy – Find those at highest risk of Type 1 diabetes and see if early intervention to protect beta cells prevents or delays onset.

Identify through genetic testing
- HLA DQ and HLA DR alleles are the major determinant of type 1
- 1 million currently at risk
The Honeymoon
- By diagnosis, 15-40% of beta cell function remains
- Length of honeymoon varies
  10-15% of teens and adults still have clinically significant insulin production > 5 yrs after DM onset (DCCT, NEJM 1993)
- Medalist study: 2/3’s with measurable insulin > 50 yrs after dx (King, Diabetes, YEAR)
  Rate of beta cell loss is correlated with age Younger pts tend to have shorter honeymoons

Remaining Beta Cells
- Can serve one well while it lasts…even if on supplemental insulin.
- Better overall glucose control lower HbA1C, less glycemic excursion, lower risk for severe hypoglycemia

Research on Type 1
- Primary Prevention – what triggers type 1?
  Viruses
  Hygiene (too much?)
  Lack of breastfeeding
  Early exposure to foods?
- Intervention – Secondary and Tertiary
- Cure
The Hygiene Hypothesis

- In studies, mouse raised in clean environment is higher risk for DM than one raised in dirty one
- "Clean living" may increase risk for autoimmune diseases
- Risk is higher in urban than rural settings
- Inverse correlation with immunizations, antibiotic use
- Daycare, other early exposures, lower risk for DM

The Environmental Determinants of Diabetes in the Young (TEDDY) Consortium

- The main mission of the TEDDY consortium, an international group of clinical centers, is to identify infectious agents, dietary factors, or other environmental factors—including psychosocial events—that trigger type 1 diabetes in those who are genetically susceptible.
TEDDY – to determine if…

- Can reduce the risk of type 1 diabetes w/
  - Avoid early cows milk exposure
  - Avoid introduction of gluten grains < 6mo
  - Adequate vitamin D
  - Reduce nitrate exposure
  - Others

Take Home Message

- Get Dirty
- Breastfeed if possible.
- Avoid early exposure to cows milk and cows milk based formula and gluten? – year of life for those at high risk
How to Get Screened?
www.DiabetesTrialNet.org

- How to get families linked to screening?

Why participate in Screening?
- Contribute to understanding
- Prevent DKA – Earlier diagnosis safer
- Start insulin sooner, may prolong honeymoon
- Early education and transitions
- Eligible for intervention studies

Type 1 – Intervention Studies
- Trial Net – Oral insulin
- GAD Vaccine (glutamic acid decarboxylase)
- START Trial – Thymoglobulin
- CD3 Monoclonal Antibodies
- Stem Cell
3 Types of Pancreas Transplants

- A combined pancreas and kidney transplant – most common – 75%
- A solitary pancreas transplant - less common – usually done after kidney transplant –
- An islet transplant — beta cells isolated from 2 pancreases, injected into portal vein of liver (lowers BG for a period of time)

Other “Cures”? www.JDRF.org

Closed loop system "artificial pancreas"

Prevention Strategies Type 2
Getting to Health

- Promoting healthy communities to decrease type 2
  - National Initiatives
  - Legislation in communities and states
  - Diabetes Educator’s emerging role in health promotion

Thoughts on Diabetes, Weight, Social Change

- "The only way on a societal basis to reduce the prevalence of obesity is through community action" – Dr. Frieden, CDC
- Poverty, Obesity, Diabetes inter-related

Will Legislation/ Policy/ Community Action Halt the Epidemic?

- Restaurant Calorie labeling
- Sugar tax – no Big Gulps
- Healthy foods in schools
- No Happy Meal toy unless make healthy choice (San Francisco, CA)
- Salt restriction
- Blue Zone (smaller plates, sidewalks)
- Let’s move
Soda Tax?

- Penny an ounce for every soda, sugar sweetened beverage sold.
- Initial projections estimate that tax on beverage distributors would raise $1.7 billion a year.
- Funds for CA cities/schools to pay for childhood obesity prevention programs in state.
- [www.publichealthadvocacy.org](http://www.publichealthadvocacy.org)

Water Making a Come Back?

[PotterLovesWater.com](http://PotterLovesWater.com)

Let'sMove.Gov

1. Help Parents Make Healthy Family Choices
2. Create Healthy Schools
3. Provide Access to Healthy and Affordable Food
4. Promote Physical Activity

[America's Move to Raise a Healthier Generation of Kids](http://America's Move to Raise a Healthier Generation of Kids)
National Salt Reduction Initiative

- 80% of salt intake from prepared foods
- Only 11% comes from own saltshakers
- Coalition of local and state health authorities and orgs working with food manufacturers and restaurants to **voluntarily** reduce the amount of salt
- The goal - reduce Americans’ salt intake by 20% over 5 years.

Diabetes Prevention Programs

- Delay or Prevent Type 2 Diabetes
- Save $5.7 billion over 25 years
- Programs
  - Partnering with YMCA
    - CDC now recognizes Diabetes Prevention Programs

*Health Affairs* 31, No 1 2012 p50-60

In Conclusion

"Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has."

— Margaret Mead
Level 2 – Diabetes Educator Course

- April 11-13, Modesto, CA
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