Is Primary Prevention of T1D A Realistic Expectation?

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T1D incidence is doubling every 20 years
What environmental factors are responsible?

Incidence /100,000/ yr
in children 0-14 yr

TEDDY Ann NYAS 2008
Two-step model of pre-T1D

Genetic susceptibility

Islet autoimmunity (IA):
PERSISTENT autoantibodies insulin, GAD_{65}, IA-2, or ZnT8

Clinical Diabetes

ADA / WHO

Trigger
virus? diet?

Promoters?
Multiple islet autoantibodies predict progression to diabetes in children
Ziegler A, Rewers M, Simell O et al. JAMA. 2013;2473

Nearly all children positive for 2+ islet autoantibodies develop diabetes in 15 yrs
Primary Prevention (before islet autoantibodies appear)

- Prevent triggering of islet autoimmunity
- Diabetes diagnosis
Secondary Prevention (in subjects with islet autoantibodies)

Islet autoantibodies

Delay diagnosis of diabetes

Beta cell function

Time
When does islet autoimmunity begin?
Late onset of islet autoimmunity

*DAISY*

Environmental TRIGGER            DIABETES
Phenotypes of Type 1 Diabetes

- **β-cell function**: 100%
- **Insulin dependence**:
  - Early T1D
  - Classical T1D
  - Adult T1D

Trigger of autoimmunity
Candidate environmental causes:

- Hot enteroviruses
- ↓ childhood infections = hygiene
- ↑ food
  - microbiota
- ↓ intake of Ω-3 fatty acids
- ↓ intake of vit. D
- mycotoxins
- rotavirus
- cow’s milk
- gluten

Not routine immunizations

Rewers, June 2014
Find Prevention for T1D!

- 424,000 newborns screened
- 8,677 high-risk children intensively followed until 15 yrs

- Find the environmental trigger (virus, dietary factor)
- Develop vaccine/ elimination diet
- Public health screening and prevention to eradicate diabetes

Currently funded by the NIH
TEDDY protocol

Clinic visits every 3 months (including ab+ children older than 4):

Blood for: GADA, IAA, IA-2A, ZnT8; DNA, mRNA, infectious agents, HbA1c, PBMC, erythrocytes, storage plasma/serum;

Nasal swabs, tap water, toenail clippings, and salivary cortisol. urine samples; DNA from FDRs

Interviews: medications, immunizations, infections, family history; maternal pregnancy diet; child’s 24 hr recall, 3 day FFQ; negative life events, parental anxiety, depression, physical activity. Accelerometer;

Stool samples collected monthly -> quarterly

Blood
Dietary Factors

Fetal
- Nitrates, nitrites, nitrosamines
- Coffee/tea
- Cod liver oil
- Vitamin D
- Birth size
- Tubers, root vegetables

Infancy
- Breast-feeding
- Timing of exposure to:
  - cow’s milk
  - cereals/gluten
  - solid foods
  - root vegetables
  - berries
- Vitamin D
- Cod liver oil
- Weight/height gain

Childhood
- Cow’s milk
- Coffee/tea
- Nitrates, nitrites, nitrosamines
- Vitamin C
- Vitamin D
- Vitamin E
- Omega-3 fatty acids
- Nicotinamide
- Zinc
- Weight/height gain
Infant diet and the risk of islet autoimmunity

Cow’s milk < 3 month
DAISY
DIPP
BABYDIAB

Cereal < 4 or >6 mo; DAISY

Gluten < 3 months; BABYDIAB

Ω-3 FA intake; DAISY
Ω-3 FA erythrocyte wall; DAISY
no association with progression to T1D

Maternal Vit D suppl. DAISY
DIPP

Infant Vit D intake DAISY (2012)
Infant Vit D blood levels; DIPP (2008)

Hazard Ratio

0.12 0.25 0.5 1 2 4 8
Clinical Trials of Infant Diet Modification
None has succeeded, YET!!!

TRIGR (Trial in Genetically at Risk)
Weaning to hydrolyzed vs. intact cow milk formula

BABY-DIET
Delay in gluten exposure 6m -> 12m

NIP (Nutritional Intervention to Prevent T1D) TrialNet
Ω-3 FA docosahexanoic acid (DHA)

FINDIA - milk formula with low cow’s insulin content

Vitamin D supplementation
Larger TRIGR Study - Casein Hydrolysate Does NOT Delay Beta-Cell Autoimmunity

- 2159 high-risk infants newborns in 15 countries
  - High-risk HLA haplotypes
  - First-degree relative with T1D
  - Screened regularly for islet autoantibodies
**Intervention:**

Gluten introduction
Delayed until age 12 months
vs. standard 6 months

**Eligibility**

Age <2 months, no gluten
2 T1D first degree relatives
or
1 relative AND high-risk HLA
Small Overlap of T1D and Celiac Disease Among TEDDY subjects

Persistent confirmed Islet Ab+ 264

Persistent TG Ab+ 329

T1D 83

CD 200

Feb 2012
BABYDIET Study Population

Children screened by HLA-genotyping on cord blood

- Children eligible for follow-up, offered to participate in the study
  - Consented to participate
    - Randomized to control group
      - Lost to follow-up
    - Randomized to late-exposure group
      - Lost to follow-up
  - Children with low-risk genotypes, excluded from the study

- Total
  - Initial screening: 1,168
  - Eligibility for follow-up: 169
  - Consented to participate: 150
  - Randomized: 150
    - Control group: 77
      - Lost to follow-up: 14
    - Late-exposure group: 73
      - Lost to follow-up: 16
  - Excluded due to low-risk genotypes: 999
BABYDIET – Reported Exposures

- Gluten
- Solid foods
- Age at first exposure
- Duration of exclusive breastfeeding

Graphs showing the age at first exposure to gluten and solid foods, with controls and late-exposure groups, and their respective p-values.
BABYDIET – Results
Development of Islet Autoantibodies to insulin, GAD, IA-2

Any autoantibodies

Multiple autoantibodies

Control group
Late gluten exposure
Child’s weight gain, BMI and growth are NOT related to islet autoimmunity (IA) or progression to T1D

**Islet Autoimmunity**
- BMI > age 2 y: DAISY 2009
- Weight gain velocity > age 2 y: DAISY 2009
- Weight < age 2 y: TEDDY 2013
- Height < age 2 y: TEDDY 2013

**Progression to T1D**
- BMI > age 2 y: DAISY 2009
- Weight gain velocity > age 2 y: DAISY 2009
- Weight < age 2 y: TEDDY 2013
- Height < age 2 y: TEDDY 2013

Similar results from BABYDIAB 2010
Enteroviral infections (EV) and the risk of islet autoimmunity (IA) or progression to T1D

**EV and islet autoimmunity**
- DAISY, Graves 2003 (n=26)
- MIDIA, Tapia 2010 (n=27)
- DIPP, Salminen 2004 (n=12)
- DIPP, Salminen 2003 (n=41)
- VIGR, Al-Shaheeb 2010 (n=13)

**EV and progression to T1D**
- DAISY, Stene 2010 (n=50)
- DIPP, Oikarinen 2011 (n=38)
Environmental toxins from food, water processing

- Vacor (rodentocide)
- Mycotoxins (*Streptomyces*)
  - Streptozotocin
  - Bafilomycin

Common scab disease
Summary:

• Unknown environmental factors are doubling the incidence of T1D every 20 years

• Triggers and promoters of progression to diabetes are largely unknown

• Autoantibody testing may help to pin-point the trigger

• Islet autoimmunity usually starts in early childhood, but may develop at any age → different T1D phenotypes

• 84% of children positive for ≥2 islet autoantibodies will develop diabetes in the next 15 years (70% in 10 yrs)
Summary:

• Little evidence to support the ‘accelerator hypothesis’ or link between obesity and T1D
• Feeding babies with cow’s milk formulas does not cause T1D
• Cereals to be added between 4-6 month of life while breast feeding
• Omega free fatty acids may be protective from early childhood IA
Summary:

- Presence of enterovirus in **blood** predicts T1D in **some** cases
- Routine immunizations /timing unrelated to T1D
Conclusion:

- Primary prevention is a realistic expectation
- Lot’s of work remain to be done
Questions

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