THE RISE OF DIABETES IN YOUTH
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American Diabetes Association
Conference
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IS diabetes in children increasing?
Short answer . . .
however . . . it’s complicated

Agenda
- TYPE 1
  T1D  T2D
- TYPE 2
- Summary and discussion of future goals for further study

Type 1a Diabetes Mellitus
- One of the most common chronic diseases in children
  – ¼ cases present in adults
- Still the most common cause of diabetes in children
  – 2/3 of new diagnoses in patients 19 years or younger in the US
  – 193,000 Americans under age 20 are estimated to have diagnosed diabetes, approximately 0.24% of that population.
  – In 2011—2012, the annual incidence of diagnosed diabetes in youth was estimated at 17,900 with type 1 diabetes, 5,300 with type 2 diabetes.

Epidemiology
- Very variable. Factors that influence T1D risk:
  - Geographical variation
    - Latitude factors: In Europe and China, risk increases as distance from equator increases; not true in US
    - Environmental factors: When patients move from an area of low to high incidence, risk increases
  - Still very variable incidence, even between neighboring areas of similar latitude

Geographical Epidemiology

Highest yearly incidence:
- Finland – 46 per 100,000 children < 15 years
- Sardinia – 40 per 100,00 children < 15 years
- Sweden – 47 per 100,000 children
- Venezuela – 0.1 – 0.5 per 100,000 children < 15 years
- China – 0.1 – 0.5 per 100,000 children < 15 years

500 fold difference!

500 fold difference!
Epidemiology – US & Canada

• Ethnic variability
  US:
  - Newfoundland: 36 per 100,000
  - Quebec: 15 per 100,000
  - Canada’s rates are even higher than US:
    - Newfoundland: 36 per 100,000
    - Quebec: 15 per 100,000

Epidemiology – age and gender

• Well-known bimodal distribution:
  - Peak at 4-6 and second peak 10-14
  - 48% children present before 10 years
  - NO gender differences overall
    - Exceptions:
      - 3:2 male:female in older males of European origin
      - 3:2 male:female ratio in children under 6 in one MA study

Trends over time: Is T1D rising?

• Reported increases of 2-5% per year in Europe, Middle East, and Australia
• Over past 30 years, incidence has increased by several times

Trends over time: US

• Overall incidence rising in most age and ethnic groups
  - Average annual increase 2%
  - Higher rate of rise in non-Hispanic white (2.7%/yr) but also significant in Hispanic (1.6%/yr)
  - As of now: no clear reason for this increase

The Rise

• Primarily in younger children
• European report (1989-2003): overall 3.9% increase
  - Ages 0-4: 5.4%
  - Ages 5-9: 4.3%
  - Ages 10-14: 2.9%
• Philadelphia report (1985-2004):
  - Incidence in <5 increased by 70%
  - If trends continue, number of new cases in children <5 may double in some regions

The Rise

• Seen in multiple locations:
  - Swedish study: increase in diagnosis for children born in or after 2000
  - New Zealand study: trend toward older age at dx
Risk Factors

- Genetics
  - Genetic susceptibility: **necessary** but not **sufficient**
- Environment
  - Must be responsible for most of the recent rise given how quickly rates have risen

Genetic risk factors

- No FH: 0.4%
- Offspring of affected mother: 1-4%
- Offspring of affected father: 3-8%
- Offspring of both parents: ~30%
- Non-twin sibling: 3-6%
- Dizygotic twin: 8%
- Monozygotic twin: 30% within 10 years; 65% by age 60

Genetics / Ethnicity

- Large 2009 study looking at prevalence of both diabetes types

<table>
<thead>
<tr>
<th>Type 1 Diabetes</th>
<th>Prevalence 2009, 0 - 19</th>
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<tbody>
<tr>
<td>Non-Hispanic White</td>
<td>2.55 / 1000</td>
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<tr>
<td>Non-Hispanic Black</td>
<td>1.62 / 1000</td>
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<tr>
<td>Hispanic</td>
<td>1.29 / 1000</td>
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<tr>
<td>Asian/Pacific Islander</td>
<td>0.6 / 1000</td>
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<tr>
<td>Native American</td>
<td>0.35 / 1000</td>
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Genetics / Ethnicity

- Most of the genetic variation is attributed to genetic polymorphisms of the **MHC** (major histocompatibility complex)
- HLA region on chromosome 6 – contains genes that code for MHC class II molecules expressed on the cell surface of antigen-presenting cells such as macrophages
- Binding of antigen allows it to be presented to antigen receptors on T cells, the main effective cells of the autoimmunity in T1D

Other known genetic associations

- Preproinsulin
- Insulin gene (repeat sequence in 5' region of the gene)
- PTPN22 – involved in T-cell receptor signaling
- CTLA-4
- Interferon-induced helicase
- IL2 receptor (CD25)
- KIA0035
- ERBB3e
- Additional loci: undefined gene in 12q region, BACH2, PRKCQ, CTSH, CLQTNF6
- Some loci also confer shared risk of celiac disease: RGS1, IL18RAP, CCR5, TAGAP, SH2B3, PTPN2

HLA subtypes

- More than **90%** of type 1 DM patients carry either:
  - HLA-DR3-DQ2
  - HLA-DR4-DQ8
  - 30% carry both
  - **5%** risk of developing type 1 DM compared with 0.3% overall
- **40%** of controls carry these – so not a reliable marker, but indicates increased risk
- Other alleles confer protection:
  - HLA-DQB*0602
- **BIG part of explanation for geographic/ethnic differences!**
CCR5 example

Known that a 32-bp deletion in CCR5, a chemokine receptor, results in a loss of function

Homozygotes for CCR5 → 2-fold decrease in risk for type 1 DM

Genetics + Environment

Genetic susceptibility + Exposure to environmental agents → immune response leading to beta-cell destruction

However . . . search for the environmental culprits has been elusive.

Potential factor: Viral

- Viral infections [especially enterovirus]
  - Examination of 75 patients who died within several weeks of dx found no evidence of acute or persisting infection from Coxackie, EBV, mumps, or CMV
  - However: Coxackie B IgM found in 39% children with newly diagnosed T1D compared with 6% controls
  - Coxackie virus antibody titers were higher in pregnant women whose children developed T1D
  - Enteroviral infections were nearly 2x more common in siblings who developed T1D compared to siblings who remained unaffected
  - Possible association between enteroviral infections during pregnancy → persistence infection and islet autoimmunity in mother and offspring
- Homology between human GAD and F2C protein of Coxackievirus B4 → potential mechanism for molecular mimicry
- However, conflicting data exists:
  - One report shows Coxackie B viruses associated with GAD antibodies but not T1D

Other Potential factors

- Immunizations: bacterial and viral antigen vaccination shown to confer no associated risk
  - Meta-analysis of 23 studies investigating 16 vaccines concluded that childhood vaccines do not increase risk
  - BCG vaccine at one point postulated as protective → no evidence of this on several trials conducted worldwide

Other Potential Factors

- Intestinal Microbiome
  - Relatively new but very interesting area of research
  - May be impacted by factors such as C-section history, early childhood diet, and use of antibiotics
  - Some studies have shown lower microbial diversity in children with islet autoimmunity compared to healthy controls
  - Research in this area still quite young but certainly increasing

Other Potential Factors: Diet

- Has been proposed that some component of bovine serum albumin (present in cow’s milk-based formulas + cow dairy) may trigger an autoimmune response
- Some suggestion that exposure to beta-casein (specific cow’s milk protein) could be involved in pathogenesis
- Studies are conflicting:
  - Finnish study showed increased risk associated with early introduction of dairy + high milk consumption in childhood
  - Cross-sectional study found no association
  - Prospective studies looking at breastfeeding have not found risk associations
Other Potential Factors: Diet

• Most of the prospective birth cohort studies failed to find protective effect of breastfeeding for T1D
  – However – children who were still breastfed at time of introduction to grains had a reduced risk of islet autoimmunity and T1D

Rewers M and Ludvigsson J. Lancet 2016; 387(10035)

Other Potential Factors: Diet

• In high-risk infants, early OR late exposure to grains may impact risk of developing islet cell autoantibodies
  – Higher risk of grains given prior to 3 months OR after 7 months
  – 4-6 month window – safest
  – Effect of gluten varies among various studies
    • Randomized trial of gluten-free diet at 6-12 months did not reduce development of islet autoimmunity in genetically high-risk infants or decrease levels of antibodies already present

Rewers M and Ludvigsson J. Lancet 2016; 387(10035)

Other Potential Factors: Diet

• Omega-3 fatty acids may have a protective effect
  – Norwegian study: Children with T1D less likely to be given cod liver oil during infancy
  – US study showed that higher omega-3 fatty acid intake + levels in erythrocyte membrane predicted lower risk of islet autoimmunity
  – Intervention study in high-risk infants underway

• Nitrates in drinking water
  – Studies in Colorado and UK have shown T1D correlates with concentration of nitrates in water
    • 30% higher in areas with nitrate concentrations > 14.8 mg/L compared to below 3.2 mg/L
    • Not seen in German study

Rewers M and Ludvigsson J. Lancet 2016; 387(10035)

Other Potential Factors: Diet

• Vitamin D deficiency
  – One European study (EURODIAB study) found vitamin D supplementation in infants to be protective; proposed immunomodulatory effect; others did not find any association or protective effect
  – Could be one factor influencing seasonality and latitude effects

Rewers M and Ludvigsson J. Lancet 2016; 387(10035)

Seasonal variations?

• Higher reported incidence in winter vs summer
  – Not consistent – another study showed no variation in girls and higher summer incidence in boys
  – Complex as social factors (school calendar, etc) may impact timing of diagnosis

Rewers M and Ludvigsson J. Lancet 2016; 387(10035)

Other potential factors: Hygiene/SES

• Postulated that perhaps increased hygiene/fewer childhood infections → rise of autoimmunity
  • However – infection data in prospective trials has not supported this
    – Colorado study (DAISY) reported association between islet autoimmunity and early childhood GI infections (but not respiratory)
  • One promising hypothesis is that decreased herd immunity to enteroviruses might be due to changes in exposure/hygiene

Rewers M and Ludvigsson J. Lancet 2016; 387(10035)
Perinatal factors

- Study of 892 children with diabetes / 2291 controls in Europe
- Increased risk:
  - Maternal age > 25
  - Pre-eclampsia
  - Neonatal respiratory distress
  - Jaundice
- Protective factors:
  - Short birth length + low birth weight

Summary of environmental factors

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<tr>
<th>Environmental Factors</th>
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<tbody>
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<td>Overweight</td>
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<td>Puberty</td>
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<td>Low physical activity</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Glucose overload</td>
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<tr>
<td>Psychological stress mediated through cortisol</td>
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“Accelerator”/Beta-cell stress hypotheses

- Proposes that excess weight gain leads to insulin resistance in early childhood and could initiate islet autoimmunity
  - Causality evidence lacking, but theories interesting
  - Theorized that insulin resistance and rising blood glucose might accelerate beta-cell apoptosis directly or induce more antigen activity in those predisposed genetically
  - Rapid growth might increase insulin demand causing beta-cell stress and increased presentation of autoantigens

Beta-cell stress hypothesis

- Proposes that factors causing increased insulin demand could play an important role in development of T1D
  - Overweight
  - Puberty
  - Low physical activity
  - Trauma
  - Infections
  - Glucose overload
  - Psychological stress mediated through cortisol

HIPS: Linking beta cell stress to T1D

- States related to insulin oversecretion → generation of neoautoantigens via post-translational modifications of islet proteins
  - Proinsulin, chromogranin A, islet amyloid polypeptide (IAPP), GAD

HIPS: Linking beta cell stress to T1D

- Recently, a new class of naturally occurring autoantigens called hybrid insulin peptides (HIPS) have been identified
  - Made from C-peptide fragments + chromogranin/IAPP
  - CD4 cells have been identified that react to these hybrid peptides
  - Molecular crowding of these peptides (due to more insulin secretion) → promotion of HIP formation → increased type 1 risk in context of insulin oversecretion
Why is this question so difficult?

- Process progresses over many months, during which the patient is asymptomatic and euglycemic
  - Genetic markers present from birth
  - Immune markers detectable after onset of the autoimmune process
  - Metabolic markers can be detected with tests once enough beta cell damage has occurred
  - Long latent period due to the number/extent of beta cells that must be lost before symptoms occur
- Makes identification of triggering factors very difficult

Type 2 Diabetes

- Incidence has increased since the early 1990s in children and adolescents
- Tightly linked to rise in childhood obesity – perhaps some good news coming?

Pathogenesis

- Type 2 DM requires
  - Insulin resistance **AND**
  - Relative impairment in insulin secretion
- Considerable overlap with type
  - Many cases are not clear-cut
  - Rise of “double diabetes” in which features of both diseases are present

Epidemiology

- Rise in prevalence in T2DM is occurring worldwide in parallel with increasing obesity
  - Early 1990s: T2DM was 3% of pediatric diabetes in US
  - 2003: T2DM represented 20% and – in some areas – nearly half of the cases among adolescents 15-19 years

Global data

- Japan: study of children ages 6-15
  - Before 1981: 1.73/100,000; After: 2.76/100,000
  - Adolescents 6.43/100,000; younger 1.73/100,000

- Thailand
  - T2DM 5% 1985-1995; 18% 1996-1999
  - Obesity 5.8% to 13.3% between 1990-1996

- Argentina: T2DM 0% - 4.3% between 1996-2001
United States

- Large recent study of data: SEARCH for Diabetes in Youth Study - 2002-2012
- 2846 with type 2 DM ages 10-19 identified looking at 5 study centers in the US
  - Rates of type 2 DM increased by 7.1% annually from 2002-2012
  - 9 cases/100,000 youths/yr in 2002 → 12.5 cases/100,000 youths in 2012
  - Increase highest in blacks, Asians/Pacific Islanders, Native Americans
  - Adjusting for age/sex/race/ethnic group annual increase in T2D 4.8%/yr

Mayer et al, NEJM 2017; 376(15):1419

T2DM Risk Factors

- More straightforward than T1!
- Obesity
- Positive family history
- Racial/ethnic group
- Female gender
- Co-occurrence of other conditions associated with insulin resistance or use of medications linked to insulin resistance/T2DM

Is the obesity rise finally slowing?

- Rates of childhood obesity have stabilized at about 17% across years 2003 – 2014
- Severe obesity however continues to increase
  - 9.1% adolescents 2013-2014
  - Latency effect – because T2DM takes time to develop, incidence rates are behind obesity trends


Obesity and T2DM

- Compared to adults, association is even stronger in children
  - 80% youths with T2DM obese (BMI > 95%)
- Central/upper body adiposity more powerful predictor than BMI alone

Genetic Susceptibility

- Very strong genetic component
  - 50-75% T2DM in at least one parent
  - Any offspring of a parent with T2D has an estimated 20% risk of developing T2D by late adulthood
  - 30% if both parents affected
- Susceptibility is polygenic
- Monozygotic twin concordance rates 90%

Barnet AH et al. Diabetologia 1981; 20:87
Genetic susceptibility loci

• Genes involved in pancreatic development/insulin synthesis: “reserve”
  – TCF7L2, SLC30A8, HHEX, KCNJ11, NOTCH2
• Beta cell signaling: KCNQ1 – potassium channel – also associated with long QT
• Beta cell survival: Variants in WFS1
  • Mutants cause Wolfram syndrome: rare disorder with DI, nonautoimmune DM, optic atrophy, deafness
• MODY
  • GCK (MODY2) - glucokinase
  • PDX1 (MODY4) – beta cell transcription factor

Ethnicity Variation in T2D

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<th>Ethnicity</th>
<th>Incidence/100,000 in 2012</th>
<th>Prevalence 2009 - 10-19y</th>
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<tr>
<td>Non-Hispanic White</td>
<td>3.9</td>
<td>0.17 / 1000</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>12.6</td>
<td>1.06 / 1000</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18.2</td>
<td>0.79 / 1000</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>12.2</td>
<td>0.34 / 1000</td>
</tr>
<tr>
<td>Native American</td>
<td>46.5</td>
<td>1.2 / 1000</td>
</tr>
</tbody>
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* Pima adolescents: 51/1000!

30.5% adjusted increase in overall prevalence T2DM between 2001 - 2009

Mayer et al, NEJM 2017; 376(15):1419
Dabalea D et al, JAMA 2014 311(17):1778-86

Age and Gender

• Girls are 1.3 – 1.7x more likely than boys to develop T2D during adolescence
• Hypothesis: related to increased risk of insulin resistance seen in adolescent girls with PCOS
• Puberty common age of onset
  – Stage of physiologic insulin resistance
  – Insulin sensitivity decreased; partially related to increased growth hormone activity

Prenatal Factors: SGA/Undernutrition

• Prenatal undernutrition increases risk of type 2 DM in adult offspring
  – Low birth weight: Associated with insulin resistance
  – Theory of “thrifty” genotype in which insulin resistance might improve survival during states of caloric deprivation
  – Premature infants (small or appropriate for gestational age) are at increased risk for type 2 DM/insulin resistance
  – Highest risk are former SGA infants that develop obesity later in life

Hyperglycemic/Overnutritive Prenatal Environment

• HIGH birth weight also increases risk (>4 kg)
  • Same risk as low birth weight – U-shaped curve
• Gestational diabetes: Abnormal intrauterine metabolic environment increases risk of T2DM
  • Affects development of adipose tissue in utero
  • May alter beta cell development
  • 4 fold increase of childhood-onset T2 DM in Canadian study

Silverman, Rizzo, Cho, Metzger Diabetes Care 2008; 21 Suppl 3:S14
T1DM / T2DM Interplay

- Risks are also increased for T2DM in offspring of T1DM
  - Adolescents born to mothers with T1D were heavier than those born to non-diabetic mothers: BMI 24.6 vs 20.9
  - Macrosomia present in infancy often resolved by 1 year of age but then recurred in childhood
  - Offspring of T1D mothers WITHOUT T1D had impaired glucose tolerance compared to controls; not seen in offspring of T1D fathers
    - Also taller, heavier, and with high BMI

Summary

- Both type 1 and type 2 diabetes are increasing in youth
  - Type 2 rise correlating with obesity which has finally leveled off; perhaps T2DM plateau coming in future
  - T1D rise is clear and at this point, ongoing

- More studies needed on environmental factors are clearly needed (diet; prenatal factors; environmental influences) so that risk-lowering interventions can be pursued along with therapeutic trials

Questions?

References