Developmental origins of type 2 diabetes in children

DCPNS
April 16, 1010
Is there an early window of opportunity?

Target pre-pregnancy to impact risk of type 2 diabetes for future generations of children in Manitoba
Developmental origins of health and disease

“The current epidemic in obesity, diabetes and many related medical conditions present one of the greatest ever challenges to global health. Evidence … indicates that much of our predisposition to these chronic diseases of adulthood arises at the earliest times of life. Events before birth and environmental influences in childhood interact with our genome, modified by messages resulting from the health experiences of our ancestors”.

Michael G. Ross UCLA. 2009
Objectives

At the end of this presentation:

• Describe the history of type 2 diabetes in children in Atlantic Canada and contrast that experience with type 2 diabetes with other parts of Canada and especially Manitoba

• Identify the unique genetic and prenatal environmental factors associated with type 2 diabetes in youth in Manitoba
Outline

- Case study: Rosemary and her family
- Classification of diabetes
- Type 2 diabetes in children Canada 2010
- Type 2 diabetes in children Manitoba 2010
- Transcription Factor diabetes in Oji-Cree
- Gene-environment interactions in diabetes
Topics not included…

- Epidemiology and prevention of obesity and type 2 diabetes in children
- Social determinants of health
- Co-morbidities: steatosis, dyslipidemia, hypertension, smoking, skin infections, periodontitis, reproductive health
- Treatment and long term outcomes
- Evolutionary theories
- Epigenetics


Sellers, Moore, Dean, Ped Clinics North America Dec 2009
Rosemary and her family

- Rosemary age 39 has had type 2 diabetes since age 15y, taking metformin & glyburide, BMI 32.5, BP 150/90, A1C 8.7%
- Rosemary's mother age 60, type 2 diabetes for 25 years, on insulin, ESRD
- Rosemary's 4 children age 4-15y, 2 have type 2 diabetes at age 9 & 11y
Rosemary's Journey

Family Services

External medical specialists:
- Endocrinologist
- Orthopedics
- Gastroenterologist

Health Professionals:
- Physiotherapy
- Pharmacist

Foot Care
Eye Care

Diabetes care: children

Emergency Room

Employment Income Assistance

Primary Care Doctor:
- Nurse
- Dietitian
- Social Worker
- Therapist
- Outreach Worker

Diabetes care & ESRD: Gramma
Classification of diabetes

Type 1 diabetes
Type 2 diabetes
Gestational diabetes
Other types:

- genetic, endocrine disorders, drugs,
- pancreatic diseases, mitochondrial

Can J Diab, Dec 2008; 27: supplement
www.diabetes.ca
Classification of diabetes

Type 1 diabetes

**Type 2 diabetes**

Gestational diabetes

Other types:
- genetic
- endocrine disorders
- drugs
- pancreatic diseases
- mitochondrial

Can J Diab, Dec 2008; 27: supplement
www.diabetes.ca
Incidence of type 2 diabetes in Canada CPSP 2004-2006

Amed S et al, Diabetes Care, April 2010
Ethnic Distribution of Children < 18 years with T2DM

- Caucasian: 25%
- Aboriginal: 44%
- Asian
- African/Caribbean

Amed S et al, Diabetes Care, 2010
Demographics of children with T2DM in Canada

<table>
<thead>
<tr>
<th>T2DM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN AGE (YRS)</td>
<td>13.7</td>
</tr>
<tr>
<td>FEMALE:MALE</td>
<td>1.4:1</td>
</tr>
<tr>
<td>ETHNICITY (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>25.1</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.8</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>0.4</td>
</tr>
<tr>
<td>African/Caribbean</td>
<td>10.1</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>44.1</td>
</tr>
<tr>
<td>Asian</td>
<td>10.1</td>
</tr>
<tr>
<td>Mixed</td>
<td>6.2</td>
</tr>
<tr>
<td>FAMILY HISTORY (%)</td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} \degree relative</td>
<td>48</td>
</tr>
<tr>
<td>2\textsuperscript{nd} \degree relative</td>
<td>85.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ETHNICITY</th>
<th>AGE ≤ 10 YRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>8.8%</td>
</tr>
<tr>
<td>African/Caribbean</td>
<td>4.4%</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>11%</td>
</tr>
<tr>
<td>Asian</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

Amed S, Diabetes Care, 2010
## Risk factors & co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Aboriginal</th>
<th>Other Ethnicity</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Age (Yrs)</strong></td>
<td>12.9</td>
<td>14.3</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>% Female</strong></td>
<td>64</td>
<td>46.9</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>% + Family History DM</strong></td>
<td>94.7</td>
<td>94.9</td>
<td>1</td>
</tr>
<tr>
<td><strong>% Obese</strong></td>
<td>91.8</td>
<td>98.3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>% Acanthosis Nigricans</strong></td>
<td>74.2</td>
<td>84.4</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>% DKA</strong></td>
<td>10.1</td>
<td>12.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

### % Comorbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Aboriginal</th>
<th>Other Ethnicity</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCOS</strong></td>
<td>1.12</td>
<td>15.1</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>24.3</td>
<td>45.7</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>27.3</td>
<td>28.3</td>
<td>1</td>
</tr>
<tr>
<td><strong>ALT &gt; 90</strong></td>
<td>24.1</td>
<td>20.4</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Micro/Macroalbuminuria</strong></td>
<td>16.7</td>
<td>14.3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Mean BMI Z-Score</strong></td>
<td>1.96 (1.81, 2.10)</td>
<td>2.21 (2.04, 2.36)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Mean A1C (%)</strong></td>
<td>10.1 (9.4, 10.7)</td>
<td>9.6 (8.8, 10.4)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

![Bar chart showing the number of cases of diabetes in Nova Scotia from 1992 to 2007.](chart.png)
Referrals type 2 diabetes
DER-CA 1986-2009
Gender at diagnosis of type 2 diabetes in youth
Evolution of T2DM in children in Manitoba 1986-2010

- Age
- Gender
- BMI
- Treatment (Sellers)
- Community and family awareness
- Primary prevention activities (McGavock)
- Outcome surveillance (E Sellers, A Dart)
- Genetic-environment interaction:
  Hepatic Nuclear Factor 1α (HNF1α)
Sandy Lake, Ontario

Hegele et al, 1999

HNF 1α transcriptional activator of many genes

HNF 1α G319S [S319]
GG or GS or SS
8.7% gen pop
21% adults T2DM
34% T2DM <35y
Each copy T2DM 7 y earlier
PPV 95% by age 50y

Hegele et al, 2003

HNF 1α transcript reduced by 66% in vitro

Triggs Raine et al PNAS, 2002
Harries et al, Diabetes, 2008

REDUCED INSULIN SECRETION
Insulin Secretion

Insulin Sensitivity

High

Low

Resistant

Sensitive

Normal glucose tolerance

IGT

Type 2 diabetes

95th

50th

5th
Transcription factor diabetes in Manitoba (HNF1α)

- DER-CA: 29% youth had S319 (GS or SS)
- 70% with S319 from ILTC (vs 30%)
- 80% of youth from ILTC had S319 (vs 29%)
- S319 polymorphism dose dependent clinical features:
  - BMI lower
  - Acanthosis nigricans less frequent
  - Mean A1c higher

Sellers E, Triggs-Raine B, Greenberg C, Dean HJ, Diabetes Care 2002;25:2202-6
Insulin Secretion

- High
- Low

Insulin Sensitivity

- Resistant
- Sensitive

Normal glucose tolerance

IGT

Type 2 diabetes

95th

50th

5th
Monogenic diabetes
Maturity Onset Diabetes of the Young (MODY)

- Prior to 2000 thought to be rare
- Now estimated to be 5%
- 6 known types
- Autosomal dominant inheritance
- Lean habitus
- Onset before age 25yrs
Transcription Factor Diabetes
HNF 1α - (MODY-3)

• Severe defect in insulin secretion
• Average age of diagnosis = 20.4 years
• Lean, no acanthosis nigricans
• Severe microvascular complications (kidney, eyes, amputations)
• Treat with insulin or oral drugs that secrete insulin
## Transcription Factor Diabetes Impact on Birthweight

<table>
<thead>
<tr>
<th>Mother</th>
<th>Infant</th>
<th>Birthweight</th>
<th>Risk T2DM in offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>+gene T2DM</td>
<td>-</td>
<td>LGA</td>
<td>+</td>
</tr>
<tr>
<td>+gene T2DM</td>
<td>+ gene</td>
<td>AGA</td>
<td>++++</td>
</tr>
<tr>
<td>-</td>
<td>+ gene</td>
<td>SGA</td>
<td>++</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>AGA</td>
<td>-</td>
</tr>
</tbody>
</table>
Gene–environment interaction in monogenic diabetes

HNF 1α

• Exposure to intrauterine hyperglycemia is associated with earlier diagnosis of diabetes in offspring

• Offspring with HNF1α mutation
  - mother affected: diabetes at age 15 y 57%
  - mother not affected: diabetes at age 15 y 0%

Prenatal and early infancy risk factors for type 2 diabetes

SEARCH study USA

2001-2007 “population based” ascertainment
All incident cases of diabetes
Multiethnic population in 6 centres
Identified 331 youth with type 2 diabetes

Those whose mothers had diabetes during pregnancy had a younger age of diagnosis (1.68 years, p=0.18)

Pettit DJ et al, Diabetes Care, 2008
Type 2 Diabetes in offspring

Obesity in offspring

PIMA Dabelea 1998
Prenatal and early infancy risk factors for type 2 diabetes

Manitoba
case-controlled study 46 cases & 92 controls

Pre-pregnancy maternal diabetes OR=14.4 **
Gestational diabetes OR=4.4 **
Breastfeeding >12 months OR=0.24 **
Maternal prepregnancy BMI>25 OR=1.29 NS
BW <2500g OR=3.45 NS
BW >4000g OR=0.53 NS

Young et al, Arch Ped Adol Med 2002
Next Generation cohort

- Is this genetic or prenatal or postnatal environment or unique gene-environment?
- Established cohort in June 2003
- Offspring of mothers diagnosed with pre-pregnancy type 2 diabetes
- Cohort + prospective new births
- Growth surveillance annually
- Screening for diabetes ≥7 y annually
The Next Generation cohort

Mother

1. Currently live in Manitoba
2. First Nation heritage
3. Dx of T2DM < 19 years of age
4. Dx of T2DM prior to pregnancy

OFFSPRING
The Next Generation cohort  Aug 2009
Prevalence of T2DM in offspring of mothers with *pre-gestational* T2DM

IDF 20th World Diabetes Congress, Montreal QC, October 20th, 2009
Offspring at diagnosis of type 2 diabetes

<table>
<thead>
<tr>
<th>Age at Dx</th>
<th>A₁C %</th>
<th>BMI z score</th>
<th>HNF-1α genotype</th>
<th>Weight Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 y 8 m</td>
<td>7.1</td>
<td>2.3</td>
<td>SS</td>
<td>Obese</td>
</tr>
<tr>
<td>11 y 2 m</td>
<td>11.3</td>
<td>2.8</td>
<td>GS</td>
<td>Obese</td>
</tr>
<tr>
<td>12 y 5 m</td>
<td>8.3</td>
<td>1.7</td>
<td>SS</td>
<td>Overweight</td>
</tr>
<tr>
<td>10 y 10m</td>
<td>7.7</td>
<td>2.1</td>
<td>GS</td>
<td>Obese</td>
</tr>
<tr>
<td>10 y 1m</td>
<td>7.3</td>
<td>2.1</td>
<td>SS</td>
<td>Obese</td>
</tr>
<tr>
<td>9 y 6 m</td>
<td>10.9</td>
<td>2.2</td>
<td>GS</td>
<td>Obese</td>
</tr>
<tr>
<td>13 y 6 m</td>
<td>11.4</td>
<td>1.2</td>
<td>GS</td>
<td>Normal</td>
</tr>
<tr>
<td>12 y 8 m</td>
<td>11.0</td>
<td>2.3</td>
<td>GS</td>
<td>Obese</td>
</tr>
<tr>
<td>9 y 10 m</td>
<td>9.4</td>
<td>2.2</td>
<td>GS</td>
<td>Obese</td>
</tr>
<tr>
<td>~10 y</td>
<td>9.4</td>
<td>2.0</td>
<td>6 GS 3 SS</td>
<td>1 normal 1 overweight 7 obese</td>
</tr>
</tbody>
</table>
BMI of offspring Aug 2009

IDF 20th World Diabetes Congress, Montreal QC, October 20th, 2009
Growth patterns 2003-2009

IDF 20th World Diabetes Congress, Montreal QC, October 20th, 2009
Summary of Next Generation

~90% offspring are overweight or obese

~50% offspring ≥ age 10 have T2D < age 18y

10 years is average age of diagnosis

100% offspring with T2D have 1 or 2 copies of S319
Diabetes in pregnancy

• **Inadequate insulin response to:**
  – The demand of insulin resistance in pregnancy normal 2-3 fold increased insulin response
  – Exaggerated by maternal obesity
  – Exaggerated by decreased insulin secretion eg. HNF polymorphism or decreased beta cell mass

Continuum from maternal obesity to GDM to type 2 diabetes effect on abnormal fetal organogenesis and fetal metabolic response
Diabetes in Pregnancy

Insulin Secretion

High

Low

Insulin Sensitivity

Resistant

Sensitive

Normal glucose tolerance

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Type 2 diabetes

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5th

Diabetes in Pregnancy

Insulin Sensitivity

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Diabetes in Pregnancy: Vicious Cycle

- Mother with diabetes
- Obesity
- HNF G319S
- Infant of diabetic mom
- Child / woman with diabetes
Epigenetics is an attractive mechanism linking early life exposures with alterations in gene expression which may persist throughout life without a change in DNA sequence.”

Protein transcription is inhibited in inactive chromatin. Histone deacetylase activity leads to DNA methylation, which inhibits transcription. Translation is also inhibited. Gluckman et al. (NEJM, 2008)
Conclusions of Next Gen

- Type 2 diabetes in children is complex
- Transcription factor diabetes in Oji-Cree is unique (and not MODY-3)
- Gene-intrauterine environment interactions are important in determining expression of disease
- Transcription factor diabetes affects insulin secretion capacity but insulin sensitivity can be modified
“Intergenerational observational case studies will provide a substantial advance in knowledge. ... One major limitation is the problem of confounding.”

MG Gillman, Harvard, DOHaD, 2009
Future Directions
Next Gen cohort study

- Recruit offspring of fathers with type 2 diabetes to compare the risk of obesity and type 2 diabetes
  
  BSc (med) 2010-11

- Plan diabetes prevention trial using intensive lifestyle in before and during pregnancy with a life course approach to focus on future generations
Future of Pharmacogenetics?

- Sulfonylurea drugs for beta cell secretion
- Glucagon-like peptide (GLP-1) for beta cell regeneration
- Measurement of beta cell mass
- Measurement of confounders
Gardens in the North 1938
Aboriginal Diabetes Initiative*
Health Canada

- 2005-2010 $190 million
- Community Programs Directorate, FNIHB, Health Canada
- >600 communities
- ADI workers

* funding expires March 31, 2010
Objectives

At the end of this presentation:

• Describe the history of type 2 diabetes in children in Atlantic Canada and contrast that experience with type 2 diabetes with other parts of Canada and especially Manitoba

• Identify the unique genetic and prenatal environmental factors associated with type 2 diabetes in youth in Manitoba
Take home messages

• Consider screening for type 2 diabetes in all Oji-Cree children age ≥ 7y in all clinical settings FBG ± oGTT

• Document a detailed family history of type 2 diabetes in every child at risk
Intergenerational effects on metabolism

Pediatric Academic Societies
May 4, 2010, Vancouver, BC
MS Kramer & MW Gillman

Developmental Origins of Health and Disease

www.DOHaD.org
Historical perspective of DOHaD theories

- 1962 Thrifty gene  Neel
- 1993 Thrifty phenotype  Barker
  - Animal models of IUGR ++
  - U shaped curve for BW & risk T2D
- 2008 Developmental plasticity = the ability of an organism to develop in various ways depending on the environment  Gluckman, NEJM 2008
Our bodies of evidence.
Rosemary’s Journey

Family Services

External medical specialists:
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Health Professionals:
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Foot Care
Eye Care

Emergency Room

Employment Income Assistance

Diabetes care: children

Primary Care Doctor:
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- Dietitian
- Social Worker
- Therapist
- Outreach Worker

HAC

Diabetes care & ESRD: Gramma
THANK YOU FOR YOUR ATTENTION