Lessons from conducting research in an American Indian community: The Pima Indians of Arizona

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Pittsburgh,
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What did we learn in 1963?

• RA (and AS) common in this population
  – We provided care and treatment for the affected
• Community willing to take part in research
• Diabetes appeared to be a very common problem
• Further assessment of diabetes and its complications is needed
1965 Diabetes survey

- 75g OGTT
- Anthropometry
- Height and weight
- Medical history (+ medical record review)
- Physical examination- B.P., ophthalmoscopy, (joints) etc.
- and in those age30+: Retinal photos, ECG,
- Plasma glucose, serum creatinine, cholesterol
- Urine glucose & protein (and if +ve, protein/creatinine ratio)
Prevalence of Diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>259</td>
<td>319</td>
</tr>
<tr>
<td>25-34</td>
<td>124</td>
<td>175</td>
</tr>
<tr>
<td>35-44</td>
<td>133</td>
<td>174</td>
</tr>
<tr>
<td>45-54</td>
<td>85</td>
<td>106</td>
</tr>
<tr>
<td>55-64</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>104</td>
<td>67</td>
</tr>
</tbody>
</table>
DISTRIBUTION OF PLASMA GLUCOSE LEVELS IN PIMA INDIANS BY DECADE

MALES

PERCENT

TWO HOUR PLASMA GLUCOSE (MG./100ML)
Retinopathy and 2hr Plasma Glucose Levels in Pima Indians Aged 15-74yrs
Outcome of 1,223 Pregnancies—
Normal, Prediabetic and Diabetic Pima Indians

- Nondiabetic
- Prediabetic
- Diabetic

Percent

Stillbirths

Neonatal Deaths

Perinatal Mortality
What did we learn in 1965?

- The Pima have the world’s highest reported prevalence of diabetes
  - Diabetes has a major impact on the community
- Plasma glucose levels show a bimodal distribution
  - Current criteria for diagnosis seem inappropriate
- Retinopathy and nephropathy are frequent complications
- Pregnancy in the diabetic is associated with considerable excess perinatal mortality
- Further assessment of determinants of diabetes and its complications is indicated
- A longitudinal study could elucidate risk factors for diabetes and its complications
  - Very little known about the development and course of the disease
• Addressing a problem that community perceived as important
• Discussed ideas for longitudinal study with community leaders
  – Ask for their suggestions
  – Become aware of local cultural sensitivities
• Obtain appropriate community approval and endorsement (beyond the IRB)
  – E.g. Tribal council
Initial Goals of Longitudinal Study

- Characterize clinical features of diabetes mellitus in Pima Indians
- Identify risk factors for diabetes mellitus
- Determine its pathogenesis
- Distribution and determinants of its complications
Establishing the Longitudinal Population-based Study

Detailed census of community including identification of parents, siblings and children

Examine all aged 5 years and over
Repeat examination at two-yearly intervals
  1. 75g OGTT
  2. Anthropometry-Height and weight
  3. Medical history (+ medical record review)
  4. Physical examination- B.P., ophthalmoscopy, etc.
     - and in those age15+: Retinal photos, ECG,
  5. Plasma glucose, serum creatinine, cholesterol
  6. Urine glucose & protein (and if +ve, protein/creatinine ratio)

Initiate Pregnancy study - Third trimester GTT and examination of newborn-birth weight and congenital anomalies
Risk Factors for Diabetes
Diabetes in Pima by Parental Diabetes

<table>
<thead>
<tr>
<th>Diabetes in Parents</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Father</td>
<td>20</td>
</tr>
<tr>
<td>Mother</td>
<td>40</td>
</tr>
<tr>
<td>Both</td>
<td>60</td>
</tr>
</tbody>
</table>
Incidence of Diabetes by BMI in Pima Indians

Five-year Incidence of Type 2 Diabetes in Pimas aged 25-44yrs by BMI

Adapted - Knowler AJEpid 1981;113:144-56.
Type 2 DM and Current Leisure Activity in Pima Indians, aged 37-46 years

Prevalence (%) vs. Physical Activity (Low, Medium, High) for MEN and WOMEN.
Pathogenesis
Five-year Incidence of Type 2 Diabetes in Pima Indians with Normal Glucose Tolerance by fasting insulin levels
Insulin concentrations during development of IGT and Type 2 diabetes in Pima Indians
Diabetes Incidence (cases/1000 p-yr) by Insulin Sensitivity and Secretion

- High Sensitivity
- Mid Sensitivity
- Low Sensitivity

- High Secretion
- Mid Secretion
- Low Secretion

Incidence vs. Sensitivity

- Incidence range from 0 to 100

High Incidence
Mid Incidence
Low Incidence
Complications
Incidence of Proteinuria by Duration of Diabetes

2h glucose (mg/dl)
- >450
- 250-449
- <250

Systolic BP (mm Hg)
- >160
- 140-159
- <140

Cases/1,000 Person-Years

Duration of Diabetes (years)

Kidney Int 35:681-687, 1989
Incidence of End-Stage Renal Disease in Diabetic Patients, 1984-93

Relative Incidence
- Whites 1.0
- Blacks 2.1x
- Pima 9.2x

Age-sex-adjusted

Cases per 100,000/year

Whites
Blacks
Pima Indians
Pregnancy study

- Perinatal mortality
- Congenital defects
- Long-term effects of diabetic pregnancy on offspring
- Type 2 diabetes in childhood and adolescence
Prevalence of Diabetes in Children if Mother had Diabetes while Pregnant

Mother's Diabetes
- Prediabetic
- Diabetic

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td>30</td>
</tr>
<tr>
<td>25-29</td>
<td>70</td>
</tr>
</tbody>
</table>
Diabetes Prevalence in Pima Indian Children

1965-1969

1998-2002

% with Diabetes

Age (years)
Risk Factors
for Diabetes in Children and Adolescents
Ten-year cumulative incidence of diabetes in Pima Indians aged 5-19 years by Parental diabetes

McCance DR et al, Diabetologia 37; 617-23, 1994
Prevalence of Diabetes by Exposure to Diabetes in Utero

Sib Pairs Discordant for Diabetes and Intrauterine Exposure to Diabetes

<table>
<thead>
<tr>
<th>Born Before</th>
<th>Born After</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>21</td>
</tr>
</tbody>
</table>

OR = 3.0, p < 0.01
Percent of Offspring exposed to Diabetes in utero in three time intervals

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967-76</td>
<td>2</td>
</tr>
<tr>
<td>'77-86</td>
<td>4</td>
</tr>
<tr>
<td>'87-96</td>
<td>8</td>
</tr>
</tbody>
</table>
Prevalence of Type 2 Diabetes in Pima Indians aged 20-39yrs by Birth Weight

Age-Adjusted Birth Weight (g)

Prevalence of diabetes (%)

<2500: 30%
-3000: 20%
-3500: 15%
-4000: 10%
-4500: 15%
>4500: 30%
Parental Risk of Diabetes according to birth weight of children

Lindsay, RS et al, Diabetes 49:445-449, 2000
Prevalence of Type 2 Diabetes and Infant Feeding

* Adjusted for age, sex, birth date, obesity, birth weight, parental diabetes and maternal diabetes in pregnancy

**Breast Fed**
- > 2 months
- Never

**Odds Ratio** = 0.42
(95% CI = 0.18-0.96)
Prevalence of Diabetes in 5-19 year old Pima Children by Relative Weight
Cumulative Incidence of Nephropathy by Age at Diagnosis and Attained Age

Incidence (%) vs. Attained Age (years)

Age at Diagnosis
- 15-24
- 25-34
- 35-44
Death rates in Pima Indians with onset of diabetes <20 years

- Deaths/1000 pyrs
- Age (years)

- Diabetes
- No diabetes
Consequences of youth-onset type 2 diabetes

- Pregnancies are likely to be diabetic pregnancies
- Children will develop diabetes at an early age
- High likelihood of vascular complications by 30-40 years of age
- Likely to develop ESRD in the 40 year age range
- Premature mortality
Prevention
Diabetes Incidence Rates by Ethnicity (DPP)

Cases per 100 person-yr

- **Lifestyle**
- **Metformin**
- **Placebo**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Cases per 100 person-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (n=1768)</td>
<td>8.0</td>
</tr>
<tr>
<td>African American (n=645)</td>
<td>8.0</td>
</tr>
<tr>
<td>Hispanic (n=508)</td>
<td>12.0</td>
</tr>
<tr>
<td>American Indian (n=171)</td>
<td>12.0</td>
</tr>
<tr>
<td>Asian (n=142)</td>
<td>8.0</td>
</tr>
</tbody>
</table>
Ongoing Intervention studies

• DPPOS
• Look AHEAD
• Early intervention in prevention of renal disease
Some Achievements from the Pima Indian Study

- Identified phenotypic (and etiologic) differences in Type 1 (IDDM) and Type 2 diabetes mellitus

- Established criteria for definition and diagnosis of diabetes mellitus (Now the International Criteria)
Some Achievements from the Pima Indian Study

- Established obesity as a major risk factor for type 2 diabetes
- Established importance of insulin resistance as a key feature of Type 2 diabetes
- Demonstrated that blood pressure predicts development and progression of diabetic retinopathy and nephropathy
Some Achievements from the Pima Indian Study

- Demonstrated that intrauterine environment programs the development of obesity and diabetes in offspring
- Established nature of relationships of diabetes to low and high birth-weight
- Established that infant feeding practice is an important determinant of diabetes risk
- Established that type 2 diabetes can be prevented or delayed by lifestyle intervention or metformin
- Identified several genetic loci that confer genetic susceptibility to diabetes
Pima Indians of the Gila River Indian Community have contributed enormously to knowledge and understanding of the causes of Type 2 diabetes and its complications, ways in which the disease is now treated, and possible ways by which it may be prevented.
Guidelines for successful community-based programs

- Address a problem that community perceives as important
- Discuss ideas with community leaders
  - Ask for their suggestions
  - Become aware of local cultural sensitivities
- Obtain appropriate community approval and endorsement beyond the IRB
  - E.g. Tribal council
Guidelines for successful community-based programs

• Engage local community members in the work to the greatest extent possible
• Start slowly (and simply) to build confidence
• Explain the goals and procedures to participants in simple understandable language—best done by a local community member
• Try to provide a “service” to the community that is not readily available
• Provide feedback to participants and the community—never enough
Guidelines for successful community-based programs

• Be prepared for delays in approval process
• Can the work be done in conjunction with or as a component of other ongoing activities?
Thank you