Reducing Acute and Chronic Events from Diabetes
Jaime A. Davidson, MD, FACP, MACE
Prof. of Medicine
Division of Endocrinology, Diabetes and Metabolism
Touchstone Diabetes Center
Agenda

- The problem: diabetes trends, terminology, etc
- The patho-physiology
- Differences and similarities in DM2
- Clinical trials in Latino/Hispanic populations
- Conclusions
Agenda

- The problem: diabetes trends, terminology, etc
- The patho-physiology
- Differences and similarities in DM2
- Clinical trials in Latino/Hispanic populations
- Conclusions
The Global Burden of Diabetes

For the first time in the history of mankind non-communicable diseases have become the leading cause of global mortality and morbidity (60%).

Diabetes is now responsible for 3.2 million deaths each year and it has overtaken HIV/AIDS which is responsible for 3 million deaths per year (WHO 11 May 2004)

BMJ 2009;339:b2857
Health care burden associated with diabetes in United States

- Most common cause of end-stage renal disease (ESRD) in adults
- Most common cause of blindness
- Most common cause of amputations
- 2–5-Fold increased risk for CVD

In the aggregate, costs attributed to diabetes total more than $174 billion dollars per year.*

Prevention! Prevention!

Primary and Secondary
Actual and Projected Diagnosed Diabetes in the United States, 1990-2050

Type 2 Diabetes in Younger Adults

- Increasing
- Serious
- 25-30% requiring insulin
- Direct costs as high as T1D
- Early onset complications
- Cultural and economic implications
Causes of death in people with diabetes (USA)

- Ischemic heart disease: 40%
- Other heart disease: 15%
- Diabetes: 13%
- Malignant neoplasms: 13%
- Cerebrovascular disease: 10%
- Pneumonia/influenza: 4%
- All other: 5%

Diabetes: worst treated US illness

Percentage NOT receiving recommended care

- Diabetes: 55%
- Colorectal cancer: 46%
- Congestive heart failure: 36%
- High blood pressure: 35%
- Coronary artery disease: 32%

Opportunity to Improve US Diabetes Treatment Standards

“The age-adjusted death rate for diabetes in the USA has increased 30% since 1980.”

The Lancet, Vol. 356, August 26, 2000
Type 2 diabetes is already a major healthcare burden

4 + Million

The number of deaths annually from diabetes¹

5-10 years

The average reduction in life expectancy of a person with type 2 diabetes¹

US$58 billion

The economic burden of lost productivity due to type 2 diabetes in the USA alone²

1. World Heart Federation Fact Sheet on Diabetes and Cardiovascular Disease
Is it a new Problem? NO!
Prevalence of Diabetes in US by Ethnic Groups

Males/Females age 45-74 years

- European
- Asian-American
- Japanese-American
- African-American
- Mexican-American
- Cuban-American
- Pimas

Harris et al, Diabetes 1987; 36:523
Fujimoto et al, Diabetes 1987; 36:721
Flegal et al, Diabetes Care 1991; 14:628
Knowler et al, Diabetes Care 1993; 16:216
Latino/Hispanics in the United States

- Fastest growing minority group
- Beginning in 1996, the growth of Latino children surpassed African American children
- Combining US born Latinos, with legal Latino residents and temporary workers plus those without proper documentation, the number exceeds 70 million, making the United States the third largest Latino country in the World
Changes in US Ethnicity Pattern 1997 to 2000: Latino-Hispanics are the Emerging Minority

Absolute change in percentage of total populations

- White
- Latino
- African-American
- Native-American, Eskimo, Aleut
- Asian and Pacific


Percent of Population 1980
Hispanic or Latino

Source: U.S. Census Bureau, Decennial Census, 1980
Latinos? SI!!!
USA Advertising expenses:

<table>
<thead>
<tr>
<th>Category</th>
<th>Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast food</td>
<td>US$ 3.5 billion</td>
</tr>
<tr>
<td>Food, confectionary and beverages*</td>
<td>US$ 5.8 billion</td>
</tr>
<tr>
<td>*incl. $785.5 for top 5 soda brands</td>
<td></td>
</tr>
<tr>
<td>Automobile industry</td>
<td>US$ 15.5 billion</td>
</tr>
<tr>
<td>Total</td>
<td>US$ 24.8 billion</td>
</tr>
</tbody>
</table>

versus

USA 2001 Budgets for:

<table>
<thead>
<tr>
<th>Agency</th>
<th>Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>US$ 5.1 billion</td>
</tr>
<tr>
<td>FDA</td>
<td>US$ 1.3 billion</td>
</tr>
<tr>
<td>Total</td>
<td>US$ 6.4 billion</td>
</tr>
</tbody>
</table>

Welch, Diabetes Care, 2003
Agenda

- The problem: diabetes trends, terminology, etc
- The patho-physiology
- Differences and similarities in DM2
- Clinical trials in Latino/Hispanic populations
- Conclusions
## There Are 3 Main Types of Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 2</th>
<th>Type 1</th>
<th>Gestational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typically over/ obese</td>
<td>Typically lean (but not always)</td>
<td>Usually overweight/ obese</td>
<td></td>
</tr>
<tr>
<td>Usually older than 40 but increasingly found in young people</td>
<td>Half younger than 20, half older than 20 at diagnosis</td>
<td>Pregnant women</td>
<td></td>
</tr>
<tr>
<td>Slow onset</td>
<td>Abrupt onset</td>
<td>Diagnosed during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Usually do not need insulin at diagnosis (but often need it later)</td>
<td>Always need insulin</td>
<td>Treated with diet/exercise or insulin, depending on severity</td>
<td></td>
</tr>
<tr>
<td>Often have family history</td>
<td>Frequently have family history</td>
<td>Increases risk of type 2 diabetes later in life</td>
<td></td>
</tr>
<tr>
<td>Asians, Blacks, Latinos, at higher risk</td>
<td>Most patients white</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HLA genetic markers or islet antibodies</td>
<td>Positive for genetic markers and/or antibodies</td>
<td>No HLA genetic markers or islet antibodies</td>
<td></td>
</tr>
<tr>
<td>90% to 95% of diabetic population</td>
<td>1% to 5% of diabetic population</td>
<td>4% of pregnant women except minorities (Latinas 10 %+)</td>
<td></td>
</tr>
</tbody>
</table>
Pathogenesis of Type 2 Diabetes: An Evolving Concept

- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Increased HGP
- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Decreased Incretin Effect

Result: Hyperglycemia
At what age does it start?
Adolescent Obesity and Metabolic Impairment

Control
- n=20
- Age=12 y
- BMI=18 kg/m²
- Wt (kg)=42

Overweight
- n=31
- Age=12 y
- BMI=24 kg/m²
- Wt (kg)=57

Moderately Obese
- n=244
- Age=13 y
- BMI=33 kg/m²
- Wt (kg)=86

Severely Obese
- n=195
- Age=11 y
- BMI=41 kg/m²
- Wt (kg)=100

BMI=body mass index.
Metabolic Characteristics: Glucose

Control Overweight Moderately Obese Severely Obese

85 86 87 88 89 90 91 92

85 86 87 88 89 90 91 92
Metabolic Characteristics: Insulin
Triglycerides

- **Total**
  - Control: 48
  - Overweight: 83
  - Moderately Obese: 104
  - Severely Obese: 97

- **Black**
  - Overweight: 77
  - Moderately Obese: 77
  - Severely Obese: 78

- **Latino**
  - Overweight: 99
  - Moderately Obese: 99
  - Severely Obese: 106
### HDL-Cholesterol

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Black</th>
<th>Latino</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>58</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Overweight</td>
<td>47</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>Moderately</td>
<td>41</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Severely Obese</td>
<td>40</td>
<td>43</td>
<td>38</td>
</tr>
</tbody>
</table>
Systolic Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Black</th>
<th>Latino</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>116</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately Obese</td>
<td>121</td>
<td>125</td>
<td>117</td>
</tr>
<tr>
<td>Severely Obese</td>
<td>124</td>
<td>124</td>
<td>120</td>
</tr>
</tbody>
</table>
Agenda

- The problem: diabetes trends, terminology, etc
- The patho-physiology
- **Differences and similarities in DM2**
- Clinical trials in Latino/Hispanic populations
- Conclusions
# Early vs Late Intervention in Type 2 Diabetes

Early diagnosis and intensive glucose control therapy from the start are the key to long-term risk reduction in diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Goal: FPG &lt;108 mg/dL</th>
<th>N=4209</th>
<th>Newly diagnosed with T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS 80</td>
<td>Intervention endpoint: 7.0%</td>
<td>17 yr</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Follow-up: 7.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.5% from BL in 3 months

Macrovascular Benefit

No

Yes

Lasting Benefits of Early, Intensive Intervention: UKPDS “Legacy Effect”

<table>
<thead>
<tr>
<th>Any Diabetes Endpoint</th>
<th>Microvascular Disease</th>
<th>Myocardial Infarction</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>-12</td>
<td>-25</td>
<td>-16</td>
<td>-6</td>
</tr>
<tr>
<td>( P=0.029 )</td>
<td>( P=0.0099 )</td>
<td>( P=0.052 )</td>
<td>( P=0.44 )</td>
</tr>
<tr>
<td>-9</td>
<td>-24</td>
<td>-15</td>
<td>-13</td>
</tr>
<tr>
<td>( P=0.040 )</td>
<td>( P=0.001 )</td>
<td>( P=0.014 )</td>
<td>( P=0.007 )</td>
</tr>
</tbody>
</table>

Mortality Risk from the ACCORD Study

Conventional
Intensive

Lessons?

ADA 2011
Inert, esp. in relation to effort, movement, action, and similar; inactivity; laziness.*

* Diccionario Webster
At insulin initiation, the average patient had
• 5 years with HbA$_1c$ >8%
• 10 years with HbA$_1c$ >7%

Meta-analysis: Improved Glucose Reduction in Macro-vascular Events

Meta-analysis of Randomized Clinical Trials: Conventional vs Intensive Interventions

**Macrovascular**
- T1DM (8 randomized studies)
- T2DM (6 randomized studies)

**Cardiovascular**
- T1DM (8 randomized studies)
- T2DM (6 randomized studies)

**Periferal Vascular**
- T1DM (8 randomized studies)
- T2DM (6 randomized studies)

**Cerebrovascular**
- T1DM (8 randomized studies)
- T2DM (6 randomized studies)

**T1DM N = 1800**
**T2DM N = 4472**

**Combined Incidence**
- Any macrovascular event
  - T1DM 0.38 (95% CI, 0.26-0.56)
  - T2DM 0.81 (95% CI, 0.73-0.91)

Retinopathy* in Type 2 Diabetes
Prevalence in U.S. Adults Aged ≥ 40Yrs

* Any retinopathy in patients with diagnosed type 2 diabetes.
Diabetic Retinopathy

Impact

- Leading cause of new blindness in the US (5,000 cases a year)
- Leading cause of blindness worldwide (30,000-40,000 cases a year)
- $75 million annual cost in terms of health care and time lost from work
Measuring the Meaning of Vision Loss

Severe vision loss:
- <5/200 on 2 consecutive visits
- No letters can be read

Legal blindness:
- 20/200

At 20/80 patients have trouble reading and cannot drive in many states

Moderate vision loss:
- 3-line loss (15 letters)
- Eg, 20/20 declines to 20/40

Normal vision: 20/20
- From 20 feet, patient can read this line on chart

Impact of Vision Loss

Visual acuity:

Normal: 20/20

Severe Vision Loss: 5/200

Legal blindness: 20/200

Moderate Vision Loss: 20/40

Images: Courtesy of Daniel Palanker, PhD
Nontraumatic Lower Extremity Amputation and Type 2 Diabetes

Clinical Syndromes of DM Neuropathy
Neuropathic Ulcers

- Major source of morbidity
- Caused by loss of protective sensation and repetitive trauma (i.e. walking)
- Occur over areas of increased pressure (i.e. metatarsal heads or under calluses)
- Hammer-claw toe deformity of foot causes increased pressure on metatarsal heads
Social and Economical Issues

- Social
  - False disease beliefs and perceptions
  - Cultural idiosyncrasies
  - Language differences
  - Practitioner bias, prejudice, stereotyping
  - Geographic variations in clinical practice
  - Health insurance
  - Accessibility of services
Why More Complications?

- Language barriers: 25% of us do not speak English; communication is a big problem
- Distrust of health care providers that are not Latinos
- Economics may be a factor, if you do not ask how can you know
- Different health care beliefs
  - Symptom improvement equals a cure, so patients discontinue drug use
  - More medications = worsening of the condition
The problem: diabetes trends, terminology, etc
The patho-physiology
Differences and similarities in DM2
Clinical trials, etc in Latino/Hispanic populations
Conclusions
Economic Issues

- Economic
  - Funding
  - Accessibility of services
  - Medical insurance

Photo credit: US Census Bureau
Clinical Trials in Latinos

- Are you expecting lots of references
- Are you expecting significant differences
- Have you heard “We can not entice minority patients to participate in clinical trials”
- The most representative Latino in the US is from Mexican origin, would you be satisfied with trials done in Mexico
Clinical Trials in Latinos

- Rosiglitazone added to Glyburide treated patients inadequately controlled with SU monotherapy
- 144 patients enrolled for a 24 w multicenter, randomized trial
- Basal A1c 9.4%
- A1c reduction 1.5%
- 25.8% (Gly+Rosi) achieved an A1c <7% compared with placebo (Gly+Placebo) 1.4%
- Most common side effect edema and weight gain

*A 24 w, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and tolerability of combination therapy with rosiglitazone and sulfonylurea in African American and Hispanic American patients with type 2 diabetes inadequately controlled with sulfonylurea monotherapy.
Davidson JA et al Clin Ther 29(9):1900-14, 2007*
Insulin

- Several trials indicating the following
- Higher A1c levels at the initiation of the study
- Less patients achieving targets of <7% (40% vs 53% for Caucasians)
- Insulin requirements usually higher
- A1c lowering greater than Caucasians (-2.17% vs 1.84%) as expected for a greater A1c at baseline

Impact of race/ethnicity on the efficacy and safety of commonly-used insulin regimens: a post hoc analysis of clinical trials in Type 2 diabetes
Davidson JA et al. Endocrine Practice;16:818-28, 2010
Agenda

- The problem: diabetes trends, terminology, etc
- The patho-physiology
- Differences and similarities in DM2
- Clinical trials in Latino/Hispanic populations
- Conclusions
No Difference In Complications When Good Control Is Achieved

- **San Luis Valley Study: Caucasian and Latino (n=279)**
  - Similar glucose control in both study groups
  - Similar severity of retinopathy, nephropathy and diabetic neuropathy

- **Cruickshanks and Alleyne: Caucasian + African-Caribbean (n=131)**
  - After adjusting for duration of diabetes, there were no differences in total background retinopathy or other complications between the study groups

Glucose Control Matters In All Patients!

Hamman RF et al. *Diabetes*. 1989; 38;1231.
Solutions

Together we can work and improve the problem

It is OUR PROBLEM!
Summary and Conclusions

- Type 2 diabetes and its complications are highly prevalent in the US Latino population and other minorities.
- Increasing occurrence in Latino children and adolescents.
- Cultural sensitivity important for improvement.
- Prevention and early detection, early and aggressive therapy critical.
- Barriers must be identified and overcome.
- More research is urgently needed, very few clinical trials target the US Latino community.