Type 1 DM, 2015-
No Longer a Disease of Youth

Dace Trence, MD
April, 2015
Epidemiological Data

- Type 2 diabetes mellitus remains dominant form
- Overall incidence of type 1 diabetes increasing by 2–5% per year worldwide
- As a result of improved diabetes management, an increased proportion of individuals with type 1 diabetes are living into later decades of life


Gale EM. Diabetes 51:3353-3361, 2002
Cumulative incidence of diabetes from three U.K. birth cohorts. Progressive left shift in age of onset of the disease

- Type 1 diabetes is commonly diagnosed in childhood
- ~25% of people with type 1 diabetes are diagnosed as adults
- Some even as late as the ninth decade of life

Gale EM. Diabetes 51:3353-3361, 2002

Three Year Follow-Up in Kronenberg, Sweden

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Kronoberg All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>New cases</td>
</tr>
<tr>
<td>Years</td>
<td>n</td>
</tr>
<tr>
<td>Type 1</td>
<td>At risk</td>
</tr>
<tr>
<td>0–9</td>
<td>20 493</td>
</tr>
<tr>
<td>10–19</td>
<td>22 686</td>
</tr>
<tr>
<td>20–29</td>
<td>21 949</td>
</tr>
<tr>
<td>30–39</td>
<td>22 749</td>
</tr>
<tr>
<td>40–49</td>
<td>23 332</td>
</tr>
<tr>
<td>50–59</td>
<td>23 970</td>
</tr>
<tr>
<td>60–69</td>
<td>17 017</td>
</tr>
<tr>
<td>70–79</td>
<td>15 150</td>
</tr>
<tr>
<td>80–100</td>
<td>9 756</td>
</tr>
<tr>
<td>0–19</td>
<td>43 179</td>
</tr>
<tr>
<td>20–100</td>
<td>133 923</td>
</tr>
<tr>
<td>0–100</td>
<td>177 102</td>
</tr>
<tr>
<td>0–39</td>
<td>87 877</td>
</tr>
<tr>
<td>40–100</td>
<td>89 225</td>
</tr>
</tbody>
</table>

Type 1 Diabetes: What have we learned?

- Can occur at any age (NOT “juvenile-onset”)
- Can occur in overweight people
- Best identified using immune and genetic markers
  - Immune markers: GAD, ICA-512, IAA, ZnT8
  - Genetic markers: high-risk, no-risk and low-risk HLA types
- Long pre-clinical period

Natural History of Type 1 DM

Genetic risk

Environmental Insult

Autoimmune attack

Normal islet function

Onset clinical diabetes

“preclinical period”

TIME (months or years)
22 y/o: brother type 1 DM serial testing with glucose load 1980-1986

C-peptide

- Commonly present early in course of Type 1
- In adulthood, better clinical outcomes and can achieve lower A1C levels with less serious hypoglycemia than without detectable C-peptide concentrations

Predictive Value of Developing Type 1 DM

Goals of Treatment

- Short Term:
  - Symptom control-
    - Fatigue, weight loss, polyuria, polydipsia
  - Frequent infections: Yeast, UTI, skin
  - Metabolic stability-
    - Diabetic ketoacidosis
    - Sensorium changes
    - Coma

- Long term:
  - Prevent complications
    - Microvascular: eye, kidney, nerve
    - Macrovascular: CVD

**A1C Targets Suggested by Different Organizations**

Optimal target: A1C <6% (normal range)

- **AACE target:** A1C <6.5%
- **EASD target:** A1C <6.5%
- **ADA target:** A1C <7% (general)
  A1C <6%* (individual patient)

*As close to normal (<6%) without significant hypoglycemia.

**Barrier: hypoglycemia!!!!!**

ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes, AACE = American Association of Clinical Endocrinologists.

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**Diabetes Complications and Control Trial:**

**DCCT: study design**

![DCCT study design diagram](image)

DCCT. NEJM 1993;29:977-86
Intensive Therapy Reduces Risk of Retinopathy and Nephropathy

DCCT: treatment conditions

Conventional group (n = 730):
- Aim: to avoid symptoms of hyper / hypoglycaemia
- 1 or 2 insulin injections per day
- Daily self-monitoring
- Initial diet and exercise education
- Quarterly visits

Intensive group (n = 711):
- Aim: symptom-free + plasma glucose 3.9-6.7 mmol/L before meals, < 10 mmol/L after meals, > 4.0 mmol/l at 03.00 a.m. and HbA1c < 6.5%
- ≥ 3 insulin injections / day or insulin pump
- ≥ 4 daily blood glucose tests
- Hospitalisation for initiation
- Comprehensive education programme
- Frequent dietary instructions
- Monthly clinic visits

DCCT: intensive therapy significantly reduces and maintains HbA$_{1c}$

Intensive
Conventional

Conventional group encouraged to switch to intensive treatment

DCCT  Year

DCCT end EDIC


DCCT: intensive therapy reduces microvascular complications

Retinopathy: 76% reduction
Microalbuminuria*: 34% reduction

Intensive
Conventional

Patients (%)

Patients (%)

Years

Adapted from: N Engl J Med 1993;329:977–86

*urinary albumin excretion ≥10 mg per 24 hours
Therapy and Cardiovascular Complications

Swedish Registry 1998-2011:
Type 1 DM, mean age 36 at entry

DCCT/EDIC Study mortality data

- 27 year follow-up data
- Relatively few deaths
- Better glycemic control protects - “metabolic memory”
- Most deaths due to CVD, with added risk if smoking, diabetes dx a later age, renal dysfunction

JAMA 2015;313:45-53.

DCCT: the price of improved diabetic control – hypoglycaemia

Adapted from: N Engl J Med 1993;329:977–86
Risk of Hypoglycemia among Frequently Used Conventional Agents

For All Therapies, the Significance of Differences between Levels Is $p<0.0001$

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Percentage of Patients Reporting ≥1 Hypoglycemic Event per Year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet Alone</td>
<td>0.8%</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.7%</td>
</tr>
<tr>
<td>SU</td>
<td>7.9%</td>
</tr>
<tr>
<td>Basal Insulin only</td>
<td>21.2%</td>
</tr>
<tr>
<td>Basal + Bolus Insulin</td>
<td>32.6%</td>
</tr>
</tbody>
</table>

SU = sulfonylurea.

Hypoglycemia Is Common in Patients Treated with Insulin

- T1DM (N=294):
  - 0.9 episodes/year
  - 87.9% non-severe hypoglycemia
  - 0.3 episodes/year
  - 18.2% severe hypoglycemia

- T2DM BT (N=179):
  - 0.3 episodes/year
  - 42.1% non-severe hypoglycemia

- T2DM BBT (N=95):
  - 0.3 episodes/year
  - 29.6% non-severe hypoglycemia

- T2DM Other (N=62):
  - 0.4 episodes/year

Patients aged >15 years reporting hypoglycemia to a general practitioner or specialist in Spain (N=630). BBT = basal-bolus insulin therapy; BT = basal insulin therapy; Other = other insulin regimen (eg, premixed insulin therapy).
**Classification of Hypoglycemia**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycemia</td>
<td>Assistance required from another person to administer CHO, glucagon, or other resuscitative measure. In the absence of measured plasma glucose, neurological recovery following resuscitative measures is considered sufficient evidence that the event was induced by hypoglycemia.</td>
</tr>
</tbody>
</table>
| Documented symptomatic hypoglycemia | Typical symptoms of hypoglycemia with measured plasma glucose ≤ 70 mg/dL.  
| Asymptomatic hypoglycemia | No symptoms of hypoglycemia, but measured plasma glucose ≤ 70 mg/dL.  
| Probable symptomatic hypoglycemia | Typical symptoms of hypoglycemia, but no measured plasma glucose available.  
| Relative hypoglycemia     | Typical symptoms of hypoglycemia, with measured plasma glucose > 70 mg/dL.  

All degrees of hypoglycemia should be considered as serious.

CHO, carbohydrate

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**Asymptomatic Hypoglycemia May Go Unreported**

- In a cohort of patients with diabetes, more than 50% had asymptomatic (unrecognized) hypoglycemia, as identified by continuous glucose monitoring
- Other researchers have reported similar findings

How Often Does Hypoglycemia Occur in Diabetes?

Survey 409 US patients with T1DM (n = 200) and with T2DM (n = 209)


Hypoglycemia in the over 65 y/o with T2DM

Review of hospitalizations for hyper, hypoglycemia for 1999-2011 in Medicare population

When Does Hypoglycemia Occur with Diabetes?

1/5 of all nonsevere hypoglycemia occurs nocturnally

Survey 409 US patients with T1DM (N=200) and with T2DM (N=209)

Economic Consequences of Hypoglycemia

Retrospective analysis of 536,581 patients with type 2 diabetes from 2004 to 2008 showed hypoglycemia cost over $52 million

Bron M, et al. 71st Scientific Sessions of the ADA; 2011 June 24-28; San Diego, CA; Abstract# 1175-P.
Clinical Consequences of Hypoglycemia

- Hospital admissions
  - In a prospective study of well-controlled elderly T2DM patients, 25% of hospital admissions for diabetes were for severe hypoglycemia
- Increased mortality
  - 9% in a study of severe sulfonylurea-associated hypoglycemia
- Road accidents caused by hypoglycemia
  - 45 serious events per month

Testing Made Small and Simple

<table>
<thead>
<tr>
<th># of Readings</th>
<th>48 %</th>
<th>24 %</th>
<th>44 %</th>
<th>24 %</th>
<th>4 %</th>
<th>2 %</th>
<th>2 %</th>
<th>2 %</th>
<th>2 %</th>
<th>2 %</th>
<th>Aggregate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>375</td>
<td>341</td>
<td>329</td>
<td>264</td>
<td>264</td>
<td>264</td>
<td>264</td>
<td>264</td>
<td>264</td>
<td>264</td>
<td>375</td>
</tr>
<tr>
<td>75th Percentile</td>
<td>318.50</td>
<td>311.75</td>
<td>318.75</td>
<td>249.50</td>
<td>249.50</td>
<td>249.50</td>
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<td>249.50</td>
<td>249.50</td>
<td>249.50</td>
<td>316.00</td>
</tr>
<tr>
<td>Median</td>
<td>287.50</td>
<td>302.00</td>
<td>308.50</td>
<td>235.00</td>
<td>235.00</td>
<td>235.00</td>
<td>235.00</td>
<td>235.00</td>
<td>235.00</td>
<td>235.00</td>
<td>285.50</td>
</tr>
<tr>
<td>25th Percentile</td>
<td>259.00</td>
<td>284.00</td>
<td>298.25</td>
<td>220.50</td>
<td>220.50</td>
<td>220.50</td>
<td>220.50</td>
<td>220.50</td>
<td>220.50</td>
<td>220.50</td>
<td>276.50</td>
</tr>
<tr>
<td>Minimum</td>
<td>169</td>
<td>150</td>
<td>266</td>
<td>206</td>
<td>206</td>
<td>206</td>
<td>206</td>
<td>206</td>
<td>206</td>
<td>206</td>
<td>150</td>
</tr>
<tr>
<td>Mean</td>
<td>290</td>
<td>296</td>
<td>308</td>
<td>235</td>
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<td>235</td>
<td>235</td>
<td>235</td>
<td>235</td>
<td>235</td>
<td>291</td>
</tr>
<tr>
<td>Std Dev</td>
<td>45.21</td>
<td>38.19</td>
<td>20.51</td>
<td>29.00</td>
<td>29.00</td>
<td>29.00</td>
<td>29.00</td>
<td>29.00</td>
<td>29.00</td>
<td>29.00</td>
<td>42.73</td>
</tr>
</tbody>
</table>

Events
- Hypo (<60)
  - 0
- Hyper (>180)
  - 23

Above Target(<140)
- 100% 24%
- 100% 22%
- 100% 2%
- 100% 2%
- 100% 2%
- 100% 2%

On Target(100-140)
- 0%
- 0%
- 0%
- 0%
- 0%
- 0%
- 0%

Below Target(<100)
- 0%
- 0%
- 0%
- 0%
- 0%
- 0%
- 0%
Physiologic Insulin Secretion

Insulin

- Basal: background
- Bolus: prandial or combined with correction
- Correction: with prandial or independent

1960s to 1970s: The Evolution of Physiologic Insulin Replacement
Physiologic Insulin Replacement

Morning Afternoon Evening Night

INSULIN EFFECT

REG basal

prandial

LISPRO (aspart, glulys) REG NPH/Lente

B L S HS B

MEALS

Type I Diabetes (Trence), NWGEC Spring 2015
**Insulin Effect**

<table>
<thead>
<tr>
<th>Morning</th>
<th>Afternoon</th>
<th>Evening</th>
<th>Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro/Aspart/glulys</td>
<td>Lispro/Aspart/GL</td>
<td>Lispro/Aspart/GL</td>
<td>Insulin Glargine</td>
</tr>
</tbody>
</table>

**Insulin Pens**

- More convenient than traditional vial/syringe
- Easier to use for those with visual/motor skill impairments
- Less injection pain (Needles not dulled by insertion into vial before insertion into the skin)
- Most insurance companies covering insulin pens
- But more expensive! (2 X)

INSULIN EFFECT

Morning Afternoon Evening Night

Bolus Bolus Bolus

CSII with LISPRO/ASPART

Basal Infusion

MEALS

B L S HS B
Continuous glucose monitoring

Moving to a New Era…

Continuous Glucose Monitoring

Time

Glucose (mg/dL)

0 50 100 150 200 250 300 350 400

9:00 11:00 13:00 15:00 17:00 19:00 21:00 23:00 1:00 3:00 5:00 7:00 9:00

Type I Diabetes (Trence), NWGEC Spring 2015
DexCom SC Glucose Sensor

Slowly Closing the Loop…
1 month CGM: ave 141/ SD64
6 months CGM: 123/49

Week 1 on sensor-augmented pump
Mean = 162

Week 2 on sensor-augmented pump
Mean = 115
Complications of Diabetes

- Hyperglycemia
- Chronic microvascular macrovascular
- Diabetic ketoacidosis
- Infections: urinary, vaginal, skin

**Retinopathy:**
Most common cause blindness in US
15 yrs DM 1, 50% have more severe form DR
20 yrs DM 2, on insulin, 20% have PDR
Screening:
DM 1, 5 yrs post diagnosis but after puberty
DM 2, yrly, if photos normal, then q 4yrs
unless proteinuria, severe hyperglycemia
Diabetic retinopathy
Neovascularization
Hemorrhage

Diabetic retinopathy
Neovascularization
Meta-analysis: Diabetic Retinopathy Outcomes in Studies Before, After 1985

Data from studies reporting outcomes after four years


Nephropathy:

- 30-40% DM 1 will develop
- 5-10% DM 2 develop
- Protein in urine earliest marker
- Microalbumin (albumin/creatinine ratio)
- False positives: exercise
  - UTI
  - large protein intake
  - HTN

Challenges in the Management of Type 1 Diabetes in Older Adults

- Type 1 Diabetes (T1D) Exchange clinic registry reported characteristics of older adults with type 1 diabetes followed in diabetes centers across US.
- 50 to < 65 years (n = 2,066), mean A1C 7.7% (27% had an A1C < 7.0%, 46% had an A1C < 7.5%, and 11% had an A1C ≥ 9.0%), mean self-reported blood glucose testing was 5.5/day.
- ≥ 65 years of age (n = 683), mean A1C 7.4% (34% A1C < 7.0%, 52% A1C < 7.5%, and 8% had A1C ≥ 9.0%)
- Mean self-reported blood glucose testing 5.6 times daily.

Dhaliwal R et al Diabetes Spectrum 2014; 27,

- Greater frequency of self-monitoring of blood glucose (SMBG) associated with lower A1C levels in both those who used an insulin pump vs insulin via injections.
- Diabetic ketoacidosis (DKA) was lower with increasing age and was not associated with duration of diabetes.
- DKA was more likely in those with higher A1C levels and lower socioeconomic status.
- No relationship between DKA and pump versus injection use.
Hypoglycemia

- Severe hypoglycemia, defined as an episode requiring assistance for treatment, has been associated with cardiac abnormalities including arrhythmias and brain damage.
- Hypoglycemia unawareness or poor awareness are major risk factors for severe and recurrent hypoglycemia in type 1 diabetes and are of particular concern in the elderly because of increased risk of falls, cognitive impairments, and cardiovascular disease.
- With aging and long duration of diabetes, there is impairment of counterregulatory hormone release.
- Confusion, dizziness, falling, weakness, difficulty with communication, and poor coordination and balance may not be recognized as possible symptoms of hypoglycemia.

- T1D Exchange: 18.6% with diabetes ≥ 40 years of age (n = 758) self-reported having had a seizure or loss of consciousness in previous 12 months.
- Duration of DM associated with occurrence of severe hypoglycemia, also lower education status, lower household income, lack of private insurance, and race (greater in non-Hispanic blacks and Hispanics than in non-Hispanic whites).
- Injection users had more severe hypoglycemia than pump users.
- Self-reported severe hypoglycemia lowest with mean A1C 7.0–7.5%.
U.K. Hypoglycemia Study

- 46% prevalence over 12 months of severe hypoglycemia in adults with type 1 DM of > 15 yrs’ duration (mean age 53 years, A1C 7.8%).
- Severe hypoglycemia more common in presence of nephropathy, neuropathy, and depression and with the use of nonselective β-blockers and alcohol.

Recent study of adults ≥ 69 yrs (both type 1 and 2 with an A1C > 8%)
- 72 hours of continuous glucose monitoring (CGM), 65% experienced hypoglycemia at least once.

Arch Intern Med 2011;171:362–364,
### Challenges specific to older adults:

| Cognitive dysfunction | · Screening for cognitive impairment (e.g., Mini-Mental State Exam, Mini-Cog)  
· Screening for adverse effects of medications  
· Laboratory testing (screening for vitamin B₁₂ deficiency and hypothyroidism)  
· Consideration of structural neuroimaging | · Cognitive aids  
· Audio reminders (e.g., devices with alarms)  
· Visual reminders (e.g., dry erase board for refrigerator)  
· Simplification of medication regimen  
· Assistance with insulin administration  
· Consideration of fixed mealtime insulin dosing (if eating is reliable and consistent meals can be provided) |

| Chronic pain | · History  
· Physical examination | · Adequate pain management |

| Vision impairment | · Vision assessment  
· Eye examination by eye care professional | · Use of assistive devices (e.g., talking meter, magnifier fitted for syringe or pump screen, or hand or wallet magnifier)  
· Use of insulin pens (count clicks for dosing)  
· Improved lighting  
· Use of vibration and memory features on pumps  
· Instruction handouts printed in large type size  
· Use of dark colored paper under the syringe or pen (to provide contrast)  
· Referral to low-vision specialist |

<p>| Hearing impairment | · Hearing assessment | · Hearing aids |</p>
<table>
<thead>
<tr>
<th>Concerns</th>
<th>Assessments</th>
<th>Possible Interventions</th>
</tr>
</thead>
</table>
| Polypharmacy      | • Review of medication list  
                       • Review of prescription plan formulary and ability to pay for medications | • Titration of medication doses (use lowest doses possible)  
                       • Discontinuation of inappropriate medications and those no longer needed  
                       • Review of possible adverse effects of medications on blood glucose and perception of hypoglycemia |
| Nutrition         | • Assessment of adequacy of diet and nutrients  
                       • Celiac screening, if indicated  
                       • Assessment of the need for carbohydrate consistency  
                       • Assessment of ability to shop and prepare meals  
                       • Assessment of ability to pay for food | • Dietary counseling  
                       • Referral to a nutritionist  
                       • Reminders for meals  
                       • Referral to social services (e.g., Meals on Wheels or in-home care) |

<table>
<thead>
<tr>
<th>Concerns</th>
<th>Assessments</th>
<th>Possible Interventions</th>
</tr>
</thead>
</table>
| Diabetes-related distress | • Assessment of nonadherence, adverse effects of medications, social issues, financial issues, and transportation concerns | • Diabetes education  
                       • Referral to diabetes educator/nurse  
                       • Increased attention by educators (more frequent visits or phone calls between office visits)  
                       • Referral to social services  
                       • Pharmacy assistance program  
                       • Pharmacy delivery program  
                       • Transportation assistance |
| Social support     | • History                                                                  | • Family meeting  
                       • Referral to social services  
                       • Stress reduction  
                       • Referral to community resources |
### Table 2. Glycemic Management of Type 1 Diabetes in Older Adults

<table>
<thead>
<tr>
<th>Health Status</th>
<th>Fasting and Preprandial Blood Glucose Goal (mg/dl)</th>
<th>Bedtime Blood Glucose Goal (mg/dl)</th>
<th>AIC Goal (%)</th>
<th>Insulin Therapy Options</th>
</tr>
</thead>
</table>
| Healthy (few chronic illnesses and intact cognition and functional status) | 90–130 | 90–150 | < 7.5 | • MDI  
• CSII  
• CSII-CGM |
| Frail Complex/intermediate health (several chronic illnesses or mild to moderate cognitive impairment or two or more instrumental ADL deficits) | 90–150 | 100–180 | < 8.0 | • MDI  
• CSII  
• CSII-CGM  
• Fixed dose |
| Poor health (end-stage chronic disease(s) or moderate to severe cognitive impairment or two or more ADL deficits) | 100–180 | 110–200 | < 8.5 | • MDI  
• Fixed dose |
| Long-Term Care Facility Residents | 100–180 | 110–200 | < 8.5 | • MDI  
• Fixed dose |

ADL - activities of daily living; CSII - continuous subcutaneous insulin infusion; MDI - multiple daily injections.

### Table 3. Management of Cardiovascular Risk Factors in Older Adults With Type 1 Diabetes

<table>
<thead>
<tr>
<th>Health Status</th>
<th>Blood Pressure (mmHg)</th>
<th>Lipids (LDL goal &lt; 100 mg/dl in general; &lt; 70 mg/dl in those with cardiovascular disease)</th>
<th>Aspirin Therapy (75–162 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (few chronic illnesses and intact cognition and functional status)</td>
<td>&lt; 140/80</td>
<td>Statin therapy recommended unless contraindicated or not tolerated</td>
<td>Recommended for secondary prevention and for primary prevention with one additional risk factor unless contraindicated</td>
</tr>
<tr>
<td>Frail Complex/intermediate health (several chronic illnesses or mild to moderate cognitive impairment or two or more instrumental ADL deficits)</td>
<td>&lt; 140/80</td>
<td>Statin therapy recommended unless contraindicated or not tolerated</td>
<td>Recommended for secondary prevention and for primary prevention with one additional risk factor unless contraindicated</td>
</tr>
<tr>
<td>Poor health (end-stage chronic disease(s) or moderate to severe cognitive impairment or two or more ADL deficits)</td>
<td>&lt; 150/90</td>
<td>Statin therapy recommended unless very limited life expectancy, contraindicated, or not tolerated</td>
<td>Consider benefit vs. risk from adverse effects (especially bleeding)</td>
</tr>
<tr>
<td>Long-Term Care Facility Residents</td>
<td>&lt; 150/90</td>
<td>Consider benefit with very limited life expectancy</td>
<td>Consider benefit vs. risk from adverse effects (especially bleeding)</td>
</tr>
</tbody>
</table>
Additional Concerns:

- Literacy
- Income/coverage (donut hole)
- Comprehension level
- Denial of disease
- Technology averse
- Social isolation
- Fear

“Too often we underestimate the power of a touch, a smile, a kind word, a listening ear, an honest compliment, or the smallest act of caring, all of which have the potential to turn a life around.”

— Leo Buscaglia