Hyperglycemia and Diabetic Microvascular Complications (DMC)

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Hyperglycemia and DMC: Outline

- Overview of DMC
  - Impact
  - Risk factors

- Glycemic control and DMC
  - Risk reduction benefits
  - Evidence
    - Diabetes Control and Complications Trial (DCCT)
    - United Kingdom Prospective Diabetes Study (UKPDS)
  - Recommended targets
  - Limitations

- Targeting postprandial glucose (PPG) control

- Roundtable discussion
Overview of DMC
DMC in the United States

• Nervous system damage occurs in 60% to 70% of people with diabetes
• Each year, between 12,000 and 24,000 people lose their sight as a result of diabetic retinopathy
• Diabetes is the leading cause of end-stage renal disease (ESRD)

Impact of Diabetic Neuropathy

• More hospitalizations are due to neuropathy than all other diabetic complications combined

• Diabetic neuropathy is the most common peripheral neuropathy in developed nations

• Diabetic neuropathy contributes to 50%-70% of all nontraumatic amputations in the United States

• About 82,000 nontraumatic lower-limb amputations were performed in people with diabetes in 2002

Impact of Diabetic Retinopathy

- Frequently present at diagnosis of type 2 diabetes
- Progresses, resulting in:
  - Microaneurysms
  - Retinal hemorrhages
  - Blindness
- May include diabetic macular edema (DME)
- US cost of blindness due to diabetes $500 million

Impact of Diabetic Nephropathy

• Diabetic nephropathy occurs in 20%-40% of patients with diabetes
• It is the leading single cause of end-stage renal disease (ESRD)
• Approximately 25% of people with type 1 diabetes and 5%-10% with type 2 diabetes develop ESRD
• The total estimated costs for treatment of patients with ESRD in the US was $15.6 billion in 1997

ADA. Diabetes Care. 2005;28(suppl 1):S4-S36.
## Risk Factors for DMC

<table>
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<tr>
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<tbody>
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<td><strong>Neuropathy</strong></td>
<td>• Hyperglycemia</td>
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<td>• Blood pressure</td>
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<td>• Smoking</td>
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<td>• Alcohol intake</td>
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<td>• Hypertension</td>
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Glycemic Control and DMC
Intensive Glycemic Control Reduces DMC Risk

• Maintenance of near-normal glucose levels* in patients with type 1 diabetes:
  – Reduces retinopathy development and progression
  – Reduces kidney damage
  – Reduces nerve damage

• Other studies have shown similar benefits of intensive glycemic control in patients with type 2 diabetes

*Mean A1C = 7.3%.

DMC Risk Reduction per 1% Decrease in A1C

<table>
<thead>
<tr>
<th>Study</th>
<th>Retinopathy</th>
<th>Nephropathy</th>
<th>Neuropathy</th>
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<tbody>
<tr>
<td>DCCT</td>
<td>27%-38%</td>
<td>22%-28%</td>
<td>29%-35%</td>
</tr>
<tr>
<td>Kumamoto</td>
<td>28%</td>
<td>50%</td>
<td>↑NCV*</td>
</tr>
<tr>
<td>UKPDS</td>
<td>19%</td>
<td>26%</td>
<td>18%</td>
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*NCV = Nerve Conduction Velocity.

DCCT: Objective and Study Design

- Objective: Determine whether maintaining blood glucose levels near normal range decreases severity and frequency of DMC in type 1 diabetes patients

- Study design
  - N = 1,441 type 1 diabetes patients
  - Randomized, controlled trial
  - Mean duration: 6.5 years
  - Primary and secondary prevention cohorts
  - Conventional and intensive therapy regimens
  - Regular assessment of retinopathy, nephropathy, and neuropathy

## DCCT: Eligibility and Exclusion Criteria

<table>
<thead>
<tr>
<th>PRIMARY PREVENTION</th>
<th>SECONDARY INTERVENTION</th>
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<tbody>
<tr>
<td><strong>AGE</strong></td>
<td>13-39 Y</td>
</tr>
<tr>
<td><strong>DURATION</strong></td>
<td>1-5 Y</td>
</tr>
<tr>
<td><strong>RETINOPATHY</strong></td>
<td>NONE</td>
</tr>
<tr>
<td><strong>ALBUMINURIA</strong></td>
<td>&lt;40 mg/ 24 h</td>
</tr>
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</table>

**EXCLUSION CRITERIA:** hypertension, hypercholesterolemia, severe diabetic complications or medical conditions

DCCT: Conventional Therapy Regimen

INTENDED TO MIMIC CONVENTIONAL CARE

• Clinical goals: No symptoms of hyper- or hypoglycemia
• 1 or 2 injections per day
• Daily self-monitoring
• Quarterly hemoglobin A1C
• Pregnant women treated intensively
• Diet and exercise education
• Quarterly visits

DCCT: Intensive Therapy Goals

• Same clinical goals as conventional therapy (no symptoms of hyper- or hypoglycemia)

PLUS

• Maintain blood glucose levels as close to nondiabetic range as possible

• Preprandial  Postprandial  Weekly 3 AM

70-120 mg/dL  <180  >65

• A1C <6.05% (mean + 2 SD)

DCCT: Intensive Therapy Methods

• ≥3 daily injections or insulin pump
• 4 or more blood-glucose tests daily
• Frequent dietary instruction to help achieve goals
• Monthly clinic visits

DCCT: Summary of Results

• Median A1C: 7.3% and 9.1% for intensive and conventional, respectively

• Retinopathy
  – Development reduced by 76% in primary prevention cohort
  – Progression reduced by 54% in secondary prevention cohort

• Nephropathy (primary and secondary cohort results combined)
  – Microalbuminuria development decreased by 39%
  – Albuminuria development decreased by 56%

• Neuropathy (clinical exam, nerve conduction, or autonomic function)
  – Prevalence reduced by 69% in primary prevention cohort
  – Prevalence reduced by 57% in secondary prevention cohort

• Increase in hypoglycemia and weight gain

The risk for development of DMC is increased at all A1C values above the normal range.
DCCT: Applying Results to Clinical Populations

- Patient population typical of type 1 diabetes patients seen in practice
- Start intensive treatment as soon as safely possible
- Aim for A1C of ≤7%
- Hypoglycemia and weight gain are increased with intensive glycemic control

UK Prospective Diabetes Study 35 (UKPDS 35): Objective and Study Design

- Objective: Determine relation between glycemia and the risk of microvascular and macrovascular complications over time

- Study design
  - Prospective, observational study
  - Intensive (FPG* <6 mmol/L) vs conventional (FPG <15 mmol/L) therapy
  - Median follow-up of 10 years

*FPG = fasting plasma glucose.

UKPDS 35: Study Population and Results

• Population
  – N = 3,642 for relative risk analysis
  – Newly diagnosed type 2 diabetes patients
  – Mean age 53 years
  – Exclusion criteria: ketonuria, evident cardiovascular disease, serum creatinine >175 µmol/L, severe retinopathy, malignant hypertension, uncorrected endocrine abnormality, severe concurrent illness

• Results
  – A1C: 7% (intensive) vs 7.9% (conventional)
  – 1% A1C reduction leads to 37% decrease in risk of DMC
  – No glycemic threshold for risk of DMC

No Lower A1C Threshold for Increased DMC Risk in Type 2 Diabetes Patients

UKPDS 35: Applying Results to Clinical Populations

- UKPDS 35 is an epidemiological study meant to estimate expected results in practice
  - Estimates are consistent with the actual trial results
  - Existing hyperglycemia-induced tissue damage may pose limitations
- Study population likely to be at lower risk for complications
  - Newly diagnosed
  - Old and ill patients excluded
- Patients seen in practice may have other characteristics of excluded patients

Postprandial Glucose as a Therapeutic Target
Targeting PPG to Improve Glycemic Control

• Recommended glycemic targets are difficult to achieve
• Even with near-normal, long-term glucose levels, patients may experience postprandial hyperglycemia
• Glucose levels are routinely assessed by A1C and premeal blood glucose testing
• Routine assessment may not provide an indication of postprandial hyperglycemia
• PPG excursions may contribute to DMC
## Recommended Glycemic Targets

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<tr>
<th>Glycemic Target</th>
<th>ADA</th>
<th>ACE</th>
<th>IDF</th>
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<tbody>
<tr>
<td>A1C (%)</td>
<td>&lt;7.0</td>
<td>≤6.5</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>90-130*</td>
<td>&lt;110*</td>
<td>&lt;100‡</td>
</tr>
<tr>
<td>Postprandial glucose (mg/dL)</td>
<td>&lt;180*†</td>
<td>&lt;140*†</td>
<td>&lt;135‡</td>
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*Plasma equivalent.
†2 h.
‡Self-monitored blood glucose.

ADA. *Diabetes Care*. 2005;28:S4-S36.
Recommended Glycemic Targets Are Difficult to Achieve

• ~60% of people with diabetes have A1C >7% (NHANES/NHANES III)

• <5% of patients receiving intensive therapy maintained A1C within normal levels (DCCT)

• Only 28% of insulin-treated patients maintained A1C <7% (UKPDS)

FPG and PPG Contributions to Hyperglycemia (FPG and PPG): Objective and Study Design

- **Objective:** Calculate relative FPG and PPG contributions to hyperglycemia based on diurnal glycemic profiles at various A1C levels

- **Study design**
  - Overnight fast with test breakfast (8 AM) and lunch (12 PM)
  - Blood samples at 8 AM, 1 PM, 2 PM, and 5 PM

FPG and PPG: Study Population and Results

• Study population
  – N = 290
  – Type 2 diabetes
  – Stable diet and/or metformin therapy
  – Patients on acarbose or insulin were excluded
  – Divided into quintiles based on A1C

• Results
  – FPG and PPG increase with A1C
  – Relative contribution of PPG to hyperglycemia was greatest at lower A1C
  – Relative contribution of FPG to hyperglycemia was greatest at higher A1C
  – PPG contributes ~30% to hyperglycemia at high A1C

FPG and PPG: Contribution to A1C

As patients approach target A1C, the need to manage PPG increases

FPG = Fasting Plasma Glucose
PPG = Postprandial Plasma Glucose

FPG and PPG: Applying Results to Clinical Populations

- Patient population seems consistent with patients seen in practice
- PPG control is important in patients with mild or moderate hyperglycemia (fairly well-controlled)
- PPG contribution to hyperglycemia in poorly controlled patients is still ~30%

Postprandial Blood Glucose: ADA Consensus Statement

• Individuals with diabetes should be tested for PPG in the following circumstances:
  – Suspected postprandial hyperglycemia
    • Premal glucose targets are obtained
    • A1C indicates poor glycemic control
  – Monitoring treatment aimed specifically at lowering PPG
  – Hypoglycemia

ADA. Diabetes Care. 2001;24:775-778.
Postprandial Blood Glucose: ADA Consensus Statement

• Elevated PPG concentrations may contribute to suboptimal glycemic control

• Outstanding questions:
  – Does postprandial hyperglycemia play a unique role in the pathogenesis of diabetes complications?
  – Should PPG be a therapeutic target?

• Additional research is necessary to clarify the role of PPG in the medical management of diabetes

ADA. Diabetes Care. 2001;24:775-778.
Postprandial Hyperglycemia: Expert Panel Position Statement

- The potential importance of PPG control in the development of diabetes complications is widely recognized
- PPG may disproportionately contribute to DMC
- Targeting chronic and acute glucose fluctuations is necessary in the prevention and management of DMC
- 2-hour PPG measurement is practical and recommended
- Additional research is needed to clarify epidemiological associations between PPG and excess mortality

Agents That Target PPG Control

• Pharmacological treatments to improve PPG levels may be beneficial, particularly in patients who have difficulty attaining target A1C levels despite good FPG control

• No study has evaluated the effect of oral antihyperglycemics targeting PPG on diabetes complications

• Agents that target postprandial hyperglycemia
  – Short-acting insulin analogues
  – α-glucosidase inhibitors
  – Short-acting insulin secretagogues
  – Glyburide-metformin tablets
  – Amylin replacement therapy
  – Incretin mimetics


Summary

• DMC cause substantial morbidity and mortality
• Tight glycemic control reduces the risks of DMC development and progression in type 1 and type 2 diabetes patients
• Tight glycemic control is difficult to achieve
• FPG and PPG levels contribute to glycemic control
• Evidence suggests that therapeutically targeting postprandial hyperglycemia may be beneficial
  – Improves overall glycemic control
  – Questions remain as to unique benefit in preventing complications