Management of Type 2 Diabetes Mellitus in the Elderly

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Incidence and Prevalence of Diabetes in the United States

County-level Estimates of Diagnosed Diabetes for Adults aged ≥ 20 years:
United States 2007
County-level Estimates of Obesity among Adults aged ≥ 20 years: United States 2007C

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2008

Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

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Estimated lifetime risk of developing diabetes for individuals born in the United States in 2000

Narayan et al. JAMA, 2003

Percentage of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, by Age, United States, 1980-2007


Distribution of Age at Diagnosis of Diabetes Among Adult Incident Cases Aged 18-79 Years, United States, 2008

Incidence of Diagnosed Diabetes per 1,000 Population Aged 18-79 Years, by Sex and Age, United States, 1997-2008


Etiology of Type 2 Diabetes and The Importance of Glycemic Control

Type 2 Diabetes

- Current American Diabetes Association (ADA) definition:
  - Type 2 diabetes is a metabolic disorder characterized by hyperglycemia resulting from a combination of resistance to insulin action and an inadequate insulin secretory response.
  - Type 2 diabetes involves two primary pathogenic processes:
    - Progressive decline in pancreatic islet function (↓ insulin secretion and inadequately suppressed glucagon secretion)²,³
    - Diminished tissue response to insulin (insulin resistance)²,⁴

1 ADA. Diabetes care. 29(Suppl): S43-S48
4 Ahren B and Pacini G. Diabetes Obes Metab. 2005;7:2-8
Tight Glycemic Control Reduces Incidence of Microvascular Complications

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>DCCT*1</th>
<th>Kumamoto*2</th>
<th>UKPDS*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>76%</td>
<td>69%</td>
<td>21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>34%</td>
<td>70%</td>
<td>34%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>69%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Primary prevention cohort

DCCT = Diabetes control and Complications Trial
UKPDS = United Kingdom Prospective Diabetes Study


Intensive Glycemic Control in Type 2 Diabetes Reduces Risk of Complications (UKPDS)

Risk Reduction With 1% Decline in Updated Hba1c

- Death related to diabetes
- Cataract extraction
- Heart failure
- Stroke
- Hospitalization
- Microvascular disease

Relative Risk Reduction (%)

UKPDS 35: Prospective observational analysis of UKPDS patients (n=4,585) incidence analysis; median 10 years of follow-up. MI = myocardial infarction, PVD = peripheral vascular disease.
Tight Glycemic Control Reduces Long-Term Cardiovascular Risk (DCCT/EDIC Study)

- Intensive Treatment Group:
  - ≥3 insulin injections/day or insulin pump, frequent blood glucose monitoring, and HbA1c ≤6%

- Conventional Therapy Group:
  - ≤2 insulin injections/day and daily urine/blood testing

Relative Risk Reduction (%)

- Aggregate CV Events: 42% vs 57%
- Nonfatal MI, Stroke, and CV Death: **

Subanalysis of most severe outcomes

DCCT/EDIC Study Research Group


Current Treatment goals for Glycemic Control

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>ACE</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>&lt;6%* (individual goal)</td>
<td>≤6.5% (general goal)</td>
<td>≤6.5%*</td>
</tr>
<tr>
<td>FPG</td>
<td>&lt;180 mg/dl</td>
<td>&lt;140 mg/dl</td>
<td>&lt;140 mg/dl</td>
</tr>
<tr>
<td>PPG</td>
<td>&lt;110 mg/dl</td>
<td>&lt;110 mg/dl</td>
<td>&lt;145 mg/dl</td>
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</table>

*Referenced to a nondiabetic range of 4-6% using DCCT assay.

- ADA. Diabetes Care. 2006; 29(suppl): S4-S42
- ACE. Endocr Pract. 2002;8(Suppl): S5-S11
- IDF. Global Guidelines for Type 2 Diabetes. 2005

Unmet Therapeutic needs in Type 2 Diabetes

- Durable HbA1c control
- Addressing islet dysfunction (i.e., addressing both insulin and glucagon secretion)
- Minimum risk of treatment-limiting adverse events
  - Minimum risk of hypoglycemia
  - Minimum risk of weight gain
  - No increased risk of edema
  - No increased risk of heart failure

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**Pathophysiology of Type 2 Diabetes**

**Characteristics of β-cells and α-cells**

- **β-cells**
  - Comprise about 60% of the endocrine mass of the pancreas
  - Located in the central portion of the islet
  - Produce insulin and amylin
  - Insulin released in response to elevated blood glucose levels

- **α-cells**
  - Comprise about 25% of the endocrine mass of the pancreas
  - Located in the periphery of the islet
  - Produce glucagon
  - Glucagon released in response to low blood glucose levels

**Progression Reflecting Imbalance Between Insulin Supply and Demand**

- IGT = Impaired glucose tolerance; IFG = impaired fasting glucose; NGT = normal glucose tolerance
**B-cell Function Declines Regardless of Intervention In Type 2 Diabetes**

- B-cell function measured by homeostatic assessment

**B-cell Mass Is Decreased in Obese persons with IFG and Type 2 Diabetes**


**Medical Therapy in Type 2 Diabetes**

- Inzucchi SE, JAMA 2002;287:360-372
- DeFronzo RA. Br J Diabetes Vasc Dis 2003;3(suppl);S24-S40
- Ovalle F, Bell DS, Diabetes Care, 2004;27:2585-2589
- Vilsbøll T, Holst JJ. Diabetologia; 2004; 47:357-366
- Drucker DJ. Diabetes educator. 2006;32 (suppl):72S-81S

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Diagnostic Criteria for Type 2 DM

- Hemoglobin A1c ≥ 6.5%
- Fasting blood glucose ≥ 126 mg/dl
- 2-hour glucose level ≥ 200 mg/dl during OGTT
- Random blood glucose levels of ≥ 200 mg/dl in a patient with typical clinical symptomatology for hyperglycemia or hyperglycemic crisis

AACE/ACE A1C Position Statement, Endocr Pract. 2010;16(No2)

Management of Type 2 Diabetes
Outpatient management

GLP-1 analogs and DPP-4 inhibitors

- Incretin analogue- GLP-1 (Glucagon-like peptidase - 1) analogs
- Incretin inhibitor: DPP-4 (dipeptidyl peptide-4) inhibitors
The "Incretin Effect" in Normal Subjects


The Incretin Effect in Type 2 Diabetes


GLP-1 and GIP

- In humans, the major incretins are:
  - Glucagon like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic polypeptide (GIP)
- Both GLP-1 and GIP increase insulin secretion
- Only GLP-1 suppresses glucagon secretion
- Effects on insulin and glucagon occur mainly when blood glucose levels are elevated
- Both GLP-1 and GIP are rapidly inactivated by dipeptidyl peptidase 4 (DPP-4)
GLP-1 Demonstrates Multiple Effects in patients with Type 2 Diabetes

- Improves glucose-dependent insulin secretion
- Decreases plasma glucagon concentration
- Decreases fasting and postprandial plasma glucose concentrations
- Lowers HbA1c
- Delays gastric emptying
- Reduces appetite and food intake


Management of Type 2 Diabetes Mellitus in the Elderly - GLP-1 analogs and DPP-4 inhibitors

- Incretin analogue: Exenetide (Byetta), Liraglutide (Victoza)
- Incretin inhibitor: DPP-4 sitagliptin (Januvia), saxagliptin (Onglyza)

GLP-1 analogues and DPP-4 Inhibitors

- Pros: weight neutral, reduce both postprandial and fasting plasma glucose, reduce HbA1c by 1.6%.
- Cons: Injectable, multiple doses, requires refrigeration (Byetta), GI complaints
- Risks: acute pancreatitis, C cell hyperplasia with long acting GLP-1 analogs (caution in people with hx of medullary thyroid cancer)
Management of Type 2 Diabetes Mellitus in the Elderly - Thiazolidinediones

- Pioglitazone (Actos)
- Rosiglitazone (Avandia)

Thiazolidinediones (Actos and Avandia)

- Short term studies demonstrated reduction in HbA1c, collectively by 2%
- Lower incidence of hypoglycemia
- Weight gain similar to Insulin therapy
- Pioglitazone has a favorable lipid profile
- Improved ratio of Proinsulin to Insulin
- Pioglitazone ameliorated fatty liver with increase in Insulin sensitivity

Thiazolidinediones (Actos and Avandia) - Cons

- Increase incidence of congestive heart failure
- New black box warning of increased myocardial ischemia with rosiglitazone
- Marginally beneficial effect with pioglitazone (PROactive study*)
- Edema
- Increase risk of osteoporosis
- Cost

*Charbonnel B. Diabetes Care 2004;27:1647-1653
Management of Type 2 Diabetes Mellitus in the Elderly - Insulin

- Bedtime Insulin to reduce the fasting blood glucose level to the optimal range of 80-130

Bedtime Insulin

- Insulins:
  - Glargine (Lantus)
  - Detemir (Levemir)
  - NPH Insulin (Humulin or Novolin N)

Bedtime Insulin

- Bedtime Insulin
  - Safe
  - Easy to administer
  - Single injection
  - Easily titrated to target
  - Achieved the Hba1c goal
  - Amenable to community-care-based setting and cost effective

- Treating to Target (4-T trial) showed less hypoglycemia compared to twice daily or short times three times daily injections.


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### Current treatments for Type 2 Diabetes: Review

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<td>Inhibits hepatic glucose production</td>
<td>GI complaints</td>
<td>Monitor HbA1c @ 3 months, FPG @ 2 weeks. Bile acid synthesis inhibitors required in patients with renal disease.</td>
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<tr>
<td>Metformin</td>
<td>Decreases FFA and glucagon</td>
<td>Tend to hypoglycemia</td>
<td>FPG at 4 weeks</td>
<td>Reduces by 0.5% HbA1c</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Inhibits glucagon</td>
<td>Not usually significant</td>
<td>FPG at initiation</td>
<td>Possible side effects</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Infrequent use due to the amount of potential side effects or non-melanoma</td>
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<tr>
<td>Pramlintide</td>
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### AACE/ACE Diabetes Algorithm for Glycemic Control

![AACE/ACE Diabetes Algorithm](image)

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### Table I: Summary of Key Benefits and Risks of Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Benefit 1</th>
<th>Benefit 2</th>
<th>Benefit 3</th>
<th>Risk 1</th>
<th>Risk 2</th>
<th>Risk 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
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<tr>
<td>B</td>
<td>Medium</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
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<tr>
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<td>Low</td>
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*Note: The table above illustrates a summary of key benefits and risks associated with various medications. Further details are available in the full report. The information is subject to change and may vary based on individual circumstances.*