Twin Epidemic of Diabetes and Obesity

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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE
MANAGEMENT OF DIABETES MELLITUS

AACE Diabetes Mellitus Clinical Practice Guidelines Task Force

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Acknowledgments
We would like to recognize Elliot Sternthal, MD, FACE, and Joseph Vassallo, MD, for their review of these guidelines and thoughtful comments.
“Success is going from failure to failure without losing your enthusiasm.”

-Sir Winston Churchill
Obesity Trends* Among U.S. Adults
BRFSS, 1985
(*BMI ≥30, or ~30 lbs. overweight for 5’4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1986
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1987
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1988
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1989

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%          10%–14%
Obesity Trends* Among U.S. Adults
BRFSS, 1990

(*BMI $\geq$ 30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1991

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults

BRFSS, 1992

(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1993

(*BMI $\geq$ 30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1994

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1995

(*BMI ≥30, or ~ 30 lbs. overweight for 5′ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1996

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1997

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1998

(*BMI \geq 30, or \sim 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1999
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Obesity Trends* Among U.S. Adults

BRFSS, 2000

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2001

(*BMI $\geq 30$, or ~ 30 lbs. overweight for 5’ 4’’ person)
Obesity Trends* Among U.S. Adults
BRFSS, 2002

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2003

(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2004

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2005

(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2006

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2007

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2008
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Prevalence of Type 2 Diabetes Is Escalating

Type 2 diabetes progression is a multifactorial challenge.
In humans, beta-cell mass increases with obesity, decreases with type 2 diabetes.

Adapted from Butler et al. Diabetes 2003;52:102–10
IFG, impaired fasting glucose. Data are mean ± SE
Global Projections for Diabetes 1995-2010

Global Prevalence of Diabetes Projected to More Than Double by 2030

Top 10: Prevalence of diabetes* (20-79 age group) in 2007 (with 2025 prevalence)

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>Prevalence (%)</th>
<th>2007</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nauru</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahrain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuwait</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonga</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mauritius</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Comparative prevalence

SOURCE: DIABETES ATLAS THIRD EDITION, © INTERNATIONAL DIABETES FEDERATION, 2006
Prevalence estimates of diabetes, 2007

SOURCE: DIABETES ATLAS THIRD EDITION, © INTERNATIONAL DIABETES FEDERATION, 2006
Type 1 Diabetes

Absolute Insulin Deficiency

Autoimmune

Beta Cell under autoimmune attack
Type 2 Diabetes
Relative Insulin Deficiency
Insulin Resistance
(impaired insulin action)
Obesity is a Prime Risk Factor for Hypertension, CKD, DM2 and Dyslipidemia
DCCT: The Closer to Goal, the Higher the Risk of Hypoglycemia

Severe hypoglycemic events per 100 patient-years

A1C (%)

Correlation Between Weight Gain and Treatment

Type 1 Patients in DCCT,\(^1\)
Baseline to Year 1

Type 2 Patients in UKPDS,\(^2\)
Baseline to 15 Years

\(*P<.0001.\)

% of ideal body weight = comparison of patients’ actual weights to their ideal body weights based on 1983 Metropolitan Life Insurance norms.

Complications and Effects of Severe Hypoglycemia

Plasma glucose level

- Increased Risk of Cardiac Arrhythmia¹
  - Abnormal prolonged cardiac repolarization—↑QTc and QT dispersion
  - Sudden death

- Progressive Neuroglycopenia²
  - Cognitive impairment
  - Unusual behavior
  - Seizure
  - Coma
  - Brain death

# 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>HbA$_{1c}$</td>
<td>&lt;6.0%*</td>
<td>≤6.5%*</td>
<td>&lt;6.5%*</td>
</tr>
<tr>
<td></td>
<td><em>(Individual goal)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;7.0%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>(General goal)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG</td>
<td>90-130 mg/dL</td>
<td>&lt;110 mg/dL</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td>PPG$^\dagger$</td>
<td>&lt;180 mg/dL</td>
<td>&lt;140 mg/dL</td>
<td>&lt;145 mg/dL</td>
</tr>
</tbody>
</table>

*Referenced to a nondiabetic range of 4.0% to 6.0% using a DCCT-based assay
$^\dagger$Upper limit of normal = 6.0%

**ADA** = American Diabetes Association; **ACE** = American College of Endocrinology; **IDF** = International Diabetes Federation; **FPG** = fasting plasma glucose; **PPG** = postprandial plasma glucose
FPG and PPG Contribute to A1C Management

N=290 non-insulin-using patients with type 2 diabetes.
FPG=fasting plasma glucose; PPG=postprandial plasma glucose.
Mortality Risk With Increasing PPG, Regardless of FPG Levels

*Adjusted for age, sex, and study center.
Diagnostic Criteria Associated with Glucose Abnormalities

<table>
<thead>
<tr>
<th>FPG</th>
<th>2-Hour PG on OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td><strong>Diabetes Mellitus</strong></td>
</tr>
<tr>
<td>126 mg/dL</td>
<td>11.1 mmol/L</td>
</tr>
<tr>
<td>100 mg/dL</td>
<td>7.8 mmol/L</td>
</tr>
<tr>
<td><strong>Impaired Fasting Glucose</strong></td>
<td><strong>Impaired Glucose Tolerance</strong></td>
</tr>
<tr>
<td>7.0 mmol/L</td>
<td>200 mg/dL</td>
</tr>
<tr>
<td>6.1 mmol/L</td>
<td>140 mg/dL</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td><strong>Normal</strong></td>
</tr>
</tbody>
</table>

Adapted from The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. 
Recommendations of the 2003 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

- Impaired fasting glucose (IFG): $\geq 100 \text{ mg/dL}$
- Normal fasting plasma glucose (FPG): $< 100 \text{ mg/dL}$
- FPG and 2-h plasma glucose (2-h PG) tests preferred for diagnosis of diabetes
  - 2-h PG test is more sensitive than FPG
  - FPG test is more reproducible, less costly, and more convenient than 2-h PG

Response and Beta-Cell Balancing Beta-Cell Workload
Insulin Is Enhanced and Glucagon Is Suppressed

Healthy Subjects (n = 14)

Carbohydrate Meal

Insulin (μU/mL)

Glucagon (pg/mL)

Glucose (mg/dL)

Time (min)

Mean (SE)
Response and Beta-Cell Balancing Beta-Cell Workload
Insulin Is Enhanced and Glucagon Is Suppressed

Healthy Subjects (n = 14)
Type 2 Diabetes (n = 12)

Carbohydrate Meal

Insulin (μU/mL)
Glucagon (pg/mL)
Glucose (mg/dL)

Time (min)

Mean (SE)
Plasma Glucose and Insulin Responses in Patients With Normal Glucose Tolerance, Impaired Glucose Tolerance, and Type 2 Diabetes

Diabetes Mellitus Reduction

Obesity as a Risk Factor for CAD

The Importance of Abdominal Fat

Android Obesity

Gynoid Obesity
Which has higher cardiovascular risk?
The Apple

- Waist circumference
  women >35 in (88 cm)
  men >40 in (102 cm)
Visceral Fat Distribution: Normal vs Type 2 Diabetes

Normal

Type 2 Diabetes

Courtesy of Wilfred Y. Fujimoto, MD.
Leptin - low, normal or high?
↑ Leptin/ ↓ Adiponectin

- Proportional to fat mass
- Women > men
- Homer > most people
**Pharmacologic Agents for Diabetes**

**Marketed Since 1990**

<table>
<thead>
<tr>
<th>Category</th>
<th>Agents and Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas/Secretagogues</td>
<td>- Glipizide GITS (Glucotrol XL) - 1992&lt;br&gt;- Repaglinide (Prandin) - 1998&lt;br&gt;- Glimepiride (Amaryl) - 1995&lt;br&gt;- Nateglinide (Starlix) - 2000</td>
</tr>
<tr>
<td>Biguanides</td>
<td>- Metformin (Glucophage) - 1995&lt;br&gt;- Metformin/glyburide (Glucovance) - 2000&lt;br&gt;- Metformin/rosiglitazone (Avandamet) - 2002&lt;br&gt;- Metformin/glipizide (Metaglip) - 2002&lt;br&gt;- Metformin/pioglitazone (ACTOplus met) - 2005</td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitors</td>
<td>- Acarbose (Precose) - 1995&lt;br&gt;- Miglitol (Glyset) – 1999</td>
</tr>
<tr>
<td>Thiazolidinediones (glitazones)</td>
<td>- Rosiglitazone (Avandia) - 1999&lt;br&gt;- Pioglitazone (Actos) – 1999</td>
</tr>
<tr>
<td>Bile acid sequestrant (SE-BAS)</td>
<td>- Colesevelam (Welchol) – 2007</td>
</tr>
<tr>
<td>Dopamine D&lt;sub&gt;2&lt;/sub&gt; RA</td>
<td>- Bromocriptine – 2009</td>
</tr>
</tbody>
</table>
## Pharmacologic Agents for Diabetes Marketed Since 1990 (cont’d)

<table>
<thead>
<tr>
<th>Category</th>
<th>Agents and Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin</strong></td>
<td>Lispro (Humalog) – 2000</td>
</tr>
<tr>
<td></td>
<td>Lispro/Protamine (75/25) – 2000</td>
</tr>
<tr>
<td></td>
<td>Aspart (Novolog) – 2001</td>
</tr>
<tr>
<td></td>
<td>Aspart/NPH (75/25) – 2002</td>
</tr>
<tr>
<td></td>
<td>NPH/Regular (70/30) – 1990</td>
</tr>
<tr>
<td></td>
<td>Glargine (Lantus) – 2000</td>
</tr>
<tr>
<td></td>
<td>Glulysine (Apidra) – 2005</td>
</tr>
<tr>
<td></td>
<td>Detemir (Levemir) – 2006</td>
</tr>
<tr>
<td></td>
<td>Exubera – 2006 **</td>
</tr>
<tr>
<td><strong>Amylin analogue</strong></td>
<td>Pramlintide (Symlin) - 2005</td>
</tr>
<tr>
<td><strong>Glucagon-like peptide 1 (GLP) agonist</strong></td>
<td>Exenatide (Byetta) - 2005</td>
</tr>
<tr>
<td></td>
<td>Liraglutide (Victoza) - 2010</td>
</tr>
<tr>
<td><strong>Dipeptidyl peptidase IV (DPP IV) inhibitors</strong></td>
<td>Sitagliptin (Januvia) - 2006</td>
</tr>
<tr>
<td></td>
<td>Saxaglptin (Onglyza) - 2009</td>
</tr>
</tbody>
</table>
# Typical A1C Reduction by Treatment Regimen

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of Administration</th>
<th>Year of Introduction or FDA Approval</th>
<th>Efficacy as Monotherapy, Measured as a Reduction in the Glycated Hemoglobin Concentration (A1C) percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Parenteral</td>
<td>1921</td>
<td>≥2.5</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>Pulmonary</td>
<td>2006</td>
<td>1.5</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>1946</td>
<td>1.5</td>
</tr>
<tr>
<td>Metformin*</td>
<td>Oral</td>
<td>1995</td>
<td>1.5</td>
</tr>
<tr>
<td>Alpha-glycosidase inhibitors</td>
<td>Oral</td>
<td>1995</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Oral</td>
<td>1997</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Glinides</td>
<td>Oral</td>
<td>1997</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Oral</td>
<td>2006</td>
<td>0.5-0.9</td>
</tr>
</tbody>
</table>

*Metformin has been available in other countries since 1957, but was approved in the United States in 1995.

GLP=glucagon-like peptide; DPP-IV=dipeptidyl peptidase IV.

The shape of things to come
"I'm Lovin' it!"
Actor Michael Moore, Director

Super Size Me
A Film of Epic Proportions

Fast Food Nation
The Dark Side of the All-American Meal

New York Times BESTSELLER
7-11 Fountain Drinks

- 32 oz
- 44 oz
- 52 oz
- 64 oz

Sugar content: 48 teaspoons!
After a short visit to the United States, Michaelangelo's David returns to Italy
Just to let you know how my diet's going.
Low-CHO vs. Low-Fat Diets

- Meta-analysis of 5 trials/n=447
- **Weight loss**
  Clinically irrelevant differences
- **Lipids/lipoproteins**
  - Low-fat diet: more favorable changes in Total-C (10 mg/dl) and LDL-C (7.7 mg/dl)
  - Low-CHO diet: more favorable changes in TG(31 mg/dl) and HDL-C (3.1 mg/dl)
- **Glucose/Insulin**
  No differences in people with T2 DM (HbA1c)

Arch Intern Med 2006;166:285-293
Diet, weight loss and lipids

- 5-10% weight loss required for metabolic benefits
- Atkins, Ornish, Weight Watchers and Zone diets are equally effective
- Adherence to diet rather than the diet determines success
- High protein or monounsaturated fat diet may be best

JAMA 2005;294:2455-2464
Trans Fatty Acids and CV Disease

- Impact on LDL-C and HDL-C
  - trans fat worse than saturated fat
  - $\uparrow$LDL-C, $\downarrow$HDL-C, $\uparrow$TC/HDL-C ratio
- Adverse effects with 2-7 g/d
- Limit to < 0.5 g/d or eliminate trans FA
- 50% reduction in dietary trans FA reduces CV events by 10-12%; elimination of trans FA, reduces CV events by 19-22%

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥ 160</td>
<td>≥ 100</td>
</tr>
</tbody>
</table>

No Stage 3

ATP III: The Metabolic Syndrome*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td></td>
</tr>
<tr>
<td>(Waist circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>TG</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

*Diagnosis is established when ≥3 of these risk factors are present.

Exercise

“An agent with blood pressure and lipid-lowering, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight reducing, insulin sensitizing, glucose-lowering, tranquilizing, hypnotic and antidepressant qualities”

Modified from WC Roberts, EIC
Am J Cardiol 1984;53:261
Exercise or lack thereof . . .
Physical activity

- 60% of adults do not engage in the recommended amount of activity
- 25% of adults are not active at all
- 14% of youth report no recent physical activity
Walking the dog
Diagnostic Criteria Associated with Glucose Abnormalities

<table>
<thead>
<tr>
<th>FPG</th>
<th>2-Hour PG on OGGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>Impaired Glucose Tolerance</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Diabetes Mellitus</td>
</tr>
</tbody>
</table>

- FPG:
  - 126 mg/dL (11.1 mmol/L)
  - 100 mg/dL (6.1 mmol/L)

- 2-Hour PG on OGGT:
  - 200 mg/dL (11.1 mmol/L)
  - 140 mg/dL (7.8 mmol/L)

Summary of Revisions for the 2006 Clinical Practice Recommendations

Beginning with the 2005 supplement, the Clinical Practice Recommendations contained only the “Standards of Medical Care in Diabetes” and selected other position statements. This change was made to emphasize the importance of the “Standards” as the best source to determine ADA recommendations. The position statements in the supplement are updated yearly. Position statements not included in the supplement will be updated as necessary and republished when completed. A list of the position statements not included in this supplement appears on p. S75.

Format changes
- Page numbers now appear in the “Contents” for ease in locating particular sections
- Recommendations are now listed at the beginning of each section

Additions to the Standards of Medical Care in Diabetes
- Medical nutrition therapy (MNT)—extensively enhanced

- Diabetes self-management education (DSME)
- Physical activity
- Neuropathy

Summary of Revisions to Standards of Medical Care for Diabetes
- Assessment of glycemic control
  - Use of point-of-care testing for HbA$_1c$ (A1C) allows for timely decisions on therapy changes, when needed (E)

- Glycemic goals
  - The A1C goal for patients in general is <7% (B)
  - The A1C goal for the individual patient is an A1C as close to normal (<6%) as possible without significant hypoglycemia (E)

- Nephropathy
  - To reduce the risk of nephropathy, protein intake should be limited to the recommended dietary allowance (RDA) (0.8 g/kg) (B)
  - Serum creatinine in those with any degree of chronic kidney disease (CKD) should be measured at least annually for the estimation of glomerular filtration rate (GFR) in all adults with diabetes regardless of the degree of urine albumin excretion.

The serum creatinine alone should not be used as a measure of kidney function but rather used to estimate GFR and stage the level of CKD (E)

Members of the Professional Practice Committee
- Vivian Fonseca, MD, Chair
- Evan M. Benjamin, MD
- Lawrence Blonde, MD
- Kenneth Copeland, MD
- Marjorie L. Cypress, MS, RN, CDE
- Hertzl C. Gerstein, MD, Msc, FRCPC
- Irl Hirsch, MD
- Steven Kahn, MB, ChB
- Elizabeth Mayer-Davis, MS, PhD, RD
- James Meigs, MD, MPH
- Michael P. Pignone, MD, MPH
- Janet H. Silverstein, MD
- Geralyn R. Spollett, MSN, C-ANP, CDE
- Judith Wylie-Rosett, RD, EdD
- Nathaniel G. Clark, MD, MS, RD (Staff)
Why Estimate GFR From SCr, Instead of Using SCr for Kidney Function?

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>SCr (mg/dL)</th>
<th>eGFR (mL/min/1.73 m²)</th>
<th>CKD Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>M</td>
<td>B*</td>
<td>1.3</td>
<td>91</td>
<td>1</td>
</tr>
<tr>
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<td>M</td>
<td>W†</td>
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<td>50</td>
<td>F</td>
<td>W</td>
<td>1.3</td>
<td>46</td>
<td>3</td>
</tr>
</tbody>
</table>

*B = black; †W = all ethnic groups other than black.

eGFR Versus Creatinine in Patients Receiving Metformin

<table>
<thead>
<tr>
<th>Patients with Abnormal Renal Function (%)</th>
<th>Abnormal Serum Creatinine (W &gt;1.4, M &gt;1.5)</th>
<th>Abnormal eGFR (&lt;60 mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Men</td>
<td>7</td>
<td>13</td>
</tr>
</tbody>
</table>

\( n = 4838. \)

Diabetes is the most common primary diagnosis in patients with kidney failure.

ESRD = end-stage renal disease.
USRDS 2004 Annual Data Report. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government. Available at: www.usrds.org.
Annual Transition Rates in Patients With Type 2 Diabetes in the UKPDS

No Nephropathy: 1.4%
- Microalbuminuria: 2.0%
  - Albuminuria: 2.8%
  - Elevated Creatinine or Renal Replacement Therapy: 2.3%

Death: 19.2%

UKPDS = The United Kingdom Prospective Diabetes Study.
Patterns of Insulin Response to IV Glucose: Non-diabetic and Diabetic Individuals

- Insulin Secretion vs. Time, minutes
- IV Glucose Stimulus
- 1st Phase
- 2nd Phase
- Non-Diabetic
- Type 2 Diabetes

- Time, minutes
In type 2 diabetes, mealtime insulin secretion is blunted and delayed.

Complications of Type 2 Diabetes

**Heart**
- Coronary heart disease
- Cardiovascular disease

**Blood Vessels**
- Peripheral artery disease
- Intermittent claudication

**Kidneys**
- Microalbinuria
- Nephropathy

**Nerves**
- Chronic sensorimotor distal symmetric polyneuropathy
- Gastroparesis

**Eyes**
- Retinopathy
- Glaucoma

**Hyperglycemia**

The Dallas Heart Study Population

Nondiabetic

Patients (%)

CKD Stage: None 1-2 3-5

Diabetic

 Patients (%)

CKD Stage: None 1-2 3-5

CAC = coronary artery calcification.
Normal Retina (No Apparent Retinopathy)
Nonproliferative Diabetic Retinopathy

Courtesy EyeTel’s DigiScope®
Proliferative Diabetic Retinopathy

Courtesy EyeTel’s DigiScope®
Diabetic Macular Edema

Courtesy EyeTel’s DigiScope®
Microvascular Damage Leads to Diabetic Peripheral Neuropathy (DPN)

Examination of tissues from patients with diabetes reveals capillary damage, including occlusion in the vasa nervorum\(^1,2\)

Reduced blood supply to the neural tissue results in impairments in nerve signaling that affect both sensory and motor function\(^2\)

Symptoms and Signs of Diabetic Peripheral Neuropathy

**Symptoms**
- Numbness or loss of feeling (asleep or “bunched up sock under toes” sensation)
- Prickling/Tingling
- Aching pain
- Burning pain
- Lancinating pain
- Unusual sensitivity or tenderness when feet are touched (allodynia)

**Signs**
- Diminished vibratory perception
- Decreased knee and ankle reflexes
- Reduced protective sensation such as pressure, hot and cold, pain
- Diminished ability to sense position of toes and feet

Symptoms and signs progress from distal to proximal over time.
How Far Would You Go to Minimize the Impact of Diabetic Peripheral Neuropathy?

Clawing toes, callus, superficial ulceration

Plantar ulcer, callus

Calluses scraped away, revealing ulcers

Images: 1,2. Rayaz A Malik, MBChB, PhD, MRCP. 3. Edward J Bastyr, III, MD.
Less Chronic Complications

- DCCT type 1 DM
- UKPDS type 2 obese
- Kumamoto type 2 lean

Improve insulin Resistance

- ↓ Glucose and lipotoxicity (metabolic toxicity)

Improve βeta-Cell function

- ↓ βeta cell fatigue ?
- ↑ βeta cell mass ?
Evidence for Effects of Good Glycemic Control on Complications, Including Nephropathy

<table>
<thead>
<tr>
<th>Complication</th>
<th>DCCT A1C: (9 → 7%) N = 1441</th>
<th>Kumamoto (9 → 7%) N = 110</th>
<th>UKPDS (8 → 7%) N = 5102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>↓ 76%</td>
<td>↓ 69%</td>
<td>↓ 21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>↓ 54%</td>
<td>↓ 70%</td>
<td>↓ 34%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>↓ 60%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

DCCT = The Diabetes Control and Complications Trial.
Intensive therapy reduced HbA$_1$c by 0.9% over 10+ years

Conventional

Intensive

Every 1% A1C drop can reduce long-term diabetes complications

Correlation between a 1% A1C decrease and reduced risk of complications

- Microvascular complications: 35%
- Diabetes-related deaths: 25%
- Myocardial infarction: 18%
- All-cause mortality: 7%

Impact of A1C Reduction

According to the UKPDS (N=3642)

- For every 1% reduction in A1C, there is a 37% decrease in relative risk of microvascular complications
- For every 1% reduction in A1C, there is a 14% decrease in relative risk of fatal and nonfatal MI
- Lower the glycemia, lower the risk of vascular complications

UKPDS = UK Prospective Diabetes Study
The DCCT Trial: Effect of Intensive Therapy on HbA$_{1c}$

Intensive therapy reduced HbA$_{1c}$ by 1.8% over 10 years

- Conventional: 8.9%
- Intensive: 7.1%

DCCT: Diabetic Complication Event Rates

<table>
<thead>
<tr>
<th>Event</th>
<th>Conventional</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy Progression 1</td>
<td>55.0%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Laser Rx 1</td>
<td>29.8%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Microalbuminuria 2</td>
<td>23.9%</td>
<td>16.4%</td>
</tr>
<tr>
<td>Albuminuria 2</td>
<td>5.1%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Clinical Neuropathy 3</td>
<td>13.4%</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

76% Risk Reduction
59% Risk Reduction
39% Risk Reduction
54% Risk Reduction
64% Risk Reduction

Distribution of HbA1c in the Former DCCT Intensive and Conventional Groups During EDIC

Mean HbA1c during EDIC
- Conventional: 8.2%
- Intensive: 8.0%

p = .0019

DCCT Closeout 1 2 3 4 5 6 7 8
p < .0001 .0001 .0001 .002 .04 .037 .59 .83

Cumulative Incidence of New Clinical Albuminuria >300 mg/24 h During EDIC

83% risk reduction

EDIC Year

Cumulative Incidence (%)

1 - 2
0
2 - 4
4 - 6
6 - 8
8 - 10
10 - 12

DCCT/EDIC Research Group. JAMA. 2002;287:2563-2569
## Advanced Kidney Outcomes by Year 8 of EDIC Reduced by Intensive Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive (n = 676)</th>
<th>Conventional (n = 673)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine &gt;2 mg/dL</td>
<td>5* (0.7%)</td>
<td>19 (2.8%)</td>
</tr>
<tr>
<td>Dialysis or Transplant</td>
<td>4 (0.6%)</td>
<td>7 (1.0%)</td>
</tr>
</tbody>
</table>

EDIC = Epidemiology of Diabetes Interventions and Complications.  
*P = 0.004.  
Carotid Intima-Media Thickness With Intensive Insulin Therapy
DCCT-EDIC

Mean change in intima-media thickness (mm)

-0.20
-0.15
-0.10
-0.05
0
0.05
0.10

Common carotid artery

Combined internal and carotid artery

P=0.01

P=0.02

Intensive treatment (n=618)
Conventional treatment (n=611)

EDIC Findings: Cardiovascular Events

Non-Fatal MI, Stroke, or CVD Death

Risk reduction 57%
95% CI: 12% to 79%
P = 0.02

Endocrine Functions of Adipocytes

- Leptin
- Fatty acids
- Adiponectin
- Resistin
- TNFα
- IL-6
- RBP4
- Omentin
- Angiotensinogen
- ASP
- PAI-1

ASP = acylation-stimulating protein; IL-6 = interleukin-6; PAI-1 = plasminogen activator inhibitor 1; RBP4 = retinol binding protein 4.

Rondinone CM. Endocrine. 2006;29:81–90.
Antuna-Puente B et al. Diabetes Metab. 2008;34:2–11.
Targets of “Angry” Fat

- ↑ PAI-1, ↑ adipokines, ↑ FFA, ↓ adiponectin
- ↑ FFA, ↑ glucose
- ↑ Adipokines, ↑ FFA
- ↑ Adipokines, ↑ FFA
- ↑ Adipokines

- ↑ Endothelial dysfunction
- ↑ \(\beta\) -cell apoptosis
- Nonalcoholic steatohepatitis
- ↑ Skeletal muscle insulin resistance
- ↑ Cardiac hypertrophy and other effects
- ↑ Alzheimer’s disease

FFA = free fatty acids.

Effects of PPARγ Agonist Activity of Thiazolidinediones

TZD = thiazolidinedione; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein.
Molecular Mechanisms of Action of Metformin

- Stimulation of AMPK
- Phosphorylation of insulin receptor and IRS2
- Inhibition of enzymes in gluconeogenic pathway

Decreases glucose production

Augments glucose uptake

- Enhanced muscle uptake of insulin
- Increased insulin receptor tyrosine kinase activity
- Increased GLUT4 activity

IRS2 = insulin receptor substrate-2.
Obesity as a Risk Factor for CAD

The Importance of Abdominal Fat

Android Obesity

Gynoid Obesity
Which has higher cardiovascular risk?
The Apple

- Waist circumference
  women >35 in (88 cm)
  men >40 in (102 cm)
Visceral Fat Distribution: Normal vs Type 2 Diabetes

Normal

Type 2 Diabetes

Courtesy of Wilfred Y. Fujimoto, MD.
Leptin - low, normal or high?
↑ Leptin/ ↓ Adiponectin

- Proportional to fat mass
- Women > men
- Homer > most people
# Pharmacologic Agents for Diabetes Marketed Since 1990

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs and Details</th>
</tr>
</thead>
</table>
| **Sulfonylureas/Secretagogues**| - Glipizide GITS (Glucotrol XL) - 1992  
- Repaglinide (Prandin) - 1998  
- Glimepiride (Amaryl) - 1995  
- Nateglinide (Starlix) - 2000 |
| **Biguanides**                  | - Metformin (Glucophage) - 1995  
- Metformin/gliburide (Glucovance) - 2000  
- Metformin/rosiglitazone (Avandamet) - 2002  
- Metformin/glipizide (Metaglip) - 2002  
- Metformin/pioglitazone (ACTOplus met) - 2005 |
| **Alpha-glucosidase Inhibitors**| - Acarbose (Precose) - 1995  
- Miglitol (Glyset) – 1999 |
| **Thiazolidinediones (glitazones)**| - Rosiglitazone (Avandia) - 1999  
- Pioglitazone (Actos) – 1999 |
| **Bile acid sequestrant (SE-BAS)**| - Colesevelam (Welchol) – 2007 |
| **Dopamine D2 RA**              | - Bromocriptine – 2009 |
## Pharmacologic Agents for Diabetes Marketed Since 1990 (cont’d)

| Insulin                          | Lispro (Humalog) – 2000  
|                                | Lispro/Protamine (75/25) – 2000  
|                                | Aspart (Novolog) – 2001  
|                                | Aspart/NPH (75/25) – 2002  
|                                | NPH/Regular (70/30) – 1990  
|                                | Glargine (Lantus) – 2000  
|                                | Glulysine (Apidra) – 2005  
|                                | Detemir (Levemir) – 2006  
|                                | Exubera – 2006 **  
| Amylin analogue                 | Pramlintide (Symlin) - 2005  
| Glucagon-like peptide 1 (GLP) agonist | Exenatide (Byetta) - 2005  
|                                | Liraglutide (Victoza) - 2010  
| Dipeptidyl peptidase IV (DPP IV) inhibitors | Sitagliptin (Januvia) - 2006  
|                                | Saxagliptin (Onglyza) - 2009  

## Typical A1C Reduction by Treatment Regimen

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of Administration</th>
<th>Year of Introduction or FDA Approval</th>
<th>Efficacy as Monotherapy, Measured as a Reduction in the Glycated Hemoglobin Concentration (A1C) percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Parenteral</td>
<td>1921</td>
<td>≥2.5</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>Pulmonary</td>
<td>2006</td>
<td>1.5</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>1946</td>
<td>1.5</td>
</tr>
<tr>
<td>Metformin*</td>
<td>Oral</td>
<td>1995</td>
<td>1.5</td>
</tr>
<tr>
<td>Alpha-glycosidase inhibitors</td>
<td>Oral</td>
<td>1995</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Oral</td>
<td>1997</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Glinides</td>
<td>Oral</td>
<td>1997</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Oral</td>
<td>2006</td>
<td>0.5-0.9</td>
</tr>
</tbody>
</table>

*Metformin has been available in other countries since 1957, but was approved in the United States in 1995.
GLP=glucagon-like peptide; DPP-IV=dipeptidyl peptidase IV.
Global Prevalence of Diabetes Projected to More Than Double by 2030

The Americas
2000: 33 million
2030: 67 million

Europe
2000: 33 million
2030: 48 million

Africa and Middle East
2000: 22 million
2030: 61 million

Asia and Australia
2000: 83 million
2030: 190 million

World
2000: 171 million
2030: 366 million

Diabetes Is the Most Common Primary Diagnosis in Patients with Kidney Failure

ESRD = end-stage renal disease.
USRDS 2004 Annual Data Report. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government. Available at: www.usrds.org.
Prevalence of Diabetes Macrovascular & Microvascular Complications

- Heart Attack: 9.8%
- Chest Pain: 9.5%
- Coronary Heart Disease: 9.1%
- Congestive Heart Failure: 1.1%
- Stroke: 1.8%
- Chronic Kidney Disease: 27.8%
- Foot Problems: 22.9%
- Eye Damage: 18.9%

- Diagnosed Diabetes
- Normal Blood Sugar Levels
EVERY 24 HOURS there are:

- 4,100 new cases of diabetes,
- 810 deaths due to diabetes,
- 230 amputations,
- 120 kidney failures, and
- 55 new cases of blindness

Association of Diabetes, Chronic Kidney Disease, and Secondary Hyperparathyroidism

- Diabetes has become epidemic in our society
- Diabetes is the leading cause of CKD
- CKD is also very prevalent and often unrecognized.
- eGFR should be ascertained to identify pts with CKD
- CKD is associated with many comorbid conditions including diabetes, hypertension, dyslipidemia and SHPT
- CKD is also associated with increased mortality
- Treatment of comorbid conditions can reduce progression and improve outcomes for those with CKD
## Specific Interventions for Comorbidities in Patients With Diabetes and CKD

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Intervention</th>
<th>Target Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Glycemic control</td>
<td>AACE A1C ≤6.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADA A1C &lt;7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>BP control</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Maintain lipids to target</td>
<td>LDL-C &lt;70 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TG &lt;150 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDL-C &gt;40 mg/dL</td>
</tr>
<tr>
<td>Secondary HPT</td>
<td>PTH control</td>
<td>CKD stage 3 = 35-70 pg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 = 70-110 pg/mL</td>
</tr>
<tr>
<td>Anemia</td>
<td>Reach Hgb goal</td>
<td>11-12 g/dL</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Dietary modification</td>
<td>Adequate energy intake</td>
</tr>
</tbody>
</table>

A1C = glycosylated hemoglobin; HPT = hyperparathyroidism; PTH = parathyroid hormone; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; Hgb = hemoglobin.
Metabolic and Pathologic Comorbidities as They Begin to Appear in CKD Stage 3

## Why Estimate GFR From SCr, Instead of Using SCr for Kidney Function?

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<thead>
<tr>
<th>Age</th>
<th>Gender</th>
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- 810 deaths due to diabetes,
- 230 amputations,
- 120 kidney failures, and
- 55 new cases of blindness

Proportion of Patients With A1C >6.5% (2003-2004)

National average = 67%

- Top 10 worst
- States where data for A1C >9% are available
- All other states

The shape of things to come
Global Projections for Diabetes 1995-2010

World
2000=151 million
2010=221 million
Increase: 46%

Global Prevalence of Diabetes Projected to More Than Double by 2030

The Americas
2000: 33 million
2030: 67 million

Europe
2000: 33 million
2030: 48 million

Africa and Middle East
2000: 22 million
2030: 61 million

Asia and Australia
2000: 83 million
2030: 190 million

World
2000: 171 million
2030: 366 million

Nationwide Diabetes Prevalence Categories

Top 10: Prevalence of diabetes* (20-79 age group) in 2007 (with 2025 prevalence)

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nauru</td>
<td>31</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>19</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>18</td>
</tr>
<tr>
<td>Bahrain</td>
<td>17</td>
</tr>
<tr>
<td>Kuwait</td>
<td>16</td>
</tr>
<tr>
<td>Oman</td>
<td>15</td>
</tr>
<tr>
<td>Tonga</td>
<td>15</td>
</tr>
<tr>
<td>Mauritius</td>
<td>14</td>
</tr>
<tr>
<td>Egypt</td>
<td>13</td>
</tr>
<tr>
<td>Mexico</td>
<td>12</td>
</tr>
</tbody>
</table>

*Comparative prevalence

SOURCE: DIABETES ATLAS THIRD EDITION, © INTERNATIONAL DIABETES FEDERATION, 2006
National Incidence of Diabetes

Estimates based on 2003 data.

India
China
U.S.
Russia
Japan

Incidence (millions)

International Diabetes Federation: http://www.idf.org/home/index.cfm?node=37
Obesity is a Prime Risk Factor for Hypertension, CKD, DM2 and Dyslipidemia
Adipose Tissue as an “Endocrine Organ”? 

- Leptin 
- Resistin 
- FFA 
- PAI$_1$ 
- Angiotensinogen 
- TNF-$\alpha$ 
- Adipsin 
- Adiponectin 
- IL-6 
- Cortisol
Obesity as a Risk Factor for CAD
The Importance of Abdominal Fat

Android Obesity

Gynoid Obesity
Which has higher cardiovascular risk?
The Apple

- Waist circumference
  - women >35 in (88 cm)
  - men >40 in (102 cm)
Visceral Fat Distribution: Normal vs Type 2 Diabetes

Normal vs Type 2 Diabetes

Courtesy of Wilfred Y. Fujimoto, MD.
### Pharmacologic Agents for Diabetes Marketed Since 1990

<table>
<thead>
<tr>
<th>Classification</th>
<th>Medication</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas/Secretagogues (meglitinides)</strong></td>
<td>Glipizide GITS (Glucotrol XL)</td>
<td>1992</td>
</tr>
<tr>
<td></td>
<td>Repaglinide (Prandin)</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td>Glimepiride (Amaryl)</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Nateglinide (Starlix)</td>
<td>2000</td>
</tr>
<tr>
<td><strong>Biguanides</strong></td>
<td>Metformin (Glucophage)</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Metformin/glyburide (Glucovance)</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Metformin/rosiglitazone (Avandamet)</td>
<td>2002</td>
</tr>
<tr>
<td></td>
<td>Metformin/glipizide (Metaglip)</td>
<td>2002</td>
</tr>
<tr>
<td></td>
<td>Metformin/pioglitazone (ACTOplus met)</td>
<td>2005</td>
</tr>
<tr>
<td><strong>Alpha-glucosidase Inhibitors</strong></td>
<td>Acarbose (Precose)</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Miglitol (Glyset)</td>
<td>1999</td>
</tr>
<tr>
<td><strong>Thiazolidinediones (glitazones)</strong></td>
<td>Rosiglitazone (Avandia)</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone (Actos)</td>
<td>1999</td>
</tr>
</tbody>
</table>
### Pharmacologic Agents for Diabetes Marketed Since 1990 (cont’d)

| Insulin                  | Lispro (Humalog) – 2000  
|                         | Lispro/Protamine (75/25) – 2000  
|                         | Aspart (Novolog) – 2001  
|                         | Aspart/NPH (75/25) – 2002  
|                         | NPH/Regular (70/30) – 1990  
|                         | Glargine (Lantus) – 2000  
|                         | Glulysine (Apidra) – 2005  
|                         | Detemir (Levemir) – 2006  
|                         | Exubera – 2006  
| Amylin analogue         | Pramlintide (Symlin) - 2005  
| Glucagon-like peptide 1 (GLP) agonist | Exenatide (Byetta) - 2005  
| Dipeptidyl peptidase IV (DPP IV) inhibitors | Sitagliptin (Januvia) - 2006  
|                         | Vildagliptin (Galvus) – FDA approval pending  

the Natural History Of Type 2 Diabetes

IGT = impaired glucose tolerance.
Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota.
Beta-Cell Function Declines as Type 2 Diabetes Progresses: Hypothetical Model

The Natural History of Type 2 Diabetes Mellitus

- Beta Cell Function
- Metabolic Toxicity
- Recovery
- GLP-1 (Incretins), TZD, Metformin

Intensive Treatment
EFFECTS OF DURATION OF TYPE 2 DIABETES MELLITUS ON INSULIN SECRETION

Farhad Zangeneh, MD,1 Punet S. Arora, MD,1 Peter J. Dyck, MD,2 Lynn Bekris,3 Ake Lernmark, PhD,2 Sara J. Achouhade,3 Ann L. Oberg, PhD,3 and Robert A. Rizza, MD,1

ABSTRACT

Objective: To gain insight into the effects of duration of type 2 diabetes on insulin secretion in patients with type 2 diabetes mellitus.

Methods: C-peptide concentrations were measured every 2 years before and after intravenous injection of 1 mg of glucagon in 89 patients with type 2 diabetes (51 men and 38 women) as part of the Rochester Diabetic Neuropathy Study in those subjects who participated in follow-up (median, 12 years; range, 6 to 14 years).

Results: Although insulin secretion decreased over time (P < 0.001) in the group as a whole, both the pattern and the rate of decline in C-peptide concentration differed considerably among the study subjects. Insulin secretion, whether measured as fasting C-peptide, 6-minute C-peptide, or postglucagon increment in C-peptide concentrations, declined with increasing duration of diabetes in approximately half of the patients but either increased or remained essentially constant over time in the other half. The decrease in insulin secretion was not associated with a deterioration in glycemic control because hemoglobin A1c also declined (P < 0.005) during the same interval.

Conclusion: We conclude that insulin secretion decreases over time in many patients with type 2 diabetes. Because the rate of decline is variable, the predictive value of any single measurement is limited. These data indicate that although a decrease in insulin secretion over time is characteristic of type 2 diabetes mellitus, it is not inevitable. (Endocr Pract. 2006;12:388-393)

INTRODUCTION

Diabetes develops when the secretion of insulin is insufficient to maintain plasma glucose concentrations within the normal range (1). Type 1 diabetes results from immune destruction of pancreatic beta cells (2,3). The cause of beta cell loss in patients with type 2 diabetes is less well defined and is likely to be multifactorial. Although it is generally accepted that type 2 diabetes is associated with a progressive loss of insulin secretion over time (4-9), no published studies have documented the rate of loss of insulin secretion in patients who have had type 2 diabetes longer than 10 years.

Many studies have examined the pattern of insulin secretion within the first 5 to 10 years after diagnosis of diabetes. For example, the United Kingdom Prospective Diabetes Study (UKPDS) (5) and the Belfast Diet Study (4) used homeostasis model assessment of beta cell function to analyze insulin secretion in patients with newly diagnosed type 2 diabetes. Both studies showed that beta cell function (an index of insulin secretion) decreased during the 5 to 10 years after diagnosis of diabetes and that this decrease was associated with a deterioration in glycemic control (4,5). Skad el al (6) also reported that fasting and 2-hour postglucagon insulin concentrations in Pima Indians decreased during the first 5 to 7 years after diagnosis of diabetes. Similarly, Niskanen et al (8) reported that the cumulative incidence of insulin deficiency, defined as a plasma C-peptide concentration of less than 0.7 nmol/L after intravenous injection of 1 mg of glucagon, increased from 3% at 5 years after diagnosis of diabetes to 7% at 10 years after diagnosis. Furthermore, Mourits-Jarvis et al (9) reported that the postglucagon increment in C-peptide level decreased by 35% in patients of sub-Saharan African origin during the first 10 years after diagnosis of type 2 diabetes. In contrast, Borg et al (7) noted that when antibody-positive subjects (that is,
Response and Beta-Cell Balancing Beta-Cell Workload

Insulin is enhanced and glucagon is suppressed.

Mean (SE)
Response and Beta-Cell Balancing Beta-Cell Workload
Insulin Is Enhanced and Glucagon Is Suppressed

- Healthy Subjects (n = 14)
- Type 2 Diabetes (n = 12)

Mean (SE)
Plasma Glucose and Insulin Responses in Patients With Normal Glucose Tolerance, Impaired Glucose Tolerance, and Type 2 Diabetes


Table:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Plasma Glucose (mmol/L)</th>
<th>Plasma Insulin (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>11.0</td>
<td>500</td>
</tr>
<tr>
<td>IGT</td>
<td>16.5</td>
<td>375</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>11.0</td>
<td>250</td>
</tr>
</tbody>
</table>

Graph:

- Plasma Glucose
- Plasma Insulin

- NGT
- Type 2 DM
- IGT
The Incretin Effect
Beta-Cell Response to Oral vs IV Glucose

Crossover of Healthy Subjects (n = 6)

- Oral Glucose
- Intravenous (IV) Glucose

Plasma Glucose (mg/dL)

C-peptide (nmol/L)

Mean (SE): *P<0.05
Data from Nauck MA, et al. J Clin Endocrinol Metab. 1986;63:492-498
The Incretin Effect Is Diminished in Type 2 Diabetes

GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

Beta cells: Enhances glucose-dependent insulin secretion

Data from Nauck MA, et al. Diabetologia. 1996;39:1546-1553
Data from Drucker DJ. Diabetes. 1998;47:159-168
Acutely Improving Beta-Cell Response
BYETTA Restored First-Phase Insulin Response

Insulin (pM/kg/min)

Healthy Controls (n = 12)

Type 2 Diabetes (n = 13)

Placebo
BYETTA

See Important Safety Information included in this presentation
Mean (SE), Evaluable
Data from Fahs S, et al. Diabetologia 2004;47(suppl 1):A279
Rosiglitazone Restores β-cell Insulin content in Pancreatic Islets
Pioglitazone Preserves Pancreatic Islet Structure: KKAγ Mice: Photomicrographs - Pancreatic Islets

A. Untreated KKAγ Mouse
   Sparsely granulated β-cells

B. Pioglitazone-Treated KKAγ Mouse
   Pronounced granulation of the β-cells and restored structural integrity

Diani AR et al. Diabetes 2003; 52 (Suppl 1) abstract
Patterns of Insulin Response to IV Glucose: Non-diabetic and Diabetic Individuals

- **1st Phase**: Immediate Insulin Secretion in response to IV Glucose Stimulus.
- **2nd Phase**: Delayed Insulin Secretion.

**Non-Diabetic**

- Peaked Insulin Secretion at -5 to 20 minutes.
- Steady Insulin Secretion until 90 minutes.

**Type 2 Diabetes**

- Consistent Insulin Secretion with no significant peaks or valleys.

![Graph showing patterns of insulin response to IV glucose](image-url)
In type 2 diabetes, mealtime insulin secretion is blunted and delayed.

Diabetes Management

Complications of Type 2 Diabetes

Heart
- Coronary heart disease
- Cardiovascular disease

Blood Vessels
- Peripheral artery disease
- Intermittent claudication

Kidneys
- Microalbuminuria
- Nephropathy

Eyes
- Retinopathy
- Glaucoma

Nerves
- Chronic sensorimotor distal symmetric polyneuropathy
- Gastroparesis

The Dallas Heart Study Population

Nondiabetic

Diabetic

Patients (%)

CKD Stage: None 1-2 3-5 None 1-2 3-5

CAC = coronary artery calcification.
Normal Retina (No Apparent Retinopathy)

Courtesy EyeTel’s DigiScope®
Nonproliferative Diabetic Retinopathy
Proliferative Diabetic Retinopathy

Courtesy EyeTel’s DigiScope®
Diabetic Macular Edema

Courtesy EyeTel’s DigiScope®
Microvascular Damage Leads to Diabetic Peripheral Neuropathy (DPN)

- Examination of tissues from patients with diabetes reveals capillary damage, including occlusion in the vasa nervorum\(^1,2\)
- Reduced blood supply to the neural tissue results in impairments in nerve signaling that affect both sensory and motor function\(^2\)

---

Symptoms and Signs of Diabetic Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Numbness or loss of feeling</td>
<td>• Diminished vibratory perception</td>
</tr>
<tr>
<td>(asleep or “bunched up sock</td>
<td>• Decreased knee and ankle reflexes</td>
</tr>
<tr>
<td>under toes” sensation)</td>
<td>• Reduced protective sensation such as</td>
</tr>
<tr>
<td>• Prickling/Tingling</td>
<td>pressure, hot and cold, pain</td>
</tr>
<tr>
<td>• Aching pain</td>
<td>• Diminished ability to sense position of</td>
</tr>
<tr>
<td>• Burning pain</td>
<td>toes and feet</td>
</tr>
<tr>
<td>• Lancinating pain</td>
<td></td>
</tr>
<tr>
<td>• Unusual sensitivity or</td>
<td></td>
</tr>
<tr>
<td>tenderness when feet are</td>
<td></td>
</tr>
<tr>
<td>touched (allodynia)</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms and signs progress from distal to proximal over time.
How Far Would You Go to Minimize the Impact of Diabetic Peripheral Neuropathy?

Clawing toes, callus, superficial ulceration¹

Plantar ulcer, callus²

Calluses scraped away, revealing ulcers³

Images: 1,2. Rayaz A Malik, MBChB, PhD, MRCP. 3. Edward J Bastyr, III, MD.
Less Chronic Complications

- DCCT type 1 DM
- UKPDS type 2 obese
- Kumamoto type 2 lean

Improve insulin Resistance
- ↓ Glucose and lipotoxicity (metabolic toxicity)

Improve βeta-Cell function
- ↓ βeta cell fatigue?
- ↑ βeta cell mass?
Evidence for Effects of Good Glycemic Control on Complications, Including Nephropathy

<table>
<thead>
<tr>
<th>Complication</th>
<th>DCCT A1C: (9 → 7%) N = 1441</th>
<th>Trial Kumamoto (9 → 7%) N = 110</th>
<th>Trial UKPDS (8 → 7%) N = 5102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>↓ 76%</td>
<td>↓ 69%</td>
<td>↓ 21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>↓ 54%</td>
<td>↓ 70%</td>
<td>↓ 34%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>↓ 60%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

DCCT = The Diabetes Control and Complications Trial.
Diabetes Management

The UKPDS Trial: Effect of Intensive Therapy on HbA$_{1c}$

Intensive therapy reduced HbA$_{1c}$ by 0.9% over 10+ years

![Graph showing reduction in HbA$_{1c}$ levels over time with intensive therapy compared to conventional therapy.]

Every 1% A1C drop can reduce long-term diabetes complications

Correlation between a 1% A1C decrease and reduced risk of complications

<table>
<thead>
<tr>
<th>Cardiovascular complications</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvascular complications</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes-related deaths</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Impact of A1C Reduction

According to the UKPDS (N=3642)

- For every 1% reduction in A1C, there is a 37% decrease in relative risk of microvascular complications
- For every 1% reduction in A1C, there is a 14% decrease in relative risk of fatal and nonfatal MI
- Lower the glycemia, lower the risk of vascular complications

*UKPDS = UK Prospective Diabetes Study
Intensive therapy reduced HbA1c by 1.8% over 10 years.

Conventional: 8.9%

Intensive: 7.1%

DCCT: Diabetic Complication Event Rates

Distribution of HbA1c in the Former DCCT Intensive and Conventional Groups During EDIC

<table>
<thead>
<tr>
<th>EDIC year</th>
<th>Conventional</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

Mean HbA$_{1c}$ during EDIC
Conventional 8.2%
Intensive 8.0%

$p = .0019$

Cumulative Incidence of New Clinical Albuminuria >300 mg/24 h During EDIC

83% risk reduction
$p < .0001$

Conventional

Intensive

## Advanced Kidney Outcomes by Year 8 of EDIC Reduced by Intensive Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive (n = 676)</th>
<th>Conventional (n = 673)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine &gt;2 mg/dL</td>
<td>5* (0.7%)</td>
<td>19 (2.8%)</td>
</tr>
<tr>
<td>Dialysis or Transplant</td>
<td>4 (0.6%)</td>
<td>7 (1.0%)</td>
</tr>
</tbody>
</table>

EDIC = Epidemiology of Diabetes Interventions and Complications.

*P = 0.004.

Carotid Intima-Media Thickness With Intensive Insulin Therapy DCCT-EDIC

Mean change in intima-media thickness (mm)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Common carotid artery</th>
<th>Combined internal and carotid artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive treatment (n=618)</td>
<td>0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>Conventional treatment (n=611)</td>
<td>-0.05</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

P=0.01

P=0.02

EDIC Findings: Cardiovascular Events

**Non-Fatal MI, Stroke, or CVD Death**

- Risk reduction 57%
- 95% CI: 12% to 79%
- P = 0.02


The National Diabetes Education Program

www.ndep.nih.gov

A joint program of NIH and CDC
## Major Goals for Diabetes Management

<table>
<thead>
<tr>
<th>Goals</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic control</td>
<td>Prevent/limit microvascular complications</td>
</tr>
<tr>
<td>Controlled lipid metabolism and blood pressure</td>
<td>Prevent/limit macrovascular complications</td>
</tr>
<tr>
<td>Balanced food intake and energy output</td>
<td>• Control weight</td>
</tr>
<tr>
<td></td>
<td>• Improve overall health</td>
</tr>
</tbody>
</table>

Summary of Revisions for the 2006 Clinical Practice Recommendations

Beginning with the 2005 supplement, the Clinical Practice Recommendations contained only the “Standards of Medical Care in Diabetes” and selected other position statements. This change was made to emphasize the importance of the “Standards” as the best source to determine ADA recommendations. The position statements in the supplement are updated yearly. Position statements not included in the supplement will be updated as necessary and republished when completed. A list of the position statements not included in this supplement appears on p. 575.

Format changes
- Page numbers now appear in the “Contents” for ease in locating particular sections
- Recommendations are now listed at the beginning of each section

Additions to the Standards of Medical Care in Diabetes
- Medical nutrition therapy (MNT)—extensively enhanced
- Diabetes self-management education (DSME)
- Physical activity
- Neuropathy

Summary of Revisions to Standards of Medical Care for Diabetes
- Assessment of glycemic control
- Use of point-of-care testing for HbA1c (A1c) allows for timely decisions on therapy changes, when needed (E)
- Glycemic goals
- The A1c goal for patients in general is <7% (B)
- The A1c goal for the individual patient is an A1c as close to normal (<6%) as possible without significant hypoglycemia (E)
- Nephropathy
- To reduce the risk of nephropathy, protein intake should be limited to the recommended dietary allowance (RDA) 0.8 g/kg (B)
- Serum creatinine in those with any degree of chronic kidney disease (CKD) should be measured at least annually for the estimation of glomerular filtration rate (GFR) in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine alone should not be used as a measure of kidney function but rather used to estimate GFR and stage the level of CKD (E)

Members of the Professional Practice Committee
Vivian Fonseca, MD, Chair
Evan M. Benjamin, MD
Lawrence Blonde, MD
Kenneth Copeland, MD
Marjorie L. Cypress, MS, RN, CDE
Hertzel C. Gerstein, MD, Msc, FRCP
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Elizabeth Mayer-Davis, MS, PhD, RD
James Meigs, MD, MPH
Michael P. Pignone, MD, MPH
Janet H. Silverstein, MD
Geralyn R. Spollett, MSN, C-ANP, CDE
Judith Wylie-Rossett, RD, EdD
Nathaniel G. Clark, MD, MS, RD (Staff)
## 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><strong>HbA₁c</strong></td>
<td>&lt;6.0%* (Individual goal)</td>
<td>≤6.5%*</td>
<td>&lt;6.5%*</td>
</tr>
<tr>
<td></td>
<td>&lt;7.0%* (General goal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FPG</strong></td>
<td>90-130 mg/dL</td>
<td>&lt;110 mg/dL</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td><strong>PPG†</strong></td>
<td>&lt;180 mg/dL</td>
<td>&lt;140 mg/dL</td>
<td>&lt;145 mg/dL</td>
</tr>
</tbody>
</table>

*Referenced to a nondiabetic range of 4.0% to 6.0% using a DCCT-based assay
†Upper limit of normal = 6.0%

ADA = American Diabetes Association; ACE = American College of Endocrinology; IDF = International Diabetes Federation; FPG = fasting plasma glucose; PPG = postprandial plasma glucose
HbA$_{1C}$ Predicts CVD Mortality in Men

p<0.001 age-adjusted death rates for linear trend.

Just to let you know how my diet’s going.

Leggett
Diabetes Management

**Importance of Weight Control**

- Excess body weight is principal risk factor for type 2 diabetes
- Obesity alters insulin receptors
- Obesity promotes insulin resistance and impaired glucose tolerance

**Moderate weight loss (4.5 to 9 kg) lowers hyperglycemia, hyperlipidemia, and hypertension**

Low-CHO vs. Low-Fat Diets

- Meta-analysis of 5 trials/n=447

- Weight loss
  Clinically irrelevant differences

- Lipids/lipoproteins
  Low-fat diet: more favorable changes in Total-C (10 mg/dl) and LDL-C (7.7 mg/dl)
  Low-CHO diet: more favorable changes in TG(31 mg/dl) and HDL-C (3.1 mg/dl)

- Glucose/Insulin
  No differences xc in pts with T2 DM (HbA1c)

Arch Intern Med 2006;166:285-293
Diet, weight loss and lipids

- 5-10% weight loss required for metabolic benefits
- Atkins, Ornish, Weight Watchers and Zone diets are equally effective
- Adherence to diet rather than the diet determines success
- High protein or monounsaturated fat diet may be best

JAMA 2005;294:2455-2464
Adverse Effects of Low-Fat Diets on HDL-C

Subjects on the very-low-fat diets had lower HDL-C levels without significantly lower LDL-C levels. This study’s findings confirm the epidemiologic observation that dietary fat increases HDL-C concentrations.

Trans Fatty Acids and CV Disease

• Impact on LDL-C and HDL-C
  trans fat worse than saturated fat
  ↑LDL-C, ↓HDL-C, ↑TC/HDL-C ratio

• Adverse effects with 2-7 g/d

• Limit to < 0.5 g/d or eliminate trans FA

• 50% reduction in dietary trans FA reduces CVEs by 10-12%; elimination of trans FA, reduces CVEs by 19-22%

Omega-3 Fatty Acids
Miracle substance or what?

• 48 RCTs and 41 cohort studies analyzed
• Trial results: inconsistent
• Pooled estimate: no evidence of reduced mortality or combined CV events
• Conclusion: Omega-3 fatty acids do not have a clear effect on all-cause mortality, CV events or cancer

Hooper et al BMJ pub online 3/24/06
Reduction of *Homocysteine*

- Folic acid and B vitamins reduce Hcy levels by ~30% but do not reduce CV events
  - 3 RCT:
    - 3680 patients with stroke (VISP)$^1$
    - 3749 patients with recent MI (NORVIT)$^2$
    - 5522 patients with diabetes (HOPE-2)$^3$

1. *JAMA* 2004;291:565-575
Exercise

“An agent with blood pressure and lipid-lowering, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight reducing, insulin sensitizing, glucose-lowering, tranquilizing, hypnotic and antidepressant qualities”

Modified from WC Roberts, EIC
Am J Cardiol 1984;53:261
Exercise or lack thereof . . .
Physical activity

- 60% of adults do not engage in the recommended amount of activity
- 25% of adults are not active at all
- 14% of youth report no recent physical activity
Walking the dog
Summary of Concepts

• Diabetes is an emerging pandemic with global health and economic consequences

• Poorly controlled diabetes leads to long-term health complications

• Control of blood pressure, lipid levels, glycemia, and weight are cornerstones of diabetes management
Medical Nutrition Therapy (MNT) for Diabetes Management
MNT for Diabetes Management

Factors Affecting Glycemic Control

• Nutrition
  • Physical activity
  • Medication
  • Self-care
    – Blood glucose monitoring
    – Behavior modification
## Recommended Macronutrient Distribution

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>ADA* (% Energy)</th>
<th>EASD† (% Energy)</th>
<th>Diabetes UK (% Energy)</th>
<th>CDA‡ (% Energy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>15-20</td>
<td>10-20</td>
<td>≤1 g/kg body weight</td>
<td>15-20</td>
</tr>
<tr>
<td>Fat</td>
<td>25-35</td>
<td>25-35</td>
<td>&lt;35</td>
<td>≤30</td>
</tr>
<tr>
<td>SFA</td>
<td>&lt;7</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>≤10</td>
</tr>
<tr>
<td>MUFA</td>
<td>individually tailored</td>
<td>60-70 for CHO + cis-MUFA individually tailored</td>
<td>10-20 cis-MUFA</td>
<td>should be used in meal plan when possible</td>
</tr>
<tr>
<td>PUFA</td>
<td>~10</td>
<td>≤10</td>
<td>n–6 &lt;10 n–3, consume fish once or twice weekly</td>
<td>&lt;10</td>
</tr>
<tr>
<td>CHO</td>
<td>45-65 (CHO + fat); Individually tailored</td>
<td>45-60 (CHO + fat); Individually tailored, ↓ GI and ↑ fiber foods</td>
<td>45-60 emphasize foods with ↓ GI</td>
<td>50-60 ↓ GI foods may be helpful</td>
</tr>
</tbody>
</table>
MNT for Diabetes Management

2006 ADA MNT Recommendations

- People with diabetes should receive individualized MNT to reach treatment goals

- Monitoring the amount and type of CHO is key strategy in achieving glycemic control

- Use of glycemic index may provide additional benefit over consideration of total CHO alone

Primary Goal: Achieve and maintain optimal metabolic outcomes — glycemic control and lipid levels

- Moderate postprandial blood glucose (PPG) response
- Achieve and maintain healthy weight
- Address individual nutrition needs

Optimal glycemic management requires targeting PPG, FPG, and A1C—the glucose triad

Strive for Ideal: Address BOTH FPG and PPG

At A1Cs ranging from 7.3–8.4%, overall glycemia is impacted equally by FPG and PPG\(^1\)*

A1C =

*The relative contribution of fasting and postprandial blood glucose varies with A1C range.

FPG and PPG Contribute to A1C Management

N=290 non-insulin-using patients with type 2 diabetes.
FPG=fasting plasma glucose; PPG=postprandial plasma glucose.
Mortality Risk With Increasing PPG, Regardless of FPG Levels

*Adjusted for age, sex, and study center.
Postprandial glucose levels impacted by:

- Carbohydrate amount
  - Meal spacing
- Carbohydrate types
  - Slowly digesting
  - Low glycemic-index (GI) foods
Points of absorption of slowly and rapidly digested carbohydrate in the gastrointestinal tract

Slowly Digested CHO

Rapidly Digested CHO

Glycemic Effects of Regular vs Modified Maltodextrin

Slowly Digesting Carbohydrates

• Modifications to starch may result in slow glucose release and/or resistance to digestion
• Resistant starch promotes reduced PPG response
The 2-hour blood sugar response of a high GI food vs a low-GI food

Reference Food

Time
Glucose, GI = 100

Test Food

Time
Lentils, GI = 40
## Benefits of Low-GI Foods

<table>
<thead>
<tr>
<th>High GI-Foods</th>
<th>Low GI-Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Elicit higher insulin levels</td>
<td>• Produce lower insulin response</td>
</tr>
<tr>
<td>• Greater intake associated with insulin resistance and elevated TG</td>
<td>• Improve glucose uptake by tissues</td>
</tr>
<tr>
<td></td>
<td>• Intake at breakfast improves glucose tolerance at lunch</td>
</tr>
</tbody>
</table>

Foster-Powell et al. *AJCN*, 2002;76:5-56; Willet et al *AJCN* 2002;76(suppl):274S-80S.
MNT for Diabetes Management

Diabetes-Specific Formulas: 20 Years of Clinical Research

- Sturmer W et al: Clin Nutr 1994;13;221-227
- Craig LD et al: Nutrition 1998;14:529-534
- Fix BM et al: Ann Nutr Metab 2001;45(suppl 1):277
Objective: Determine benefits of nutritional support and diabetes-specific formulas in patients with diabetes

Source: *Diabetes Care* 2005;28:2267-2279

Representative Studies:
MNT for Diabetes Management
Review and Meta-Analysis (Elia et al)

Analysis Overview
23 studies (784 patients)
• Type 2 diabetes (n=16)
• Type 1 and stress diabetes (n=7)
• Oral supplements (n=16)
• Tube feedings (n=7)

Study Outcomes
• Glycemic status
• Lipid status
• Medication requirements
• Nutritional status
• Quality of life
• Complications
• Mortality
### MNT for Diabetes Management

**Meta-Analysis: Glycemic Outcomes** *(Elia et al)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decrease from Baseline (compared to standard formulas)</th>
<th>Number of Studies Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPG</td>
<td>18.5 mg/dL</td>
<td>6</td>
</tr>
<tr>
<td>Peak Glucose</td>
<td>28.6 mg/dL</td>
<td>2</td>
</tr>
<tr>
<td>AUC Glucose</td>
<td>31%-45%</td>
<td>4</td>
</tr>
</tbody>
</table>

**Several studies showed significant reduction in insulin requirements (26% to 71%)**

PPG = postprandial glucose level  
AUC = area under the curve

MNT for Diabetes Management

Meta-Analysis: Conclusion (Elia et al)

• Diabetes-specific formulas associated with improved glycemic control compared to standard formulas
• Improvement seen with short- and long-term use
• Long-term use may be implicated in reducing chronic complications (e.g., CV events)
Postprandial Blood Glucose Response

Objective
• To compare blood glucose response of Glucerna® SR to standard nutritional formula in people with type 2 diabetes.

Methods
• Subjects
  – 84 patients with type 2 diabetes
• Randomized, double-blind, parallel trial
  – Glucerna® SR or standard nutritional formula
• Meal tolerance test (MTT)
  – Fasted subjects consumes 8 fl oz beverage w/in 10 minutes.
  – Blood samples obtained at time 0, and 30, 60, 90, 120, 180 and 240 min.
• Variables
  – Adjusted blood glucose response over 4 hours.
  – Adjusted peak glucose response.

Fix et al., Ann Nutr Metab 2001;45 (suppl 1):277.
Postprandial Blood Glucose Response

Fix et al., Ann Nutr Metab 2001;45 (suppl 1):277.
Clinical Trial Data

**Objective**

- To compare the effects of diet + Glucerna® SR to diet alone for weight loss, glycemic control, and lipid profile in people with type 2 diabetes

**Methods**

- Subjects
  - 171 patients with type 2 diabetes
- Baseline measurements
  - HbA$_{1c}$
  - Lipid profile
  - Body weight
- Randomized to two diet plans (± Glucerna® SR)
- 12-wk follow-up
  - Assess changes

Clinical Trial Data

Diet Plan

Diet with Glucerna® SR

Meal Plan
45-50% CHO
20% protein
30-35% fat

Phase I (weeks 1-4)
• 1000 kcal/day (F)
• 1200 kcal/day (M)

Phase II (weeks 5-12)
• 1200 kcal/day (F)
• 1500 kcal/day (M)

Diet without Glucerna® SR

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Metabolic Benefits of Glucerna® SR

**HbA$_{1c}$ vs. baseline**
-0.67%
p<0.001

**WEIGHT**
-4.08 kg
p<0.0001

**TRIGLYCERIDES vs. baseline**
-47 mg/dL
p=0.002

**TOTAL CHOLESTEROL vs. baseline**
-11 mg/dL
p=0.002
The Development of Integrated Management:

• **UKPDS**
  – Importance of intensive blood glucose control in reducing microvascular complications

• **Foundation for lifestyle intervention programs**
  • Nutrition
  • Physical activity
  • Diabetes self management education

• **Findings from lifestyle intervention programs**
  – Intensified program was as effective as insulin in controlling poorly controlled Type 2 diabetics (Aas et al 2005)
  – SLIM (2003) and DPS (2004) studies improved glucose tolerance, blood pressure, lipids and anthropometric indices
Diagnostic Criteria Associated with Glucose Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>FPG</th>
<th>2-Hour PG on OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired Fasting Glucose</td>
<td>7.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>6.1 mmol/L</td>
<td>140 mg/dL</td>
</tr>
<tr>
<td></td>
<td>126 mg/dL</td>
<td>200 mg/dL</td>
</tr>
<tr>
<td></td>
<td>100 mg/dL</td>
<td>11.1 mmol/L</td>
</tr>
<tr>
<td></td>
<td>7.8 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Diabetes Mellitus

Diabetes Prevention

The Well-Tech China Study *(Sun J et al)*

**Objective:**
To test the effectiveness of a **structured intervention** for overweight diabetes patients.

**Study Design:**

<table>
<thead>
<tr>
<th>Treatment: n= 100</th>
<th>Control: n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diabetes education</td>
<td></td>
</tr>
<tr>
<td>• Diet management, exercise guide</td>
<td></td>
</tr>
<tr>
<td>• Glucerna SR once daily as a meal replacement</td>
<td></td>
</tr>
<tr>
<td>• Glucose monitoring ≥6/wk</td>
<td></td>
</tr>
<tr>
<td>• Medical follow-up once a week</td>
<td></td>
</tr>
<tr>
<td>• Healthy lifestyle guide</td>
<td>• Diabetes education</td>
</tr>
<tr>
<td></td>
<td>• Diet management, exercise guide</td>
</tr>
</tbody>
</table>

- **Weight management**
- **Diabetes management**
- **Health & Productivity**
- **Complication risks**
- **Quality of life**

Subjects screened, randomized, and informed consent obtained

**Schedule**

**Intervention Group**

- **WK 0**
- **WK 4**
- **WK12**
- **WK24**

**Baseline**

- Diabetes and complications assessment and control, productivity, QOL, energy expenditure, diet/nutrition assessment, health exam, glucose and insulin tests

**Mid-Term**

- Diabetes and complications assessment and control, diet/nutrition assessment, health exam, glucose and insulin tests

**End**

- Diabetes and complications assessment and control, productivity, QOL, energy expenditure, diet/nutrition assessment, health exam, glucose and insulin tests

**Control Group**

- **WK 0**

Data collection, entry, processing, and analysis with all lab data
### Clinical Trial: Well-Tech China Study (Sun et al)

**High Retention and Compliance Rates**

Subject Withdraw (WD) Rate 4/150 = 2.66%

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Huadong Hosp Site</th>
<th>Minghang District</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SR</td>
<td>Control</td>
</tr>
<tr>
<td>BL</td>
<td>55</td>
<td>26</td>
</tr>
<tr>
<td>Mid</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>End</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>WD</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Clinical Outcomes

- HbA$_{1c}$
- Fasting glucose (mmol/L)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Weight (kg)
- Waist circumference (cm)
# Intra-Group Results: Well-Tech China Study (Sun et al)

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group</th>
<th>Control Group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 month</td>
<td><em>P</em> value</td>
<td>Baseline</td>
<td>6 month</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>7.1</td>
<td>6.3</td>
<td>&lt;0.0001</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td><strong>Fasting glucose (mmol/L)</strong></td>
<td>8.62</td>
<td>7.39</td>
<td>&lt;0.0001</td>
<td>8.7</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>131.2</td>
<td>123.7</td>
<td>&lt;0.0001</td>
<td>134.8</td>
<td>133.1</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>87.0</td>
<td>83.8</td>
<td>&lt;0.0001</td>
<td>88.8</td>
<td>88.6</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>75.7</td>
<td>72.8</td>
<td>&lt;0.0001</td>
<td>75.6</td>
<td>73.8</td>
</tr>
<tr>
<td><strong>Waist Circumference (cm)</strong></td>
<td>92.0</td>
<td>88.6</td>
<td>&lt;0.0001</td>
<td>91.3</td>
<td>91.4</td>
</tr>
</tbody>
</table>
Correlation Between Weight Gain and Treatment

Type 1 patients in DCCT, baseline to year 1

Type 2 patients in UKPDS

Conclusion: Well-Tech China Study (Sun et al)

Structured intervention that includes Glucerna® SR significantly reduces:

• HbA$_{1c}$
• Fasting plasma glucose
• Systolic and diastolic blood pressure
• Body weight
• Waist circumference

in overweight persons with type 2 diabetes.
Newly Presented at IDF: Change of Metabolic Syndrome* Incidence (Sun et al)

![Graph showing change from baseline for intervention and control groups. The intervention group shows a large negative change, indicating a significant improvement, while the control group shows a smaller change.

*IDF Definition

Advancing Nutrition in Diabetes Management 
June 06

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Structured intervention that includes Glucerna® SR significantly reduces:

- $\text{HbA}_{1c}$
- Fasting plasma glucose
- Systolic and diastolic blood pressure
- Body weight
- Waist circumference

in overweight persons with type 2 diabetes.
Clinical Trial: Comparison of two nutritional diabetic formulations

Objective
To compare the effects on plasma glucose, insulin, C-peptide and triglycerides in non-diabetic subjects

Study Design
• 29 obese non-diabetic subjects (BMI 34.6 ± 4.2 kg/m²) were included in a randomized and double blind trial

Product Differences

<table>
<thead>
<tr>
<th>Enterex®</th>
<th>Glucerna SR®</th>
</tr>
</thead>
<tbody>
<tr>
<td>273 kcal</td>
<td>273 kcal</td>
</tr>
<tr>
<td>9.17gm fat</td>
<td>8 gm fat</td>
</tr>
<tr>
<td>3.4 gm fibre (90% soluble)</td>
<td>1.8 gm fibre 1 gm FOS</td>
</tr>
<tr>
<td>maltodextrin</td>
<td>fructose</td>
</tr>
</tbody>
</table>

Presented at IDF December 2006; Escalante-Pulido M., et. Al.
Enterex Diabetic®

- Calories: 237 kcal
- Carbohydrate: 26.7 gr (106.8 kcal) = 45%
- Fat: 9.17 gr (82.5 Kcal) = 34.8%
- Protein: 11.9 gr (47.6 Kcal) = 20.2%
- Fiber: 3.4 gr (90% soluble)
- Maltodextrin - Sucralose
- Glycemic Index = Unknown

Glucerna SR®

- Calories: 237 kcal
- Carbohydrate: 29 gr (106.8 kcal) = 47%
- Fat: 8 gr (82.5 Kcal) = 33%
  (75% MUFA)
- Protein: 11 gr (47.6 Kcal) = 20%
- Fiber: 1.8 gr and 1.0 gr FOS (64% insoluble)
- Fructose
- Modified Maltodextrin / Fibersol
- Glycemic Index 30

Nutrient | ADA* (% Energy)
--- | ---
Protein | 15-20
Fat | 25-35
SFA | <7
MUFA | individually tailored
PUFA | ~10
CHO | 45-65 (CHO + fat); Individually tailored

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Clinical Trial: Glycemic Response on Studied Group
n=29

Glucose Response mg/dL vs Minutes

- Glucerna SR
- Enterex diabetic

* denotes statistically significant results at 30, 60, and 180 minutes

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Clinical Trial: Insulin Response on the Studies Group n=29

* denotes statistically significant results at 30, 60, and 180 minutes

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June 06

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Clinical Trial: Glucose Area Under the Curve (AUC)

$\rho = 0.0003$

$\text{mg/dl/3 hr}$

Glucerna SR  Enterex Diabetic

Presented at IDF December 2006; Escalante-Pulido M., et. Al.
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Clinical Trial: Insulin Area Under the Curve (AUC)

$p = 0.004$

Glucerna SR  Enterex Diabetic

mU/ml/3 hr

Insulin AUC

Presented at IDF December 2006; Escalante-Pulido M., et. Al.

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June 06

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Summary of Concepts

Glucerna® SR is a low-GI diabetes-specific formula that:

• Has been clinically shown to improve glycemic control in diabetic subjects via its unique blend of CHO, increased MUFA, fructose, and fiber

• Improved glycemic control and lipid profile and lowered body weight in 3-months*

• Significantly reduced HbA$_{1c}$, FPG, SBP, DBP, body weight, and waist circumference in 6-months**

• Glucerna® SR nutritional profile enabled more favorable glycemic response and insulin response*** compare to Enterex Diabetic formula

* Data on file (Study DJ19). Ross Products Division, Abbott Laboratories, Jan. 2003
** Well-Tech China Study
*** Comparison of Two Nutritional Diabetic Formulations
Advancing Nutrition in Diabetes Management

• Optimal diabetes management improves metabolic outcomes, reduces complications, and improves quality of life

• *Nutrition is an essential component of diabetes management*

• Diabetes-specific formulas can be integral to nutrition management strategies complementing medical management that improve metabolic outcomes