Diabetes: What is the scope of the problem?

Elizabeth R. Seaquist MD
Division of Endocrinology and Diabetes
Department of Medicine
Director, General Clinical Research Center
Pennock Family Chair in Diabetes Research
University of Minnesota
Diabetes Mellitus

A disorder of glucose metabolism resulting in hyperglycemia as a result of insulin deficiency or abnormal insulin secretion and action.
Impact of Type 1 and Type 2 Diabetes

Individuals diagnosed \( \uparrow \) by 1.3 million each year

Especially prevalent in African and Hispanic Americans

Shortens average life expectancy by up to 15 years

Increasingly affects all age groups

6th leading cause of death

Diabetes

Diabetes Trends* Among Adults in the U.S.,
(Includes Gestational Diabetes)

BRFSS, 1990, 1995 and 2001

1990 1995 2001

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<th></th>
<th>1990</th>
<th>1995</th>
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2002 Diabetes prevalence in US by age, gender, race

Prevalence per 100 people

- White male
- White female
- Black male
- Black female
- Hispanic male
- Hispanic female

CDC
Type 2 diabetes 90-95%

Gestational diabetes 3-5%

Other 1-2%

Type 1 diabetes 5-10%
Type 1 Diabetes Mellitus

Insulin Dependent Diabetes Mellitus (IDDM), Type I Diabetes, Ketosis-prone diabetes, Juvenile onset diabetes mellitus

• Caused by an absolute deficiency of insulin
• Occurs because of autoimmune destruction of pancreatic beta cells
• Arises in genetically susceptible individuals exposed to a triggering factor
Beta cell mass over time:

- Genetic susceptibility
- Overt immunologic abnormalities (ICA+ GAC+)
- Decreasing insulin release (Glucose normal)
- Overt diabetes (C-peptide present)
- No C-peptide

Age, y
Type 1 diabetes

• Peak time of clinical onset is at puberty but can present at any age
• Patients are usually lean
• Concordance rate for identical twins is ~50%
• Insulin therapy is required for survival
Type 2 Diabetes Mellitus

Non-insulin dependent diabetes mellitus (NIDDM), Adult onset diabetes mellitus

- Occurs because of a defect in both insulin secretion and insulin action
- Primary defect probably varies by population but failure to compensate for primary defect ultimately leads to hyperglycemia
Type 2 diabetes

- Usually presents in adulthood
- Patients are usually obese at presentation
- Concordance rate for identical twins is >90%
- Long prodrome (period of impaired glucose intolerance) often undetected
- Long-term complications may be present at time of diagnosis
Diabetic Complications

Microvascular Complications
- Diabetic Retinopathy
- Diabetic Nephropathy
- Diabetic Neuropathy

Macrovascular Complications
- Stroke
- Heart Disease
- Peripheral Vascular Disease

References:
World Health Organization, 2002; Fact Sheet N° 138
Effect of Glycemic Control on Incidence of Diabetic Complications in Patients With Type 1 Diabetes

Data derived from Rathmann W. Drug Benefit Trends. 1998;24–33.
Normal Physiology of Insulin and Glucose Response to Meals

In this graph, the time is marked from 7 am to 9 pm. The graph shows the insulin level (μU/mL) and glucose level (mg/dL) over the day. The purple line represents the normal insulin response to meals, while the orange line represents the normal glucose response to meals. Throughout the day, insulin levels rise and fall in response to meals, with peaks during breakfast, lunch, and dinner. Glucose levels also show fluctuations, particularly after meals, with lower levels during non-meal times. The basal levels of insulin and glucose are maintained at a steady state, except during meal times. This indicates the body's natural response to dietary intake.
**Figure 2.** Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.

The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.
Typical course for type 2 diabetes

**Usual sequence of interventions**

<table>
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<tr>
<th>Year</th>
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<th>Oral Agents</th>
<th>Combination Therapy with Oral agents</th>
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**Usual Clinical Course**

- Onset of Diabetes
- Diagnosis
- Development of complications
- Death
Sites of Action of Oral Antihyperglycemic Agents

**Sulfonylureas and Meglitinides**
- Stimulate pancreatic insulin secretion
- Sulfonylureas are of special value in patients who are lean and have insulinopenia
- Meglitinides are of special value in patients with postprandial hyperglycemia

**Thiazolidinediones**
- Rosiglitazone, pioglitazone
- Insulin resistance in skeletal muscle and adipose tissue
- Excess hepatic glucose output
- Thiazolidinediones are of special value in insulin-resistant, overweight patients who have dyslipidemia or who have renal impairment

**α-Glucosidase inhibitors (acarbose, miglitol)**
- Delays intestinal absorption of carbohydrates
- α-Glucosidase inhibitors are of special value in patients with postprandial hyperglycemia

**Biguanide (metformin)**
- Excess hepatic glucose output
- Insulin resistance in skeletal muscle
- The biguanide is of special value in obese patients who have fasting hyperglycemia
Role of Incretins in Glucose Homeostasis

Ingestion of food

Pancreas

Glucose-dependent

↑ Insulin from beta cells (GLP-1 and GIP)

Blood glucose

↓ Glucose production by liver

↑ Glucose uptake by muscles

GI tract

Release of gut hormones — Incretins

Active GLP-1 & GIP

Beta cells

Active GLP-1 & GIP

Alpha cells

↓ Glucagon from alpha cells (GLP-1)

Glucose dependent

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

DPP-4 = dipeptidyl-peptidase 4

Incretin therapies

- **GLP-1 analog (Exenatide)**
  Administered twice daily by subcutaneous injection
  Lowers A1c 0.5-1.0%
  Side effects are weight loss, nausea, hypoglycemia

- **DPP-1 inhibitors (vitalagliptin, sidagliptin)**
  Orally administered once a day
  Lowers A1c by ~0.5%
  Not associated with weight loss or nausea
Economic Consequences of Diabetes in the United States

Direct Costs: $92 Billion
Indirect Costs: $40 Billion
Annual Total: $132 Billion*

Indirect costs due to disability and early mortality: $40 billion
Diabetes/diabetes supplies: $23 billion
Excess prevalence of chronic complications: $25 billion
Excess prevalence of general medical conditions: $44 billion

*Approximate 2002 US Dollars

Total Per Capita Health Care Expenditure 2002

- **Diabetes:** $13,243
- **Without Diabetes:** $2,560