

The Earlier Use of Insulin in Patients with Type 2 Diabetes

**This program is supported
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Welcome to The Earlier Use of Insulin in Patients with Type 2 Diabetes. This program is supported by an educational grant from Novo Nordisk Inc. It has been accredited by the American Association of Diabetes Educators (AADE) for nurses, pharmacists, and dietitians.

Carolyn Robertson, APRN, MSN, CS



**Associate Director
New York Diabetes Program
New York, NY**

The following program is a taped presentation by Carolyn Robertson.

Ms. Robertson is a certified diabetes educator (CDE), board certified in Advanced Diabetes Management (BC-ADM). She has more than 30 years of experience in diabetes education in intensive/flexible diabetes management, with an active patient caseload for more than 20 years. Ms. Robertson was a pioneer in the intensive management of diabetic pregnancies with over 300 successful pregnancies, as well as an early pioneer in insulin pump therapy. She also has expertise in type 2 diabetes management and in the management of patients with kidney and pancreas transplantation.

At the present time, Ms. Robertson is the Associate Director of the New York Diabetes Program and is on the editorial board for *Diabetes Self-Management*, a patient oriented magazine. Ms. Robertson remains actively involved in clinical research, consultation, and mentoring. Ms. Robertson has been a local board member of both the Juvenile Diabetes Foundation Research International and the American Diabetes Association. She has published widely in peer-reviewed journals, trade journals, newsletters, as well as on the Internet. Ms. Robertson lectures frequently to local, national, and international audiences of healthcare professionals, patients, and the general public. We'll now join Ms. Robertson.

Goal

Provide rationale and evidence for early insulin initiation in the treatment of type 2 diabetes.

The ultimate goal of diabetes treatment is to ameliorate or reduce the risk of microvascular and macrovascular complications associated with the disease. To that end, therapy is focused on achieving specific blood glucose targets to minimize the risk of complications. Though oral antidiabetics (OADs) are often used as first-line agents for type 2 diabetes, insulin therapy is more efficient in lowering blood glucose as well as reducing both glucotoxicity and lipotoxicity. Consequently, insulin should be recommended and used much earlier than is current practice. This presentation will review the current understanding of the pathophysiology of type 2 diabetes as well as data from randomized controlled trials (RCTs) to support the early use of insulin therapy.

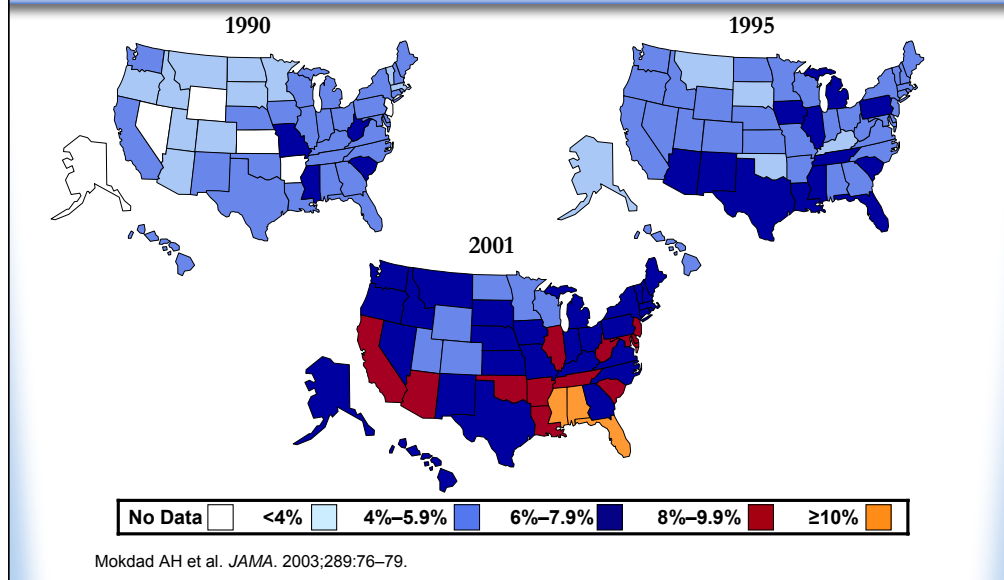
Learning Objectives

- Review epidemiological aspects of diabetes and associated economic implications
- Explain the risk factors of type 2 diabetes as well as stages of disease development and progression
- Understand the pathological changes responsible for the loss of glycemic control and insulin deficiency and resistance in type 2 diabetes
- Explain key results from various clinical studies supporting the benefits of intensive insulin therapy and their implications for disease management
- Discuss current treatment goals and options, and identify the benefits of “early” insulin therapy for optimizing glycemic control
- Recognize barriers to insulin therapy and provide solutions to overcome these barriers
- Discuss methods for initiating insulin therapy

By completing this program, the participant will be better able to:

- Review the epidemiological aspects of diabetes and associated economic implications.
- Explain the risk factors of type 2 diabetes as well as stages of disease development and progression.
- Understand the pathological changes responsible for the loss of glycemic control and insulin deficiency and resistance in type 2 diabetes.
- Explain key results from various clinical studies supporting the benefits of intensive insulin therapy and their implications for disease management.
- Discuss current treatment goals and options, and identify the benefits of “early” insulin therapy for optimizing glycemic control.
- Recognize barriers to insulin therapy and provide solutions to overcome these barriers.
- Discuss methods for initiating insulin therapy.

Diabetes Prevalence: 1990–2001



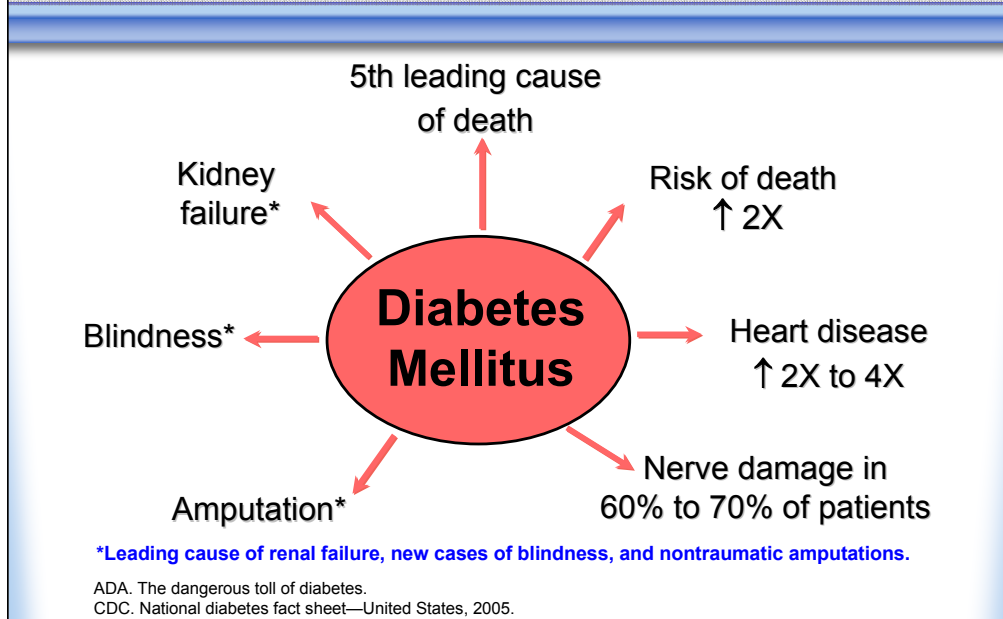
In the United States, the prevalence of diabetes has increased dramatically during the last decade. In 2001, the Centers for Disease Control and Prevention declared that diabetes was an epidemic.

The figures depict over time the number of states in which at least 6% of the adult population had a diagnosis of diabetes. In 1990, only 4 states had an age-adjusted prevalence of 6% or higher. This number increased to 46 states by 2001.

Here are some other diabetes statistics based on 2005 data:

- Approximately 20.8 million Americans (ie, 7% of population) have diabetes; of these, one third or 6.2 million Americans have undiagnosed diabetes (presumably type 2).
- 1.5 million new cases of diabetes were diagnosed in people aged 20 years or older.
- Most alarmingly is that the prevalence of type 2 diabetes, once considered “adult onset,” is increasing in children and adolescents.
- Worldwide, the incidence of diabetes is 171 million people. This number is expected to rise to more than 357 million people by the year 2020.

Complications Associated with Diabetes



The complications associated with diabetes have a huge impact on health and well-being. Fifty percent of patients with type 2 diabetes will have some type of macrovascular or microvascular complication by the time they are diagnosed with overt diabetes. The disease is the fifth leading cause of death. The risk of death increases 2-fold in patients with diabetes.

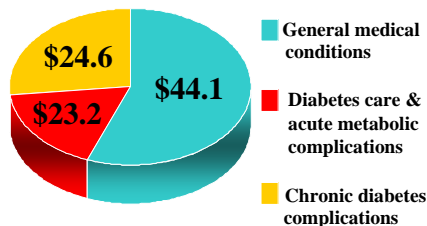
Mortality in patients with type 2 diabetes is most often due to cardiovascular disease. In general, individuals with diabetes are 2 to 4 times more likely to have a myocardial infarction or stroke compared with persons without diabetes. Diabetes is the most common cause of end-stage renal failure and new-onset blindness in adults. Peripheral neuropathy, which is present in more than 60% of individuals, increases the risk for foot amputation; in fact, diabetes is the leading cause of foot amputations not related to trauma.

Cost of Diabetes in 2002

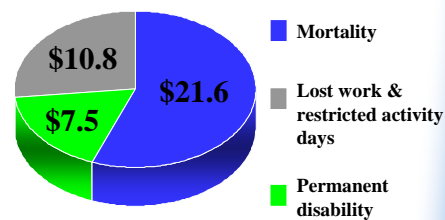
Annual Costs of Diabetes in the United States

~\$132 Billion

DIRECT COSTS
~\$91.8 Billion



INDIRECT COSTS
~\$39.8 Billion



ADA. *Diabetes Care*. 2003;26:917-932.

Not surprisingly, diabetes also has a substantial economic impact. Indeed, the management of diabetes accounts for 10% of US healthcare costs.

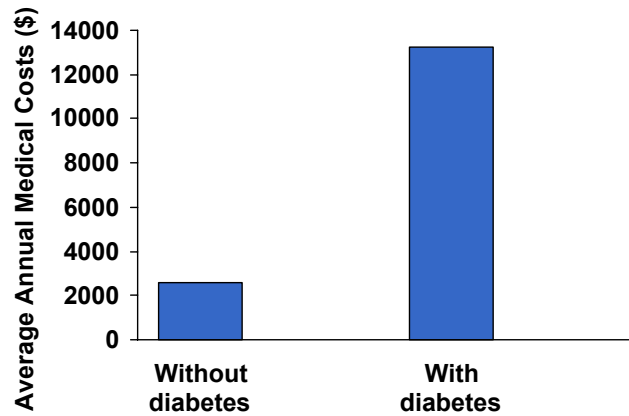
In 2002, the total direct and indirect costs attributable to diabetes were estimated to be \$132 billion. Direct costs (eg, those associated with hospitalization, medications) were estimated at almost \$92 billion annually. These costs can be broken down as follows:

- One quarter of the costs were spent on diabetes care and acute metabolic complications
- One quarter was spent to manage the chronic complications attributable to diabetes
- One half, or \$44.1 billion, was spent on the excess prevalence of general medical conditions

Indirect costs (which include lost productivity due to disability and early mortality) in 2002 are estimated at \$39.8 billion. These costs can be broken down as follows:

- \$7.5 billion for permanent disability
- \$10.8 billion for lost work and restricted activity days
- \$21.6 billion for mortality

Cost of Diabetes in 2002

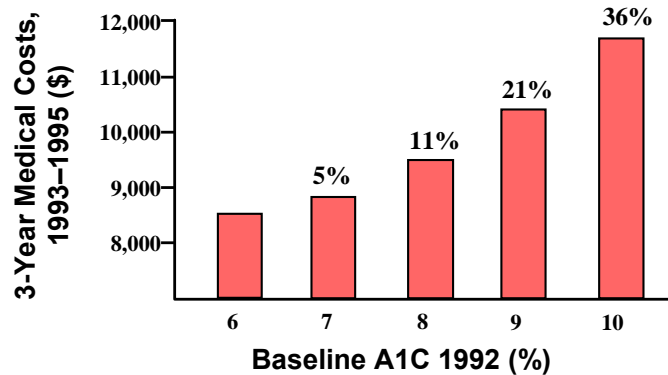


ADA. *Diabetes Care*. 2003;26:917-932.

Diabetes is expensive. In 2002, on a per-person basis, the average annual medical costs were \$2,560 for a person without diabetes and \$13,243 for a person with diabetes.

Healthcare Costs Increase with Worsening Glycemic Control

Increase in medical costs associated with rising A1C levels compared with costs for patients with A1C of 6%



Gilmer TP et al. *Diabetes Care*. 1997;20:1847-1853.

This slide demonstrates that the cost of healthcare in adults with diabetes corresponds to the level of glycemic control.

The 3-year mean of healthcare costs among 3017 adults with diabetes (mean age, 59.7 years) who were continuously enrolled in a large health maintenance organization (HMO) over a 4-year period were assessed. Both inpatient and outpatient charges for medical care were determined based on the patient's baseline A1C (mean A1C, 8.3%).

For every 1% increase in A1C above 6%, medical care costs almost doubled.

Healthcare Costs Decrease with Improved Glycemic Control

**Patients who had A1C reductions of 1% or more over a 1-year period and sustained the improvement for at least 1 additional year
versus
Patients who did not meet these criteria**

- Total annual healthcare costs were \$685–\$950 lower in the “improved” cohort
- Total costs for a 3-year period were 50%–60% higher in patients with A1Cs >10% versus patients with A1Cs ≤8%

Wagner EH et al. *JAMA*. 2001;285:182–189.

There is good news. Healthcare costs can decrease when glycemic control is improved. In a second retrospective study, total healthcare costs were significantly lower for HMO patients with diabetes who had A1C reductions of 1% or more over a 1-year period and were able to sustain the improvement for at least 1 additional year (n = 732) as compared with patients who did not meet these criteria (n = 4012).

- Costs were tracked during the 2-year A1C monitoring period and for an additional 3 years.
- Total annual healthcare costs were \$685–\$950 lower in the “improved” versus the “unimproved” cohort; the difference fell short of significance at the end of the 2-year monitoring period but was statistically significant ($P < 0.05$) for each of the subsequent 3 years.
- Total costs for a 3-year period were 50%–60% higher in patients with A1Cs >10% compared with those with A1Cs ≤8%.
- Improvement in glycemic control also reduced the number of physician visits.

Risk Factors Associated with Type 2 Diabetes

- **Advancing age**
- **Family history**
- **Ethnicity**
- **Obesity**
- **Hypertension**
- **Dyslipidemia**
 - High LDL and triglycerides, low HDL
- **Polycystic ovary syndrome**
- **Gestational diabetes**
- **High fasting or postprandial glucose**

Type 2 diabetes is a heterogeneous and polygenic disorder that results from the interaction of genetic and environmental or behavioral causes.

Diabetes is often asymptomatic for long periods of time before being diagnosed. Therefore, identifying at-risk individuals can assist in early diagnosis and interventions to minimize complications. Risk factors include increasing age, family history, certain ethnic groups (eg, Native Americans, African Americans, Asian Americans, Pacific Islanders, and Hispanic Americans are at higher risk), and weight. The presence of hypertension, dyslipidemia, polycystic ovary syndrome as well as a history of gestational diabetes are also risk factors for type 2 diabetes.

An estimated 41.1 million Americans have prediabetes, a condition that often precedes diabetes. This condition is associated with increased fasting plasma glucose (FPG) and postprandial plasma glucose.

Pathophysiology of Type 2 Diabetes

A Dual Defect

- **Insulin resistance**
 - ♦ Insulin receptor defects
 - ♦ Impaired glucose uptake
 - ♦ Elevated free fatty acids
 - ♦ Hyperinsulinemia (compensatory)
- **Insulin deficiency**
 - ♦ Glucotoxicity
 - ♦ Lipotoxicity
 - ♦ Apoptosis

Gerich JE. *Eur J Clin Invest.* 2002;32(Suppl 3):46–53.
Petersen KF, Shulman GI. *Am J Cardiol.* 2002;90(Suppl 5A):11G–18G.

Type 2 diabetes occurs as a result of multiple pathophysiologic defects involving both insulin resistance and insulin deficiency.

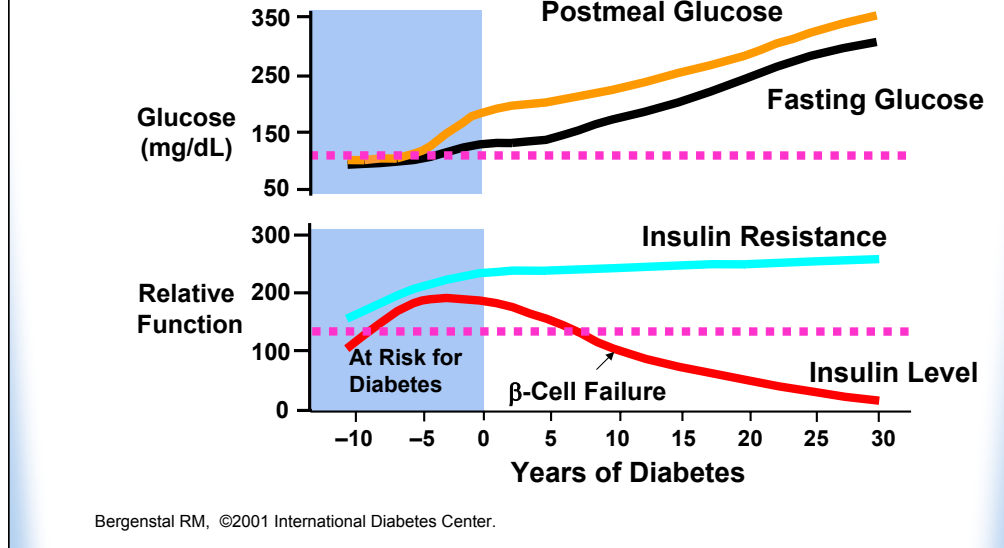
Insulin resistance can be the result of downregulation of cell surface insulin receptor levels, which can lead to abnormalities in glucose transport within the muscles and liver. As a result, free fatty acids (FFAs) increase. This further impairs glucose uptake, causing the system to compensate by increasing insulin secretion.

Chronically elevated plasma glucose and lipids also results in glucose and lipid toxicity which can lead to a loss of β -cell mass and function. The decline in insulin secretion leads to further increases in both postprandial and fasting glucose levels. Central adiposity, high plasma FFAs, and intracellular lipids further exacerbate insulin resistance and decrease β -cell function and encourage lipotoxicity.

Repeated stimulation of β -cells may lead to desensitization to glucose, exhaustion (depletion of insulin), and, eventually, cell death through apoptosis (or programmed cell death).

Increased hepatic output of glucose occurs much later during the transition from impaired glucose tolerance to overt diabetes.

Progression of Type 2 Diabetes



This slide depicts the progressive course of type 2 diabetes. Most patients have had the disease for 10 or more years before diabetes is diagnosed. During this 10-year period (depicted by the blue shaded areas), insulin resistance begins to creep up. The initial impact is on the postprandial glucose levels. With time, fasting glucose levels also begin to rise. After years of having type 2 diabetes, insulin resistance remains increased but eventually levels off. β -Cell function on the other hand starts to deteriorate.

As the disorder continues to progress, there is increasing β -cell failure. Endogenous insulin levels significantly decrease, making insulin replacement therapy an important consideration in patients with type 2 diabetes.

Since diabetes is characterized by dual defects, the treatment of type 2 diabetes should correct both the insulin resistance and the insulin deficiency simultaneously. Thus, from a physiologic standpoint, initiating insulin as a first-line treatment for type 2 diabetes would seem most appropriate.

Test Your Understanding

Which of the following statements is TRUE?

- A. The majority of indirect costs associated with diabetes are related to lost workdays.**
- B. Type 2 diabetes arises from insulin deficiency as well as increased insulin sensitivity.**
- C. β -Cell function progressively deteriorates over time while insulin resistance reaches a plateau.**

Now, let's take a moment to test your understanding.

Which of the following statements is TRUE?

- A. The majority of indirect costs associated with diabetes are related to lost workdays.
- B. Type 2 diabetes arises from insulin deficiency as well as increased insulin sensitivity.
- C. β -Cell function progressively deteriorates over time while insulin resistance reaches a plateau.

Test Your Understanding

If you answered “C” ... you are correct!

β -Cell function progressively deteriorates over time while insulin resistance reaches a plateau.

If you answered “C” ... you are correct!

β -Cell function progressively deteriorates over time while insulin resistance reaches a plateau.

Rationale for Aggressive Therapy

Landmark Trials

As mentioned previously, the goal of diabetes management is to reduce the risk for developing complications, which is achieved through improving glycemic control. These next slides provide the support from several landmark RCTs that have provided compelling evidence that tight control of blood glucose levels can slow the rate of development of diabetes-related complications.

Lowering A1C Reduces Complications

	DCCT (Type 1)	Kumamoto (Type 2)	UKPDS (Type 2)	DCCT/EDIC (Type 1)
A1C	9% → 7%	9% → 7%	8% → 7%	9% → 8%
Retinopathy	↓63%	↓69%	↓17%–21%	↓72%–87%
Nephropathy	↓54%	↓70%	↓24%–33%	↓53%–92%
Neuropathy	↓60%			
Macrovascular	↓41%*		↓16%*	↓42%–57%

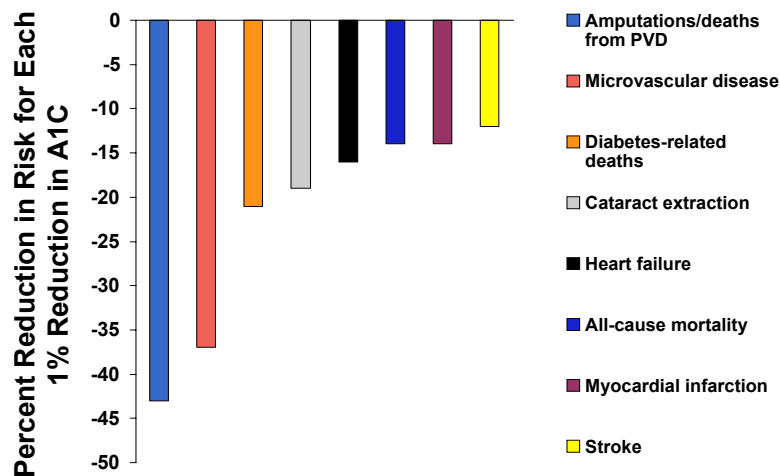
*Not significant because of small number of events.

The RCTs displayed on this slide have studied the impact of intensive therapy on the incidence of long-term, diabetes-related complications. The Diabetes Complications and Control Trial (DCCT) evaluated complications in patients with type 1 diabetes, whereas the Kumamoto study and the United Kingdom Prospective Diabetes Study (UKPDS) were focused on type 2 diabetes.

In all the studies, a reduction of the A1C in the treatment groups was associated with a statistically significant reduction of microvascular complications, including reduced incidence of retinopathy, neuropathy, and nephropathy. The DCCT, Kumamoto, and UKPDS did not elucidate a statistically significant reduction in macrovascular complications. The authors suggest that this may have been due to the small number of events that occurred over the 6- to 10-year follow-up period.

More recently, however, a significant reduction in macrovascular complications with intensive therapy in type 1 diabetes was observed in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study, which was a very long-term (17-year) follow-up to the DCCT. Clinicians are hypothesizing that periods of good control, even when they are not maintained, may offer cellular memory, which reduces the future risk of macrovascular disease.

UKPDS Key Findings



Stratton IM et al. *BMJ*. 2000;321:405-412.

PVD = peripheral vascular disease.

The UKPDS included a prospective observational analysis that evaluated endpoints and deaths related to type 2 diabetes among the more than 4500 individuals during a 10-year period. An important observation was that the incidence of clinical complications was significantly associated with glycemia. Each 1% reduction in A1C was associated with significant reductions in risk of 43% for amputations and death from peripheral vascular disease and 37% for microvascular complications. There was also a 21% reduction for deaths related to diabetes; 19% reduction in the risk of needing a cataract extraction; 12% to 16% decrease in the incidence of heart failure, all-cause mortality, and, finally, both fatal and nonfatal stroke and myocardial infarction.

UKPDS Key Findings (cont'd)

Although monotherapy increased the proportion of patients that attained the A1C goal (<7%) by 3-fold,

- only 50% could maintain this goal for 3 years
- only 25% could maintain this goal for 9 years
- the majority of patients needed multiple agents to maintain the target A1C goal
- the majority of patients eventually required insulin to obtain A1C levels <7%

Turner RC et al. *JAMA*. 1999;281:2005–2012.

Further analysis of the UKPDS determined the percentage of patients in each group achieving American Diabetes Association (ADA) goals for A1C and FPG. Patients were followed up every 3 months for 9 years.

Although monotherapy with either diet alone, insulin, sulfonylurea, or metformin initially increased the proportion of patients that attained the A1C goal (<7%) by 3-fold, the majority of patients could not maintain this target goal over time. Only 50% could maintain the A1C for 3 years; this number declined to 25% after 9 years.

The majority of patients needed multiple agents to maintain the target A1C goal. A young age at diagnosis, high baseline obesity, hyperglycemia, and triglyceridemia were associated with an increased likelihood of needing multiple therapies. The authors also concluded that due to progressive β -cell decline, the majority of patients eventually required insulin to obtain A1C levels <7%.

UKPDS Key Findings (cont'd)

- **Lowest risk in patients with A1C <6%; no threshold**
- **53% of patients receiving sulfonylurea therapy in the UKPDS required insulin after 6 years**
- **Insulin and sulfonylureas do not increase cardiovascular risk**

Stratton IM et al. *BMJ*. 2000;321:405–412.
Wright A et al. *Diabetes Care*. 2002;25:330–336.
UKPDS. *Lancet*. 1998;352:837–853.

The UKPDS also demonstrated that individuals with the lowest risk of complications had A1C levels <6%. However, there was no apparent threshold for reductions in A1C for any type of complication associated with diabetes.

More than half of the individuals who received sulfonylureas needed insulin added to their regimen after 6 years because their FPG exceeded 108 mg/dL, despite maximal doses of sulfonylureas. (A threshold of 108 mg/dL was defined as the upper limit of normal for the investigator's reference range.)

The UKPDS also verified the safety of the combination of insulin and sulfonylureas. There was no increase in cardiovascular risk when these drugs were used together.

Glycemic Control

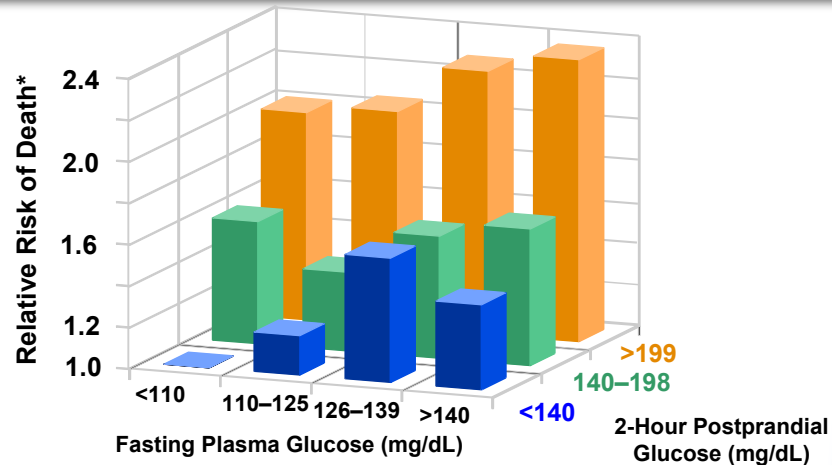
Normal A1C $\leq 6.0\%$

A1C = PPG + FPG

ADA. *Diabetes Care*. 2001;24:775-778.

The long-term impact of hyperglycemia on glycemic control is best measured via A1C, which is a function of both fasting and postprandial glucose (PPG) exposure. Normal A1C is $\leq 6\%$ — this represents an average blood glucose level of 135 mg/dL or lower. On average, a 1% increase in A1C corresponds to an increase in mean plasma glucose of ~ 35 mg/dL.

DECODE Trial: The Role of PPG



*Adjusted for age, sex, study center.

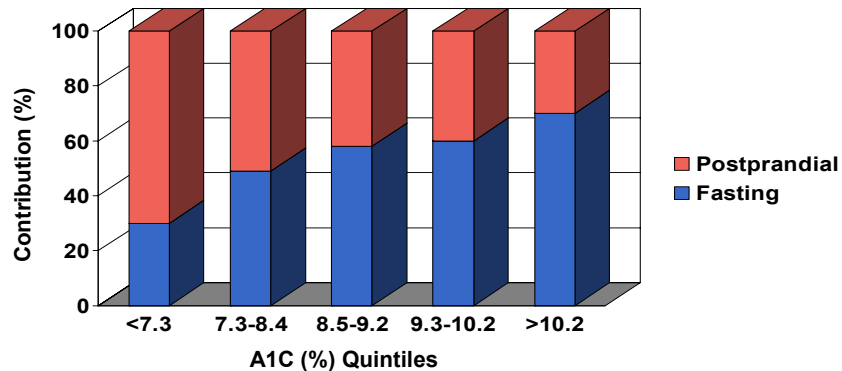
Adapted from DECODE Study Group. *Lancet*. 1999;354:617-621.

Although PPG may be responsible for up to 40% of daytime hyperglycemia, most therapies and monitoring schemes focus on fasting glucose. However, postprandial hyperglycemia is equally, if not more, important.

The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) study demonstrated the impact of PPG on diabetes complications. This multinational research study assessed the relationship of fasting and postprandial blood glucose levels and risk of death. Thirteen prospective European cohort studies involving more than 25,000 individuals were studied for a mean follow-up of 7.3 years. In all three levels of fasting glucose comparison, as depicted by the horizontal bar, there was no additional increase in risk noted. However, using the 2-hour postchallenge plasma glucose, there was a significant increased risk at all three postprandial levels. Individuals who had an FPG <110 mg/dL but a 2-hour postmeal glucose ≥ 200 mg/dL had an almost 2-fold increased risk of death.

Postprandial Control

PPG excursions become more predominant in patients with good control of fasting glucose



Monnier L et al. *Diabetes Care*. 2003;26:881-885.

Other studies have determined that postprandial hyperglycemia is common in individuals with type 2 diabetes and that it is even present in many individuals who have an A1C value close to target.

A study published in 2003 followed 290 patients with type 2 diabetes and compared the fasting and postprandial contributions to glycemic control in individuals not responding to therapy with two OADs. In mild to moderate hyperglycemia, which was defined as A1C <8.4% in the study, 60% to 80% of the glucose contribution came from postmeal excursions. It was not until the A1C was >8.5% that the fasting blood glucose made the higher contribution. These results strongly suggest that PPG measurements are not only warranted but necessary if improved glucose control is the goal. However, additional studies are needed to confirm these findings.

Current Treatment Goals

	ADA	AACE
A1C	<7%	≤6.5%
Fasting/preprandial glucose (mg/dL)	90–130	<110
Postprandial glucose (mg/dL)	<180*	<140†
Blood pressure (mm Hg)	<130/80	<130/85
LDL-cholesterol (mg/dL)	<100 (<70)‡	<130
HDL-cholesterol (mg/dL)	>40	>35
Triglycerides (mg/dL)	<150	<200

*Peak postprandial capillary plasma glucose.

†2-hour postprandial glucose.

‡The ADA recommends an LDL <70 mg/dL in individuals with overt cardiovascular disease.

American Diabetes Association. *Diabetes Care*. 2006;29:(Suppl 1):S4–S42.

American Association of Clinical Endocrinologists. *Endocr Pract*. 2002;8:(Suppl 1):40–82.

American Association of Clinical Endocrinologists. *Endocr Pract*. 2000;6:162–213.

The treatment goals for diabetes include more than optimizing A1C and fasting blood glucose levels. Preventing complications requires treatment goals for blood pressure and plasma lipids as well as glucose postmeals.

You may notice that the target goals differ somewhat between the guidelines of the ADA and the American Association of Clinical Endocrinologists (AACE). The ADA favors tighter control of lipids and blood pressure whereas the AACE favors tighter control of glycemia.

Regardless of which standard is adopted, diabetes care will demand continuous medical care and comprehensive self-management to achieve these goals and to prevent complications.

Monitoring

The ADA recommends:

• Self-monitored blood glucose	Varies (≥ 1 /day)
• A1C ♦ Every 3 months if goals not met or therapy changed	At least 2X/year
• Microalbumin	Annual
• Dilated eye examination	Annual
• Visual foot examination	Each visit
• Comprehensive foot examination	Annual
• Blood pressure	Each visit
• Lipid monitoring	At least annually

American Diabetes Association. *Diabetes Care*. 2006;29(Suppl 1):S4–S42.

To facilitate achievement of these goals, the ADA has established guidelines for standards of care for individuals. These standards are reviewed yearly and are updated frequently to keep the guidelines timely and appropriate. In addition to outlining the frequency for measurements of control (ie, A1C and self-monitored blood glucose), the standards also encompass diagnostic testing for identifying diabetes-related complications. These recommendations should be individualized for each patient. Patients who are pregnant will need different standards than patients who are elderly and frail.

Quality of Care

Inadequate diabetes control and management is common in the United States

• A1C >7%	57%
• BP >140/90 mm Hg	34%
• LDL >130 mg/dL	58%
• No A1C test	71%
• No dilated eye examination	37%
• No foot examination	45%

Saaddine JB et al. *Ann Intern Med.* 2002;136:565–574.

Despite the availability of guidelines and standards of care, evidence indicates that the goals identified by the ADA standards are not being met in current practice.

An analysis of data collected from 1988 to 1994 from 1026 participants with diabetes in the Third National Health and Nutritional Examination Survey (NHANES III) and 3059 individuals with diabetes in the Behavioral Risk Factors Surveillance System revealed a significant gap between the recommendations and practice.

Inadequate control of glycemia was found in 57% of patients; additionally, 34% had hypertension and 58% had elevated LDL-cholesterol. During the previous year, only 29% had an A1C test, 63% had a dilated eye examination, and 55% had a foot examination. Uninsured persons were less likely than insured persons to have adequate glycemetic control and regular eye and foot examinations.

Glycemic Control from 1988 to 2000

	1988–1994 (n = 8 million)	1999–2000 (n = 10 million)
A1C <7%	45%	36%
OADs only	45%	52%
Insulin only	24%	16%
Insulin + OADs	3.1%	11.0%
Diet alone	27%	20%

Koro CE et al. *Diabetes Care*. 2004;27:17–20.

More recent data from NHANES III and NHANES 1999–2000 involving more than 1500 patients with type 2 diabetes confirm that glycemic control continues to be undermanaged. From 1988 to 2000, glycemic control has declined, as has the use of insulin and diet alone to manage type 2 diabetes. Interestingly, during this time period, the use of OADs to manage type 2 diabetes had increased. The authors of this study concluded that “these data lend support to public health initiatives advocating early and aggressive management of diabetes.”

Test Your Understanding

Which of the following statements is TRUE?

- A. An NHANES survey showed that most patients achieve an A1C <7%.**
- B. Maintaining A1C value <7% over the long term is difficult with monotherapy.**
- C. According to the NHANES data, glycemic control has improved over time in patients with type 2 diabetes.**

Time for another short test.

Which of the following statements is TRUE?

- A. An NHANES survey showed that most patients achieve an A1C <7%.
- B. Maintaining A1C value <7% over the long term is difficult with monotherapy.
- C. According to the NHANES data, glycemic control has improved over time in patients with type 2 diabetes.

Test Your Understanding

If you answered “B”... you are correct!

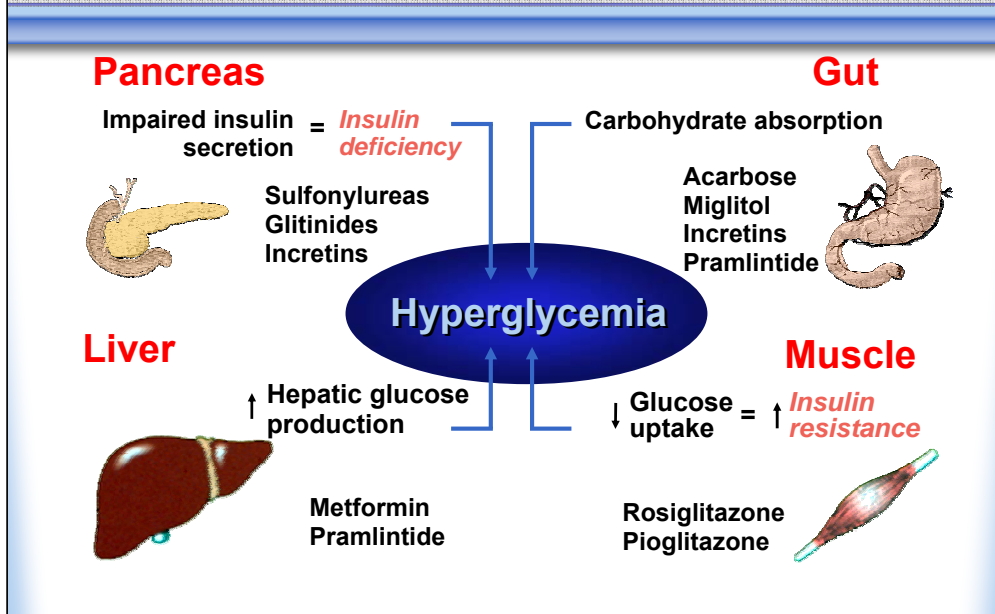
The UKPDS showed that only 50% of patients could maintain an A1C <7% for 3 years on monotherapy, and only 25% could maintain it for 9 years.

If you answered “B” you are correct.

Maintaining A1C value <7% over the long term is difficult with monotherapy.

Therapy for Type 2 Diabetes

Sites of Action



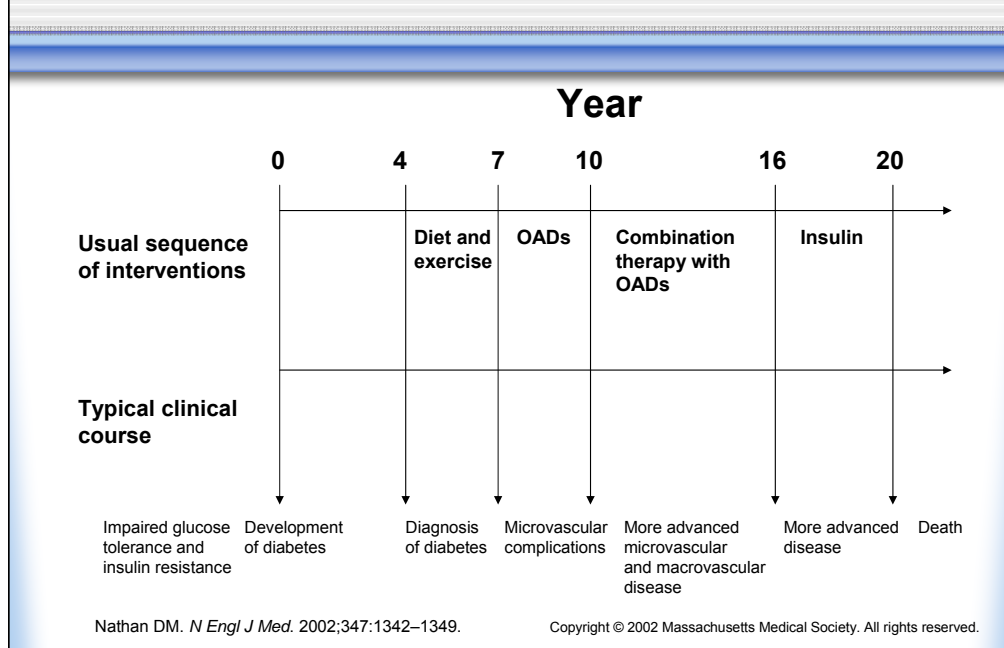
This slide depicts the sites of action of diabetes medications on specific tissues. Agents can be broadly divided into 2 classes: (1) those that augment insulin supply and (2) those that reduce insulin resistance (ie, increase the sensitivity of tissues to insulin in the skeletal muscle and liver).

Clockwise from top left: Sulfonylureas, repaglinide, and exenatide (an incretin-mimetic agent) enhance insulin secretion. α -Glucosidase inhibitors work by slowing the digestion and absorption of carbohydrates. Incretins enhance insulin secretion in a glucose-dependent manner, suppress glucagon secretion, and regulate gastric emptying. The thiazolidinediones (TZDs) (ie, rosiglitazone and pioglitazone) decrease insulin resistance in the muscles. Metformin and pramlintide exert effects that lead to reduced hepatic glucose production. Pramlintide and exenatide are new agents for the treatment of diabetes; thus, the depth of experience with these agents is limited compared with that of older agents like sulfonylureas and metformin.

Agents generally can be used alone or in combination. When used as monotherapy, the best reductions in A1C are in the 0.5% to 2.0% range. In combination, additional reductions can be in the range of 0.5% to 2.0%. The most common combination is that of a secretagogue and insulin sensitizer (eg, sulfonylurea plus metformin or a TZD).

As the disease progresses and β -cell failure becomes more pronounced, these diabetes medications will not adequately control blood glucose and insulin will be required.

Treatment of Type 2 Diabetes



In 2002, David Nathan, an endocrinologist and researcher from Boston, described the litany of traditional diabetes management. The traditional approach to the management of type 2 diabetes has been stepwise, beginning with diet and exercise, followed by antihyperglycemic monotherapy (usually OADs), and then combination therapy. Transition from one medication to another was often protracted with long periods of inadequate control before treatment was modified. Insulin was generally considered as the last alternative, presumably because of the need to administer it by injection. By the time patients with diabetes begin receiving insulin, they have had the disease for up to 15 years and have established complications. This is unfortunate, given the ability of insulin to control glycemia with no upper-dose limit.

Since this algorithm was published, the incretin or glucagon-like peptide-1 (GLP-1) mimetic (exenatide, Byetta™) and amylin analog (pramlintide, Symlin®) have become available. Their place in the treatment of type 2 diabetes is yet to be established.

Rationale for Earlier Use of Insulin

- **Inadequate control with other diabetes medications**
- **Inadequate glycemic control linked to morbidity and mortality**
- **Insulin corrects β -cell deficiency**
- **May reverse glucose toxicity**
- **Insulin is inevitable for most patients**
- **↑ costs of treating complications vs. cost of insulin therapy**

Marre M. *Int J Obes Relat Metab Disord.* 2002;26(Suppl 3):S25–S30.

There are several arguments advocating the earlier use of insulin. It has already been shown that glycemic control is not being achieved using the traditional stepwise approach.

Insulin corrects the deficiency of β -cell failure. The efficacy of oral secretagogue and incretins depends upon residual β -cell secretory function. Thus, when this becomes insufficient, they are no longer adequate in normalizing blood glucose. Since progression of type 2 diabetes is associated with β -cell failure, insulin is inevitably required by many individuals. Early use of insulin corrects the β -cell deficiency and reverses glucose toxicity.

There is no dose threshold with insulin; therefore, insulin can be dosed as necessary to achieve desired target glycemic goals to reduce the risk for developing diabetes-related complications.

As discussed previously in this presentation, the cost of diabetes-related complications is staggering and is far greater than the cost of treatment with insulin.

Insulin Therapy in Type 2 Diabetes

Advantages

- **Most effective in lowering blood glucose (unlimited ability to lower blood glucose level)**
- **Allows individualization with flexible insulin dosing**
- **Improves insulin sensitivity by reducing glucotoxicity and lipotoxicity**
- **May reduce cardiovascular risk**

Riddle M. *Am J Med.* 2000;108(Suppl 6A):1S.
Chan JL, Abrahamson MJ. *Mayo Clin Proc.* 2003;78:459-467.

Insulin therapy in type 2 diabetes is associated with several advantages over other alternatives. It is the most studied and effective drug for the treatment of diabetes. It has an unlimited ability to lower blood glucose, so that dosing is easily individualized. Insulin is also associated with reductions in glucotoxicity and lipotoxicity caused by elevated glucose and lipids, respectively. It may also reduce cardiovascular risk.

Insulin should be considered for initial therapy in patients with symptoms such as marked hyperglycemia, ketonuria, or intolerance to OADs.

Test Your Understanding

Which of the following support the use of insulin in type 2 diabetes?

- A. β -Cell failure continues to progress, making OADs less effective.**
- B. Insulin has an unlimited ability to lower blood glucose.**
- C. Flexibility of dosing allows for individualization of therapy.**
- D. All of the above.**

Now, let's take a moment to test your understanding.

Which of the following support the use of insulin in type 2 diabetes?

- A. β -Cell failure continues to progress, making OADs less effective.
- B. Insulin has an unlimited ability to lower blood glucose.
- C. Flexibility of dosing allows for individualization of therapy.
- D. All of the above.

Test Your Understanding

If you answered “D”... you are correct!

Correction of β -cell deficiency, an unlimited ability to lower blood glucose, and flexibility of dosing allowing for individualization of therapy are all advantages of insulin therapy in type 2 diabetes.

If you answered “D” you are correct.

Correction of β -cell deficiency, an unlimited ability to lower blood glucose, and flexibility of dosing allowing for individualization of therapy are all advantages of insulin therapy in type 2 diabetes.

Patient Barriers to Insulin Therapy

- **Misconceptions about insulin and disease**
- **Health beliefs/cultural mores**
- **Fear of injection and insulin (social stigma)**
- **Resist frequent monitoring**
- **Interferes with daily routines and privacy**
- **Symptoms not indicative of disease severity**
- **Do not understand goals**
- **Fear of hypoglycemia and weight gain**

Korytkowski M. *Int J Obes Relat Metab Disord.* 2002;26(Suppl 3):S18–S24.
Marre M. *Int J Obes Relat Metab Disord.* 2002;26(Suppl 3):S25–S30.
Peyrot M et al. *Diabetes Care.* 2005;28:2673–2679.

There are both patient- and physician-related barriers to using insulin in type 2 diabetes. The Diabetes Attitudes, Wishes, and Needs (DAWN) study, a survey of more than 2000 patients, has shown that many patients with type 2 diabetes believe that starting insulin means that they have failed to manage their diabetes. Further, they had low belief that insulin would help them manage their diabetes better.

Patients with diabetes may feel that insulin is the beginning of the end. They may fear the administration of medication by injection and consider using needles a stigma. Injectable therapies are invasive, and those that must be refrigerated and administered often can limit spontaneity and interfere with daily activities. Additionally, monitoring of blood glucose may be considered a nuisance or interfere with daily activities.

Given that type 2 diabetes may be asymptomatic, some patients may not understand the need for optimal glycemic control or the ramifications of lack of control and its role in preventing complications. In addition, many physicians and nurses also believed that insulin should be delayed until absolutely necessary. Finally, individuals fear that they will experience hypoglycemia and will gain weight.

Barriers to Insulin Therapy for Healthcare Providers

- **Lack of**
 - ♦ Training
 - ♦ Time
 - ♦ Support and resources

Especially in the primary care practice setting
- **Fear of**
 - ♦ Hypoglycemia and weight gain
 - ♦ Injection and insulin
 - ♦ Patient's anger and alienation
 - ♦ Complex treatment regimens

Miller CD et al. *Diabetes Care*. 2000;23:444-448.
Larme AC et al. *Diabetes Care*. 1998;21:1391-1396.
Korytkowski M. *Int J Obes Relat Metab Disord*. 2002;26(Suppl 3):S18-S24.
Hirsch IB et al. *Clin Diabetes*. 2005;23:78-86.

From a healthcare professional's perspective, there are challenges with insulin therapy for type 2 diabetes as well. Type 2 diabetes is often managed in the primary care setting, and many practitioners may perceive insulin therapy as too complex to manage in a busy practice. In one survey, diabetes was rated as significantly harder to treat than hypertension and angina. Healthcare professionals are concerned about patient annoyance with having to use insulin and adherence to therapy, and perhaps alienation. Other concerns of healthcare practitioners include resources for insulin education, the potential for patients to gain weight, and risk of hypoglycemia.

As a result of these concerns, one third of physicians report postponing insulin until it is absolutely essential.

Overcoming Barriers for Patients

- **Education and support**
 - ◆ Symptoms and disease progression
 - ◆ Match regimen to patient's medical needs and lifestyle
 - ◆ Manage hypoglycemia and weight gain
 - ◆ Insulin delivery devices
 - Reduce trauma and anxiety
 - ◆ Insulin analogs
- **Diabetes care team**
- **Counseling**

Korytkowski M. *Int J Obes Relat Metab Disord.* 2002;26(Suppl 3):S18–S24.
Ratner R. *Pract Diabetol.* 2004;23:14–24.

Patient education is a key factor in overcoming psychological resistance to using insulin. Patients should understand the progressive nature of the disease and the role of insulin (including deficiency and resistance). Insulin is a natural hormone that is diminished in diabetes. Its use should be described as an adjunct, not as a threat or a punishment.

The emphasis of treatment should be glycemic control and not insulin avoidance or alternatives to insulin. Indeed, introducing insulin at the time of diagnosis might reduce some of the preexisting myths of the process. Some clinicians have advocated patient self-injection with saline soon after diagnosis to mitigate the fear associated with future use of insulin. To reduce the fear of potential adverse reactions like hypoglycemia and weight gain, individuals need to learn about prevention and treatment with the first injection of insulin.

Presenting the individual with options for insulin delivery systems as well as dosing options may make the idea of insulin therapy more palatable and show that treatment can be tailored to match lifestyle concerns. Many individuals report that the use of insulin pens or dosers makes them more comfortable injecting in public. They describe them as easier to learn and state that they have more confidence in their ability to accurately prepare a dose. In addition, current needles are both thinner and smaller, assuring minimal discomfort from the injection. There are even jet injectors for those individuals who want to avoid a needle entirely.

Patients need to understand that it is high blood glucose levels and not insulin therapy that cause complications of diabetes. However, insulin cannot reverse damage that has already occurred. The goal of treating individuals sooner with insulin is to prevent a downward spiral caused by the effects of long-term hyperglycemia.

Overcoming Barriers for Healthcare Providers

- **Education and support**
 - ♦ Pathophysiology
 - ♦ Treatment options and glycemic control
 - ♦ Minimize risk of hypoglycemia
 - ♦ Minimize weight gain
- **New insulin formulations**
 - ♦ Better control and more physiological
- **ADA and AACE guidelines**
- **Increased access to team members**
- **Insulin delivery devices**
 - ♦ Easier to teach
 - ♦ Patient satisfaction

As mentioned earlier, most patients with type 2 diabetes are treated by primary care physicians (PCPs), a group of practitioners with limited time and resources to manage patients. Thus, providing more education and support on treatment options and management as well as information on new insulin formulations and delivery systems to this specialty is important.

PCPs need to have an increased awareness of the importance of glycemic control in preventing complications of type 2 diabetes, need to understand the advantages and disadvantages of the various treatment options for type 2 diabetes, be up to date on the types of insulin and insulin delivery devices, and respect patient lifestyle issues.

Commonly Used Insulin Preparations

Type	Onset (hrs)	Peak (hrs)	Duration (hrs)
Rapid-acting insulin analogs (rDNA origin)			
Humalog® (insulin lispro)	0.25–0.5*	0.8–4.3†	4–6*
NovoLog® (insulin aspart)	0.16–0.32†	1–3†	3–5‡
Apidra® (insulin glulisine)	NA	NA	NA
Short-acting human insulin (rDNA origin)			
Regular	0.5–1	2–3§	6–8

NA = not available; data presented graphically in Figure 3 of the package insert.
 *Skyler JS. *Therapy for Diabetes Mellitus and Related Disorders*. 3rd ed. 1998.
 †Product labeling/prescribing information.
 ‡Mudaliar SR et al. *Diabetes Care*. 1999;22:1501–1506.
 §Product labeling of Novolin® R puts the upper limit of peak action at 5 hrs.

There are more than 15 types of insulin preparations. This slide shows the action of rapid- and short-acting insulin formulations. Insulin analogs were developed to better mimic normal insulin action. The rapid-acting insulin analogs are characterized by both shorter onset and duration. Because of their more predictable absorption profiles and onset of action, these insulin analogs are often associated with improved glycemic control. It should be noted that the time–action profiles shown on the slide may vary and should be used as a general guideline only.

The rapid-acting formulations allow patients increased flexibility in meal timing, and the rapid onset and 3- to 6-hour duration of action have the potential to provide improved glycemic control after meals.

Commonly Used Insulin Preparations

Type	Onset (hrs)	Peak (hrs)	Duration (hrs)
Intermediate-acting human insulin (rDNA origin)			
NPH insulin	2–4	6–10*	14–18*
Long-acting insulin analogs (rDNA origin)			
Lantus® (insulin glargine)	1†	None†	10.8–24‡
Levemir® (insulin detemir)	0.8–2.0§	3.2–9.3§	5.7–23.2†
Premixed insulin analogs (rDNA origin)			
Humalog® Mix75/25™	<0.5†	2.6†	~22†
Humalog® Mix50/50™	<0.5†	2.3†	~22†
NovoLog® Mix 70/30	<0.16–0.32¶	2.4†	≤24†

*Product labeling of Novolin® N puts the range of peak action at 4–12 hrs, and duration of action up to 24 hrs.

†Product labeling/prescribing information.

‡Lepore M et al. *Diabetes*. 2000;49:2142–2148.

§Plank J et al. *Diabetes Care*. 2005;28:1107–1112.

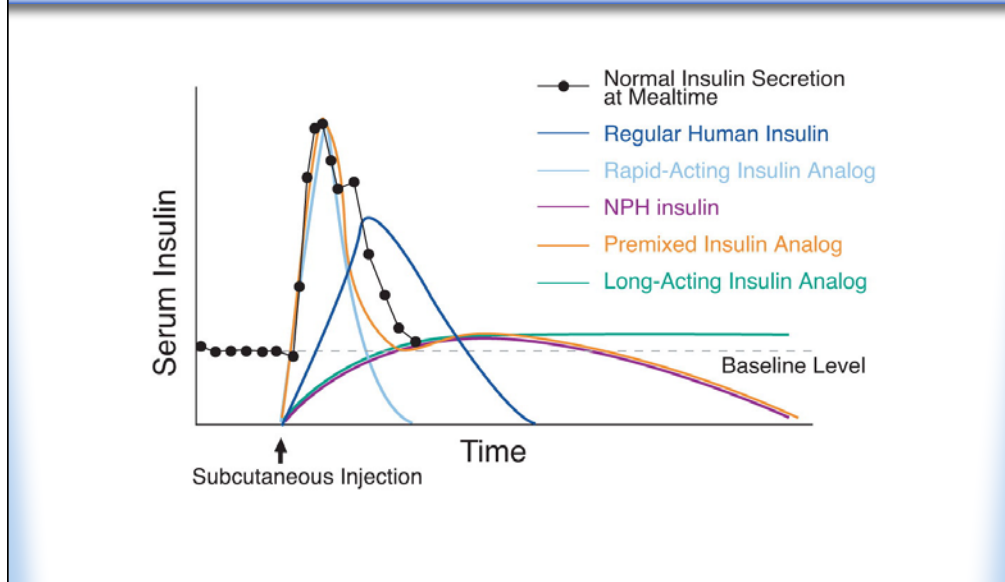
¶Weyer C et al. *Diabetes Care*. 1997;20:1612–1614.

Intermediate- and long-acting insulin formulations provide basal coverage—the insulin that is needed 24 hours a day even in the absence of food. As with the short-acting analogs, the analogs depicted here are also associated with fewer hypoglycemic episodes compared with human insulin formulations. Additionally, the time–action profiles shown here may vary and should be used as a general guideline only.

Premixed human insulin formulations are also available. They contain both a short-acting insulin (25%–30%) and an intermediate-acting insulin (70%–75%). A 50/50 formulation is also available.

The choice of a dosing regimen is often determined by the blood glucose pattern of the individual as well as the patterns of eating and activity. Glucose control can be achieved using a wide range of dosing algorithms. Through the use of a flexible insulin dosing schedule, individuals can opt for an insulin plan that fits their metabolic needs as well as their lifestyle.

Time–Action Profiles of Insulin Theoretical Representations



This slide shows the general time course of the various insulin preparations plotted against normal insulin secretion following a meal. The rapid-acting analog most closely resembles the insulin secretion that occurs at mealtimes.

Insulin Delivery Options



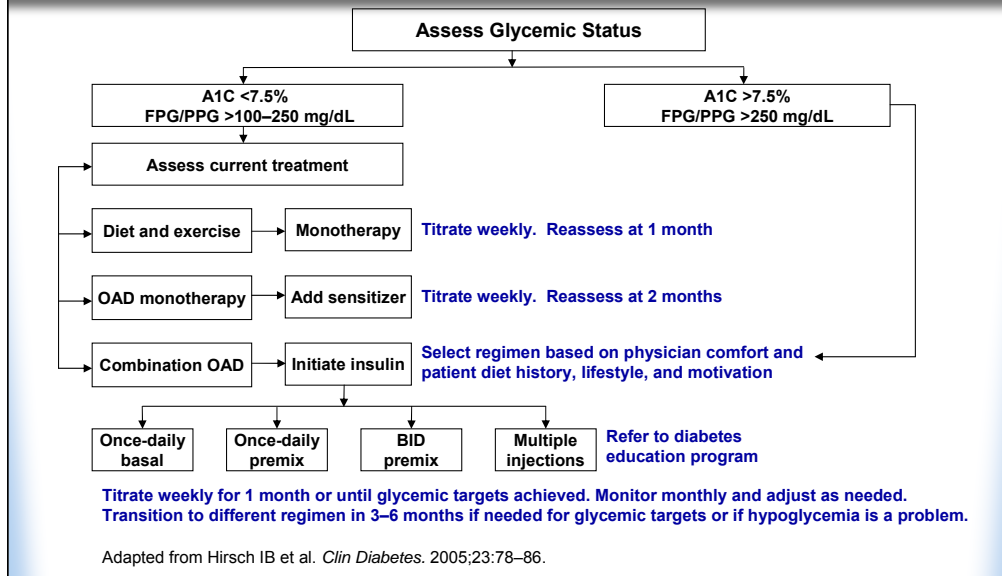
To make insulin regimens easier to use and to fit patient lifestyle, several different delivery devices are available. The traditional vial and syringe is well known but may be a barrier to patient acceptance and compliance with insulin therapy.

Insulin is also available in cartridges that can be placed into durable insulin pens and dosers. Prefilled disposable pens are another option. Both offer discreet, accurate, and flexible dosing options. Although these options are generally preferred by patients over needles and vials, this latter method of administration remains the most common insulin delivery method in the United States. Conversely, the pen is the most common insulin delivery system in Europe.

Insulin pumps are battery-powered delivery systems that enable basal doses of insulin to be delivered continuously without the need for multiple injections. The individual must still monitor the blood glucose level and make decisions about the dose required for a meal or snack. Once the decision is made, they must activate the pump to deliver that dose. However, the system does allow the individual a great deal of flexibility and permits exquisite fine-tuning of the insulin doses.

For more information about each of these delivery systems, you can refer to the ADA's annual resource guide.

Algorithm for Initiating Insulin Therapy Hirsch et al Protocol



This slide depicts a recently published suggested algorithm for initiating insulin in a primary care practice. It represents a protocol suggested by a group of clinicians in Seattle. Patients with very high blood glucose (eg, FPG >250 mg/dL) should be started on insulin immediately. Initiating treatment with oral antihyperglycemic agents is a reasonable approach for patients with less severe hyperglycemia. The authors of the algorithm suggest weekly adjustment of doses of OAD agents to achieve targeted glycemic goals. Within 3 months, if glycemic targets are not achieved, insulin therapy should be initiated. (Triple OAD therapy can be tried before this, but is usually limited by lack of efficacy and side effects.)

Though basal-bolus insulin regimens are ideal for mimicking endogenous insulin action and overall glycemic control, this group does not recommend it as first-line therapy. They comment that this regimen requires substantial motivation on the part of the patient and provider, and requires training in carbohydrate counting and insulin adjustment. However, they feel that after starting with a simpler regimen and gaining confidence with self-injection, patients can more readily transition to multiple daily injections.

A once-daily basal insulin could consist of bedtime neutral protamine Hagedorn (NPH) or a long-acting insulin analog, which could be taken any time of day but at the same time every day.

Suggested Starting Dosages Hirsch et al Protocol

Once-daily premix	10 units	Predinner
Twice-daily premix	20 units	10 units prebreakfast, 10 units predinner
Once-daily basal	10 units	Bedtime
Multiple daily injections	Individualized	Seldom used for initial insulin therapy

Hirsch IB et al. *Clin Diabetes*. 2005;23:78–86.

This slide illustrates starting doses for a variety of insulin regimens. Initiating a patient on insulin is simplified by starting with a low dose and titrating upward as needed. In general, 10 units per injection is considered a safe starting dose for once- and twice-daily regimens.

In a recently published study, the authors found that initiating a twice-daily premixed insulin analog using 5 units prebreakfast and 5 units predinner was also effective.

Suggested Titration Schedule

Hirsch et al Protocol

Once- or Twice-Daily Regimens

Blood Glucose Levels (mg/dL)(last 3–7 days)	Dosage Change (units)
<80	-2
80–109	No change
110–139	+2
140–179	+4
≥180	+6

Hirsch IB et al. *Clin Diabetes*. 2005;23:78–86.

This slide depicts the suggested dosage titration for insulin in patients with type 2 diabetes. Patients should be self-monitoring and recording blood glucose values once or twice daily depending on the regimen (before breakfast and before supper). As mentioned in the algorithm, titration should be made weekly for the first month or until glycemic targets are achieved.

For the busy practitioner, it may be easiest for patients to call/fax in their blood glucose reading, and dosage changes can be given to the patient over the phone.

Switching Regimens to Attain Glycemic Targets Hirsch et al Protocol

Current Regimen	Switch to:	Comments
Once-daily basal	Twice-daily premix	<ul style="list-style-type: none"> • Divide dose in half; give pre-breakfast and predinner • Start 18–24 hours after last basal dose
Once-daily basal	Add rapid-acting insulin at largest meal as 10% of daily dose	<ul style="list-style-type: none"> • Give rapid-acting insulin at largest meal • Reduce basal dose by 10%
Once-daily premix	Twice-daily premix	<ul style="list-style-type: none"> • Divide dose in half • Give prebreakfast and predinner
Twice-daily premix	Multiple daily injections	<ul style="list-style-type: none"> • Initiate basal dose as total daily dose/2 × 80% • Insulin prandial dose as half of total daily dose × % estimated calories at each meal

Hirsch IB et al. *Clin Diabetes*. 2005;23:78–86.

If patients are not at goal after 3 to 6 months, or if recurrent hypoglycemia limits titration, then the regimen may need to be changed.

This slide depicts some examples of transition regimens that can be employed. Once changes are made, dosages need to be titrated to goal based on glucose self-monitoring results and diet history. When titrating from once to twice daily, a larger proportion of insulin can be given at the largest meal. If recurrent hypoglycemia results, the total daily dose can be reduced by 20%.

ADA Recommendations

Adding Insulin to OAD Therapy

- Fasting levels above target
 - ♦ Single bedtime injection of detemir, glargine, or NPH
 - ♦ Starting dose 0.15 unit/kg; titrate up in 2-unit increments every 5–7 days based on fasting blood glucose (FBG)
 - ♦ Monitor blood glucose before breakfast and supper
- Fasting levels at target; values during day above target
 - ♦ Add second NPH injection before breakfast
 - Total daily dose = 0.3 X body weight (kg)
 - Divide into prebreakfast and bedtime doses
 - ♦ Add regular or rapid-acting before meals
 - Dose = 1 unit/10 grams carbohydrate in the meal

American Diabetes Association. *Practical Insulin: A Handbook for Prescribers*. Alexandria, Va: American Diabetes Association; 2002.

There are other alternative regimens for starting insulin. The ADA recommends using the fasting levels to decide how to proceed.

If fasting levels are above target, the OAD can be used to control glucose during the day, and insulin can be added to better control fasting levels. This can be achieved with a single bedtime injection of NPH or long-acting analog such as insulin detemir or insulin glargine, starting at a low dose and titrating upward as needed to achieve target fasting blood glucose (FBG).

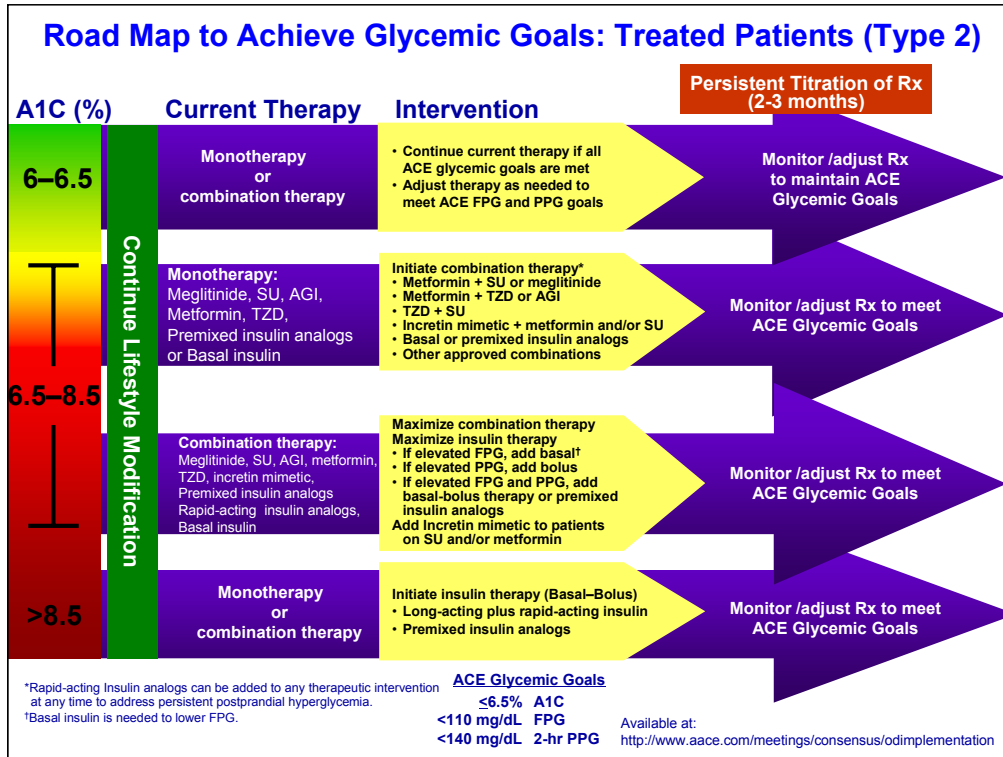
However, if fasting levels are at target, but blood glucose levels during the day are above target, recommendations include:

- A second NPH injection before breakfast (in addition to the bedtime injection) or
- A regular or rapid-acting insulin before meals. However, according to the ADA, this latter method requires carbohydrate counting.

In both cases the protocol allows for insulin to be added to sulfonylurea, metformin, or TZD therapy.



The diagram above portrays the road map for the treatment of type 2 diabetes in therapy-naive patients as developed by the American College of Endocrinology (ACE) and AACE. This map is intended to help the medical community achieve the ACE/AACE glycemic control guidelines. Although the goal of the road map is to achieve glycemic targets as quickly as possible, in some cases, clinicians may alter the recommendations to meet specific patient needs.



ACE and AACE have also created a road map for patients who are currently receiving therapy but not meeting the recommended glycemic goals. This road map aids clinicians in moving to the next step when current therapy is not adequate. As previously mentioned, in some cases, clinicians may alter the recommendations to meet specific patient needs.

Case Presentation

- EM: 46-year-old Hispanic male with type 2 diabetes diagnosed 8 years ago
- Most recent A1C 8.8%, up from 7.5% a year ago
 - ♦ Metformin added to glyburide 5 mg BID a year ago
- EM works 2 jobs, does not have time to exercise, and does not closely follow a meal plan.
 - ♦ Does not skip meals; usually has a large breakfast and dinner
- EM is willing to start on insulin, because he is concerned about diabetes complications.

Here is a case to test your understanding:

EM is a 46-year-old Hispanic male diagnosed with type 2 diabetes 8 years ago. His most recent A1C is 8.8%. One year ago his A1C was 7.5%. At that time, metformin was added to his regimen of glyburide 5 mg BID. The patient works 2 jobs, states he does not have time to exercise or closely follow a meal plan. He does not skip meals and usually has a large breakfast and dinner. He is willing to start insulin as he is concerned about developing complications of diabetes.

Case Presentation

Which of the following insulin regimens would be the most appropriate for EM to begin?

- A. Basal only**
- B. Once-daily premix**
- C. Twice-daily premix**
- D. All of the above**

Which of the following insulin regimens would be the most appropriate for EM to begin?

- A. Basal only
- B. Once-daily premix
- C. Twice-daily premix
- D. All of the above

Case Presentation

- C (twice-daily premix)
- EM eats 2 large meals daily
 - ◆ Likely causes postprandial hyperglycemia
 - ◆ This necessitates the need for a rapid-acting insulin
 - ◆ Based on EM's work schedule, a prebreakfast and predinner premixed regimen may be easiest at this time

The twice-daily premix would be a good initial choice for this patient. EM eats two large meals daily which likely results in postprandial hyperglycemia necessitating the need for a rapid-acting insulin. A prebreakfast dose of 10 units and predinner dose of 10 units premixed insulin may be easier for EM given his work schedule.

However, the insulin regimens listed in choices a and b may also be appropriate for starting EM on insulin therapy. Often, clinicians will initiate insulin therapy with a once-daily regimen and move to twice daily as the patient becomes more comfortable with administering insulin.

Ultimately, EM should be encouraged to use an insulin plan that will cover both fasting and PPG excursions.

Summary

- **Incidence of type 2 diabetes is increasing at an alarming rate**
- **Diagnosis often not until 9 to 12 years after onset of development**
 - ♦ Many already have significant microvascular and macrovascular complications
- **Current diabetes care is not optimal**
- **Starting insulin sooner or intensifying insulin therapy**
 - ♦ Insulin is most effective and safest drug (when dosed properly)
 - ♦ Physiological rationale
 - ♦ Inevitable failure of OADs

Narayan KM et al. *JAMA*. 2003;290:1884–1890.
Riddle M. *Am J Med*. 2000;108(Suppl 6A):1S.

To summarize:

- The prevalence of diabetes is increasing at an alarming rate—a 61% increase in the last 10 years. One in 3 Americans born in 2000 will develop diabetes based on present estimates.
- Type 2 diabetes is usually not diagnosed until 9 to 12 years after the onset. This means that many individuals have developed diabetes-related complications by the time of diagnosis.
- Although there are numerous classes of antidiabetic agents, and our understanding of the disease and its complications has increased over time, glycemic control remains suboptimal in the majority of patients. Earlier diagnosis and more intense monitoring of their diabetes and related parameters to achieve target goals may improve the situation.
- To counter the rising tide of complications, many healthcare professionals are advocating the use of insulin earlier in the progression of the disease than is currently practiced.
 - Insulin is the most studied and effective drug for the treatment of diabetes.
 - Development of insulin analogs with more predictable pharmacokinetic and pharmacodynamic properties has increased dosing accuracy and reduced the incidence of hypoglycemia.
 - Since other antidiabetic agents have been shown to inevitably fail in many individuals, insulin should be used as soon as it is clear that glycemic control cannot be maintained with OADs alone.

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Thank You

Please click below to return to the Main Menu and Proceed to the Post-Test