

Insulin Therapy: Sooner Rather Than Later?

This program is supported by
an educational grant from
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The following program is a taped presentation by Linda Haas.

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Ms. Haas is a past president of the American Association of Diabetes Educators (AADE) and past President, Health Care and Education of the American Diabetes Association (ADA). She received AADE's Distinguished Service Award in 1994, and ADA's Outstanding Educator of the Year Award in 1995. In 1999, she received the Veteran's Health Administration's National Award for Excellence in Nursing (Expanded Role). Ms. Haas has lectured throughout the country on diabetes management including medication management.

We'll now join Ms. Haas.

Goal

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

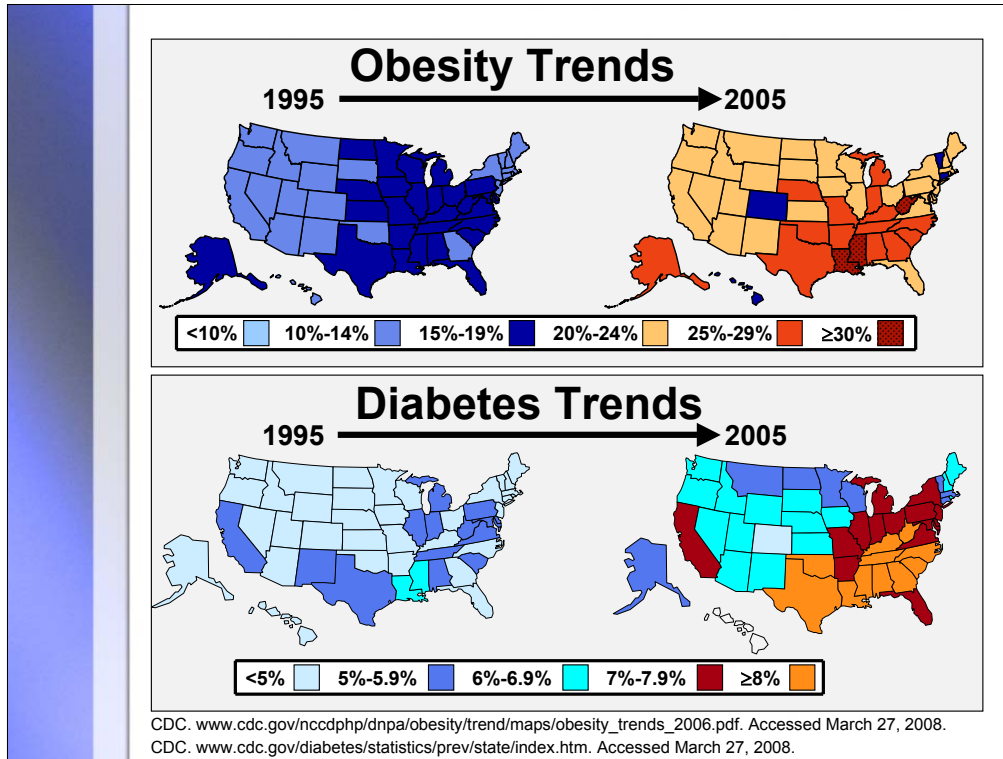
The ultimate goal of diabetes treatment is to ameliorate or reduce the risk of microvascular and macrovascular complications associated with the disease. To that end, therapy is focused on reducing blood glucose to achieve specific glycemic targets to minimize the risk of complications. Though oral antidiabetes drugs (OADs) are frequently used as first-line agents for type 2 diabetes, insulin therapy is often more efficient in lowering blood glucose and 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 to support the early use of insulin therapy.

Learning Objectives

- Review the economic and personal costs of diabetes
- Describe the progressive nature of type 2 diabetes including the risk factors contributing to the prevalence of the disease
- Discuss various clinical studies that have guided current treatment goals and identify the benefits of “early” insulin therapy for optimizing glycemic control
- Recognize barriers to insulin therapy and provide solutions to overcome these barriers
- Describe how to initiate insulin therapy using the currently available insulin preparations

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

- Review the economic and personal costs of diabetes
- Describe the progressive nature of type 2 diabetes including the risk factors contributing to the prevalence of the disease
- Discuss various clinical studies that have guided current treatment goals and identify the benefits of “early” insulin therapy for optimizing glycemic control
- Recognize barriers to insulin therapy and provide solutions to overcome these barriers
- Describe how to initiate insulin therapy using the currently available insulin preparations

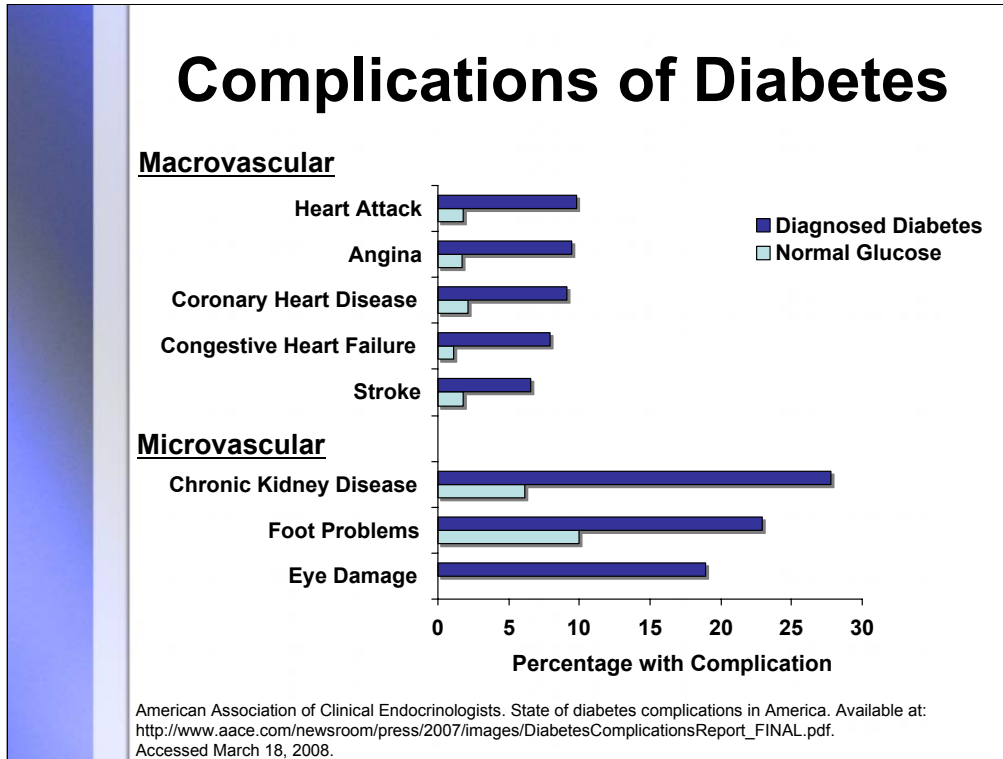


The prevalence rates of obesity and diabetes in US adults have increased dramatically and in parallel in the decade extending from 1995 to 2005.

- In 1995, the prevalence of obesity (body mass index ≥ 30 kg/m²) was less than 20% in all US states. The prevalence of diagnosed diabetes was less than 6% in all but 2 states.
- By 2005, the prevalence of obesity was less than 20% in only 4 states and 25% or higher in 17 states. The prevalence of diagnosed diabetes exceeded 8% in 11 states.

Within 10 years, the prevalence of obesity had increased by approximately 40% and diagnosed diabetes had increased by 60%.

As is apparent in these maps, the states with the highest rates of obesity also have the highest prevalence of diagnosed diabetes.



Diabetes is associated with high rates of long-term complications attributed, at least in part, to hyperglycemia. In the United States, 3 out of 5 people with diabetes have at least 1 long-term complication.

People with diabetes have a risk of cardiovascular and cerebrovascular disease that is 2 to 4 times higher than the risk for nondiabetic individuals. In addition, diabetes is the leading cause of kidney failure, blindness, and nontraumatic amputations in the United States.

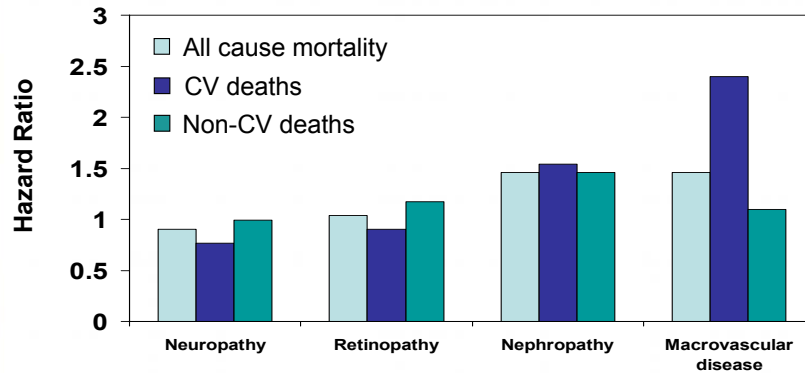
“Chronic kidney disease” refers to microalbuminuria (albumin/creatinine ratio >30) or estimated glomerular filtration rate <60 mL/min.

“Foot problems” refer to amputations of the foot or toe, or lesions or numbness of the feet.

“Eye damage” includes self-report of a diagnosis of retinopathy or damage due to diabetes. Because the National Health and Nutritional Examination Survey (NHANES) did not ask people without diagnosed diabetes about eye damage, prevalence information for people without diabetes is not available.

Mortality Associated with Diabetes Complications

- Nephropathy and macrovascular disease increase the risk of death in people with diabetes (TRIAD analysis)
- Cardiovascular (CV) causes contributed to 68% of deaths



McEwen LN et al. *Diabetes Care*. 2007;30:1736-1741.
National Center for Health Statistics. *Health, United States, 2007*. Hyattsville, Md; 2007. Accessed March 20, 2008.

The Translating Research Into Action for Diabetes (TRIAD) study analyzed data from participating health plans and provider groups serving ~180,000 patients with diabetes. Risk factors for death were ascertained by analyzing data from 8733 individuals with diabetes followed from 2000 to 2004. Of the 791 deaths occurring during that time, cardiovascular causes contributed to 68% of the deaths.

The presence of macrovascular disease increased the risk of dying from any cause by 46% and from a cardiovascular cause by 2.4-fold. In addition, nephropathy increased the risk of mortality from any cause by 45% in people with diabetes.

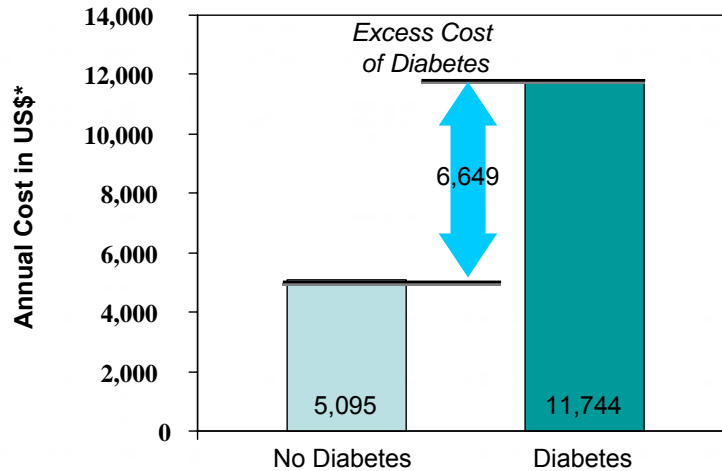
Mortality Associated with Diabetes

- Diabetes was the 6th leading cause of US deaths in 2004
- People with diabetes are twice as likely to die than nondiabetic people
- Diabetes decreases life expectancy
 - 7.5 years for men ≥ 50 years old
 - 8.2 years for women ≥ 50 years old

National Center for Health Statistics. *Health, United States, 2007*. Hyattsville, Md; 2007.
CDC. Available at: <http://www.diabetes.org/uedocuments/NationalDiabetesFactSheetRev.pdf>.
Accessed March 28, 2008.
Franco OH et al. *Arch Int Med*. 2007;167:1145–1151.

Diabetes was the sixth leading cause of US deaths in 2004 and the fifth leading cause of death due to disease. Diabetes increases the risk of dying 2-fold and, for adults 50 years of age or older, reduces life expectancy by 7.5 years for men and 8.2 years for women.

Annual Medical Cost per Patient for Diabetes in 2007

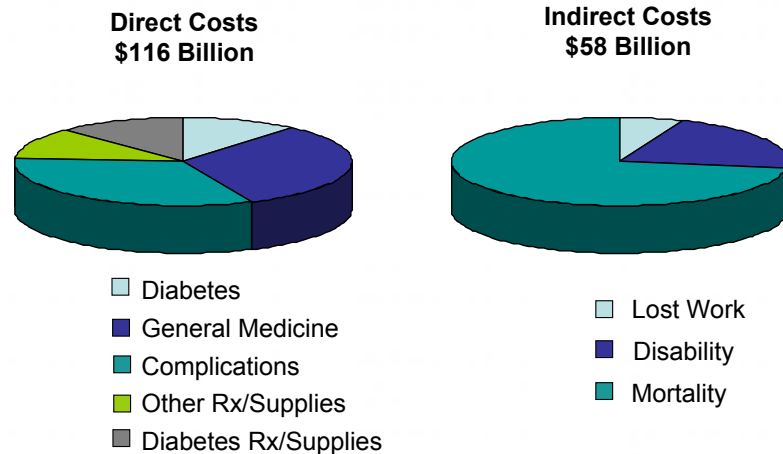


*Cost adjusted for age, sex and demographics

American Diabetes Association. *Diabetes Care*. 2008;31:1-20.

The average annual medical cost for a person with diabetes in 2007 was \$11,744 compared with \$2,935 for a person without diabetes. However, the average person with diabetes is older and sicker than the average nondiabetic person. Therefore, the more appropriate comparison is the medical cost for a matched population. As demonstrated in this graph, the medical cost for a person with diabetes is 2.3 times greater than for a similar nondiabetic individual (\$11,744 vs \$5,095). Therefore, the excess medical cost of diabetes (the difference between \$11,744 and \$5,095) is \$6,649 per person per year.

Diabetes Cost the US \$172 Billion in 2007



In 2007, diabetes cost the United States an estimated total of \$172 billion. This sum includes direct medical costs and indirect costs.

Direct medical costs totaled \$116 billion and included expenditures for:

- Inpatient care in a hospital or nursing/residential facility
- Outpatient care during visits to physician's office, podiatrist, emergency room, hospital outpatient center or hospice; outpatients transported by ambulance; outpatients receiving home care visits
- Also included in this category are outpatient prescription medications, equipment, and supplies

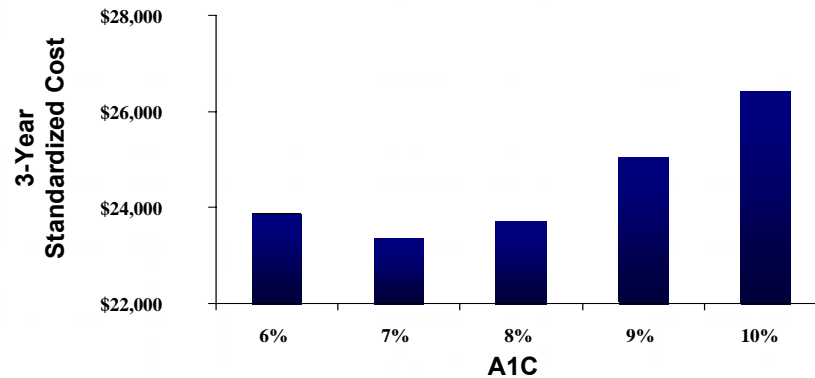
It is interesting to note that so little is spent on diabetes education that it is not even called out in these figures.

The indirect costs of diabetes totaled \$58 billion and included the estimated cost for absenteeism from work, reduced work performance, productivity lost for days not in the work force, permanent disability, and early mortality.

Clearly, diabetes exacts a large financial, personal, and societal toll in the United States.

Cost of Diabetes Care Is Related to Glycemic Control

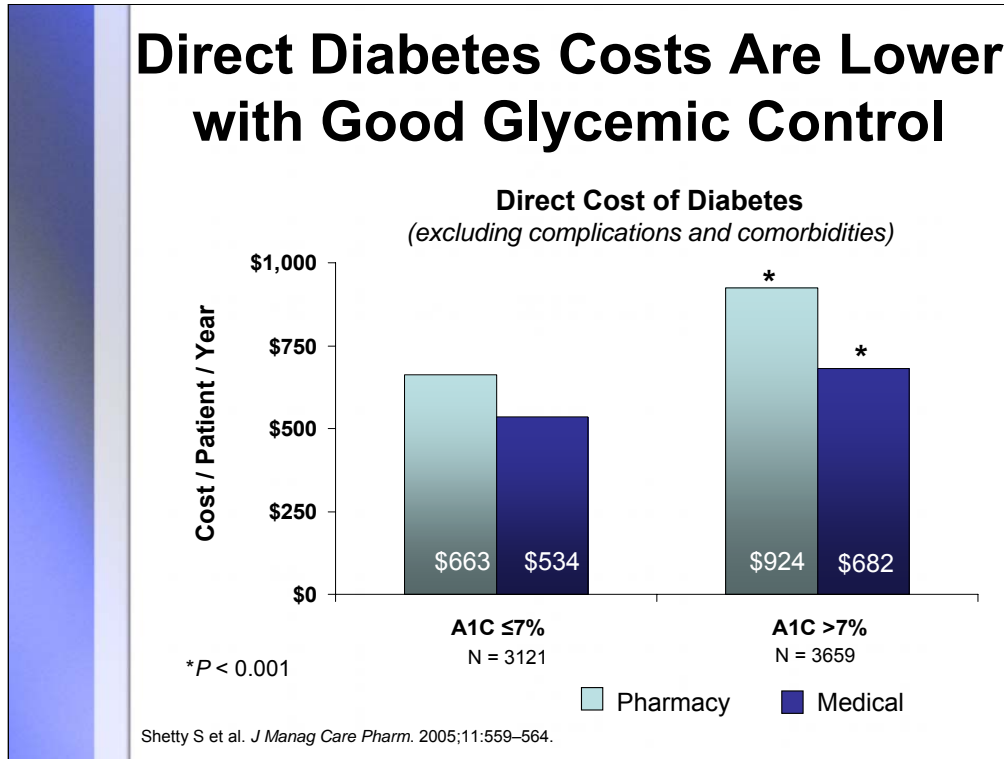
A1C	3-Yr Cost	Differential	P
6%	\$23,873		
10%	\$26,408	\$2,536	<0.05



Glimer TP et al. *Diabetes Care*. 2005;28:59-64.

The cost for diabetes care received from 1999 to 2002 by 1694 adults with diabetes depended upon the patient's level of glycemic control. Standardized costs over a 3-year period were 11% higher for patients with hemoglobin A1C (referred to as A1C) of 10% (\$26,408) compared with the costs for people with A1C of 6% (\$23,873). Medical care cost significantly more when A1C was 7.5% or higher and escalated with every 1% rise in A1C.

Direct Diabetes Costs Are Lower with Good Glycemic Control



A different retrospective analysis of patients with type 2 diabetes showed that, on average, patients who had A1C of 7% or less had lower annual costs for both medical care and prescription medications than did patients whose A1C exceeded 7%.

In this study, patients with type 2 diabetes were identified from January 1, 2002 to December 31, 2002 from a database representing a geographically diverse US population. Direct cost for diabetes care was significantly higher for the 3659 patients with A1C >7% compared with the 3121 patients with A1C of 7% or less throughout the 1-year follow-up period. The costs associated with a primary diagnosis of type 2 diabetes were significantly higher for both pharmacy use, including OADs and insulin, and medical care which included all visits to physician office, outpatient visit, inpatient, emergency room, and lab costs.

Diabetes-related costs included the total amounts paid by the member and by the health care plan. Costs for diabetic complications and comorbidities were not included.

Factors Associated with Risk of Type 2 Diabetes

- **Family history**
- **Obese or overweight**
- **Advancing age**
- **Ethnicity**
- **Physical inactivity**
- **Hypertension**
- **HDL <40 mg/dL or triglycerides >250 mg/dL**
- **Polycystic ovary syndrome**
- **Gestational diabetes or delivery of a baby >9 lb**
- **Impaired fasting glucose or impaired glucose tolerance**

HDL = high-density lipoprotein.

American Diabetes Association. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.

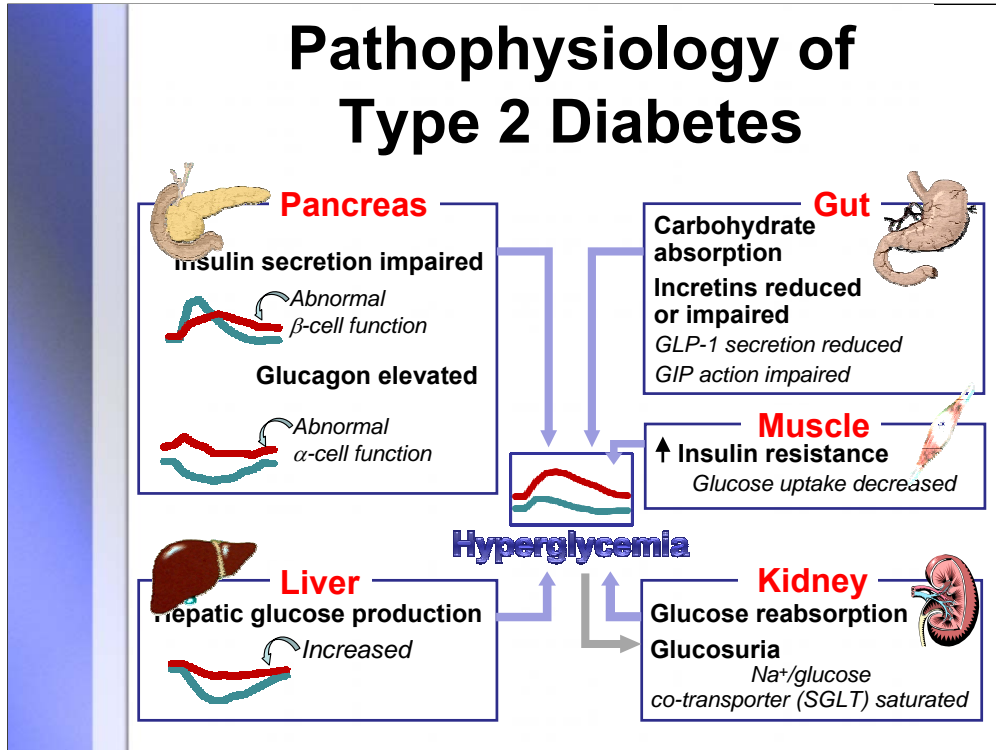
Type 2 diabetes is a heterogeneous and polygenic disorder that results from the interaction of genetic, environmental, and behavioral factors.

Diabetes is often asymptomatic for long periods of time before being diagnosed. Therefore, identifying at-risk individuals can assist in early diagnosis and initiation of interventions to minimize complications.

Factors that increase the risk of developing type 2 diabetes include family history of type 2 diabetes, higher body weight, older age, certain ethnic groups (eg, Native Americans, African Americans, Asian Americans, Pacific Islanders, and Hispanic Americans are at higher risk), and the presence of hypertension, high-density lipoprotein (HDL) cholesterol <40 mg/dL or triglycerides >250 mg/dL. For women, polycystic ovary syndrome, a history of gestational diabetes, or delivery of a baby weighing more than 9 pounds are also risk factors for type 2 diabetes. The risk of type 2 diabetes is also increased in the presence of other conditions associated with insulin resistance, such as acanthosis nigricans.

Many people have abnormalities in glucose regulation that often precede the development of type 2 diabetes. These abnormalities, now known as prediabetes, include impaired fasting glucose or IFG when the fasting plasma glucose (FPG) is between 100 and 125 mg/dL and impaired glucose tolerance or IGT when plasma glucose is between 140 and 199 mg/dL 2 hours after administration of an oral glucose tolerance test.

Pathophysiology of Type 2 Diabetes

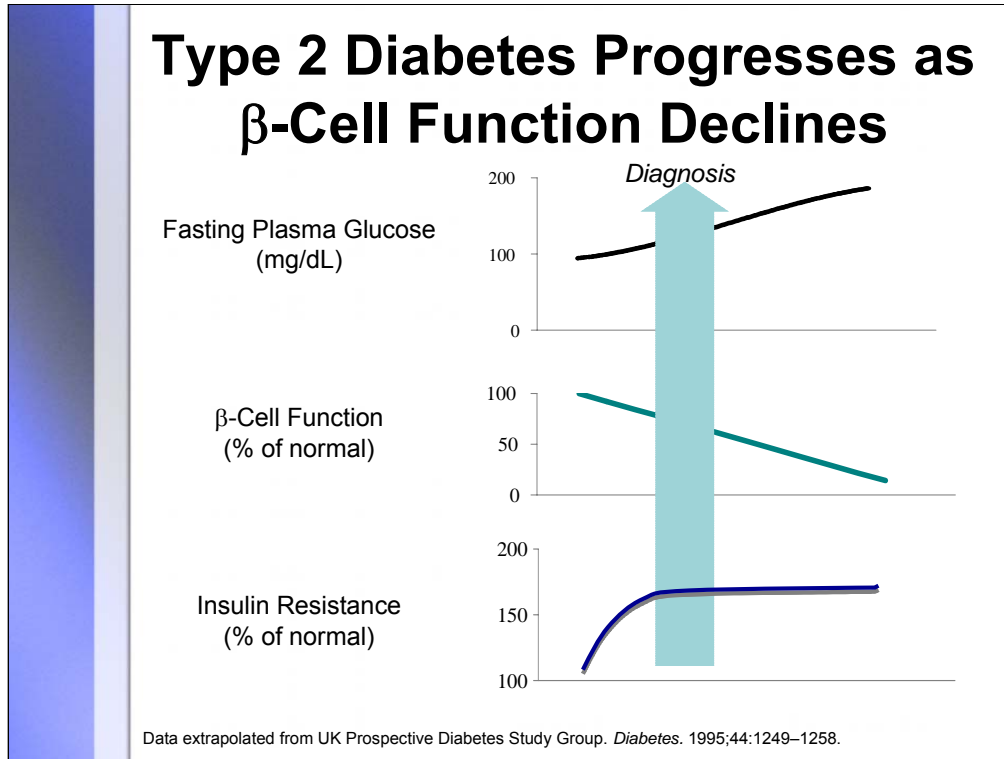


Type 2 diabetes is characterized by several abnormalities in the regulation of glucose production and utilization. Abnormal pancreatic beta-cell function impairs the normal insulin response to glucose ingestion. That is, the early insulin response is diminished and the later insulin response is prolonged. In addition, in type 2 diabetes, the normal glucose-dependent suppression of glucagon, a hormone that is secreted by the pancreatic alpha-cells and increases hepatic glucose production, is absent. Furthermore, incretin hormones, which are released from the gut, may be secreted at lower rates, or the action of these incretins may be impaired. Taken together, these hormonal abnormalities lead to inappropriately high rates of hepatic glucose production that contribute to hyperglycemia.

In addition, the liver and peripheral muscle and fat tissues are resistant to insulin action. In the liver, insulin resistance contributes to inappropriately high rates of hepatic glucose production. In the peripheral tissues, insulin resistance reduces insulin-stimulated glucose uptake.

The combination of unrestrained glucose production and diminished tissue uptake of glucose results in hyperglycemia, in both fasting and postprandial states. As will be presented later, medications for diabetes address one or more of these defects in metabolic regulation.

Another player in hyperglycemia is the kidneys. Normally, the glucose filtered out of the blood by the kidneys is actively reabsorbed via the sodium/glucose co-transporters, or SGLTs. Usually, when blood glucose concentrations are >180 mg/dL, SGLTs become saturated and glucose spills into the urine. Therefore, depending on the circumstances, the kidney may decrease plasma glucose levels or may be unable to lower plasma glucose levels due to saturation of SGLTs.



The United Kingdom Prospective Diabetes Study, or UKPDS, followed over 5,000 patients with newly diagnosed type 2 diabetes for a mean of 11 years. The patients were treated according to conventional standards or by an intensive therapy plan. During the study, hyperglycemia worsened over time in all treatment groups, whether treated by diet, sulfonylureas, metformin, or insulin.

Assessment of beta-cell function and insulin resistance using the Homeostasis Model Assessment, or HOMA, revealed a progressive loss of beta-cell function that coincided with worsening hyperglycemia. The level of insulin resistance that was already present at diagnosis did not change over time.

The diagrams shown in the present slide were extrapolated from the data gathered during the first 6 years of the UKPDS.

At the present time, there are no comparable prospective studies that have investigated the time-related changes in other contributors to the pathophysiology of type 2 diabetes, such as glucagon, incretins, or regulation of hepatic glucose production. Therefore, our current understanding of the progression of type 2 diabetes implicates beta-cell failure as the cause for continual worsening of hyperglycemia.

Test Your Understanding

Which of the following statements is TRUE?

- A. The majority of indirect costs associated with diabetes are related to disability.**
- B. Nephropathy increases the risk of death by 5-fold for people with type 2 diabetes.**
- C. Beta-cell function progressively deteriorates over time while insulin resistance is established fully at the time of diagnosis.**

Which of the following statements is true?

- A. The majority of indirect costs associated with diabetes are related to disability.
- B. Nephropathy increases the risk of death by 5-fold for people with type 2 diabetes.
- C. Beta-cell function progressively deteriorates over time while insulin resistance is established fully at the time of diagnosis.

Test Your Understanding

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

Beta-cell function progressively deteriorates over time while insulin resistance is established fully at the time of diagnosis.

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

Beta-cell function progressively deteriorates over time while insulin resistance is established fully at the time of diagnosis.

Lowering A1C Reduced Complications

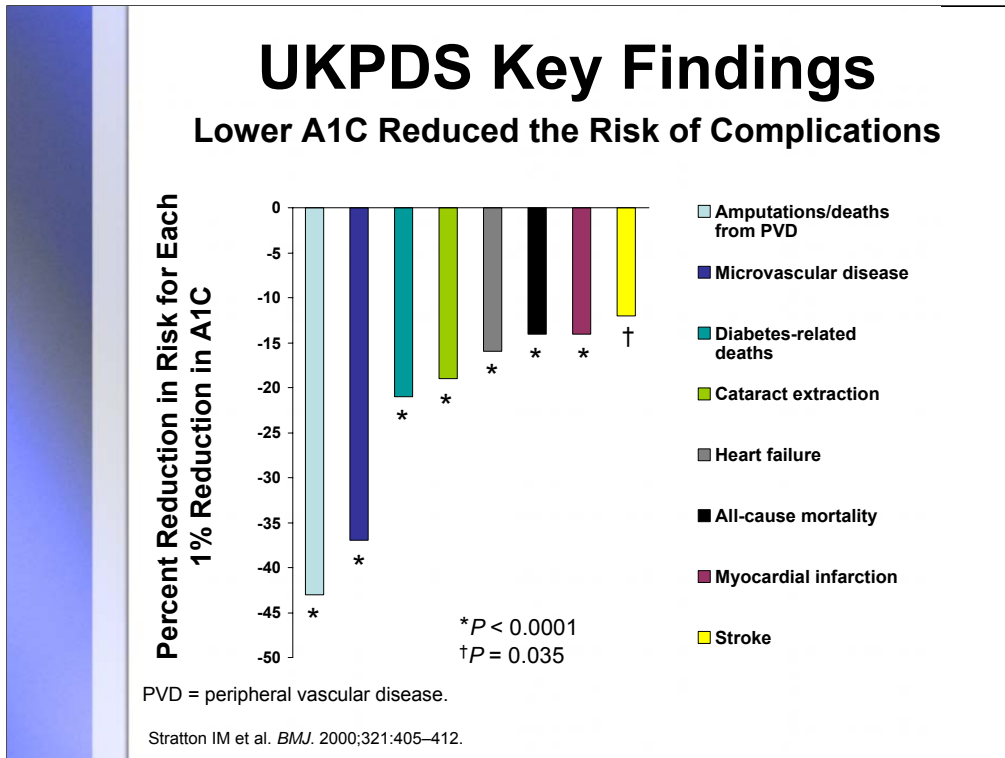
	DCCT (Type 1)	Kumamoto (Type 2)	UKPDS (Type 2)	DCCT/EDIC (Type 1)
Change in A1C	9% → 7%	9% → 7%	8% → 7%	9% → 8%
Retinopathy	↓63%	↓69%	↓17%–21%	↓72%–87%
Nephropathy	↓54%	↓70%	↓24%–33%	↓53%–92%
Neuropathy	↓60%			
Macrovascular	↓41%*		↓16%*	↓42%–57%

*Not significant because of small number of events.

Several landmark clinical trials provide evidence that better glycemic control reduces the risk of diabetic complications. These results support the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) recommendations to maintain glucose levels as close to normal as is safely possible.

The Diabetes Complications and Control Trial (DCCT) and the Kumamoto study demonstrated that using intensive insulin therapy to maintain A1C at ~7% delayed or prevented the development of microvascular complications (retinopathy, nephropathy, and neuropathy) in patients with type 1 and type 2 diabetes, respectively. The UKPDS also reported that the risk of microvascular complications was significantly reduced when insulin, oral antidiabetes medications, or both were used to keep A1C at a median of ~7% in patients with type 2 diabetes.

The risks of macrovascular complications were not significantly affected during the 6 to 10 years covered by the controlled portion of the DCCT, the Kumamoto study, or the UKPDS. However, an additional 11-year follow-up of patients who completed the controlled DCCT, the DCCT/Epidemiology of Diabetes Interventions and Complications, or EDIC study, revealed a significant association between a history of good glycemic control and reduced risk of macrovascular as well as microvascular complications. That is, the benefit of early glycemic control was still evident years later, even though A1C had not been maintained at ~7% during the follow-up period. Therefore, early intensive glycemic control conferred what has been called a “metabolic memory” that protected against long-term complications in persons with type 1 diabetes.



The UKPDS included a prospective analysis that evaluated the relationship between total glycemic exposure and the risk of complications and deaths related to type 2 diabetes. This analysis included more than 3600 individuals followed for 7.5 to 12 years.

This analysis demonstrated that the incidence of clinical complications was significantly associated with glycemic exposure. Indeed, each 1% reduction in updated A1C, defined as the average of all preceding annual A1C measurements, was associated with significant reductions in the risk of adverse events. There was a 43% reduction in amputations and deaths from peripheral vascular disease, a 37% reduction in microvascular complications, a 21% reduction in deaths related to diabetes, a 19% reduction in cataract extractions, a 16% reduction in heart failure, a 14% reduction in all-cause mortality, a 14% reduction in fatal and nonfatal myocardial infarction, and a 12% reduction in fatal and nonfatal stroke.

UKPDS Key Findings

Implications for Therapy

Monotherapy loses efficacy over time

3 Years 50% had A1C <7%

9 Years 25% had A1C <7%

Therapy adjustments are required to maintain A1C <7%

- The majority of patients needed multiple oral agents
- The majority of patients eventually required insulin
- Insulin protocols should be optimized for fasting and postprandial glycemic control

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

Analysis of the first 9 years of treatment in the UKPDS determined the percentage of patients in each treatment group that achieved the ADA goals for A1C and FPG.

Although monotherapy with either insulin, sulfonylurea, or metformin initially doubled the proportion of patients that attained the A1C goal of <7%, compared with diet alone, the majority of patients did not maintain this level of glycemic control over time. The proportion of patients who had an A1C <7% while on monotherapy declined to 50% at 3 years and 25% after 9 years. By 9 years, the majority of patients needed multiple agents or insulin to maintain the target A1C. A young age at diagnosis, high baseline obesity, the level of hyperglycemia at baseline, and hypertriglyceridemia were associated with an increased need for multiple therapies. The authors also concluded that due to progressive decline in beta-cell function, the majority of patients with type 2 diabetes eventually will require insulin delivered in a regimen that controls both fasting and postprandial hyperglycemia to obtain A1C levels <7%.

UKPDS Key Findings Summary

- **No A1C threshold for reducing the risk of diabetic complications**
 - Lowest risk in patients with A1C <6% (normal)
- **Type 2 diabetes worsens over time due to progressive β -cell failure**
 - Loss of efficacy of oral agents leads to eventual insulin use
 - Insulin therapy should address postprandial as well as fasting hyperglycemia
- **Insulin and sulfonylureas do not increase cardiovascular risk**

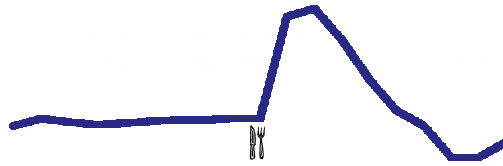
Stratton IM et al. *BMJ*. 2000;321:405–412.
UKPDS. *Lancet*. 1998;352:837–853.

The UKPDS also demonstrated that individuals with the lowest risk of complications had A1C levels <6%, a normal value. These results indicate that there is no apparent A1C threshold for any of the long-term complications associated with diabetes. This finding supports the concept of maintaining A1C as close to normal as is safely possible to reduce the risk of these complications.

The UKPDS was the first prospective study to demonstrate that progressive beta-cell failure is the primary pathophysiology underlying the continual worsening of hyperglycemia in type 2 diabetes. The consequences of the loss of beta-cell function include the eventual loss of efficacy of oral antidiabetes agents and the often inevitable need for insulin therapy. Furthermore, the UKPDS investigators discovered that a regimen using the long-acting and regular insulins that were available when the study started in 1977 was inadequate to provide the necessary control of both fasting and postprandial hyperglycemia.

Finally, the fear that insulin or sulfonylureas increased the risk of cardiovascular disease and death, a controversial finding of the earlier University Group Diabetes Program study, was not borne out by the UKPDS.

Normal Glycemic Control



Fasting
Glucose

Normal <100 mg/dL



Postprandial
Glucose

Normal <140 mg/dL

A1C

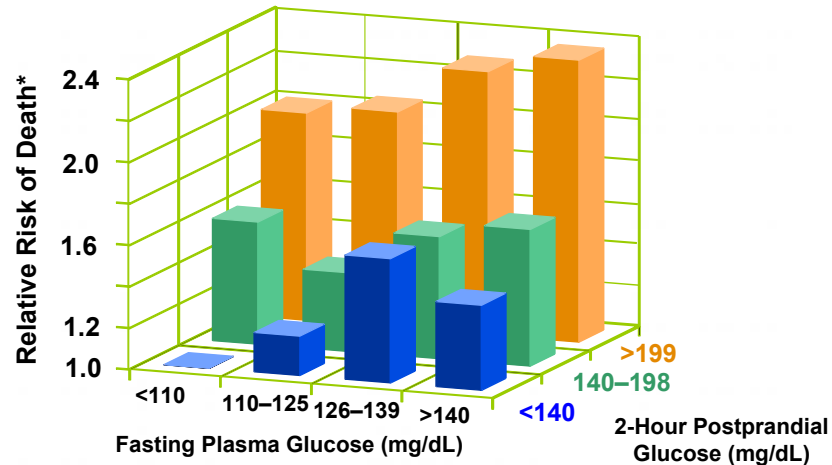
Normal $\leq 6.0\%$

American Diabetes Association. *Diabetes Care*. 2001;24:775-778.

Hemoglobin A1C, referred to as A1C, provides a measure of overall glycemic control for the preceding 2 to 3 months. A1C measures the percentage of hemoglobin molecules with glucose permanently attached as a result of both fasting and postprandial glucose, or PPG, exposure.

Normal A1C is 4% to 6% and represents a mean daily blood glucose level of 135 mg/dL or lower. On average, a 1% increase in A1C corresponds to an increase of ~35 mg/dL in mean daily glucose. Mean daily glucose is the average of several glucose measurements made at standard times during the course of a 24-hour period.

DECODE Trial: The Role of PPG



*Adjusted for age, sex, study center.

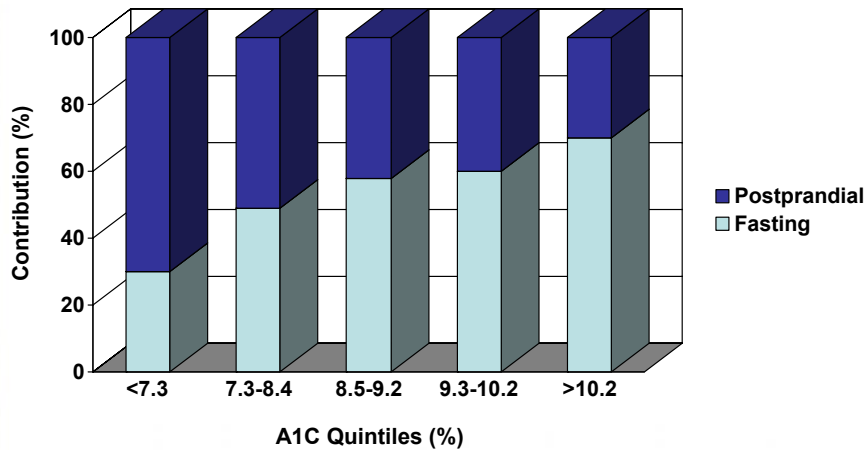
Adapted from DECODE Study Group. *Lancet*. 1999;354:617-621.

Although PPG contributes to daytime hyperglycemia, past monitoring recommendations focused on fasting glucose measurements. 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 the mortality risk for patients with diabetes. This multinational research project assessed the relationship of fasting and postprandial blood glucose levels and the risk of death reported in 13 prospective European cohort studies involving more than 25,000 individuals. The median follow-up was 7.3 years. Comparison of FPG <110 mg/dL, considered normoglycemia at the time, to three levels of fasting hyperglycemia, shown on the horizontal axis, revealed no consistent trend in the risk of death. However, within each category of FPG, higher levels of 2-hour postchallenge plasma glucose were significantly and directly related to increased risk of death. Individuals who had an FPG <110 mg/dL but a 2-hour postmeal glucose >199 mg/dL had an almost 2-fold increased risk of death than those with normal 2-hour postmeal glucose, considered <140 mg/dL. The authors concluded that postprandial hyperglycemia is a better predictor of mortality than FPG.

Postprandial Control

PPG excursions contribute more to hyperglycemia in patients with lower A1C

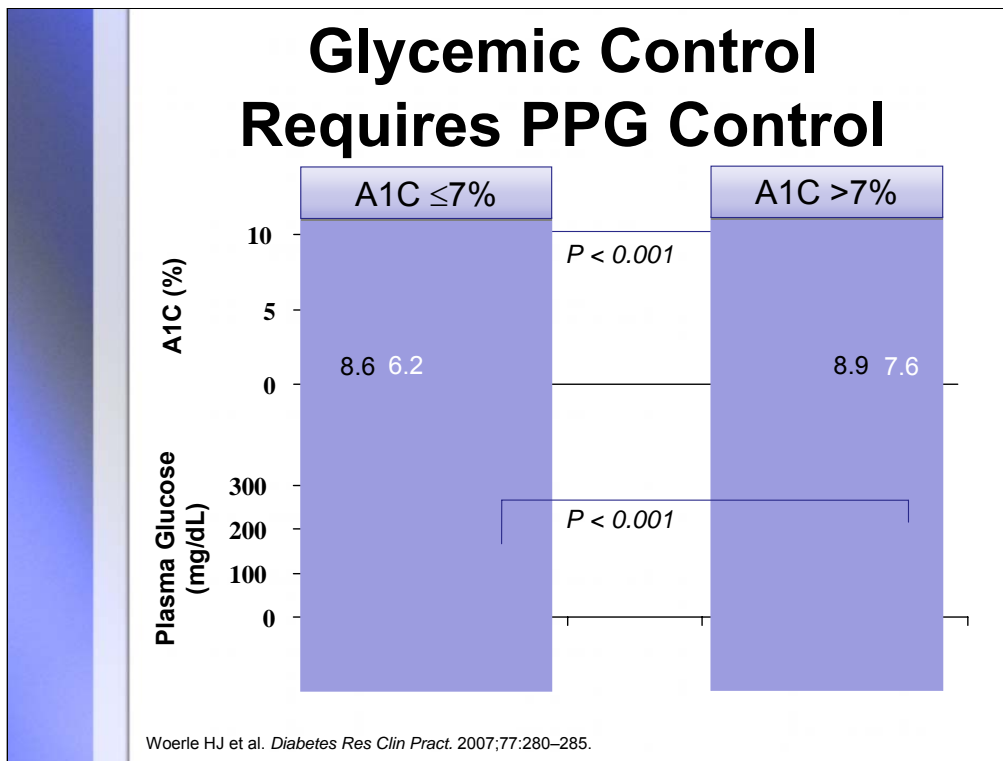


Monnier L et al. *Diabetes Care*. 2003;26:881-885.

A clinical investigation demonstrated that the postprandial contribution to hyperglycemia is greatest in patients with type 2 diabetes who have mild to moderate hyperglycemia. In the two quintiles representing the lower A1C values ($\leq 8.4\%$), postprandial excursions were responsible for 50% to 70% of the hyperglycemia of diabetes. In the patients with the highest A1C levels ($>10.2\%$), postprandial excursions contributed only 30% of the excess glucose.

This study, published in 2003, analyzed the relative contributions of fasting and postprandial hyperglycemia to A1C in 290 patients with type 2 diabetes. The patients may have been treated with diet alone or stable doses of metformin, glyburide, or both; patients taking insulin or acarbose were excluded from the analysis.

These results suggest that management of PPG is necessary for overall glycemic control for patients with type 2 diabetes who have mild to moderate hyperglycemia. The next slide shows the results of a prospective study conducted to test that hypothesis.



The necessity of PPG control for the management of hyperglycemia was demonstrated in a prospective clinical trial involving 164 patients with type 2 diabetes. The patients' existing treatments were intensified to reach FPG and PPG targets, with all major treatment changes occurring during the first 2 weeks of a 3-month follow-up. After 3 months, A1C ≤7% was achieved in 73% of the patients. Compared with the patients whose A1Cs remained >7%, those patients who attained the A1C goal had similar mean FPG but significantly lower mean PPG. Indeed, only 64% of patients attaining the goal FPG of <100 mg/dL also achieved A1C ≤7%, whereas 94% of patients reaching the PPG goal of <140 mg/dL also had A1C ≤7%.

When patients entered the study, 26% were treated with diet, 44% with OAD monotherapy or combination therapy, and 31% with NPH insulin alone or combined with OADs or short-acting insulin. Depending on their starting points, patients advanced from diet to OAD, or insulin monotherapy to metformin combined with an insulin secretagogue or NPH insulin to achieve the FPG goal of <100 mg/dL. For patients whose PPG remained >140 mg/dL, repaglinide or short-acting insulin was added or intensified before meals. At the end of the study, 30% of patients were treated with diet alone or OADs and 70% included insulin in their treatment regimen.

These results demonstrate that FPG control, while necessary, is not sufficient to provide good glycemic control, and that PPG control is essential for achieving A1C goals.

Current Treatment Goals

Parameter	ADA	AACE
A1C	<7%	≤6.5%
Fasting/preprandial glucose (mg/dL)	70–130	<110
Postprandial glucose (mg/dL)	<180*	<140†
Blood pressure (mm Hg)	<130/80	
LDL cholesterol (mg/dL)	<100 (<70 for existing CVD)	
HDL cholesterol (mg/dL)	>40 for men or >50 for women	
Triglycerides (mg/dL)	<150	

CVD = cardiovascular disease.

*Peak postprandial capillary plasma glucose

†2-hour postprandial glucose

American Diabetes Association. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.

American Association of Clinical Endocrinologists. *Endocr Pract*. 2007;13(Suppl 1):4–68.

The treatment goals for diabetes aim to reduce the risk of complications by optimizing glycemic control, reducing blood pressure, and treating dyslipidemia.

The glycemic targets are based on landmark studies showing that sustained reductions in blood glucose levels decrease the risk of developing microvascular and macrovascular complications. Because there is no threshold below which the risk of complications is zero, the targets for A1C and fasting glucose levels are intended to maintain glucose levels as near to normal as possible without an excessive risk of hypoglycemia in many patients.

Treating hypertension to reach the recommended blood pressure target has been shown to decrease the risk of both macrovascular and microvascular, in particular renal, complications in type 2 diabetes. Clinical evidence also suggests that attaining the recommended lipid goals decreases the risk of primary and secondary cardiovascular events as well as cardiovascular-related deaths.

Comprehensive diabetes care demands continuous medical care and self-management to maintain these goals and decrease the risk of complications.

Monitoring

ADA recommendations

Self-monitored blood glucose	Sufficient to achieve glycemic control
A1C if <7% if ≥7%	At least twice yearly Quarterly
Urinary albumin excretion	Annual
Serum creatinine	At least annually
Dilated eye examination	Annually or every 2-3 yr if stable
Visual foot examination	Each visit
Comprehensive foot examination	At least annually
Blood pressure	Each visit
Lipid monitoring	At least annually or every 2 yr for low-risk profile

American Diabetes Association. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.

The 2008 ADA standards of care for patients with type 2 diabetes recommend self-monitoring of blood glucose and A1C measurements frequently enough to help achieve glycemic targets. A1C should be measured at least twice a year or quarterly if the patient has changed therapy or is not at treatment goals.

Annual assessments of urinary albumin excretion and serum creatinine levels allow early detection of diabetic nephropathy. Dilated eye examinations should be conducted annually to check for diabetes-related eye damage. After 2 or 3 normal eye exams, the frequency may be reduced to every 2 to 3 years.

Each health care provider should visually inspect their patient's feet at each visit. Comprehensive foot examinations should be performed annually or more often for those patients with foot conditions that increase the risk of amputation.

Blood pressure should be measured at each visit and a lipid profile should be obtained at least annually. For individuals with a low-risk lipid profile (low-density lipoprotein [LDL] cholesterol <100 mg/dL, HDL cholesterol >50 mg/dL, and triglycerides <150 mg/dL), testing may be conducted at 2-year intervals.

Monitoring frequency should be individualized to meet the medical needs of each patient with type 2 diabetes.

Quality of Care

Inadequate diabetes control and management is common in the United States

Measurement	% of People with Diabetes (1999-2002)
A1C >7%	58
BP >130/80 mm Hg	52
LDL \geq 100 mg/dL	66
Process	
No dilated eye examination	32
No foot examination	32

Saaddine JB et al. *Ann Intern Med.* 2006;144:465-474.

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

An analysis of data collected from participants with diabetes in two federally funded national surveys, NHANES in 1999–2002, and the Behavioral Risk Factors Surveillance System, or BRFSS, in 2002, revealed a significant gap between the ADA recommendations and actual practice.

In 2002, 58% of patients had inadequate glycemic control. Additionally, 52% had poor blood pressure control and 66% of those surveyed had elevated LDL cholesterol. During the previous year, only 68% of the survey participants had a dilated eye examination or a foot examination. Therefore, there is an opportunity to provide better management of the health risks associated with diabetes by more diligent application of the standards of care.

Glycemic Control from 1999 to 2004

NHANES Analysis	1999–2000	2003–2004
A1C <7%	37%	57%*
Use of Antidiabetes Medications		
OADs only	53%	59%
Insulin only	16%	14%
Insulin + OADs	11%	9%
Diet alone	20%	18%

* $P < 0.05$.

Hoerger TJ et al. *Diabetes Care*. 2008;31:81–86.

Data from NHANES 1999–2000 and NHANES 2003–2004 revealed that overall glycemic control is improving among US adults with diagnosed diabetes. While the news is encouraging, there are still 2 out of every 5 people with diabetes who are not at the ADA's target of A1C <7%.

The pattern of use of antidiabetes treatment options is also changing. A larger percentage of people with diabetes are being treated with OADs only. Compared with NHANES 1999–2000, smaller percentages of people in 2003–2004 were treated with diet alone, insulin alone, or insulin combined with oral agents; however, these changes were not statistically significant.

Test Your Understanding

Which of the following statements is TRUE?

- A. FPG is the best predictor of mortality in people with diabetes.**
- B. Maintaining A1C value <7% over the long term is difficult with monotherapy.**
- C. Most patients with type 2 diabetes are currently treated with insulin.**

Which of the following statements is TRUE?

- A. FPG is the best predictor of mortality in people with diabetes.
- B. Maintaining A1C value <7% over the long term is difficult with monotherapy.
- C. Most patients with type 2 diabetes are currently treated with insulin.

Test Your Understanding

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

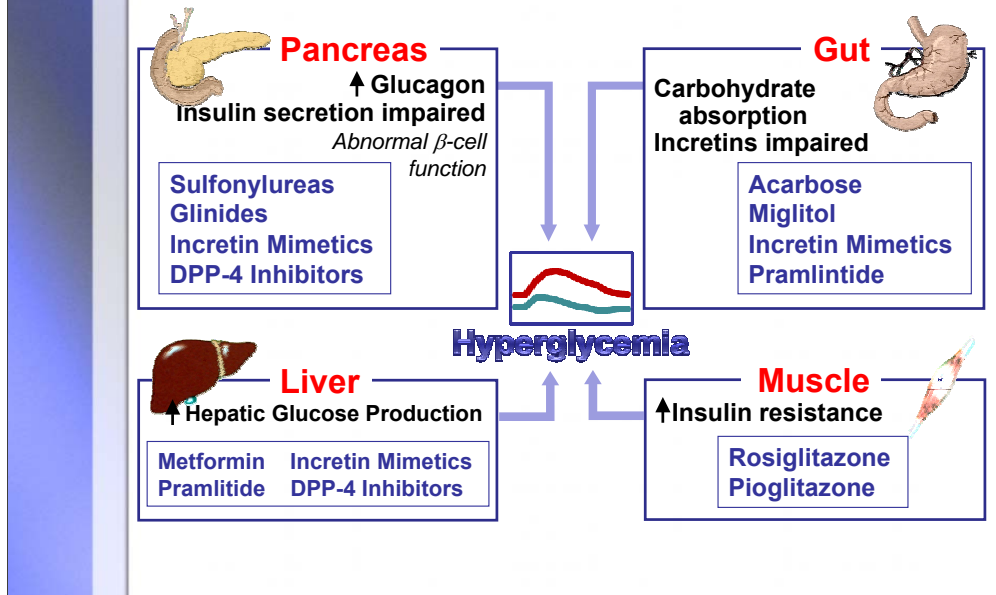
The UKPDS showed that only 50% of patients could maintain an A1C <7% for 3 years on monotherapy, and only 25% could maintain it for 9 years.

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

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.

Therapy for Type 2 Diabetes

Sites of Action



Currently available antidiabetes agents address the abnormalities in glucose regulation and utilization that contribute to type 2 diabetes pathophysiology. Sulfonylureas and glinides, such as repaglinide, act directly on the pancreatic beta-cells to stimulate insulin release. By increasing insulin levels, these agents may increase the risk of hypoglycemia and weight gain.

Other drugs that enhance insulin secretion include incretin receptor agonists such as exenatide, and the dipeptidyl-peptidase-IV (DPP-4) inhibitors, such as sitagliptin that prolong natural incretins. These agents also reduce glucagon and lower hepatic glucose production, or HGP, thus reducing glucose with a low risk of hypoglycemia or weight gain.

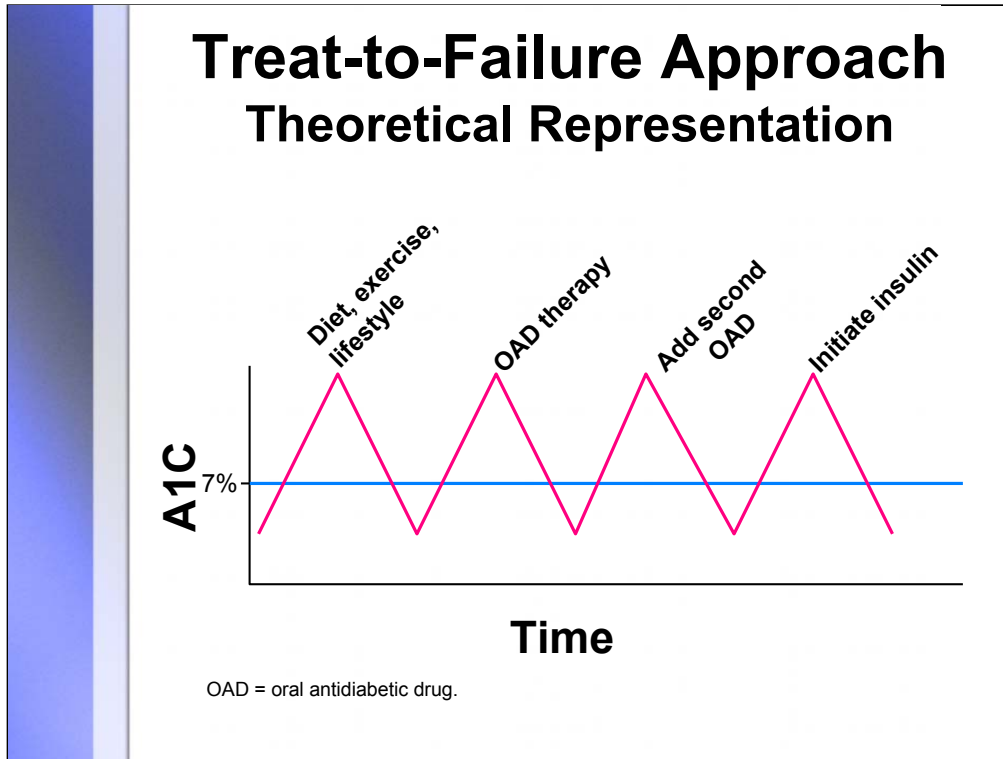
Metformin and the amylin analog, pramlintide, also reduce HGP and lower glucose. Metformin has a low risk of hypoglycemia or weight gain. However, pramlintide, which is indicated as an adjunct to mealtime insulin, has been associated with an increased risk of insulin-induced severe hypoglycemia, if insulin doses are not reduced appropriately.

The thiazolidinediones or TZDs, rosiglitazone and pioglitazone, promote glucose uptake by decreasing insulin resistance in muscle. TZDs may cause weight gain, edema, and worsen congestive heart failure.

The α -glucosidase inhibitors, acarbose and miglitol, slow the digestion and absorption of carbohydrates. Incretins and pramlintide slow gastric emptying, thereby reducing the early rise in PPG.

Antidiabetes agents used as monotherapy reduce A1C by 0.5% to 2.0%. Combinations of agents are used when monotherapy provides inadequate glycemic control, and are most effective when the drugs have synergistic mechanisms of action. Most commonly, an insulin secretagogue is combined with an agent that decreases HGP or with an insulin sensitizer, for example, a sulfonylurea plus metformin or a TZD.

As type 2 diabetes progresses due to continuing beta-cell failure, oral antidiabetes medications may eventually fail to provide adequate glycemic control and insulin may be required.



The traditional approach to the management of type 2 diabetes has been a stepwise addition of therapy, with each intervention used until the A1C increases above the ADA-recommended level of <7%. This strategy has been called the “treat-to-failure” approach since modifications are based on failure to meet glycemic targets. The initial interventions are usually diet and exercise, followed by antihyperglycemic monotherapy, usually OADs, and then combination therapy. Transition from one medication, or combination of medications, to another can often be lengthy with long periods of inadequate control before treatment is modified. Insulin is generally considered the last alternative, presumably because of the need to administer it by injection. As a result, by the time patients with diabetes begin receiving insulin, they have often had type 2 diabetes for up to 15 years and have long-term complications. This is unfortunate, given the ability of insulin to control hyperglycemia with no upper-dose limit.

The incretin or glucagon-like peptide-1, GLP-1 analog, exenatide (brand name Byetta™) and amylin analog, pramlintide (brand name Symlin®) have only recently become available, as have the DPP-4 inhibitors sitagliptin (brand name Januvia™) and vildagliptin. These agents are not represented in the diagram.

Rationale for Earlier Use of Insulin

- **Inadequate glycemic control with other diabetes medications**
- **Insulin is inevitable for most patients**
- **Inadequate glycemic control linked to morbidity and mortality**
 - Intensive glycemic control in the DCCT reduced long-term complications
- **Combinations of newer insulin analogs reproduce physiological insulin profiles**
 - Targets both fasting and postprandial glucose
- **May reverse glucose toxicity**
- **Costs of treating complications is greater than the cost of insulin therapy**

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

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

Earlier use of insulin to treat type 2 diabetes should be considered for several reasons. As presented in the previous slides, glycemic control is not sustained using the traditional stepwise approach to therapy. Because type 2 diabetes worsens over time due to the progressive loss of beta-cell function, many patients will require insulin injections to replace the loss of pancreatic insulin.

The progressive decline of beta-cell function also affects the efficacy of oral antidiabetes agents. The efficacy of oral insulin secretagogues and incretins depends upon the presence of residual beta-cell function.

Early, intensive insulin use has been shown to reverse glucose toxicity and to restore temporarily beta-cell function. In addition, the follow-up to the DCCT showed that use of insulin to achieve intensive glycemic control reduced the incidence of diabetic complications years after the study was completed.

Newer insulin analogs can be administered in combinations that mimic more closely the physiological levels of basal and postprandial insulin. Therefore, insulin regimens can be designed to safely address both fasting and postprandial hyperglycemia.

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

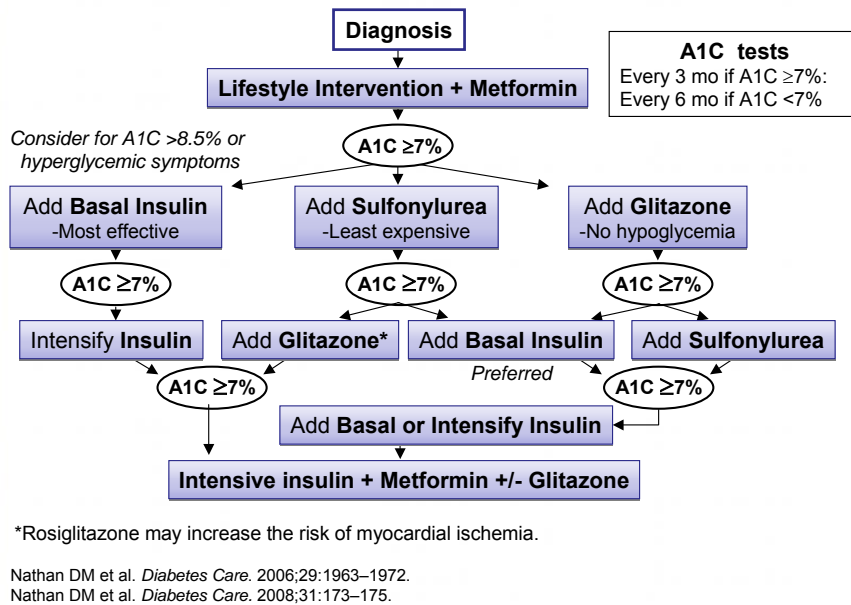
- **Most effective in lowering blood glucose (unlimited ability to lower blood glucose level)**
- **Allows individualization with flexible dosing**
- **Improves insulin sensitivity by reducing glucotoxicity and lipotoxicity**
- **Has beneficial effects on HDL cholesterol and triglycerides**
- **May reduce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

Nathan DM et al. *Diabetes Care*. 2006;29:1963–1972.

Insulin therapy in type 2 diabetes is associated with several advantages over alternative treatments. Insulin is the most effective antidiabetes therapy because there is no limit on the dosage. The amount, timing, and type of insulin injection can be individualized to address both fasting and postprandial hyperglycemia as needed while minimizing the risk of hypoglycemia.

For patients with severe hyperglycemia, insulin can reduce glucotoxicity and lipotoxicity thereby improving beta-cell function and insulin sensitivity. In addition, insulin has beneficial effects on diabetic dyslipidemia and may reduce the risk of cardiovascular complications.

ADA/EASD Consensus Algorithm for Management of Type 2 Diabetes



This slide depicts a consensus algorithm developed by the ADA and the European Association for the Study of Diabetes, or EASD. The management goal is to achieve and maintain glycemic levels as close to the nondiabetic range as is safely possible. The algorithm supports the concurrent initiation of pharmacotherapy and lifestyle interventions at the time of diagnosis, rapid adjustments in therapy, and the early addition of insulin for patients who do not maintain glycemic targets. Specifically, lifestyle interventions and metformin should be initiated in most newly diagnosed patients. Insulin and lifestyle interventions are the recommended initial therapies in the presence of severe hyperglycemia, defined as blood glucose >250 mg/dL. A second medication should be added within 2 to 3 months if the A1C is >7% after treatment with a single medication. The selection of the second agent depends in part on the A1C level; if it is >8.5%, for example, addition of basal insulin is preferred. If lifestyle, metformin, and a second agent are not effective in achieving the glycemic target, the next step is to start or intensify insulin. Adding a third oral agent may be considered, but is not recommended based on the expense and anticipated limited efficacy.

It should be noted that this algorithm was developed before the introduction of the incretin mimetics and DPP-4 inhibitors.

Test Your Understanding

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

- A. Beta-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.**

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

- A. Beta-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!

Replacement of the insulin deficit resulting from β -cell failure, an unlimited ability to lower blood glucose, and flexible dosing that allows individualization of therapy are all advantages of insulin therapy in type 2 diabetes.

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

Replacement of the insulin deficit resulting from beta-cell failure, an unlimited ability to lower blood glucose, and flexible dosing that allows individualization of therapy are all advantages of insulin therapy in type 2 diabetes.

Psychological Insulin Resistance and Clinical Inertia: Patients

- Nearly one third of patients not taking insulin would be unwilling to start even if it were prescribed
- Negative perceptions of insulin include:
 - Sense of personal failure, self-blame
 - Once initiated, insulin therapy will be permanent
 - Diabetes has become more serious
 - Anticipated pain, fear of injection
 - Fear of hypoglycemia
 - Fear of restrictions and demands associated with insulin
 - Fear of weight gain

Peragallo-Dittko V. *Diabetes Educ.* 2007;33:60S–65S.
Peyrot M et al. *Diabetes Care.* 2005;28:2673–2679.
Peyrot M et al. *Diabetologia.* 2003;46(Suppl 2):A89.
Polonsky WH et al. *Diabetes Care.* 2005;28:2543–2545.

One of the key challenges of initiating insulin therapy for type 2 diabetes is recognizing and responding to psychological insulin resistance. Psychological insulin resistance is reluctance on the part of both patients and providers to start insulin therapy when it would be beneficial.

In a recent survey of patients with type 2 diabetes, among those not currently taking insulin, 28.2% reported being unwilling to take insulin even if it were prescribed. Another study showed that more than half (57%) of patients with type 2 diabetes not currently on insulin were worried about starting insulin therapy. Moreover, 48% of those patients believed that starting insulin would mean that they had not correctly followed treatment recommendations.

Patients resist starting insulin therapy for a number of reasons including a sense of personal failure regarding management of their diabetes; beliefs that insulin therapy will become permanent or that it indicates a worsening of their disease; and fears of injection, weight gain, or hypoglycemia.

Psychological Insulin Resistance and Clinical Inertia: Providers

- Over 50% of nurses and primary care physicians report delaying insulin therapy until absolutely necessary
- Delaying insulin therapy is more common among US physicians than physicians in other countries
- Specialists are less likely to delay initiating insulin
 - Delay is less likely when insulin is viewed as more efficacious
- Health care providers' negative perceptions of insulin
 - Extra time will be required to manage complex treatment regimens
 - Extra training, support, and resources will be required
 - Fear of patient's hypoglycemia, weight gain
 - Fear of patient's anger and alienation

Peragallo-Dittko V. *Diabetes Educ.* 2007;33:60S–65S.
Peyrot M et al. *Diabetes Care.* 2005;28:2673–2679.
Phillips P. *Rev Diabet Stud.* 2005;2:35–39.
Polonsky WH, Jackson RA. *Clin Diabetes.* 2004;22:147–150.

Studies have documented that health care providers, like patients, also demonstrate psychological insulin resistance.

Analyses from the Diabetes Attitudes, Wishes, and Needs study showed that among diabetes care providers, over 50% of primary care physicians and nurses believe that insulin should be delayed until absolutely necessary. Delay of insulin therapy was found to be significantly less among specialists and opinion leaders who view insulin as more efficacious.

Health care providers' negative attitudes about insulin take several forms. These include concerns about complex treatment regimens being too difficult to manage in a busy primary care practice, lack of resources needed for insulin education, concerns about patients' possible weight gain or hypoglycemia, and fears that patients will be annoyed and alienated when insulin is introduced.

As a result of these concerns, health care providers may reflect and amplify patients' own fears about starting insulin, resulting in an unspoken collusion between patient and provider to postpone insulin therapy as long as possible. This collusion occurs, for example, if a clinician uses insulin as a potential punishment, threatening to prescribe it if a patient does not lose weight or otherwise adhere to a treatment program.

Replacing such negative attitudes and perceptions on the part of clinicians with a more positive and accepting view of insulin is an essential step toward achieving more effective diabetes management.

Overcoming Psychological Insulin Resistance

- Education

- Stress progressive nature of type 2 diabetes and β -cell decline
- Introduce the concept of insulin early
- Explain that insulin regimen will be matched to needs and lifestyle
- Teach management of hypoglycemia and weight gain
- Introduce a variety of insulin delivery devices
 - May reduce trauma and anxiety
- Explain advantages of insulin analogs
 - Increase flexibility in mealtimes
- Listen to understand patients' barriers and/or fears

- Diabetes-care team approach

- Including nurses, dietitians, and diabetes educators

Funnell MM et al. *Diabetes Educ.* 2004;30:274–280.
Korytkowski M. *Int J Obes Relat Metab Disord.* 2002;26(Suppl 3):S18–S24.
Peragallo-Dittko V. *Diabetes Educ.* 2007;33:60S–65S.
Ratner R. *Pract Diabetol.* 2004;23:14–24.

Patient education is a key factor in overcoming psychological insulin resistance. Patients should understand the progressive nature of type 2 diabetes and the role of insulin, including insulin resistance and progressive beta-cell decline. Insulin is a natural hormone that is diminished in diabetes. Its use should be described as one step in a treatment process, not as a last resort, nor as a threat or 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, patients can be taught management strategies for prevention and treatment.

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 about injecting insulin in public. They describe these delivery systems as easier to learn and claim more confidence in their ability to accurately prepare a dose. In addition, patients considering injecting insulin using a syringe should know that current needles are both thinner and smaller, assuring minimal discomfort from the injection.

Use of a diabetes-care team approach—including physicians, nurses, dietitians, pharmacists, and diabetes educators—helps to ensure that patients are informed and educated about their disease and its management, which is key to overcoming psychological insulin resistance.

Insulin Delivery Options

Durable Pens



Disposable Pens



Insulin Pumps



To make insulin regimens easier to use and to fit the patient's 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 and are generally preferred by patients over syringes and vials. Syringes are still used most often in the United States. Conversely, the pen is the most common insulin delivery system in Europe.

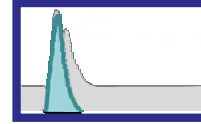
Battery-powered insulin pumps enable continuous delivery of basal doses of insulin without the need for multiple injections. The individual must still monitor blood glucose and calculate the dose, or have the pump calculate the dose, required for a meal or snack, then activate the pump to deliver that dose. However, the system does allow the individual a great deal of flexibility and permits exquisite fine-tuning of the insulin doses.

Detailed descriptions of each insulin delivery system are available in the ADA's annual resource guide.

Currently Available Insulin and Insulin Analogs: Rapid- and Short-Acting

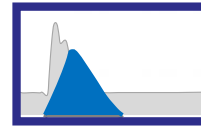
Rapid-acting insulin analogs (onset of action: 5–15 min)

- Insulin lispro (Humalog®)
- Insulin aspart (NovoLog®)
- Insulin glulisine (Apidra®)



Short-acting insulin (onset of action: 30–60 min)

- Regular human insulin (Humulin® R, Novolin® R)



Aventis. Apidra® Prescribing Information. 2005.
Skyler JS. *Therapy for Diabetes Mellitus and Related Disorders*. 2004.

Insulin and insulin analogs differ from other pharmacologic treatments for type 2 diabetes in that they can reduce any A1C level to close to the therapeutic goal. This slide and the following two slides show currently available insulin formulations.

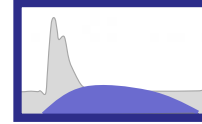
Rapid-acting insulin analogs and short-acting insulin are used to manage the increases in blood glucose associated with meals. Therefore, they are useful in multiple daily injection, or MDI, therapy that mimics the normal changes in insulin levels throughout the day. Because of a shorter time to onset, usually 5 to 15 minutes, rapid-acting insulin analogs are injected within 15 minutes of starting to eat compared with 30 to 45 minutes for regular insulin.

- The rapid-acting insulin analogs are Humalog® or insulin lispro, NovoLog® or insulin aspart, and Apidra® or insulin glulisine.
- The short-acting human insulin preparations are Novolin® R and Humulin® R.
- The analogs and human insulin preparations are of rDNA origin.

Currently Available Insulin and Insulin Analogs: Intermediate- and Long-Acting

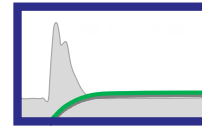
Intermediate-acting insulin (onset of action: 2–4 hr)

- NPH human insulin
(Humulin® N, Novolin® N)



Long-acting insulin analogs (onset of action: 2–4 hr)

- Insulin glargine (Lantus®)
- Insulin detemir (Levemir®)



Aventis. Lantus® Prescribing Information. 2004.
Eli Lilly. Humulin® N Prescribing Information. 2000.
Novo Nordisk. Levemir® Prescribing Information. 2005.
Novo Nordisk. Novolin® N Prescribing Information. 1999.
Skyler JS. *Therapy for Diabetes Mellitus and Related Disorders*. 2004.

Intermediate-acting insulin and long-acting insulin analogs are used to mimic basal insulin levels to lower blood glucose between meals and overnight. Intermediate-acting insulin has an onset of ~2 hours, produces peak insulin levels within 4 to 10 hours and lasts up to 18 hours. Long-acting insulin analogs are peakless and last ~24 hours. Intermediate-acting insulin and long-acting insulin analogs are usually given once or twice daily.

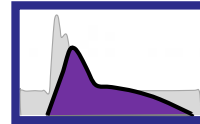
The brand names of intermediate-acting insulin, also called NPH human insulin, are Humulin® N and Novolin® N. NPH insulin is a suspension and requires extensive mixing to assure consistent absorption. A vial should be rolled at least 20 times before the insulin is withdrawn into a syringe.

The long-acting insulin analogs are insulin glargine (brand name Lantus®) and insulin detemir (brand name, Levemir®).

Currently Available Insulin and Insulin Analogs: Premixed Formulations

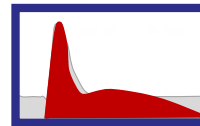
Premixed insulin (onset of action: 30–60 min)

- Humulin® 70/30
- Humulin® 50/50
- Novolin® 70/30



Premixed insulin analogs (onset of action: 5–15 min)

- Humalog® Mix75/25™
- Humalog® Mix50/50™*
- NovoLog® Mix 70/30



*Onset of action: <0.5 hr.

Eli Lilly. Humalog® Prescribing Information. 2006.
Skyler JS. *Therapy for Diabetes Mellitus and Related Disorders*. 2004.

Premixed formulations were developed for patient convenience by combining short-acting insulin with intermediate-acting insulin. Newer products are combinations of the rapid-acting insulin analogs and long-acting insulin analogs. These mixtures were designed to most closely approximate the natural insulin profile.

All mixtures are suspensions and require extensive mixing to assure consistent absorption.

There are several premixed insulin preparations. Humulin® 70/30 is 70% NPH human insulin isophane suspension, and 30% Regular human insulin injection. Humulin® 50/50 is 50% NPH human insulin isophane suspension, 50% Regular human insulin injection. Novolin® 70/30 is 70% NPH human insulin isophane suspension and 30% Regular human insulin injection.

Premixed insulin analogs are Humalog® Mix75/25™ which is 75% insulin lispro protamine suspension and 25% insulin lispro injection, Humalog® Mix50/50™, which is 50% insulin lispro protamine suspension and 50% insulin lispro injection and NovoLog® Mix 70/30, which is 70% insulin aspart protamine suspension and 30% insulin aspart.

Initiating Insulin in Type 2 Diabetes: Which Patients and When?

- **Extreme hyperglycemia** (any of the following)
 - FPG >250 mg/dL
 - Random plasma glucose consistently >300 mg/dL
 - A1C >10%
 - Ketonuria
 - Symptomatic diabetes mellitus (polyuria, polydipsia, weight loss)
- **Patients not achieving glycemic goals on oral agents**
 - Patients with A1C >8.5% or hyperglycemic symptoms on monotherapy
 - Patients receiving 2 oral agents not meeting A1C or FPG targets
 - Initiation of insulin preferred over adding third oral agent based on expected efficacy, expense, and long-term effectiveness
 - Most patients with type 2 diabetes will eventually need insulin therapy

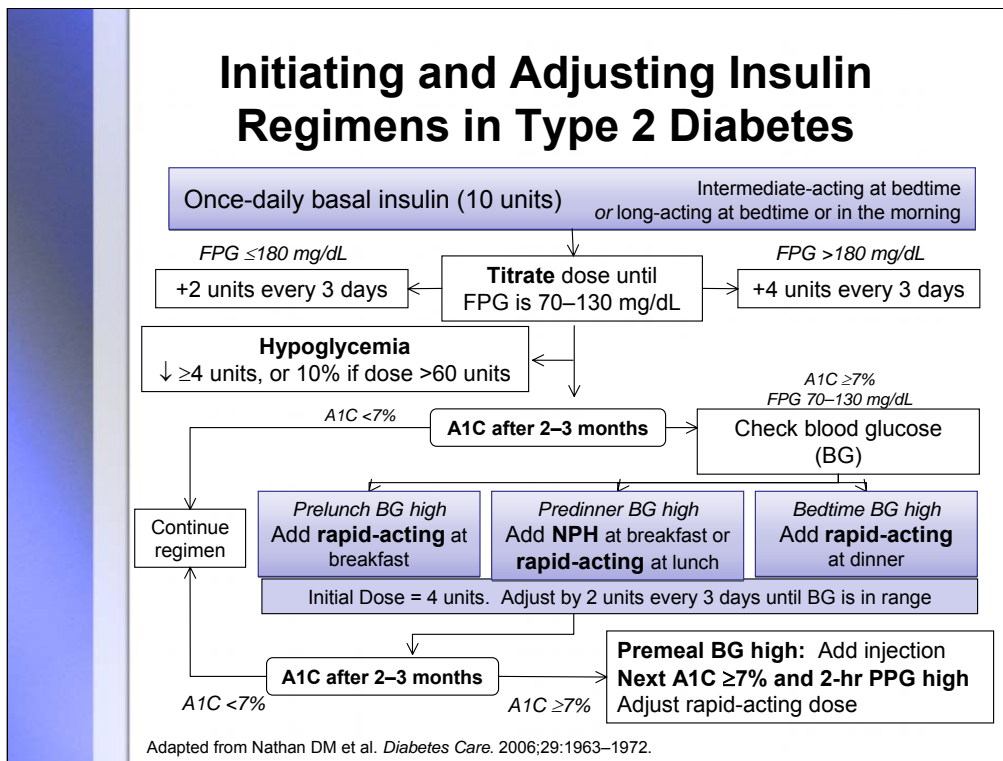
Hirsch IB et al. *Clin Diabetes*. 2005;23:78–86.
Nathan DM et al. *Diabetes Care*. 2006;29:1963–1972.

Which patients with type 2 diabetes should be started on insulin, and when insulin should be initiated can be challenging questions in diabetes management. Patients with extreme hyperglycemia should have insulin started immediately to lower glucose levels and reduce glucotoxicity. Extreme hyperglycemia may present with any of the following: FPG levels >250 mg/dL, random plasma glucose consistently >300 mg/dL, A1C >10%, ketonuria, or symptomatic diabetes with polyuria, polydipsia, and weight loss. Patients receiving oral antidiabetic agents who are not meeting glycemic targets should also be started on insulin.

In the absence of severe hyperglycemia at the time of diagnosis, the ADA now recommends concurrent initiation of lifestyle modifications and metformin pharmacotherapy when type 2 diabetes is diagnosed. Combination therapy should be initiated as soon as glycemic goals are exceeded, usually an A1C >7% on maximal doses of a single antidiabetes drug. If A1C is >8.5% or symptoms of hyperglycemia are present, the consensus ADA/EASD guidelines recommend addition of insulin to oral monotherapy rather than addition of a second oral agent.

When an A1C <7% cannot be achieved or maintained on a combination of two oral agents, initiating insulin is preferable to adding a third oral agent or exenatide. Insulin is relatively less costly and has the potential of achieving glycemic targets, even when A1C is >8%.

Most patients with type 2 diabetes will eventually require insulin therapy because of the progressive loss of beta-cell function.



The ADA/EASD consensus statement includes an algorithm for initiating and titrating insulin in type 2 diabetes. This algorithm demonstrates how to titrate the starting dose as well as how to change the insulin regimen if, despite appropriate titration, A1C levels are not at target after 2 to 3 months.

Insulin is initiated with a once-daily intermediate-acting insulin or long-acting insulin analog, dosed at 10 units or 0.15 to 0.2 unit/kg per day. The dose is then increased every 3 days based on FPG levels until FPG is between 70 to 130 mg/dL.

If A1C is $\geq 7\%$ after 2 to 3 months, and FPG is between 70 to 130 mg/dL, blood glucose levels are checked before lunch, dinner, and bedtime. Depending on the time at which blood glucose is elevated, a second injection, usually a rapid-acting insulin analog, is added at one of the mealtimes or NPH insulin is added in the morning.

If a subsequent A1C is $\geq 7\%$, the premeal blood glucose levels should be checked again and, if indicated, another mealtime injection should be added. If A1C continues to be out of range, 2-hour postprandial blood glucose levels can be checked. If the PPG level is elevated, the dose of the corresponding mealtime rapid-acting insulin analog should be increased.

Initiating Insulin: Choosing the Starting Dose

- **Once-daily basal** (intermediate-acting insulin or long-acting insulin analog)
 - 10 to 20 units/injection in the morning or at bedtime
- **Once-daily premix**
 - 10 units presupper
- **Twice-daily premix**
 - 10 units presupper, 10 units prebreakfast
- **Basal-Bolus**
 - Individualized
 - Adjust dose and incorporate carbohydrate counting

Hirsch IB et al. *Clin Diabetes*. 2005;23:78–86.
Steil CF. *The Art and Science of Diabetes Self-Management Education*. 2006:321–355.

Once the insulin regimen has been chosen, the clinician must decide on a starting dose. The best strategy is to start low and titrate up to avoid hypoglycemia.

A common starting dose for patients with type 2 diabetes who are initiating insulin is 0.15 to 0.2 unit/kg per day. However, in practice, most patients with type 2 diabetes will need higher doses to attain glycemic targets due to the presence of insulin resistance. For patients on a once-daily basal regimen, 10 to 20 units once a day is a reasonable starting dose. Those on a once-daily injection of a premixed insulin or premixed insulin analog can start with 10 units before supper. For a twice-daily premix regimen, 10 units before breakfast and 10 units before supper may be used as a starting dose. Basal-bolus (MDI) therapy involves >3 injections per day. The doses will be calculated based on the patient's meal and activity schedule. Patients on a basal-bolus regimen should be trained by a certified diabetes educator to count carbohydrates and to adjust insulin doses.

Initiating Insulin: Titrating the Dose for Once- or Twice-Daily Regimens

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

Adjust prebreakfast dose based on presupper value.
Adjust presupper (premixed)/bedtime (basal) dose based on prebreakfast value.
DO NOT increase dose if hypoglycemia (<70 mg/dL) or symptoms of hypoglycemia are present.

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

Once the patient with type 2 diabetes has initiated insulin therapy, the starting dose should be titrated as needed to achieve glycemic targets. This slide depicts one suggested titration schedule for use with patients on once- or twice-daily insulin regimens.

Using this schedule, patients should measure blood glucose once or twice daily (before breakfast and before supper) depending on the regimen. The clinician can then adjust the insulin dose based on the patient's self-reported blood glucose values. Prebreakfast dosage adjustments are based on a review of the daytime and presupper blood glucose; presupper dosage adjustments are based on a review of postsupper and prebreakfast blood glucose.

The dose should be titrated weekly until glycemic targets are achieved. If patients are not meeting glycemic targets after 3 to 6 months, or if recurrent hypoglycemia limits the dose titration, then the regimen may need to be changed.

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"> • 50% of total daily dose prebreakfast • 50% of total daily dose predinner • Start 18–24 hours after last basal dose
Once-daily premix	Twice-daily premix	<ul style="list-style-type: none"> • 50% of total daily dose prebreakfast • 50% of total daily dose predinner
Once-daily basal	Add rapid-acting insulin	<ul style="list-style-type: none"> • Rapid-acting insulin: 10% of total daily dose given at largest meal • Basal insulin: 90% of total daily dose
Twice-daily premix	Multiple daily injections	<ul style="list-style-type: none"> • Basal insulin: 40% of total daily dose (80% of half the daily dose) • Prandial insulin 50% of total daily dose divided among meals* (Example: 20% at breakfast, 20% at lunch, 60% at supper)

*The percentage of each prandial insulin dose should correspond to the percent of daily caloric intake consumed at that meal.

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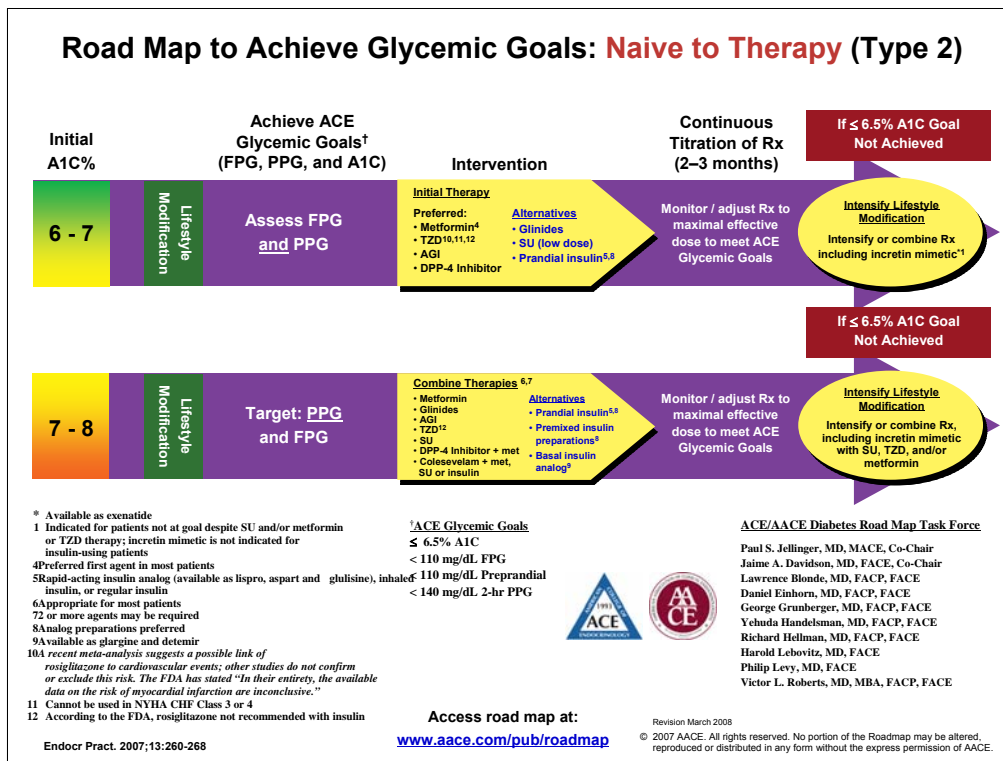
These are examples of how to transition from one type of insulin regimen to another. It is often more acceptable to a patient to start insulin therapy with a once-daily injection. Once the patient has gained experience and confidence, addition of a second injection is usually met with less resistance.

The transition from the once-daily regimens to twice-daily use of premix insulin preparations allows better management of both fasting and postprandial hyperglycemia. The addition of rapid-acting insulin before the largest meal is often a step on the way to MDI therapy.

For MDI therapy, the basal dose should be 80% of half the total daily insulin dose (or 40%). The total initial daily dose of prandial insulin dose should be half of the total daily insulin dose and should be distributed among the meals according to the anticipated caloric intake. For example, if a patient consumes 20% of total daily calories at breakfast, 20% at lunch, and 60% at supper, 20% of the total prandial insulin dose should be given before breakfast, 20% before lunch, and 60% before supper. If this patient's total daily insulin dose is 50 units, he would take 20 units as basal (80% of 1/2 of his total daily dose). He would then take 5 units before breakfast and lunch (20% of 1/2 of his total daily dose) and 15 units at dinner (60% of 1/2 of his total daily dose).

After starting a new insulin regimen, glucose self-monitoring results should be used to adjust dosages as needed to accommodate dietary patterns and to achieve and maintain glycemic targets.

If the patient experiences recurrent hypoglycemia, the total daily dose should be reduced by 20%.



This diagram portrays one of several roadmaps for the management of type 2 diabetes in therapy-naive patients, and was developed by the American College of Endocrinology, or ACE, and the American Association of Clinical Endocrinologists or AACE. These maps are intended to help the medical community achieve the ACE/AACE glycemic control guidelines. Although the goal of the roadmaps is to achieve glycemic targets as quickly as possible, in some cases, clinicians may alter the recommendations to meet specific patient needs.

This map is intended to guide treatment choices for patients with type 2 diabetes who have not been previously treated with medications. Treatment options are suggested based on initial A1C% levels.

ACE and AACE have also created roadmaps for patients who are currently receiving therapy but are not meeting the recommended glycemic goals.

These roadmaps can be found at: www.aace.com/pub/roadmap.

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 two jobs and states that 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 2 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. Ultimately, EM should be encouraged to use a twice-daily premixed insulin as this will cover both fasting and PPG excursions.

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.

Whichever insulin regimen is chosen, the metformin can be continued, but his glyburide should be discontinued if he is getting prandial coverage from insulin.

Summary

- **Type 2 diabetes is becoming more common**
 - Prevalence increases as the nation becomes older, more obese
- **Costs—personal, social and financial—are rising**
 - Glycemic control reduces complications and cost
- **Type 2 diabetes worsens due to progressive β -cell failure**
 - Therapy must compensate for continual loss of natural insulin
- **Recent guidelines promote earlier, more aggressive treatment to maintain near-normal glucose**
- **Education strategies overcome psychological insulin resistance**
- **Earlier insulin use improves glycemic control**
 - Insulin is effective and safe at all A1C levels with proper dosing
 - Available insulins allow physiological replacement
 - OADs usually fail as type 2 diabetes progresses

To summarize what we have covered:

- The prevalence of diabetes is increasing at an alarming rate showing a 60% increase in 10 years. This increase in diabetes is closely linked to an increasing prevalence of overweight and obesity.
- The direct and indirect costs of diabetes have increased 32% in 5 years from \$132 billion in 2002 to \$174 billion in 2007. Costs, both financial and personal tolls, increase with the presence of the complications associated with poor glycemic control.
- Type 2 diabetes is a challenging disease to treat because it worsens over time due to progressive beta-cell failure. Therefore, patients must be routinely monitored and therapy must be adjusted to compensate for the progressive loss of the patient's natural insulin. Because many OADs require the presence of functioning beta-cells to work, they become less effective over time.
- Two out of 5 people with diabetes have inadequate glycemic control despite the widespread use of antidiabetes medications. Recent guidelines recommend the early use of pharmacotherapy, including insulin, with rapid changes in treatment as soon as glucose levels exceed targets.
- One reason for suboptimal use of insulin is the psychological resistance to insulin use by both patients and clinicians. Educational strategies have been advanced to prepare both the patient and the clinician for the eventual necessity of treating type 2 diabetes with insulin.
- To improve glycemic control, many healthcare professionals are advocating the use of insulin earlier in the progression of the disease than is currently being practiced. This earlier use of insulin is indicated because:
 - 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.
 - Research has shown that oral antidiabetes agents often fail to maintain acceptable glucose levels over time in many individuals. The current guidelines recommend insulin use alone, or in combination, when A1C exceeds 8.5% and anytime hyperglycemic symptoms are present.