

## **An Overview of Insulin Analogs and Premixed Insulin Analogs in the Management of Diabetes**

This program is supported  
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The following program is a taped presentation by Linda Haas.

Ms. Haas is the Endocrinology Clinical Nurse Specialist at the VA Puget Sound Health Care System, Seattle Division and a Clinical Assistant Professor of Nursing at the University of Washington School of Nursing. She follows a caseload of patients with diabetes in the Endocrine Clinic and participates in four nurse-run clinics for the education and management of veterans with diabetes.

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.

## Goals and Objectives

**Goal: Provide an overview on the treatment of diabetes with insulin analogs and premixed insulin analogs.**

**After this program, participants will be able to:**

- Discuss the status of diabetes care in the United States
- Explain the rationale for insulin analog development
- List currently available insulin analogs and premixed insulin analogs
- Describe the molecular alterations of insulin analogs and their benefits over human insulin formulations
- Discuss the basic principles of initiating insulin therapy and list potential barriers to insulin treatment
- Describe the practical aspects of storing and injecting insulin
- Identify 2 possible causes of hypoglycemia and list 3 potential symptoms

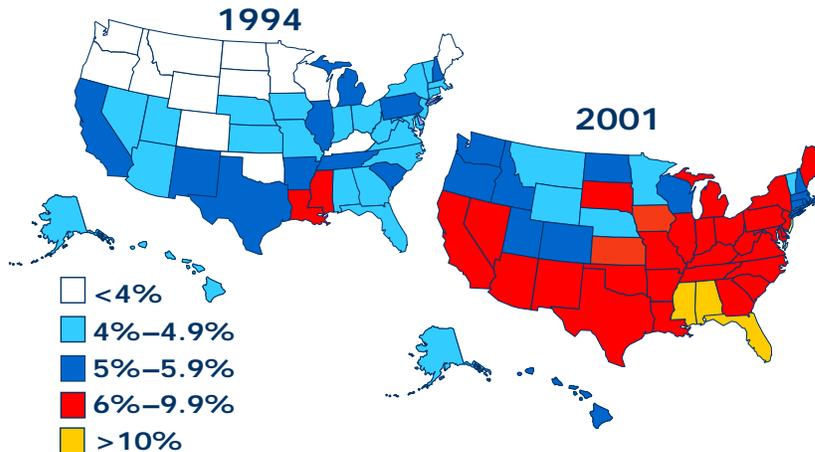
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## Diabetes 1994–2001

Age-Standardized Prevalence of  
Diagnosed Diabetes per 100 Adult  
Population



This slide shows that diabetes, a debilitating and costly disease, is reaching epidemic proportions. The prevalence of diabetes has been increasing steadily in the United States over the last few years. The number of people 20 years of age or older diagnosed with diabetes each year was recently estimated to be 1.5 million.

In 1994, the Centers for Disease Control and Prevention statistics showed that only two states had a 6% or greater prevalence rate of diabetes; in 2001, a majority of states reported a 6% to almost 10% rate, with three states reaching >10%. Additionally, in 2005, the CDC estimated that 20.8 million Americans have diabetes. That's a 14% increase in the number of persons with diabetes since 2003, a span of only two years. About 14.6 million Americans are reported to have diagnosed diabetes, while another 6.2 million are believed to have undiagnosed diabetes.

## Diabetes: Mortality, Complications, Costs

- Higher risk of death and lower life expectancy
  - 6th leading cause of death in the United States
  - Risk of death increases 2-fold in patients with diabetes
- Complications of diabetes contribute to major morbidities
  - 2 to 4 times greater risk of atherosclerotic disease
  - Single greatest cause of adult blindness, chronic renal failure, and nontraumatic amputations
- Annual healthcare costs: \$132,000,000,000
  - Person with diabetes: \$13,243
  - Person without diabetes: \$2,500

Why is diabetes so serious? This slide shows that the risk of death for people with diabetes is 1.5 to 3.6 times greater than the risk of death for people without diabetes and that the median life expectancy is about 8 years lower for adults with diabetes who are between 55 and 64 years of age. People with diabetes have a 2 to 4 times greater risk of heart disease and stroke and 65% of the deaths in people with diabetes are due to these cardiovascular diseases.

Diabetes is the leading cause of new-onset blindness in adults and, while the incidence of end-stage renal disease, or ESRD, in people with diabetes is finally declining, diabetes is still the leading cause of ESRD. In addition, more than 60% of nontraumatic amputations occur among people with diabetes.

The economic burden of diabetes in the US is substantial. Diabetes cost the US \$132 billion in 2002; that is second only to mental illness. When the annual health care costs of a person with diabetes is compared to one without diabetes, there is a five-fold increase, that is over \$13,000 for a person with diabetes, compared with \$2,500 for a person without diabetes.

## Diabetes: An Overview

- Type 1
  - 5% to 10% of patients
  - Produce minimal or no insulin
- Type 2
  - 90% to 95% of patients
  - Produce some insulin of their own at onset; production diminishes with time
- Gestational
  - First detected during pregnancy
  - Occurs in about 7% of pregnancies

There are two main types of diabetes, type 1 and type 2. Type 1 diabetes occurs in about 5%–10% of individuals diagnosed with diabetes in the US. Type 1 diabetes is an autoimmune disease, where the body destroys the part of the pancreas that makes insulin, and exogenous insulin is required to sustain life.

Type 2 diabetes accounts for 90%–95% of individuals with diabetes in the US. The majority of these patients will eventually require insulin. The incidence of type 2 diabetes increases with age, although recently there has been a dramatic increase in young people diagnosed with type 2 diabetes. It is assumed that most of the estimated 6.2 million people who are undiagnosed have type 2 diabetes.

Gestational diabetes, or GDM, is glucose intolerance that is first detected during pregnancy. GDM occurs in ~7% of pregnancies and there are about 200,000 cases each year in the US. Insulin is the treatment of choice in GDM, along with medical nutrition therapy and regular physical activity. After delivery, many women return to normal glucose tolerance; however, 5% to 10% are found to have type 2 diabetes. Alarming, women who have had gestational diabetes have a 20% to 50% chance of developing type 2 diabetes within 5 to 10 years.

## American Diabetes Association (ADA) Criteria for Diagnosis of Diabetes

- Fasting plasma glucose (FPG)  $\geq 126$  mg/dL
- or*
- Symptoms + casual plasma glucose (PG)  $\geq 200$  mg/dL
- or*
- 2-Hour PG  $\geq 200$  mg/dL during an oral glucose tolerance test (OGTT)

The American Diabetes Association (ADA) criteria for the diagnosis of diabetes are listed on this slide.

FPG is a test of fasting plasma glucose level. Fasting is defined as no caloric intake for at least 8 hrs. A test result of 126 mg/dL or greater indicates diabetes.

If a person has symptoms of diabetes, such as increased thirst and urination, especially at night, and blurred vision, and a casual blood sugar 200 mg/dL or greater, diabetes can be diagnosed. A casual blood sugar is one that is tested any time of day, regardless of caloric intake.

An OGTT, or oral glucose tolerance test, consists of a glucose load containing 75 grams of glucose dissolved in water, with the plasma glucose being tested 2 hours after drinking the glucose. A result of 200 mg/dL or above indicates diabetes.

It is important to emphasize that testing should be repeated on a subsequent day by any one of these three methods to confirm the diagnosis of diabetes.

## ADA Criteria for Prediabetes

- **IGT:** Impaired glucose tolerance detected by OGTT  
**140 to 199 mg/dL**
- **IFG:** Impaired fasting glucose detected by FPG test  
**100 to 125 mg/dL**

Prediabetes is a newly recognized condition that includes what had been called impaired glucose tolerance, or IGT, a condition where the 2-hr plasma glucose by OGTT is between 140 and 199 mg/dL, and impaired fasting glucose, or IFG, where the fasting glucose level is between 100 and 125 mg/dL. The ADA uses the term prediabetes to refer to the stage in diabetes development when glucose homeostasis can no longer be maintained, but overt diabetes has not yet developed.

Screening for diabetes and prediabetes is recommended for any adult over 45 years of age, particularly those at high risk. The recommended treatment for prediabetes is lifestyle modification including weight loss and increased activity level. For almost 60% of individuals with prediabetes, these lifestyle modifications can return elevated blood glucose levels to the normal range.

In 2004, the US Department of Health and Human Services estimated that 41 million individuals in the US had prediabetes.

## ADA and AACE Glycemic Targets

	<b>ADA</b>	<b>AACE</b>
Preprandial BG* (mg/dL)	90–130	<110
Postprandial BG* (mg/dL)	<180	<140
A1C (%)	<7	≤6.5

ADA = American Diabetes Association;  
AACE = American Association of Clinical Endocrinologists.  
\*Values are for plasma glucose.

The ADA and the American Association of Clinical Endocrinologists (AACE) both recommend targets to optimize glycemic control for adults with type 1 or type 2 diabetes. The ADA's postprandial targets are used for patients whose fasting glucose levels are within target, but whose A1C results are above target.

Aggressive efforts in the diagnosis and treatment of prediabetes and diabetes can affect the course of the disease. For example, findings from the Diabetes Prevention Program, or DPP, provided evidence that treatment involving lifestyle changes had a profound impact on those with prediabetes, reducing their risk of developing diabetes by more than 58%.

Diabetes management requires continuous medical care and comprehensive self-management training to achieve the goal of optimal glycemic control, and all appropriate treatment options should be used to help individuals with diabetes achieve this goal. However, remember these goals are guidelines, adjustments may be necessary for special populations such as the very old, children, and pregnant or lactating women.

## Landmark Trials

	DCCT (Type 1) 9% → 7%	Kumamoto (Type 2) 9% → 7%	UKPDS (Type 2) 8% → 7%
<b>A1C</b>			
<b>Retinopathy</b>	↓63%	↓69%	↓17% to 21%
<b>Nephropathy</b>	↓54%	↓70%	↓24% to 33%
<b>Neuropathy</b>	↓60%		
<b>Macrovascular*</b>	↓41%		↓16%

DCCT = Diabetes Complications and Control Trial;  
UKPDS = United Kingdom Prospective Diabetes Study.

\*Not significant because of small number of events.

The landmark randomized controlled trials, or RCTs, displayed on this slide have studied the impact of lowering A1C on the incidence of diabetes-related complications. The Diabetes Complications and Control Trial, or DCCT, studied individuals with type 1 diabetes, whereas the Kumamoto study and the United Kingdom Prospective Diabetes Study, or UKPDS, studied those with type 2 diabetes.

In each study, reduction of the A1C was associated with a statistically significant reduction of microvascular complications including a reduced incidence of retinopathy, nephropathy, and neuropathy. These studies did not show a statistically significant reduction in macrovascular complications, possibly because of the small number of events over the 6- to 10-year period of follow-up and the young subjects in the DCCT.

## Quality of Care in the United States

In a 1-year period  
<29% had an A1C test

- 57% of those tested had A1C >7%
- 34% had BP >140/90 mm Hg
- 58% had LDL >130 mg/dL

Despite strong evidence for good glycemic control from the landmark RCTs of the mid-1990s, data show that most patients in the United States are not meeting treatment and monitoring goals. That patients are not reaching goals was shown by analyses of data collected from 1988 to 1995 in 1,026 participants with diabetes in the 3rd US National Health and Nutritional Examination Survey, or NHANES III, and a later study of 3,059 patients with diabetes in the Behavioral Risk Factors Surveillance System. Among the 28.8% of patients who had an A1C test the previous year, inadequate glycemic control, defined as an A1C >7%, was found in 57%. Of the total cohorts studied, 34% had hypertension and 58% had elevated LDL cholesterol; only 63% had a dilated eye examination and only 55% had a foot examination.

Follow-up NHANES results from 1999 to 2000 showed a decline in glycemic control, from 57% of participants with an A1C >7% in 1988 to 64% with an A1C >7% in the year 2000.

## Management of Diabetes

- Medical nutrition therapy (MNT)
- Regular physical activity
- Oral antidiabetic drugs (OADs)
  - Secretagogues (stimulate insulin secretion, type 2 only)
  - $\alpha$ -Glucosidase inhibitors (delay absorption of carbohydrates, type 2 only)
  - Sensitizers (improve insulin action)
  - Incretins (stimulate insulin secretion, increase satiety)
- Insulin/insulin analogs
- Monitoring (including self-monitoring blood glucose [SMBG])
- Self-management education

Whether a patient has type 1 or type 2 diabetes, the essential components of diabetes therapy are medical nutrition therapy, regular physical activity, medications, monitoring, and self-management training.

Focusing a bit more on medications, if sufficient endogenous insulin is present in persons with type 2 diabetes, diabetes can be treated with secretagogues or  $\alpha$ -glucosidase inhibitors. Secretagogues stimulate insulin secretion, whereas  $\alpha$ -glucosidase inhibitors delay intestinal absorption of carbohydrates. In patients with type 1 or type 2 diabetes, insulin sensitizers, which improve insulin action, may be used when insulin resistance is present.

All persons with type 1 diabetes will need insulin or insulin analogs, and insulin and insulin analogs are used by many persons with type 2 diabetes. Some drug combinations have been approved for patients with type 2 diabetes and insulin is often used with secretagogues and sensitizers.

Incretins can be used to stimulate insulin secretion and increase satiety.

One can see that with the complexity of diabetes management, monitoring is necessary to ensure that treatment is appropriate and effective.

Self-management training, or SMT, is the diabetes management modality that enables people with diabetes to participate in their own care and reach glycemic and other targets.

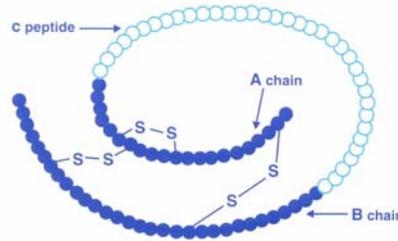
## When Is Insulin Therapy Required?

- Type 1 diabetes - from time of diagnosis
- Type 2 diabetes - when glycemic goals are not being met with other therapies. Usually the result of progressive  $\beta$ -cell failure.

When is insulin therapy needed? Patients with type 1 diabetes need insulin therapy as soon as they are diagnosed. Patients with type 2 diabetes require insulin when their glycemic goals are not being met with other therapies. This inability to reach glycemic targets is usually the result of progressive  $\beta$ -cell failure.

# Insulin

- $\beta$  cells in the pancreas synthesize, store, secrete insulin
- Endogenous human insulin molecule has 2 chains: A (21 amino acids) and B (30 amino acids)



This slide reviews the normal physiology of insulin. The  $\beta$  cells in the pancreas synthesize, store, and secrete insulin. The insulin molecule that humans make, or endogenous insulin, consists of two chains. These chains are the A chain, which consists of 21 amino acids, and the B chain, which consists of 30 amino acids. These chains are joined by a connecting peptide, called C-peptide.

The production and secretion of insulin by the pancreas is stimulated by the presence of circulating glucose. In the normal state, optimal insulin levels are maintained relative to circulating glucose concentration. However, in diabetes, the endogenous insulin supply is insufficient. When endogenous insulin is insufficient, exogenous insulin must be used. Currently, recombinant DNA technology is used to manufacture human insulin, insulin analogs, and premixed insulin analogs.

Diabetes therapy attempts to compensate for metabolic dysfunction caused by inadequate insulin secretion, or impaired insulin action due to tissue insensitivity.

## Limitations of Regular Human Insulin

- Variable absorption
- Delayed onset of action
  - Peaks 2 to 3 hours after injection
  - Needs to be dosed at least 30 mins before meal
- Prolonged duration of action
  - Slow decline after peak reached
  - Higher risk of postmeal hypoglycemia

This slide shows some of the limitations of Regular human insulin, which include variable absorption and delayed onset of action. Regular insulin peaks 2 to 3 hours after injection and should be given at least 30 minutes before meals. In addition, there may be a prolonged duration of action, with a slow decline in action after the peak is reached. These limitations can lead to a higher risk of postmeal, or postprandial, hypoglycemia.

## Limitations of Intermediate- and Long-Acting Human Insulin

- Variable absorption
- Peaks between 4 to 10 hours
- Variable duration of action (10–20 hours)
  - Requires twice-daily dosing
- Variable peaks and troughs can cause wide variation in BG

There are also limitations to intermediate- and long-acting human insulin. These limitations include, again, variable absorption, peaks between 4 to 10 hours from injection, and variable durations of action. These durations of action can range between 10 and 20 hours, and usually require twice-daily dosing. The variable peaks and troughs seen with these insulins can cause a wide variation in blood glucose levels.

## Insulin Analogs

- Insulin analogs: more closely mimic endogenous insulin activity
- Changes to a specific region of the insulin molecule involved in self-association can result in shorter- or longer-acting formulations

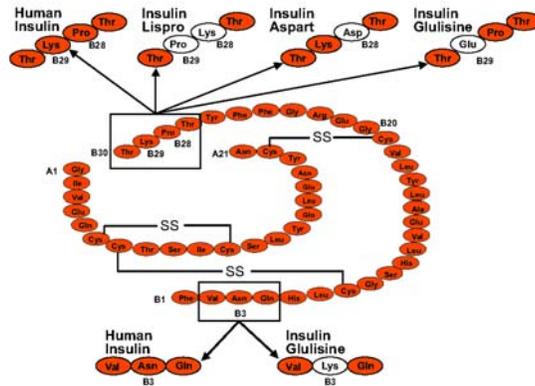
Because of the limitations of exogenous human insulin, insulin analogs were developed. An analog is a chemical compound that is structurally similar to another, but differs slightly in chemical composition. The rationale for the development of insulin analogs was to more closely mimic endogenous insulin activity. The changes made to the insulin molecule can result in either shorter- or longer-acting formulations.

## Advantages of Insulin Analogs

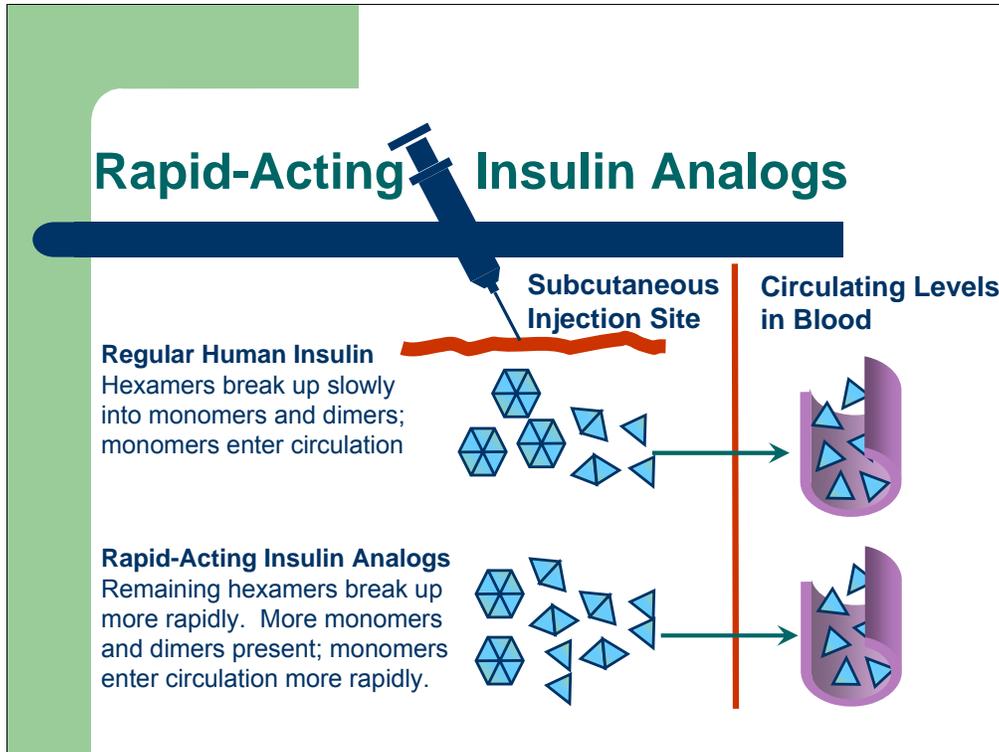
- More physiological time-action profiles
- Rapid-acting and premixed formulations can be dosed near mealtimes
- Improved postprandial glucose (PPG) control
- Long-acting analogs are “peakless”
- Reduced risk of hypoglycemia, particularly at night

The advantages of insulin analogs include more physiological time-action profiles. These more physiologic profiles mean that rapid-acting and premixed formulations can be dosed near mealtimes, which in turn can lead to improved postprandial glucose, or PPG, control. The long-acting analogs have no peaks. The lack of insulin peaks can reduce the risk of hypoglycemia, particularly at night.

## Rapid-Acting Insulin Analogs



Rapid-acting insulin analogs were developed by making slight changes to the human insulin molecule. In lispro, two amino acids, B28–proline and B29–lysine, are transposed on the B chain. In aspart, one amino acid, B28–proline, is replaced with aspartate. In glulisine, the amino acid B3– asparagine is replaced by lysine, and B29– lysine is replaced by glutamic acid.



This slide looks at how insulin is absorbed once it is injected. Commercial human insulin consists of 6-molecule aggregates called hexamers. Following subcutaneous injection of insulin, hexamers must be broken down into monomers, which consist of only 1 molecule, to be absorbed. First, the hexamers break up slowly into dimers, which consist of 2 molecules, and then into monomers to be absorbed and circulate in the bloodstream.

Rapid-acting insulin analogs have modifications on the insulin B chain which result in hexamers that break down more rapidly, so dimers and monomers are formed more quickly, and the monomers can enter the circulation more rapidly after injection.

## Benefits of Rapid-Acting Insulin Analogs

- Quick absorption and PPG-lowering activity provide potential for improved glycemic control
- Short duration of action limits potential for hypoglycemia
- More predictable time-action profile
- Increases convenience and flexibility

There are many benefits of rapid-acting analogs. Compared with Regular human insulin, rapid-acting insulin analogs are absorbed more rapidly and peak closer to meals, which can improve postprandial glucose (PPG)-lowering activity. These benefits provide the potential for improved glycemic control. Other benefits include the short duration of action, which limits the potential for hypoglycemia; the more predictable time-action profile, which is helpful in diabetes management; and the ability to inject just prior to meals, which provides convenience and flexibility.

## Premixed Insulin Analogs

A combination of a rapid-acting insulin analog and an analog in which the duration of action is prolonged by adding a protamine suspension.

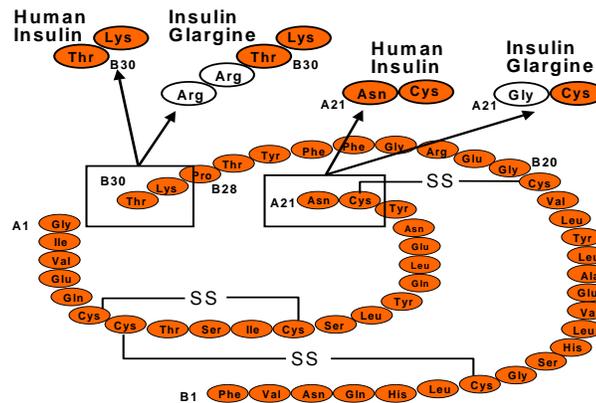
Premixed insulin analogs are insulin analog suspensions containing a specific percentage of a rapid-acting insulin analog and a larger percentage of a rapid-acting insulin analog that has had its action lengthened by a protamine suspension. Two premixed insulin analogs are 70% insulin aspart protamine suspension and 30% insulin aspart, and 75% insulin lispro protamine suspension and 25% insulin lispro.

## Benefits of Premixed Insulin Analogs

- Quick absorption and rapid PPG-lowering effects provide potential for improved glycemic control
- Eliminates difficulties associated with self-mixing 2 products
- Provides convenience and flexibility
- Can be dosed with meals

There are several benefits of premixed insulin analogs. One is that many individuals are able to achieve postprandial glycemic control with two injections a day of a premixed insulin analog, one before breakfast and one before their evening meal. Another benefit is that patients who consume most of their calories at dinnertime may only require 1 injection per day. In addition, some patients who are unable, or unwilling, to self-mix are willing and able to use this relatively simple regimen. Another benefit is that injections given immediately before the meal provide convenience and flexibility because of the rapid-acting component. Thus, these mixtures can be dosed with meals and there is no need to administer these mixtures 30 to 60 minutes before a meal as with human insulin 70/30.

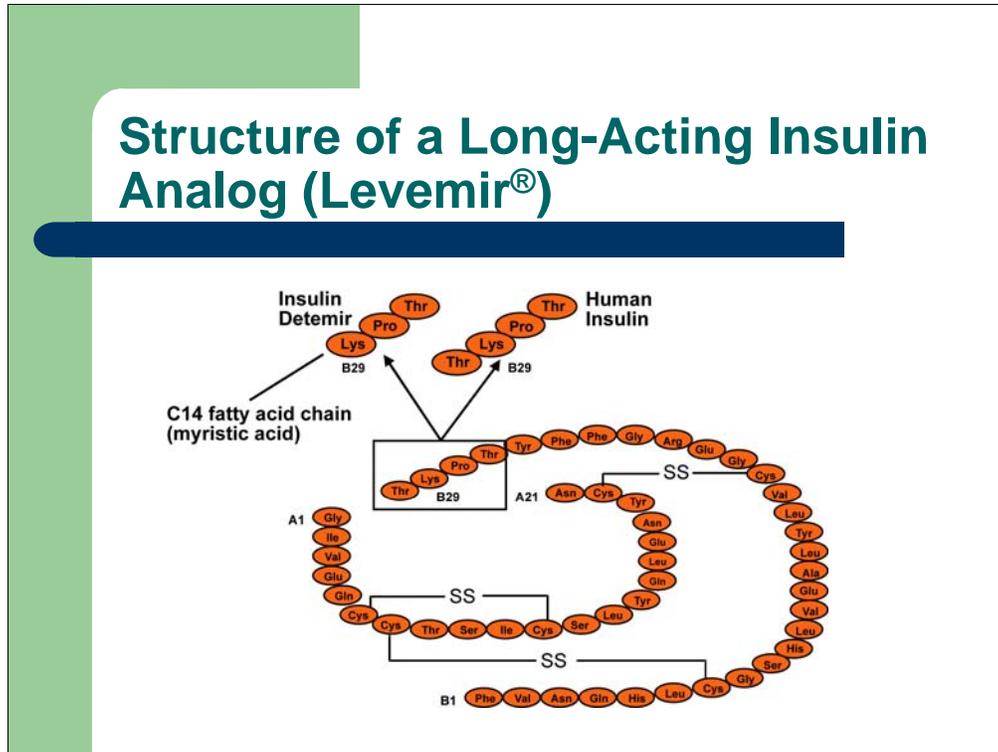
## Structure of a Long-Acting Insulin Analog (Lantus®)



The next few slides discuss the long-acting analogs. One of the currently available long-acting insulin analogs, insulin glargine, brand name Lantus®, has modifications at position 21 of the insulin A chain, where glycine replaces asparagine, and additions of arginine at positions 31 and 32 of the B chain.

These protein sequence modifications make the analog less soluble at the neutral pH of the injection site. There is also increased stability of the hexamer structure. These modifications slow the absorption and prolong the action of insulin glargine. Lantus has a pH of ~4 and is a clear solution.

## Structure of a Long-Acting Insulin Analog (Levemir®)



Insulin detemir, brand name Levemir®, is another long-acting insulin analog and is produced in yeast by a process using recombinant DNA technology. The C14 fatty acid side chain is attached to lysine at position B29 in the insulin molecule by an acylation reaction. The threonine residue at B30 has been removed and the lysine at B29 has been acylated with the 14-carbon fatty acid, myristic acid, which allows insulin detemir to reversibly bind to albumin in plasma and interstitial fluid.

Unlike insulin glargine and neutral protamine Hagedorn, or NPH, insulin detemir is soluble at a neutral pH. Thus, insulin detemir can exist as a liquid following subcutaneous injection. The protracted action occurs through self-association of insulin molecules at the site of injection. Insulin detemir is a clear, colorless, neutral solution, which means it has a pH of 7.4, and was approved by the US Food and Drug Administration in June of 2005.

## Benefits of Long-Acting Insulin Analogs

- ❑ Relatively “peakless,” with less hypoglycemia
- ❑ Timing of action more predictable than human NPH insulin
- ❑ Can provide basal coverage for up to 24 hours

The benefits of these long-acting insulin analogs include that they are relatively “peakless,” which can result in fewer hypoglycemic events. In addition, the timing of their action has been shown to be more predictable than that of human NPH insulin and these analogs can provide basal coverage for up to 24 hours.

## Brand/Generic Product Names

- **Humalog**<sup>®</sup> - insulin lispro injection (rDNA origin)
- **NovoLog**<sup>®</sup> - insulin aspart (rDNA origin) injection
- **Apidra**<sup>®</sup> - insulin glulisine (rDNA origin) injection
- **Humalog**<sup>®</sup> **Mix75/25**<sup>™</sup> - 75% insulin lispro protamine suspension and 25% insulin lispro (rDNA origin) injection
- **NovoLog**<sup>®</sup> **Mix 70/30** - 70% insulin aspart protamine suspension and 30% insulin aspart (rDNA origin) injection
- **Lantus**<sup>®</sup> - insulin glargine (rDNA origin) injection
- **Levemir**<sup>®</sup> - insulin detemir (rDNA origin) injection

With so many new insulin formulations of recombinant DNA origin currently available, it is helpful to look at their brand and generic names. The rapid-acting insulins are Humalog, which is insulin lispro; NovoLog, which is insulin aspart; and Apidra, which is insulin glulisine.

The mixtures are Humalog Mix75/25, which is 75% insulin lispro protamine suspension and 25% insulin lispro; and NovoLog Mix 70/30, which is 70% aspart protamine suspension and 30% insulin aspart.

The long-acting insulins are Lantus, which is insulin glargine; and Levemir, which is insulin detemir.

## Insulin Analogs

Product	Onset (hrs)	Peak (hrs)	Duration (hrs)
<b>Rapid-acting insulin analogs (rDNA origin)</b>			
Insulin lispro (Humalog®)	0.25–0.5*	0.8–4.3†	4–6*
Insulin aspart (NovoLog®)	0.16–0.32†	1–3†	3–5†
Insulin glulisine (Apidra®)	NA	NA	NA
<b>Long-acting insulin analogs (rDNA origin)</b>			
Insulin detemir (Levemir®)	0.8–2.0§	3.2–9.3§	5.7–23.2†
Insulin glargine (Lantus®)	1†	None†	10.8–24¶

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.

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

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

This slide shows the action profiles of the different analogs. It is critical to remember that the timing of action varies in individuals, and from time to time in the same individual. Thus, the times on this slide should be used only as guidelines.

Insulin lispro starts to work in 15 to 30 minutes, peaks in 50 minutes to 4 hours and 30 minutes, and lasts from 4 to 6 hours. Insulin aspart starts to work in 10 to 20 minutes, peaks in 1 to 3 hours, and lasts about 3 to 5 hours. Insulin glulisine's pharmacodynamic data are not listed on this slide but are presented graphically in the package insert. Rapid-acting insulin analogs are used in multiple daily injections, or MDI therapy, and in intensive insulin therapy to mimic normal insulin action. All three are approved for pump use.

The long-acting insulin analog detemir starts to work in 50 minutes to 2 hours, peaks between a little over 3 hours to 9.5 hours, and lasts between 5.5 hours and 24 hours. The long-acting insulin analog glargine starts to work in 1 hour, has no peak, and lasts between 11 hours to 24 hours.

## Premixed Insulin Analogs

Brand Name	Onset (hrs)	Peak (hrs)	Duration (hrs)
<b>Premixed insulin analogs (rDNA origin)</b>			
NovoLog® Mix 70/30	<0.16–0.32*	2.4†	≤24†
Humalog® Mix75/25™	<0.5†	2.6†	~22†

\*Weyer C, et al. *Diabetes Care*. 1997;20:1612-1614.

†Product labeling/prescribing information.

As previously mentioned, the timing of insulin action varies in individuals, and from time to time in the same individual. Thus, the times on this slide should be used only as guidelines.

## Product Availability

Brand Name	Vials	Cartridges	Devices
<b>Rapid-acting insulin analogs</b>			
Humalog®	10 mL	3.0 mL	Owen Mumford Pen, Humalog Pen (prefilled disposable)
NovoLog®	10 mL	3.0 mL	NovoPen®3, NovoPen® Junior, Innovo®, FlexPen® (prefilled disposable)
Apidra®	10 mL	–	

How are these products available? Humalog is available in 10 mL vials, which is 1000 units, and pen cartridges of 3 mL, which is 300 units. These cartridges can be used in the Owen Mumford pen and are in the prefilled disposable Humalog pen. NovoLog is also available in 10 mL vials and 3 mL cartridges, which can be used in the NovoPen3, the NovoPen Jr, the Innovo, and the FlexPen, which is prefilled and disposable. Apidra is available in 10 mL vials.

## Product Availability

Brand Name	Vials	Cartridges	Devices
<b>Long-acting insulin analogs</b>			
Lantus®	10 mL	3.0 mL	OptiClik™
Levemir®	10 mL	3.0 mL	NovoPen®, FlexPen® (prefilled disposable)
<b>Premixed insulin analogs</b>			
Humalog® Mix75/25™	10 mL		Humalog Mix75/25 Pen (prefilled disposable)
NovoLog® Mix 70/30	10 mL	3.0 mL	NovoPen®3, NovoPen® Junior, Innovo®, FlexPen® (prefilled disposable)

Lantus is available in 10 mL vials and 3 mL cartridges (which can be used in the OptiClik pen). Levemir is available in 10 mL vials, 3 mL cartridges (which can be used in the NovoPen), and as a prefilled disposable FlexPen.

## Patient Barriers to Insulin Therapy

- Perceived as last resort (failure)
- Fear of injection and insulin
  - Social stigma
- Do not understand goals
- Symptoms not indicative of disease severity
- Fear of hypoglycemia and weight gain
- Inadequate adherence
- Resist frequent monitoring
- Interference with daily routines and privacy

Insulin therapy can be challenging. Psychological insulin resistance is a real phenomenon. Individuals with diabetes, especially in certain cultures, often feel that insulin is the beginning of the end. Causes of psychological insulin resistance may include psychosocial issues, such as the stigma of using needles, and convenience factors. However, the principal cause is probably needle phobia, a fear held by providers as well as by patients.

Insulin therapy can, in fact, be a real pain both literally and figuratively. It can be intrusive, limit spontaneity, and interfere with daily activities. Thus, adhering to insulin regimens has been difficult for many patients.

Because symptom severity doesn't always parallel disease severity, many individuals do not understand the need for optimal glycemic control nor its role in preventing complications and, therefore, may resist the more frequent monitoring needed with insulin therapy. In addition, many people fear that they will experience hypoglycemia and will gain weight.

## Provider Barriers to Insulin Therapy

- Assuming patient will have needle phobia and will resist taking injections
- Concern about frequent calls from patients due to hypoglycemia
- Concern that insulin therapy will be construed by the patient as last resort (failure)

In addition to patient barriers to insulin therapy, there are provider barriers to overcome. A few examples are listed on this slide. Providers may assume that some patients have needle phobias or that patients will resist giving an injection. Providers may also be concerned about the risk of hypoglycemia and that patients may think that insulin therapy is the “end of the line.”

Many of these barriers are based on provider assumptions and can be resolved through open communication.

## Overcoming Psychological Insulin Resistance

Barriers to insulin treatment (type 2) -  
some countermeasures

- Acknowledgment of disease progression early in treatment
- Education about hypoglycemia
- Education about hyperglycemia and risk of complications
- Availability of new insulin delivery systems
  - Small needles
  - Avoidance of syringe stigma
- Improved quality-of-life issues

This slide shows some countermeasures to overcome psychological insulin resistance. One is early acknowledgment that diabetes is a progressive disease, so patients will not perceive insulin therapy as a personal failure. It is critical that insulin not be used as a threat to achieve compliance with current therapy. Another countermeasure is education about hypoglycemia. Patients can learn the cues that indicate the onset of low blood glucose and appropriate treatments. Starting insulin with a single injection may avoid an immediate hypoglycemic episode. In addition, education about hyperglycemia and the risk of complications, including discussion of maintaining glucose targets, may be helpful. Other countermeasures include the availability of new insulin delivery systems, small needles, and the ability to avoid syringe stigma. Many patients report that the use of insulin pens or dosers makes them feel more comfortable injecting in public. Another countermeasure is a frank discussion of how, in the past, insulin therapy was put off until patients already had major complications of the disease. In addition, patients are often not aware of how chronic hyperglycemia affects their lives. Many times their quality of life is diminished due to elevated blood glucose. Explaining that their fatigue, dry skin, frequent urination, and blurred vision may go away with initiation of insulin therapy is sometimes helpful.

## Basic Principles of Initiating Insulin Therapy

- Determine degree of hyperglycemia
  - Fasting and PPG monitoring
  - A1C value
- Determine body weight
- Ascertain capabilities and lifestyle needs
- Select insulin delivery system
- Calculate starting insulin dose based on weight, BG, and A1C
  - Start low (0.1 unit/kg per day commonly used)
  - Titrate up, using SMBG as directed

Once insulin therapy is decided upon, there are some basic principles to follow. The degree of hyperglycemia is determined by fasting and PPG monitoring and patients' A1C values. In addition, body weight is determined to give an indication of how much insulin a patient will need. Patients' capabilities, such as visual acuity and dexterity, should be assessed as well as their lifestyles.

Once the insulin delivery system is selected, the appropriate starting insulin dose is calculated, based on weight, BG, and A1C, and for patients with type 2 diabetes, an estimate of the degree of insulin resistance can be helpful. A basic principle for starting insulin in type 2 patients is to start low and go slow. A dose of 0.1 unit/kg per day is commonly used, and can go to 1.0 unit/kg per day or more with type 2 patients who are severely insulin resistant. The initial dose is then titrated up, no more than every 3 days, using SMBG. Patients should be told that any time new regimens are implemented or they change their eating or exercise habits, more frequent monitoring is indicated until the effects of those changes are determined.

## Considerations When Initiating Insulin Therapy

- Coverage of FPG and PPG
- Choice of formulation
  - Time-action profile
  - Number of injections
- Convenience
- Patient willingness and capability
- Carbohydrate counting with certain regimens

**Goals:** Avoid hypoglycemia, achieve glycemic control, minimize impact on lifestyle

There are other considerations when initiating insulin therapy. The regimen should provide coverage of FPG and PPG. The choice of insulin formulation used will be based on the time-action profile and the number of injections needed or desired. In addition, convenience is considered, as well as patients' willingness and ability to follow regimens. It is important to remember that carbohydrate counting is needed with certain regimens. The major goals when initiating insulin therapy are to avoid hypoglycemia, achieve glycemic targets, and minimize the impact on patients' lifestyles.

## Options for Initiating Insulin Therapy

- No set formula for initiating insulin therapy
- If goal is to improve FPG
  - Long-acting insulin analogs (basal)
- If goal is to improve PPG
  - Rapid-acting insulin analogs (bolus)
- If goal is FPG plus PPG
  - OAD + basal, premixed insulin analogs, MDI or pump
- To achieve optimal glycemic control
  - Both FPG and PPG should be targeted

There is no set formula to initiate insulin therapy; rather, certain goals are considered. If the goal is to improve FPG, long-acting analogs may be used to provide basal coverage. If the goal is to improve PPG, rapid-acting analogs can provide mealtime boluses. If the glycemic goal includes FPG and PPG, oral antidiabetes agents, such as secretagogues, and a basal insulin may be used. Alternatively, premixed analogs, MDI, or an insulin pump may be considered. It is important to remember that to achieve optimal glycemic control, both FPG and PPG should be targeted.

## Injection Techniques

### **Patients should demonstrate proper injection technique:**

- Clean hands, injection site
- Pull up fold of skin, quickly insert needle, push insulin in
- Hold a few seconds, withdraw
- Change site within same area for consistent absorption rate

Once insulin therapy is decided upon, patients should be instructed how to implement this therapy. As with all skills, there should be a demonstration of the injection technique, with the patient doing a return demonstration. Patients should demonstrate using clean hands and a clean injection site. They should pull up a fold of skin, quickly insert the needle, and push the insulin into the subcutaneous tissue. They should then leave the needle in their tissue for a few seconds, then withdraw it, holding their finger over the injection site for a few seconds. Patients should also be instructed to use different injection sites within their chosen anatomic site for more consistent absorption rates.

## Storage of Insulin Analogs

Product/Formulation	Days at Room Temperature (86°F)
Levemir®	42
NovoLog®, Humalog®, Apidra®, Lantus®	28
Humalog® Mix75/25™ Pen	10
NovoLog® Mix 70/30 FlexPen® and PenFill® Cartridges	14

An important component of education when starting insulin therapy is insulin storage. Unopened insulin products can all be stored in a refrigerator until the expiration date is reached. Patients should be aware that insulin should not be stored in a freezer nor should the insulin get too warm.

This slide shows the room temperature storage recommendations for opened analog products. Levemir can be used up to 42 days; NovoLog, Humalog, Apidra, and Lantus can be used up to 28 days. The Humalog Mix75/25 pen can be used up to 10 days and the NovoLog Mix 70/30 FlexPen and PenFill cartridges can be used up to 14 days. Some products can be stored in a refrigerator once opened; however, the package insert should be checked for specific recommendations.

Patients should be instructed that premixed insulin analogs are cloudy suspensions and rapid- and long-acting insulin analogs are clear solutions. If analogs are discolored or clear analogs are cloudy, they should be discarded.

## Insulin Pump Therapy

### □ Continuous Subcutaneous Insulin Injection (CSII)

- Alternative to MDI
- Increases convenience and flexibility
- All rapid-acting insulin analogs are approved for insulin pumps
- Used primarily by patients with type 1 diabetes but now also being used by some patients with type 2 and GDM
- Frequent BG monitoring and thorough patient training, including instruction in appropriate programming techniques, carbohydrate counting, and calculating insulin/carbohydrate ratios are required

Continuous subcutaneous insulin injection, or CSII, is considered intensive therapy. Short- or rapid-acting insulin formulations are used in pumps. All the currently available rapid-acting insulin analogs— aspart, glulisine, and lispro— are approved for pump use. For successful CSII, frequent BG monitoring and thorough patient training, including instruction in appropriate programming techniques, carbohydrate counting, and calculating insulin to carbohydrate ratios, are required. Pumps are programmed, usually by the patient, to deliver amounts of insulin or insulin analog throughout a 24-hour period; this is the basal insulin. The patient also selects an appropriate dose before each meal, based on SMBG and carbohydrate counting, and activates the pump to deliver the insulin; this is termed the bolus insulin.

## Monitoring

- SMBG
- Routine medical visits
- Blood or urine ketone testing during sickness, infection, or stress, or when BG >250 mg/dL

SMBG is essential in the daily control of hyperglycemia and to minimize the risk of hypoglycemia. The ADA recommends SMBG 3 or more times daily for patients using insulin. Patients should be instructed in the proper interpretation of SMBG results to assist them in making specific treatment changes.

Routine medical visits to monitor other parameters are especially important for the management of diabetes. These parameters include: A1C testing, at least quarterly, for assessment of overall diabetes management; management of cardiovascular risk factors, which include triglyceride and cholesterol levels, and hypertension. In addition, patients' eyes should be monitored with an annual dilated eye examination. It is also important for patients to have their feet examined. The ADA recommends that all individuals with diabetes undergo a thorough foot examination annually to assess protective sensation, foot structure, vascular status, and skin integrity.

Diabetic ketoacidosis, or DKA, and hyperosmolar hyperglycemic state are serious acute metabolic complications of diabetes. Infection is the most common precipitating factor of DKA but inadequate insulin use can also cause these conditions. Blood or urine ketone monitoring is usually limited to patients with type 1 diabetes, GDM, and lean patients with type 2 diabetes. Blood or urine ketone monitoring should be done during sick days, when any infection is present, or when there are any symptoms of DKA, such as nausea, vomiting, and abdominal pain, and when BG is >250 mg/dL for several tests. Ketones result from the breakdown of fatty acids and action is required if the test results are high. Blood tests are preferred and home blood ketone tests are now available.

## Hypoglycemia

- ❑ Most common acute complication of insulin therapy
- ❑ In most cases, food intake, physical activity, and medication are not balanced.
  - Possible causes: dosage errors (excess), missed or late meals, increased activity, illness
- ❑ Symptoms include rapid heart rate, sweating, shaking, confusion, visual disturbances, anxiety, and, possibly, hunger
- ❑ Minor hypoglycemic episodes do not cause loss of consciousness or seizures.

The most common acute complication of diabetes therapy is hypoglycemia. The most common causes of hypoglycemia are reduced food intake or excessive physical activity not matched with medication changes. Other causes of hypoglycemia are dosage errors, that is, excess dosing, missed or late meals, and increased insulin absorption due to higher skin temperatures, which can be caused by bathing or illness.

Symptoms of hypoglycemia may include rapid heart rate, sweating, shaking, confusion, visual disturbances, anxiety, and hunger. Minor hypoglycemic episodes do not cause loss of consciousness or seizures. Patients can be helped to prevent hypoglycemic episodes by learning to recognize their own personal cues, and to be aware of circumstances associated with hypoglycemia.

## Recommended Treatment of Hypoglycemia

- Consume 15 grams glucose from food, beverage, or tablet
- Check BG 15 minutes later (repeat treatment if BG level still low)
- If not eating within next hour, be cautious about additional hypoglycemic episodes
- If oral carbohydrate cannot be safely given or individual is unconscious
  - Glucagon can be administered by a friend or family member
  - IV glucose can be administered by emergency personnel

This slide shows the recommended treatment of hypoglycemia. When symptoms of hypoglycemia are first felt, usually when BG level is near 70 mg/dL, the patient should consume 15 grams of glucose from food, beverage, or tablet. If BG levels are <50 mg/dL, 20 to 30 grams of carbohydrate may be needed. Patients should test their BG level 15 to 20 minutes after hypoglycemia treatment. If their BG level remains low, the treatment should be repeated, even if symptoms have disappeared. Patients should be advised that hypoglycemia may reappear if a meal, or carbohydrate, and protein snack is not eaten within 1 to 2 hours after treatment. Food or drinks that have high fat content may take longer to raise BG levels and are not recommended for treatment.

If the person is not alert, is uncooperative, or unable to swallow, emergency measures are required. Emergency measures include application of jam or glucose gel between the cheek and gum. When the patient is able, the treatment should be followed with a snack containing carbohydrates and protein. Another emergency measure is a glucagon injection. Glucagon can be given subcutaneously or intramuscularly to stimulate hepatic glucose production. A close friend or relative, significant other, or companion should be instructed on when and how to inject glucagon. They should practice giving an injection before they are confronted with a hypoglycemic emergency. Emergency personnel can administer IV glucose. When injections or IVs are used, patients should eat or drink carbohydrate as soon as possible.

## Prevention of Hypoglycemia

- Follow meal plan and avoid missing meals
- Plan meals and snacks no more than 5 hours apart
- Know when drug effect peaks
- Carry glucose source at all times
- Monitor BG as directed

The most effective way to deal with hypoglycemia is prevention. Patients should be instructed to follow meal plans, to plan meals and snacks no more than 5 hours apart, and to know when their diabetes medications peak. In addition, they should carry a fast-acting glucose source at all times and monitor their BG levels as directed and indicated.

## Education

- All members of diabetes care team serve as teachers (including the patient)
- Each contact should be an opportunity for assessment and counseling
- Information should be consistent and sequential
- Advice:
  - Selection of appropriate tools
  - Troubleshoot problems and reassess goals
  - Simplify treatment

Self-management training is the management modality that allows people with diabetes to fully participate in their care. All members of diabetes care team, including the patient, serve as teachers. Each contact is an opportunity for assessment and counseling. It is important that information be consistent and sequential. All team members can help patients learn warning signs of hypo- and hyperglycemia and emphasize the importance of SMBG. In addition, self-management training involves the development of individualized meal plans and regular exercise routines, help in selecting appropriate products, and troubleshooting and problem solving. Whenever possible, the diabetes team should try to simplify the treatment regimen.

## Summary

- All patients with type 1 diabetes and many with type 2 require insulin
- Insulin analogs closely mimic normal insulin secretion patterns
- Both fasting BG and PPG should be treated to achieve optimal glycemic control

In summary, several landmark randomized controlled trials have illustrated the need for good glycemic control. To achieve this control, all patients with type 1 diabetes and many with type 2 will require insulin treatment. Insulin is also the treatment of choice for women with gestational diabetes.

Regular human insulin has several limitations including variable absorption, delayed onset of action, and prolonged duration of action. Intermediate- and long-acting human insulins also have limitations including variable absorption, variable duration of action, and variable peaks and troughs leading to wide variations in blood glucose. The insulin analogs and premixed insulin analogs were developed to closely mimic normal insulin secretion patterns and thus alleviate some of the limitations associated with human insulin.

And finally, when developing a treatment regimen, it is important to remember that optimal glycemic control requires treatment of both fasting blood glucose and postprandial glucose.