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# Insulin – Pharmacology, Types of Regimens, and Adjustments

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## INTRODUCTION

With the introduction of several new insulins since 1996, insulin therapy options for type 1 and type 2 diabetics have expanded. Insulin therapies are now able to more closely mimic physiologic insulin secretion and thus achieve better glycemic control in patients with diabetes. This chapter reviews the pharmacology of insulins (using a comparative approach), types of insulin regimens and therapeutic adjustment of them, and provides an overview of insulin pump therapy.

## PHARMACOLOGY

In 1922, Canadian researchers were the first to demonstrate a physiologic response to injected animal insulin in a patient with type 1 diabetes. In 1955, insulin was the first protein to be fully sequenced. The insulin molecule consists of 51 amino acids arranged in two chains, an A chain (21 amino acids) and B chain (30 amino acids) that are linked by two disulfide bonds <sup>[1]</sup> ( **Figure 1** ). Proinsulin is the insulin precursor that is transported to the Golgi apparatus of the beta cell where it is processed and packaged into granules. Proinsulin, a single-chain 86 amino acid peptide, is cleaved into insulin and C-peptide (a connecting peptide); both are secreted in equimolar portions from the beta cell upon stimulation from glucose and other insulin secretagogues. While C-peptide has no known physiologic function, it can be measured and if present, indicates a person has functioning beta-cells.

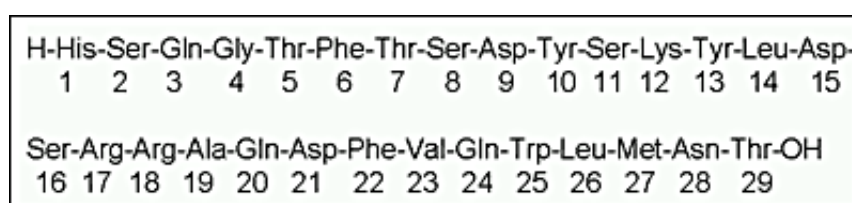


Figure 1: Insulin Structure

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Insulin exerts its effect on glucose metabolism by binding to insulin receptors throughout the body. Upon binding, insulin promotes the cellular uptake of glucose into fat and skeletal muscle and inhibits hepatic glucose output, thus lowering the blood glucose. (see [Insulin signaling and action: glucose, lipids, protein](#) )

Commercially available insulins are used for all patients with type 1 diabetes in whom insulin is required for survival, and for patients with type 2 diabetes when diet/exercise, oral agents and other injectable hypoglycemic agents (i.e., incretine mimetic agents/GLP-1 analogs) no longer provide adequate glucose control.

## Sources of Insulin

With the availability of human insulin by recombinant DNA technology in the 1980s, use of animal insulin declined dramatically. Beef insulin, beef-pork and pork insulin are no longer commercially available. The FDA may allow for personal importation of beef insulin from a foreign country if a patient cannot be treated with human insulin <sup>[2]</sup> . Beef insulin differs from human insulin by 3 amino acids and pork insulin differs by one amino acid <sup>[3]</sup> .

Currently, in the USA , most insulins used are either human insulin and/or analogs of human insulin. The recombinant DNA technique for human insulin involves insertion of the human proinsulin gene into either *Saccharomyces cerevisiae* (baker's yeast) or a non-pathogenic laboratory strain of *Escherichia coli* (E coli) which serve as the production organism. Human insulin is then isolated and purified <sup>[4][5][6][7][8][9][10][11]</sup> .

## Insulin Analogs

Recombinant DNA technology has allowed for the development and production of analogs to human insulin. With analogs, the insulin molecule structure is modified slightly to alter the pharmacokinetics properties of the insulin, primarily affecting the absorption of the drug from the subcutaneous tissue. The B26-B30 region of the insulin molecule is not critical for insulin receptor recognition and it is in this region that amino acids are generally substituted <sup>[12]</sup> . Thus, the insulin analogs are still recognized by and bind to the insulin receptor. The structures of three insulin analogs are shown in Figure 2 (insulin aspart, lispro and glulisine) and Figure 3 (insulin glargine and detemir).

# Insulin Aspart, Lispro, & Glulisine Structure

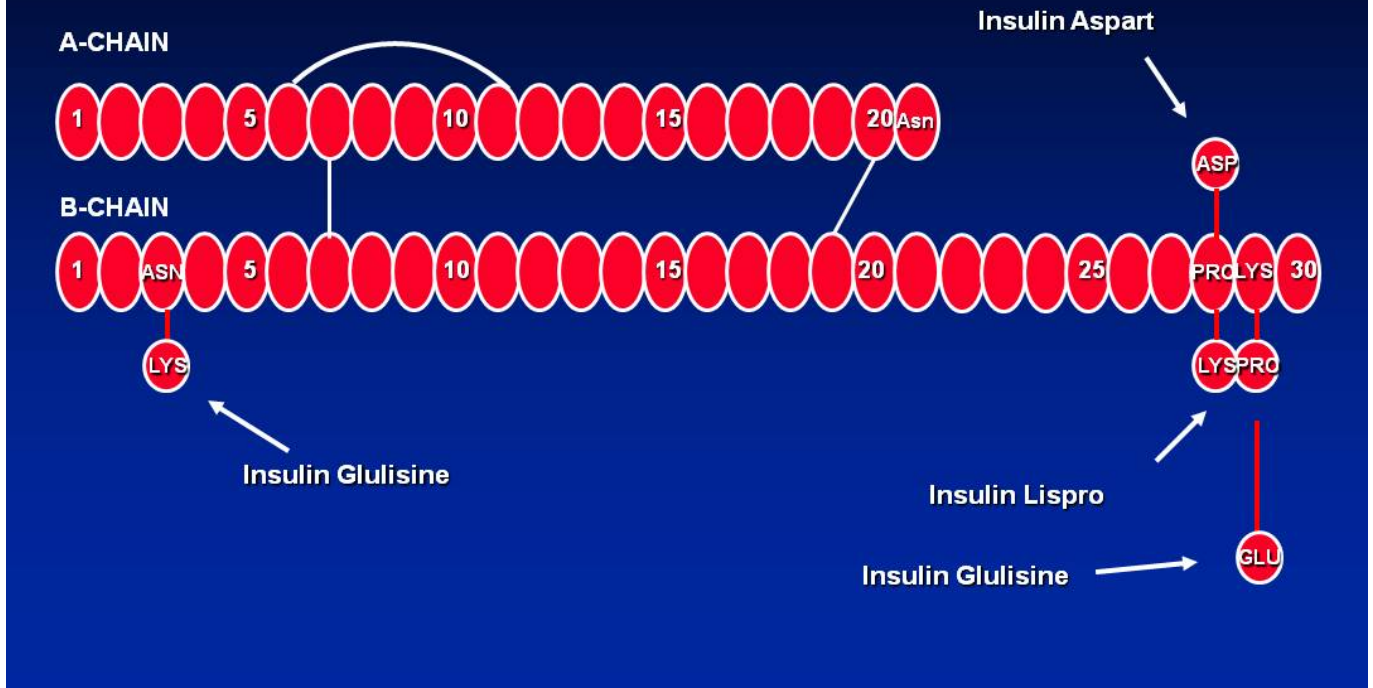


Figure 2: Insulin Aspart, Glulisine and Lispro Structures

# Insulin Glargine & Detemir Structure

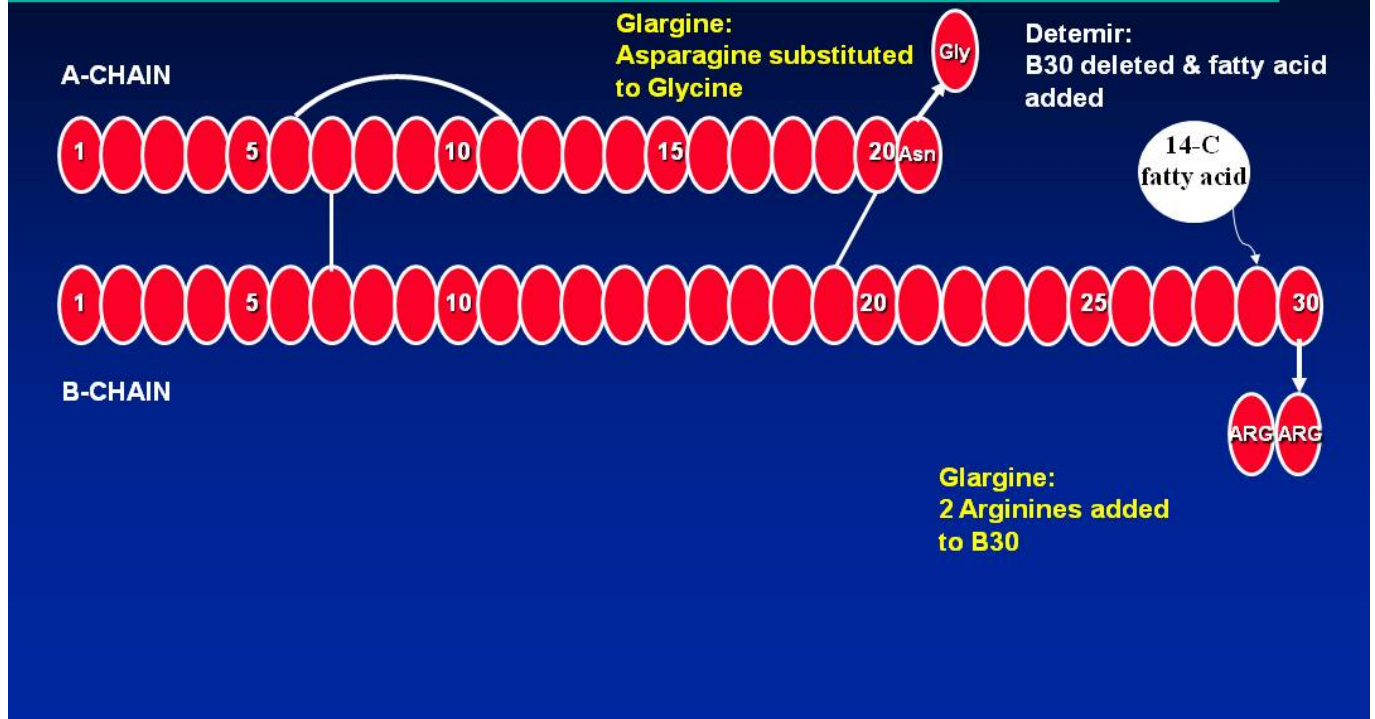


Figure 3: Insulin Glargine and Detemir Structures

Because insulin analogs are modified human insulin, the safety and efficacy profiles of these insulins have been compared to human insulin <sup>[13]</sup>. Insulin and IGF-1 receptor binding affinities (IGF- insulin like growth factor), metabolic and mitogenic potencies of insulin lispro, insulin aspart, insulin glargine and insulin detemir relative to human insulin has been assessed. Insulin lispro and aspart are similar to human insulin on all of the above parameters, except insulin lispro was found to be 1.5-fold more potent in binding to the IGF-1 receptor compared to human insulin. Insulin glargine was found to have a 6- to 8-fold increase in mitogenic potency and IGF-1 receptor affinity compared to human insulin. Insulin detemir was found to be more than 5-fold less potent than human insulin in binding to IGF-1. While the clinical significance of these differences is not known, they likely do not represent any significant concern <sup>[14]</sup>.

## Immunogenicity

Because pork and beef insulin differ from human insulin by 1 and 3 amino acids respectively, they are more immunogenic than exogenous human insulin. Older formulations of insulin were less pure, containing islet-cell peptides, proinsulin, C-peptide, pancreatic polypeptides, glucagons, and somastostatin, which contributed to immunogenicity of insulin <sup>[15]</sup>. Components

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of insulin preparations (e.g., zinc, protamine) and subcutaneous insulin aggregates are also thought to contribute to antibody formation <sup>[16]</sup>. Commercially available human insulins are now virtually free of contaminants and contain <1 ppm of proinsulin (also referred to as “purified”) <sup>[17]</sup>. Insulin side effects such as local or systemic hypersensitivity, lipodystrophy, and antibody production causing insulin resistance, are now rarely seen with exogenous human insulin <sup>[18]</sup>. Because of the availability of human insulin and the increased potential for animal source insulin to be immunogenic, animal source insulins are now rarely used and people with diabetes should be initiated on human insulin.

The rare hypersensitivity responses to insulin can be immediate-type, local or systemic IgE-mediated reactions <sup>[19]</sup>. Patients who experience a true allergic reaction to insulin often have received insulin in the past, and experience the allergic reaction after insulin is restarted. Another allergic reaction seen with animal insulins was a delayed local reaction that was IgG-mediated <sup>[20]</sup>. Insulin therapy can also result in the production of insulin antibodies of the IgG class, which neutralize insulin. An immunological insulin resistance can occur in patients with very high titers of IgG-antibodies.

Lipodystrophy seen with insulin refers to two conditions: lipoatrophy and lipohypertrophy. Lipoatrophy is an immune-mediated condition in which there is loss of fat at the insulin injection sites <sup>[21]</sup>. Lipoatrophy occurs much less frequently with purified human insulins. Treatment for patients who were on an animal insulin was injection with human insulin at the atrophied site. Lipohypertrophy is a non-immunological side effect of insulin resulting from repeated administration of insulin at the same injection site.

## Concentration

In the United States, all insulins are available in the concentration of 100 units/ml (denoted as U-100). Insulin syringes are designed to accommodate this concentration of insulin. Regular human insulin (Humulin R, Lilly) is available in a more concentrated insulin, U-500 (500 units/ml), however this preparation is used primarily in a specialized institutional setting or for rare cases of extreme insulin resistance, where very large doses of insulin (generally > 200 units per day) are required. Specific syringes for U-500 insulin are not available and extreme caution must be taken as each marked unit on a U-100 syringe will actually deliver 5 units of insulin.

Outside the United States, a less concentrated insulin preparation, U-40, (40 units/ml) is still available and sometimes used. Specific U-40 syringes are used with this insulin. It is important that patients traveling from one country to the next, be aware of the concentration of insulin they use, and that the appropriate syringe is used.

## Physical and Chemical Properties

Regular human insulin is crystalline zinc insulin dissolved in a clear solution. It may be administered by any parenteral route: subcutaneous, intramuscular, or intravenous. Insulin aspart, glulisine and lispro are also soluble crystalline zinc insulin, but are intended for

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subcutaneous (subQ) injection. NPH, or neutral protamine Hagedorn, is a suspension of regular insulin complexed with protamine that delays its absorption. Insulin suspensions should not be administered intravenously. All insulins, except insulin glargine, are formulated to a neutral pH.

Long-acting Insulin glargine is a soluble, clear insulin, and has a pH of 4.0. Its acidic pH is critical for its subQ absorption characteristics and will be discussed further under pharmacokinetics. Insulin glargine should not be mixed with other insulins, and should only be administered subcutaneously <sup>[22]</sup>.

Insulin detemir is a long-acting insulin analog that has a fatty acid coupled to it so that it binds to albumin in the subQ tissue resulting in delayed absorption, prolonging its duration of action. Like insulin glargine, insulin detemir should not be mixed with other insulins, and should be injected subcutaneously.

## Pharmacokinetics

### *Absorption*

Insulin administered via SC injection is absorbed directly into the bloodstream, with the lymphatic system playing a minor role in transport <sup>[23]</sup>. The absorption of human insulin after subQ absorption is the rate limiting step of insulin activity. This absorption is inconsistent with the coefficients of variation of T50% (time for 50% of the insulin dose to be absorbed) varying ~25% within an individual and up to 50% between patients <sup>[24][25]</sup>. Most of this variability of insulin absorption is correlated to blood flow differences at the various sites of injection (abdomen, deltoid, gluteus, and thigh) <sup>[26]</sup>. For regular insulin, the impact of this is a ~2 times faster rate of absorption from the abdomen than other subcutaneous sites <sup>[27]</sup>. The clinical significance of this is that patients should avoid random use of different body regions for their injections. For example, if a patient prefers to use their thigh for a noontime injection, this site should be used consistently for this injection. For simplicity, however, the abdomen is often recommended as the preferred site of injection because it is the least susceptible to factors affecting insulin absorption (see Table 1). Insulin aspart, glulisine and lispro appear to have less day-to-day variation in absorption rates and also less absorption variation from the different body regions <sup>[28][29][30][31]</sup>. Insulin glargine's pharmacokinetic profile is similar after abdominal, deltoid or thigh SC administration <sup>[32]</sup>.

A general principle for factors that can alter insulin absorption is that when local blood flow in the subQ tissue is changed, the absorption rate of insulin will also be affected. A factor that increases subQ blood flow will increase the absorption rate and vice versa. See **Table 1** for factors that affect insulin absorption.

**Table 1 Factors Affecting Insulin Absorption** ( <sup>[33][34][35]</sup> )

| Factor                    | Comment   |
|---------------------------|---|
| Exercise of injected area | Strenuous exercise of a limb within 1 hour of injection. Clinically significant for regular |

|  |   |
|--|---|
|  | human insulin.  |
| Local massage                            | While it is OK to press on the injection site to prevent seepage, the site should not be rubbed vigorously or massaged.                 |
| Temperature                              | Heat can increase absorption rate. Avoid the sauna, shower, hot bath soon after injection. Cold has the opposite effect.                |
| Site of injection                        | Insulin is absorbed faster from the abdomen. Less clinically relevant with rapid-acting insulins, insulin glargine and insulin detemir. |
| Lipohypertrophy                          | Injection into hypertrophied areas delays insulin absorption.   |
| Jet injectors                            | increase absorption rate.   |
| Insulin mixtures                         | Absorption rates are unpredictable when suspension insulins are not mixed adequately (i.e., they need to be resuspended).               |
| Insulin dose                             | Larger doses have delay in action and increased duration.   |
| Physical status (soluble vs. suspension) | Suspension insulins must be sufficiently resuspended prior to injection to reduce variability.  |

### ***Distribution***

Circulating insulin is distributed in equilibrium between free insulin and insulin bound to IgG antibodies [36]. The presence of insulin antibodies can delay the onset of insulin activity, reduce the peak concentration of free insulin, and prolong the biologic half-life of insulin [37].

### ***Elimination***

The kidneys and liver account for the majority of insulin degradation. Normally, the liver degrades ~60% of insulin released by the pancreas (insulin delivered through portal vein blood flow) and the kidneys ~35-45% [38]. When insulin is injected exogenously, the degradation profile is altered since insulin is no longer delivered directly to the portal vein. The kidney has a greater role in insulin degradation with subQ insulin (~60%), with the liver degrading ~30-40% [39].

Because the kidneys are involved in the degradation of insulin, renal dysfunction will reduce the clearance of insulin and prolong its effect. This decreased clearance is seen with both endogenous insulin production (either normal production or that stimulated by oral agents) and exogenous insulin administration. Renal function generally needs to be greatly diminished before this becomes clinically significant [40].

### **Pharmacodynamics**

The onset, peak, and duration of effect are the most clinically significant differences among the

insulins. Insulin pharmacodynamics refers to the metabolic effect of insulin. Commercially available insulins can be categorized as rapid-acting, short-acting, intermediate-acting, and long-acting. The current insulins available in the United States are listed in **Table 2** . Insulin pharmacodynamics (i.e., onset, peak and duration) of the various insulins) are shown in **Table 3** . It is important to note that ranges are listed for the onset, peak and duration, accounting for intra/inter-patient variability. Each patient will have an individual pattern of response. By having the patient self-monitor their blood glucose frequently, the patient-specific time-action profile of the specific insulin can be better appreciated. **Figures 4a-4c** <sup>[41][42][43][44]</sup> graphically show the time-activity profiles for the various insulins.

**Table 2 Insulins Commercially Available in the US**

| <b>Category/<br/>Name of Insulin</b> | <b>Source</b>   | <b>Brand Name<br/>(manufacturer)</b> | <b>Preparation(s)</b>              |
|--------------------------------------|-----------------|--------------------------------------|------------------------------------|
| <b>Rapid-Acting</b>                  | Recombinant DNA | Humalog (Lilly)                      | vial, cartridge,<br>disposable pen |
| Insulin Lispro                       | Recombinant DNA | Novolog (Novo Nordisk)               | vial, cartridge,<br>disposable pen |
| Insulin Aspart                       | Recombinant DNA | Apidra (sanofi-aventis)              | vial, disposable pen               |
| Insulin Glulisine                    |                 |                                      |                                    |
| <b>Short-Acting</b>                  | Recombinant DNA | Humulin R (Lilly)                    | vial                               |
| Regular                              |                 | Novolin R (Novo Nordisk)             | vial                               |
| Human                                |                 |                                      |                                    |
| <b>Intermediate-Acting</b>           | Recombinant DNA | Humulin N (Lilly)                    | vial, disposable pen               |
| NPH                                  |                 | Novolin N (Novo Nordisk)             | vial                               |
| Human                                |                 |                                      |                                    |
| <b>Long-Acting</b>                   | Recombinant DNA | Levemir ( Novo Nordisk )             | vial, disposable pen               |
| Insulin Detemir                      | Recombinant DNA | Lantus (sanofi-aventis)              | vial, cartridge,<br>disposable pen |
| Insulin Glargine                     |                 |                                      |                                    |
| <b>Insulin Mixtures</b>              | Recombinant DNA | Humulin 70/30 (Lilly)                | vial, disposable pen               |
| NPH/Regular (70%/30%)                | Recombinant DNA | Novolin 70/30 (Novo Nordisk)         | vial                               |
| Human                                | Recombinant DNA | Humalog Mix 50/50 (Lilly)            | vial, disposable pen               |
|                                      | Recombinant DNA |                                      | vial, disposable pen               |



|   |  |                                     |                      |
|---|--|-------------------------------------|----------------------|
| Lispro<br>Protamine/Lispro<br>(50%/50%) |  | Humalog Mix 75/25<br>(Lilly)        | vial, disposable pen |
| Lispro<br>Protamine/Lispro<br>(75%/25%) |  | Novolog Mix 70/30<br>(Novo Nordisk) |                      |
| Aspart<br>Protamine/Aspart<br>(70%/30%) |  |                                     |                      |

Note: All insulin analogs are available by prescription only. On August 17, 2009, Novo Nordisk announced the Novolin Innolet R, N, and 70/30 devices and the Novolin R, N and 70/30 PenFill cartridges would no longer be available after December 31, 2009.

**Table 3 Insulin Pharmacodynamics** ( [\[45\]](#) [\[46\]](#) [\[47\]](#) [\[48\]](#) [\[49\]](#) [\[50\]](#) [\[51\]](#) [\[52\]](#) [\[53\]](#) [\[54\]](#) [\[55\]](#) [\[56\]](#) [\[57\]](#) )

| Insulin           | Onset (hr)    | Peak (hr)                    | Duration (hr) | Appearance |
|-------------------|---------------|------------------------------|---------------|------------|
| Insulin Lispro    | within 15 min | ½-1½                         | 3-5           | Clear      |
| Insulin Aspart    | within 15 min | 1-3                          | 3-5           | Clear      |
| Insulin Glulisine | .25-.5        | .5-1                         | 4             | Clear      |
| Regular           | ½-1           | 2-4                          | 5-8           | Clear      |
| NPH               | 1-2           | 4-10                         | 14+           | Cloudy     |
| Insulin Detemir   | 3-4           | 6-8 (though relatively flat) | up to 20-24   | Clear      |
| Insulin Glargine  | 1.5           | flat                         | 24            | Clear      |
| Lispro Mix 50/50  | .25-.5        | .5-3                         | 14-24         | Cloudy     |
| Lispro Mix 75/25  | .25-5         | .5-2.5                       | 14-24         | Cloudy     |
| Aspart Mix 70/30  | .1-.2         | 1-4                          | 18-24         | Cloudy     |

**Note: Patient specific onset, peak, duration may vary from times listed in table,**

**Peak and duration are often very dose dependent with shorter duration of actions with smaller doses and vice versa.**

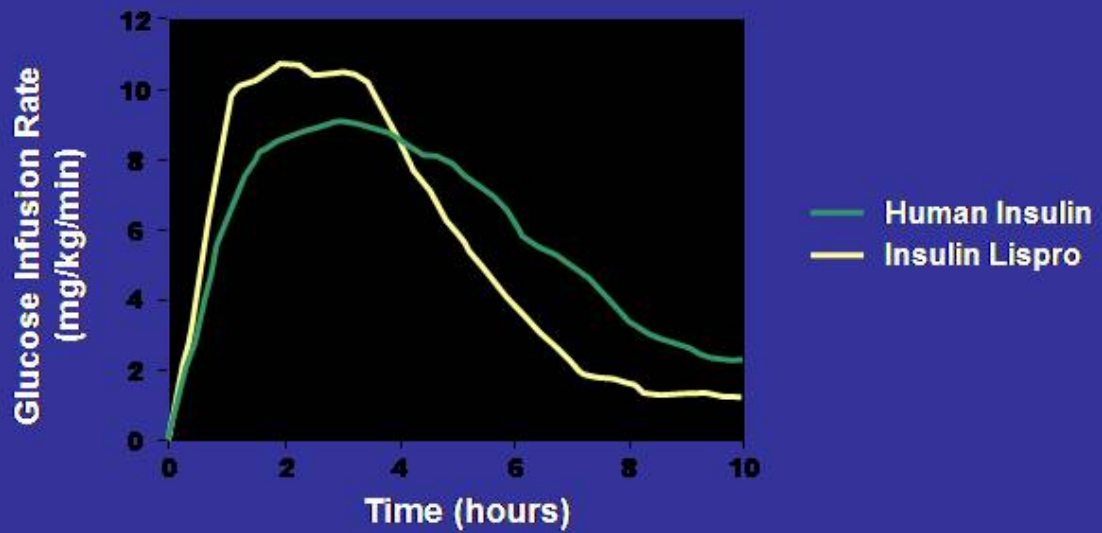
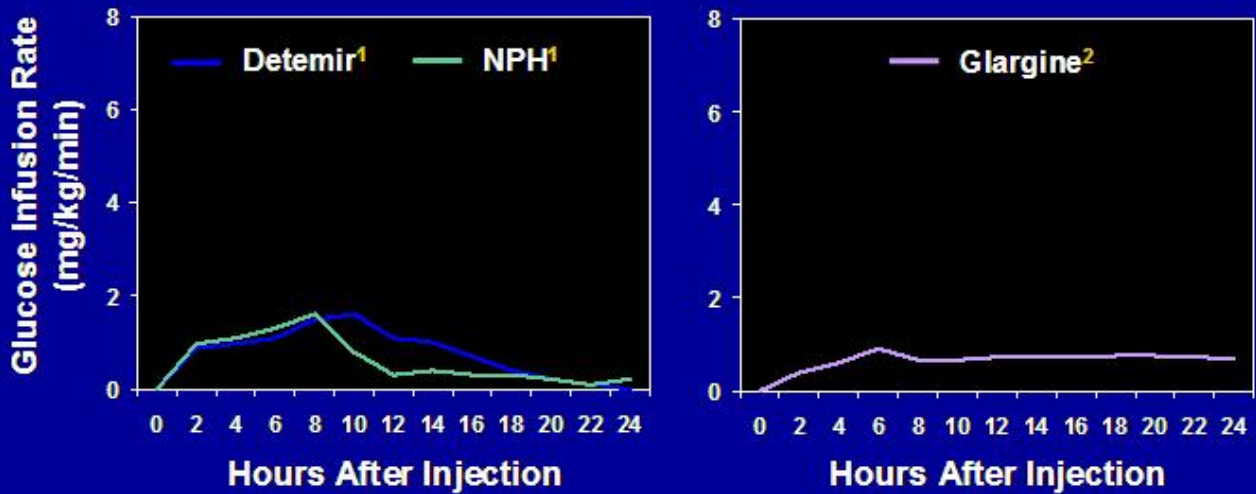


Figure 4a.

Figure 4a. Pharmacodynamic Profiles of a Rapid Insulin Analog (insulin lispro) and Regular Insulin.

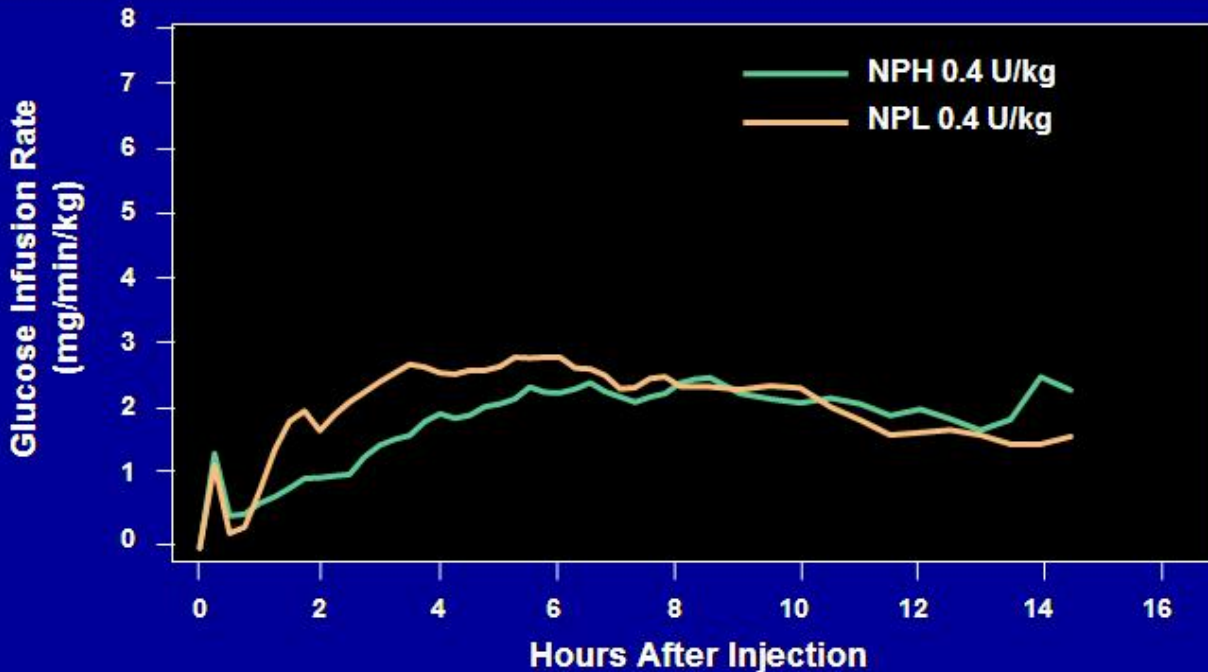


- Type 1 diabetic patients (N=12)<sup>1</sup>, Type 1 diabetic patients (n=20)<sup>2</sup>
- NPH and Glargine dose = 0.3 U/kg; Detemir dose = 0.4 U/kg

Figure 4b.

Figure 4b. Pharmacodynamic Profiles of Long-Acting and Intermediate-Acting

Basal Insulins.



• Non-diabetic patients (N=8)

Figure 4c.

Figure 4c. Pharmacodynamic Profile: Lispro NPL in Comparison with NPH

## Dose-Dependent Effect

The pharmacodynamics of regular and NPH are particularly affected by the size of the dose <sup>[58]</sup>. Larger doses can cause a delay in the peak and increase the duration of action. For example, injecting 4 units of NPH will have a significantly different time-action profile compared to 30 units of NPH.

## Rapid-Acting Insulins

### *Insulin Lispro (Humalog)*

Insulin lispro [Lys (B28), Pro (B29)] is an insulin analog that was approved in 1996 (Humalog). The B28 (proline), B29 (lysine) amino acid sequence of the insulin molecule is reversed to be lysine-proline resulting in a rapid absorption, within 15 minutes. Because it is absorbed more

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rapidly, its onset and peak are sooner (and duration shorter) compared to regular insulin. Insulin lispro is also approved for injection immediately after a meal. Because insulin lispro can be injected just before (or after) the meal versus waiting 30 minutes with regular insulin, patients may find it provides them with more flexibility and convenience for their mealtime insulin injection. Insulin lispro can be more effective in lowering postprandial blood glucose levels and has a reduced risk of hypoglycemia compared to regular insulin [59] [60] [61]. The reason insulin lispro is associated with less hypoglycemia is due to better matching of insulin effect and food absorption [62]. Insulin lispro has been studied for use in insulin pumps and, FDA approved for this indication in 2004. [63] [64] [65]. In the rare case of severe human insulin allergy, insulin lispro has been shown to be less immunogenic [66].

### ***Insulin Aspart (Novolog)***

Insulin aspart is a human insulin analog approved June 7, 2000 (Novolog). The B28 amino acid proline is substituted with aspartic acid resulting in a rapid onset of activity. Insulin aspart should be injected 5-10 minutes before the meal. Advantages listed above for insulin lispro are the same for insulin aspart [67]. The insulin aspart is FDA-approved for use in insulin pumps [68] [69].

While on a molar basis insulin aspart and lispro have identical in vivo potency compared to regular human insulin, higher peak concentrations are achieved with the rapid-acting insulins [70]. Thus, while a 1:1 conversion is often used for the initial switch from regular insulin to insulin aspart, glulisine or lispro, over time, a patient's rapid-acting insulin dose may need to be adjusted, often reduced. This dosing change is also due to the better matching of the peak of the insulin with the meal, thus achieving better post-prandial control.

### ***Insulin Glulisine (Apidra)***

Insulin glulisine is a rapid-acting insulin analogue that differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid. Chemically, it is 3B-lysine-29B-glutamic acid-human insulin. When injected subcutaneously, its onset of action is more rapid and achieves higher concentrations compared to human insulin on a unit-per-unit basis. When used as a meal-time insulin, the dose should be given within 15 minutes before a meal or within 20 minutes after starting a meal. Insulin glulisine also is being used in insulin pumps [71]. Insulin glulisine has been available in USA since 2007 and FDA-approved in 2004.

### **Short-Acting Insulin (Regular)**

Regular insulin has an onset of action of 30-60 minutes. It should be injected approximately 30 minutes before the meal. Adherence to this schedule can be inconvenient and difficult for some patients.

### **Intermediate-Acting Insulins (NPH)**

NPH, which stands for Neutral Protamine Hagedorn, was created in 1936 by Hans Christian

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Hagedorn and B. Norman Jensen. These scientists discovered that the effects of subcutaneously injected insulin could be prolonged by the addition of protamine, a protein that they obtained from the “milt” or semen of river trout. NPH insulin is categorized as an intermediate-acting insulin, whose onset of action is approximately 2 hours, peak effect at 6-14 hours, and duration of action up to 24 hours (depending on the size of the dose). Intermediate-acting insulins can serve a basal insulin and/or prandial insulin depending on time of administration. NPH insulin is available in various combinations with either regular insulin or short-acting insulins (Table 2).

## Long-Acting Insulins

Long-acting insulins serve to provide a basal (or baseline) level of insulin.

### *Insulin Glargine (Lantus)*

Insulin glargine (21A-Gly-30Ba-L-Arg-30Bb-L-Arg-human insulin) is an insulin analog approved April 20, 2000 (Lantus). It consists of two modifications to human insulin. Two arginines are added to the C-terminus of the B chain shifting the isoelectric point of the insulin from a pH of 5.4 to 6.7 [72]. This change makes the insulin more soluble at an acidic pH and insulin glargine is formulated at a pH of 4.0 [73]. The second modification is at the A21 position, where asparagine is replaced by glycine. This substitution prevents deamidation and dimerisation that would occur with acid-sensitive asparagine. When insulin glargine is injected into subcutaneous tissue, which is at physiologic pH, the acidic solution is neutralized. Microprecipitates of insulin glargine are formed, from which small amounts of insulin are released throughout a 24-hour period, resulting in a low level of insulin throughout the day [74]. The biological activity of insulin glargine is due to its absorption kinetics and not a different pharmacodynamic activity (e.g., stimulation of peripheral glucose uptake) [75].

It is critical that insulin glargine not be mixed in the same syringe with any another insulin or solution because this will alter its pH and thus affect its absorption profile. Lantus may be given at any time of day. Insulin glargine has been shown to have less nocturnal hypoglycemia when used at bedtime compared with NPH insulin [76] [77].

### *Insulin Detemir (Levemir)*

Insulin detemir is a long-acting human insulin analog for maintaining the basal level of insulin; its trade name is Levemir. It is an insulin analog in which the B30 amino acid is omitted and a C14 fatty acid chain (myristic acid) is bound to the B29 lysine amino acid. Insulin detemir is slowly absorbed due to its strong association with albumin in the subQ tissue and when it reaches the bloodstream it again binds to albumin delaying its distribution to the peripheral tissues.

## Storage

All insulins have an expiration date which is labeled on directly on the product (vials, cartridges, disposable pens and other delivery devices) applies when they are unopened and refrigerated.

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Unopened (i.e., insulin not currently in use) insulin should be stored in the refrigerator at 36°F-46°F (2°C-8°C). Insulin should never be frozen or stored in an ambient temperature greater than 86°F (30°C). An insulin vial in use may be kept at room temperature, below 86°F, or 30°C (insulin glulisine and Novo Nordisk human insulins, N, R and 70/30, should be stored up to 77°F only), for 28 days, or about 1 month (except for insulin detemir and Novo Nordisk human insulins, which can be kept for up to 42 days). Insulin cartridges, disposable pens and other delivery devices can have different storage recommendations for room temperature. Once opened, insulin cartridges and pens should not be refrigerated.

## Adverse Effects

The most significant adverse effect of insulin is hypoglycemia. In the DCCT (Diabetes Control and Complications Trial), intensive insulin therapy was associated with a 2-3 fold increase in severe hypoglycemia (i.e., a person requiring assistance) <sup>[78]</sup>. Likewise, in the UKPDS (United Kingdom Prospective Diabetes Study), insulin therapy in the intensively treated group resulted in 1.8% rate of major hypoglycemic episodes compared to 0.7% in the conventional group <sup>[79]</sup>. All patients receiving insulin should be aware of the symptoms of hypoglycemia and how to treat it.

Weight gain is another significant side effect of insulin therapy. In part, the weight gain can be a result of frequent hypoglycemic episodes in which patients often overtreat/overeat in response to hunger. Insulin, being an anabolic hormone, also promotes the uptake of fatty acids into adipose tissue. The amount of weight gain in the DCCT and UKPDS associated with insulin therapy was 4.6 kg and 4.0 kg respectively <sup>[80]</sup> <sup>[81]</sup>. However, less weight gain is encountered with long-acting insulin analogs <sup>[82]</sup> <sup>[83]</sup>.

True allergic reactions and cutaneous reactions are rare (see Immunogenicity). To avoid lipohypertrophy, patients should be instructed to rotate their insulin injection sites, preferably rotating within one area (e.g., abdomen; avoid 2-inch radius around navel) and not reusing for one week <sup>[84]</sup>.

In June 2009, 4 retrospective, epidemiologic studies assessing the risk of cancer from insulin use, glargine in particular, were published online at the European Association for the Study of Diabetes' journal website; 3 of these European studies reported an increased risk of cancer with insulin glargine. In the Germany study, a correlation between insulin dose and cancer risk was found for all insulin types (human insulin, aspart, lispro or glargine); however after adjusting for dose, insulin glargine was found to have a dose-dependent increased risk of cancer compared to human insulin (e.g., HR 1.09, 1.19 and 1.31 for a total daily doses of 10 units, 30 units and 50 units respectively). <sup>[85]</sup> The median follow-up time was only 1.63 years (1.31 years for insulin glargine) and body mass index was not accounted for. The Swedish study found a statistically significant increased risk of breast cancer only in women who used insulin glargine alone (RR 1.99), but not in those on insulin glargine plus other insulins. <sup>[86]</sup> The Scotland study demonstrated an increased risk of cancer (HR 1.55) for patients on insulin glargine alone, while those on insulin glargine plus other insulins had a slightly lower incidence of cancer (HR 0.81)

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compared to human insulin only users which was not statistically significant. <sup>[87]</sup> Finally, in the UK study, no link between insulin glargine and cancer was found. <sup>[88]</sup> These observational studies assessed large patient databases and have significant, inherent limitations to generalize their conclusions, such as the potential for different pre-treatment characteristics of the groups, selection bias, the small numbers of cancer cases found, and short duration of follow-up. Also, type 2 diabetes itself is associated with an increased risk of colon, pancreas and breast cancer. Furthermore, in a randomised, 5-year, open-label trial comparing the progression of retinopathy of NPH and insulin glargine users, no increased risk of cancer was found in the 1017 patient sample. <sup>[89]</sup> Lastly, in an analysis of 31 randomized controlled trials from the sanofi-aventis safety database (phase 2, 3, and 4 studies), insulin glargine was not associated with an increased risk of cancer, including breast cancer. <sup>[90]</sup> Of note, the main study affecting these findings is the Rosenstock et al study comparing glargine to NPH that had an approximate 5 year duration, whereas 19 of the studies included had very short durations (approximately 6 months). On July 1, 2009, the FDA issued an early communication about the safety of Lantus and is working with the manufacturer to review the collective data and determine whether additional studies need to be performed. ***At this time, these data do not provide conclusive evidence of an increased risk of cancer associated with insulin glargine.***

## TYPES OF REGIMENS

### General Principles

#### *Type 1 Diabetes*

With decreasing beta cell function resulting in decreased insulin production, people with type 1 diabetes may require insulin for survival. In general, insulinopenic type 1 diabetics generally require 0.5-1.0 units per kg of body weight per day of insulin <sup>[91]</sup>. Insulin therapy is often initiated at 0.5-0.75 units/kg/day <sup>[92]</sup>. During the early stages of type 1 diabetes, patients will require less insulin because the beta cells are still producing some insulin; insulin requirements can be in the range of 0.1-0.6 units per kg per day <sup>[93]</sup> <sup>[94]</sup>. Intensive insulin therapy (defined as 3 insulin injections daily) is indicated for people with type 1 diabetes as this has been shown to provide better glycemic control than 1 or 2 daily injections and reduce the development and progression of microvascular complications <sup>[95]</sup>.

#### *Type 2 Diabetes*

Many patients with type 2 diabetes will eventually require insulin therapy. Since type 2 diabetes is associated with insulin resistance, insulin requirements can exceed 1 unit/kg/day. In the UKPDS, by 9 years less than 25% of patients treated with a sulfonylurea as monotherapy were able to maintain A1C levels <7.0%; the majority of patients required insulin therapy within 9 years of diagnosis <sup>[96]</sup>. When initiating insulin therapy in patients with type 2 diabetes, insulin is often used in combination with the oral medications a patient is taking. Often an intermediate to long-acting insulin (e.g., NPH, insulin glargine, or insulin detemir) is added at bedtime or 70/30 insulin before dinner <sup>[97]</sup>. The rationale is that insulin, by suppressing hepatic glucose output during the night, will control the fasting blood glucose (FPG), while the oral medication(s)



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continues to control prandial glucose levels and glucose throughout the day <sup>[98]</sup>. Typically, a starting dose of 10 units is utilized, or ~0.1-0.2 units/kg <sup>[99]</sup>. The intermediate to long-acting insulin is titrated to achieve the FPG target (see Adjustments below). If the patient has poor glycemic control during the day, daytime insulin can be initiated; twice-daily regimen of insulin or multiple daily injections can be used. At this point, the patient is experiencing beta-cell failure. If the patient is taking an insulin secretagogue (e.g., glyburide, repaglinide, etc), it should be discontinued, as insulin will now be replaced exogenously. However, the insulin sensitizing oral agents (e.g., metformin) should be continued. Another option is to discontinue the insulin secretagogue when insulin therapy is started to simplify the medication regimen and to avoid potential hypoglycemia. <sup>[100]</sup>.

## Goals of Therapy

Before starting a patient on insulin, or adjusting their current insulin therapy, it is important to establish glycemic goals tailored to the patient. The American Diabetes Association currently recommends the following glycemic goals <sup>[101]</sup>:

Preprandial plasma glucose 70-130 mg/dl

Postprandial plasma glucose <180 mg/dl

A1C <7%

For example, if a patient's preprandial blood glucose levels have been in the high 200's, an initial goal might be to lower them to 150 mg/dl. Upon achieving this, a lower goal can be set (e.g., 90-130 mg/dl). In the DCCT, retinopathy initially worsened during the first year in patients (with type 1 diabetes) who received intensive therapy <sup>[102]</sup>. This is thought to be due to rapid lowering of glucose levels. Thus in patients with proliferative retinopathy or those with high A1C (e.g., >10%), slower lowering of glucose is warranted <sup>[103]</sup>. Another example of individualizing glycemic goals is a patient with hypoglycemic unawareness; glycemic goals should be less aggressive as glucose levels should not border around 70 mg/dl too closely.

## Replacement Strategies

### *Physiologic Insulin Replacement*

A functioning pancreas releases insulin continuously, to supply a basal amount to suppress hepatic glucose output between meals and overnight, and also releases a bolus of insulin prandially to promote glucose utilization after eating <sup>[104]</sup>. Replacing insulin in a manner that attempts to mimic physiologic insulin release is often referred to as the basal/bolus concept. This physiologic replacement requires multiple daily injections (3 or more) or use of an insulin pump. Basal insulin requirements are approximately 50% of the total daily amount. Prandial insulin is ~10-20% of the total daily insulin requirement at each meal <sup>[105]</sup>. Providing basal-bolus insulin regimens allow patients to have flexibility in their mealtimes and achieve better glycemic control.

## *Non-Physiologic Insulin Replacement*

When insulin is given once or twice daily, insulin levels do not mimic physiologic insulin release patterns. For people with type 2 diabetes, in whom basal insulin replacement is not as critical, once or twice daily regimens can still work satisfactorily with reasonable glycemic control achieved.

## **Examples of Regimens**

### *Once Daily Insulin Regimen (for patients with type 2 diabetes on oral agents)*

NPH ( **Figure 5a** ), insulin glargine ( **Figure 5b** ), or insulin detemir are most often given at bedtime (however insulin glargine can be administered anytime of the day); or for patient who eat large amounts of carbohydrates at dinner, an insulin mixture, regular and NPH or a premixed insulin, can be given prior to dinner ( **Figure 5c** ).

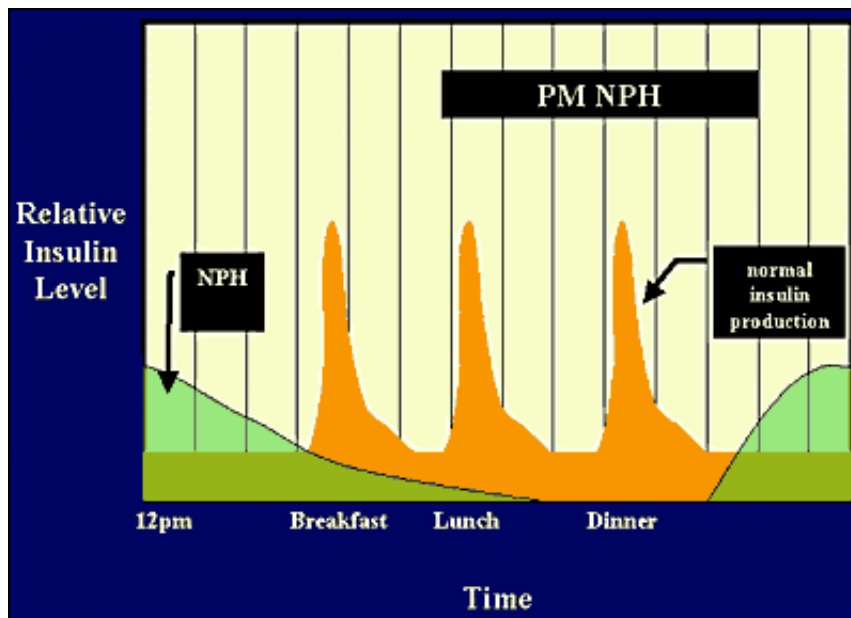


Figure 5a.

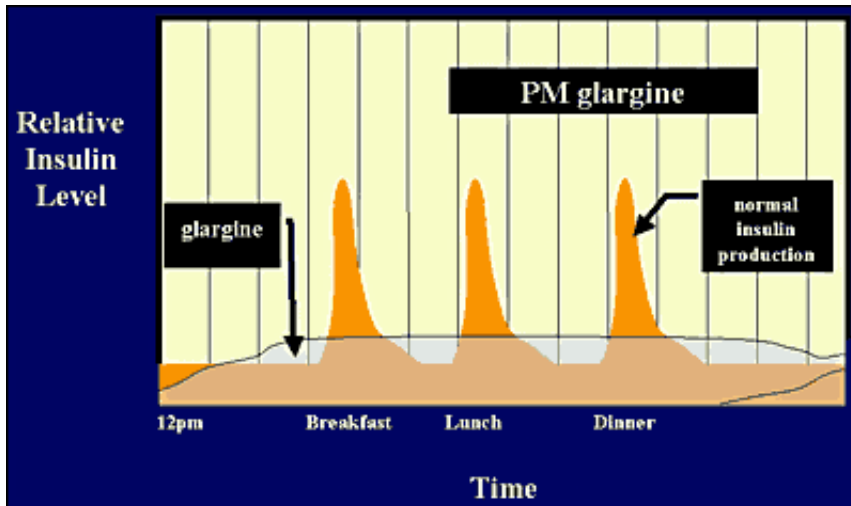


Figure 5b.

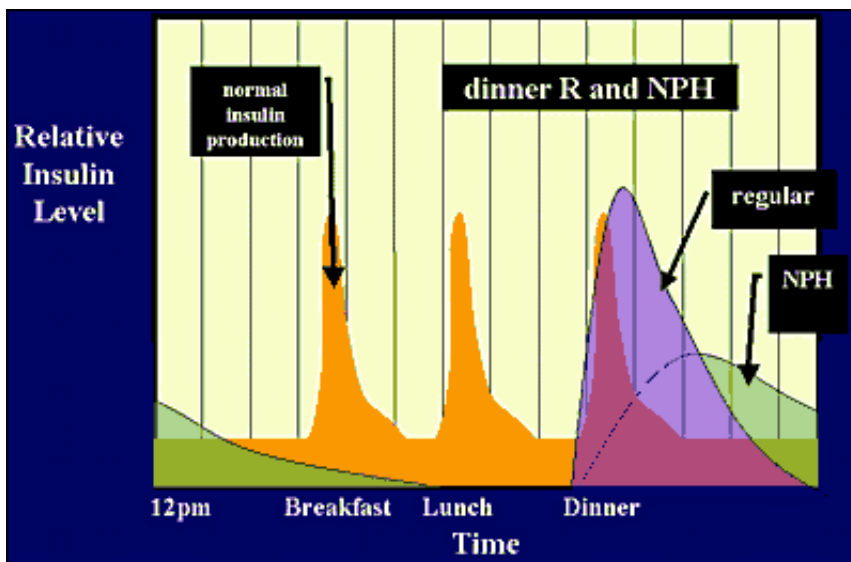


Figure 5c.

***Twice-daily Insulin Regimen (Split-Mixed and Pre-Mixed Regimens)***

Two-thirds of the insulin dose is given in the morning before breakfast and one-third is given before dinner. Premixed insulins can be used or a mixture of a short-acting insulin (e.g., regular, insulin aspart/glulisine/lispro) and an intermediate-acting insulin (e.g., NPH) ( **Figure 6a** ) <sup>[106]</sup> .

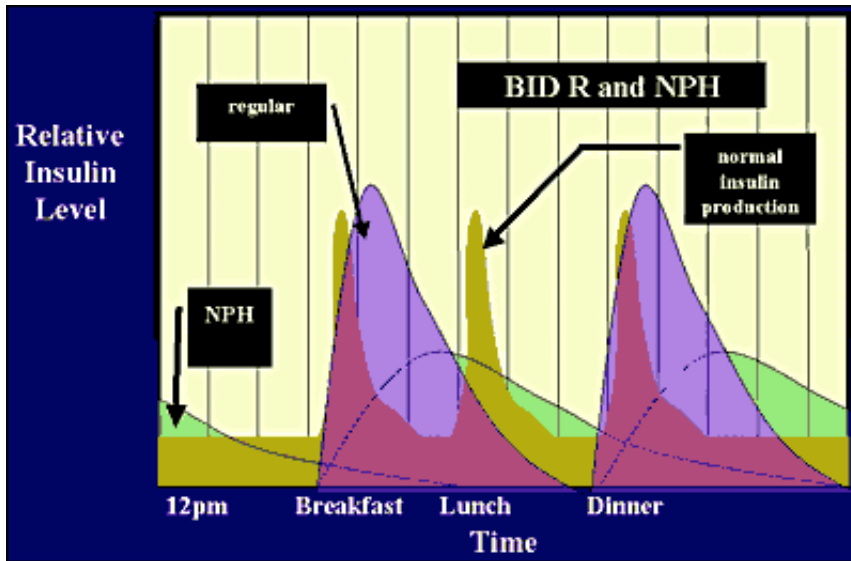


Figure 6a.

- 2/3 total daily dose at breakfast: given as 2/3 NPH and 1/3 Regular (or insulin aspart/gulisine/lispro)
- 1/3 total daily dose at dinner: divided in equal amounts of NPH and Regular (or insulin aspart/gulisine/lispro)

For patients who experience nocturnal hypoglycemia when NPH is administered at dinner with a short-acting insulin, moving the NPH dose to bedtime helps reduce the risk for nocturnal hypoglycemia <sup>[107]</sup>. Conversely, NPH at dinner can result in fasting hyperglycemia due to dissipation of insulin activity and the dawn phenomenon. Moving the NPH dose to bedtime can help resolve this problem <sup>[108]</sup> ( **Figure 6b** ). An obvious limitation to using premixed insulin is reduced flexibility in dosing; if the dose is adjusted, both types of insulin in the mixture are adjusted.

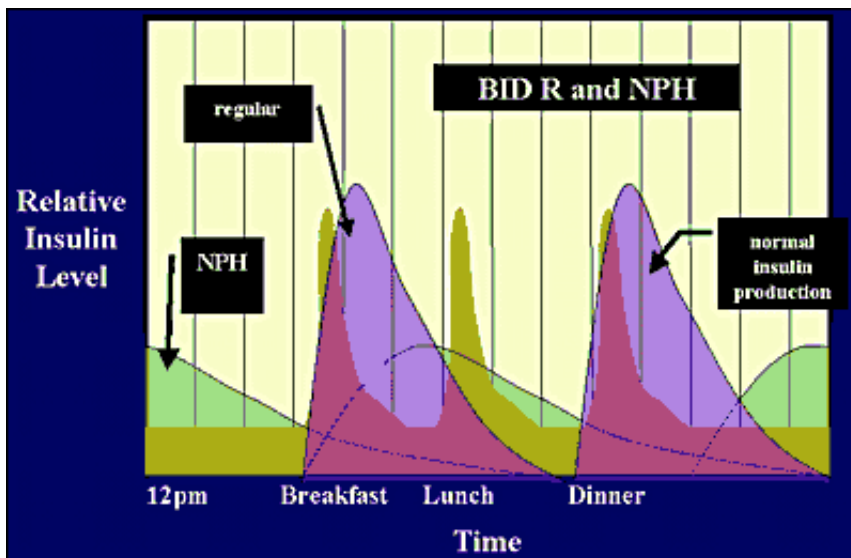


Figure 6b.

### ***Multiple Daily Injection Regimen: Basal plus Prandial Insulin***

Many different types of regimens are possible with multiple daily injections. Regular, insulin aspart, glulisine and lispro are used to provide prandial insulin. NPH, insulin glargine, and insulin detemir are used to provide basal insulin.

- Regular, insulin aspart/glulisine/lispro before meals and NPH, insulin glargine or insulin detemir at bedtime ( **Figure 7a, 7b** ).
- Insulin aspart/glulisine/lispro before meals and NPH twice daily (breakfast and bedtime) ( **Figure 8** ).

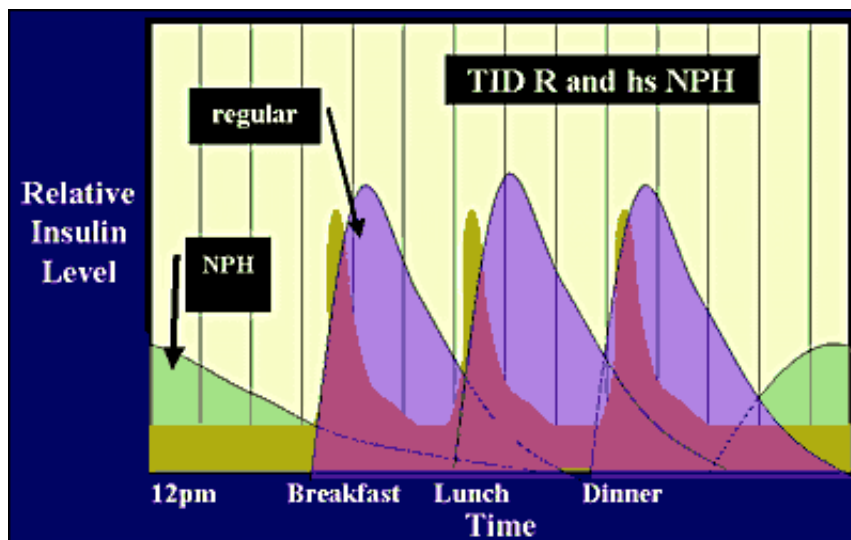


Figure 7a.

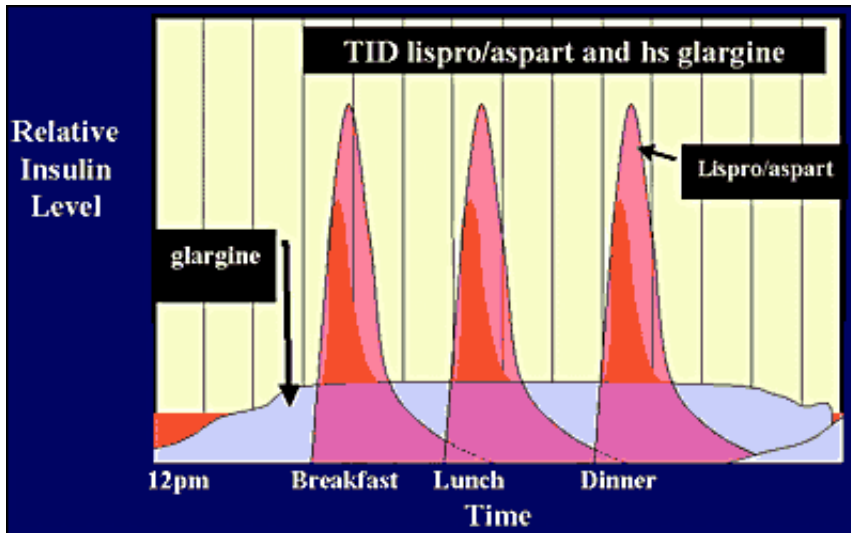


Figure 7b.

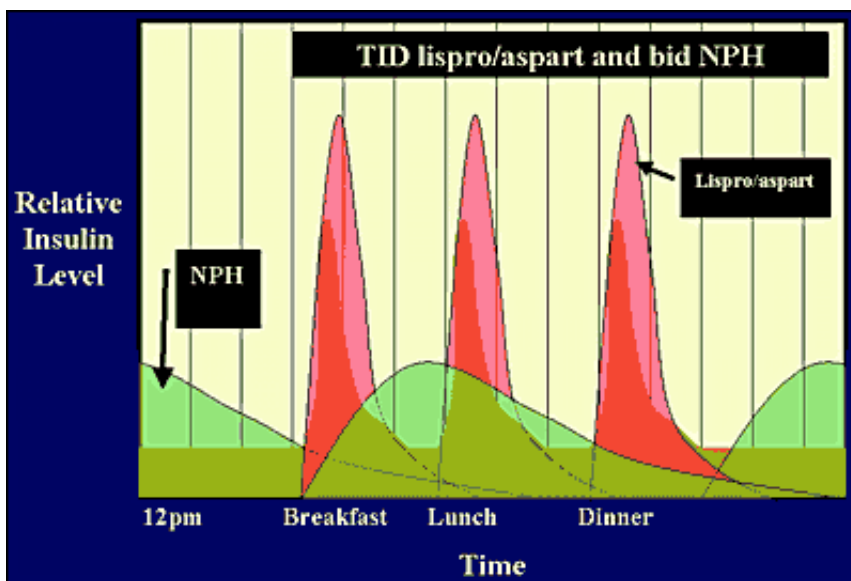


Figure 8.

### *Insulin Pumps*

Insulin pump or continuous subcutaneous insulin infusion (CSII) therapy is another option for intensive insulin therapy. While pump therapy used to be reserved for primarily type 1 diabetes, patients with type 2 diabetes are now using insulin pumps <sup>[109]</sup>. Patients initiated on insulin pump therapy need to be very knowledgeable about diabetes management and be practicing self-management. Patients already know how to count carbohydrates and adjust their insulin

doses. Potential advantages of insulin pumps include less weight gain, less hypoglycemia, and better control of fasting hyperglycemia due to the dawn phenomenon compared to multiple daily injections <sup>[110]</sup><sup>[111]</sup><sup>[112]</sup><sup>[113]</sup>.

### ***Timing of Prandial Insulin Injection***

The lag time from injecting regular insulin and eating is approximately 30 minutes; while insulin aspart/glulisine/lispro can be injected within 15 minutes of eating. Depending on the level of hyperglycemia before meals, the lag-time can be increased. Rapid acting insulins allow patients to adjust insulin to match their lifestyle rather than having to adapt the timing of meals to a more fixed insulin regimen <sup>[114]</sup>.

## **Adjustments**

Insulin doses should be adjusted to achieve glycemic targets. It is always best to err on the conservative side when dosing insulin at initiation or when adjusting current insulin therapy. Typically a 10-20% increase or decrease in an insulin dose is appropriate. If a patient is experiencing hypoglycemia, adjustment of the insulin dose causing the hypoglycemia should be addressed preferentially over other insulin dose adjustments. Hyperglycemia is a domino effect: if a patient is hyperglycemic in the morning, chances are they remain hyperglycemic throughout the day. Therefore, adjust the earliest time of hyperglycemia first <sup>[115]</sup>.

### ***Adjustment of Intermediate to Long-Acting Insulin***

When a dose of intermediate or long-acting insulin is adjusted, it is recommended to wait at least 2-5 days before further changes in the dose to assess the response <sup>[116]</sup>.

### ***Adjustment of Once-Daily Evening Insulin***

The FPG is used to adjust the intermediate to long-acting insulin given in the evening. A common weekly titration schedule used is <sup>[117]</sup>:

- If the FPG is >140 mg/dl: Increase by 4 units
- If the FPG is 120-140 mg/dl: Increase by 2 units

For insulin glargine, the following titration schedule has been studied and shown to cause less nocturnal hypoglycemia compared to bedtime NPH insulin. In this study, insulin was titrated, using a forced titration schedule, to target a FPG of  $\hat{\text{A}}\text{E}$  100 mg/dl <sup>[118]</sup>.

| Forced Titration Schedule                                     |                       |
|---|-----------------------|
| Start with 10 units bedtime basal insulin dose; adjust weekly |                       |
| FPG (mg/dL)   | Increase insulin dose |
| 100-120   | 2                     |
| 120-140   | 4                     |

|  |   |
|--|---|
| 140-180  | 6 |
| ≥ 180  | 8 |
| Decrease insulin dose (e.g., 2-4 units/day) if hypoglycemia occurs. (modified recommendation from reference 112) |   |

### ***Supplemental Insulin for Correction of Hyperglycemia***

Regular insulin, insulin aspart/glulisine/lispro can be used to correct for hyperglycemia <sup>[119]</sup>. In general, 1-2 units of insulin will lower the blood glucose by 30-50 mg/dl. Often 1 unit for every 50 mg/dl above the glucose target is a starting supplemental dose, adjusting for insulin sensitivity <sup>[120]</sup>. An example of a supplemental insulin regimen is as follows: For every 50 mg/dl above the premeal glucose target (e.g., 150 mg/dl), add 1 unit of insulin <sup>[121]</sup>. So, if a person's premeal glucose was 250 mg/dl, 2 units of insulin would be added to the usual dose of premeal insulin. Supplemental insulin can also be used for snacks <sup>[122]</sup>.

### ***Carbohydrate Counting***

A more sophisticated type of insulin regimen is one in which a patient doses their prandial insulin based on the number of carbohydrates eaten at the meal. By learning how to count their carbohydrates, and dosing their insulin accordingly, patients are afforded flexibility in their meals. A starting insulin-to-carbohydrate ration often used is 1 unit of insulin for every 15 grams of carbohydrate <sup>[123]</sup>. This ratio is adjusted based on insulin sensitivity and may be different for each meal. Carbohydrate counting is too difficult for some patients. In these patients, meal portion sizes and estimates of carbohydrate servings (15 grams) are concepts that can be learned. Medical nutrition therapy is a critical component of therapy for patients on insulin.

A comprehensive diabetes education class, that teaches self-management skills, such as how to dose prandial insulin by matching it to the amount of carbohydrate intake are an excellent resource to facilitate patients in adopting an intensive insulin therapy regimen <sup>[124]</sup>.

### ***Adjustments for Exercise***

Exercise improves insulin sensitivity. Thus, when a patient exercises, it is often necessary to decrease the insulin dose (and increase caloric intake). For morning exercise, the pre-breakfast insulin dose should be reduced (~25% depending on the duration and intensity of the exercise). For late-morning/early-afternoon and evening exercise, the pre-lunch and pre-dinner insulin dose should be reduced respectively <sup>[125]</sup>. The effect of exercise on insulin sensitivity can last for many hours; so several insulin doses may need to be adjusted.

### ***Self-Monitoring of Blood Glucose***

Patients who were not self-monitoring their blood glucose (SMBG) levels prior to insulin need to be educated how to do this, how to interpret their glucose readings, and how to treat hypoglycemia if it occurs. Involvement of diabetes educator is extremely useful when initiating patients on insulin to provide comprehensive self-management training. The ADA currently



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recommend that people with type 1 diabetes SMBG at least 3 times daily and those with type 2 diabetes at least daily [126]. Most glucose meters are now plasma-referenced, correlating better to the ADA's glyceic goals. Plasma glucose concentrations are approximately 10-15% higher than whole blood glucose concentrations [127].

## SICK DAY GUIDELINES

A common misconception among patients is that if they are sick enough that they don't eat or even vomit, they should not take their diabetes medications, insulin included. Patients should be instructed to continue their insulin therapy, maintain fluid intake, eat smaller meals as tolerated, and test their glucose levels every 1-4 hours (ketones as well for people with type 1 diabetes). Insulin therapy should be adjusted based on the glucose levels. If the glucose is >240 mg/dl with moderate to large ketonuria, patients should contact their provider immediately [128].

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