

Variability in Insulin Action: Mechanisms, Implications, and Recent Advances

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Citation

T Ganiats. *Variability in Insulin Action: Mechanisms, Implications, and Recent Advances*. The Internet Journal of Family Practice. 2006 Volume 5 Number 2.

Abstract

An important drawback of conventional human insulin formulations is their variable absorption and unpredictable insulin activity. Modern insulin analogs offer several clinical advantages over conventional human insulin therapies, including a more predictable and physiologically accurate profile of insulin absorption and action. Accumulating evidence suggests that insulin therapies exhibiting less within-patient variability are associated with greater convenience, a reduced risk of hypoglycemia, and in some cases, reduced weight gain.

CONFLICT OF INTEREST

The author has served on advisory boards for Novo Nordisk and Eli Lilly in 2006. Also, he has worked on research projects with Amgen and Schering-Plough.

INTRODUCTION

Although insulin is the most effective treatment for diabetes mellitus when properly dosed,¹ older insulin formulations have significant limitations that often make clinicians and patients reluctant to initiate this highly effective therapy. Today, modern insulin analogs offer equivalent efficacy or modestly improved efficacy compared with conventional insulin therapies, but without many of these limitations.² Insulin analogs have the potential to improve the balance between predictable glycemic control and tolerability.

The primary goal of insulin therapy is to safely match the insulin needs of the individual, which generally can be accomplished by reproducing the physiologic pattern of insulin secretion observed in healthy individuals. In healthy people, there is a low and constant, or basal, output of insulin, which controls fasting glucose levels.³ Insulin secretion also increases rapidly within 15 to 45 minutes of initiation of a meal, controlling postprandial glucose excursions. Ideally, insulin therapy should meet the basal and postprandial needs of patients in a physiologic fashion.

Several types of insulin therapies are available to meet these needs. Older insulin formulations include regular human insulin and neutral protamine Hagedorn (NPH). NPH is an intermediate-acting insulin traditionally used to control

fasting plasma glucose, while regular human insulin is a short-acting insulin used to control mealtime glycemic excursions. A major limitation of both regular human insulin and NPH is that they do not accurately reproduce physiologic insulin secretion. For example, regular human insulin has a slow onset of action and a delayed peak of action. NPH exhibits a significant peak in action and a relatively short duration of action, both of which limit its ability to cover basal insulin needs.^{2,4} Moreover, both regular human insulin and NPH exhibit considerable variation within an individual patient.^{5,6,7} This variability in insulin action means that identical doses of subcutaneous insulin injections do not always lead to the same glycemic effects, even if dietary intake and physical activity are controlled.⁷ Therefore, the pharmacokinetic profiles of conventional human insulin formulations and the unpredictable nature of these profiles can result in insulin levels that are not appropriately matched to the patient's needs.⁸

The introduction of recombinant DNA technologies has allowed the development of insulin analogs, which, through their more physiologic pharmacokinetic profiles, have revolutionized insulin therapy. Rapid-acting insulin analogs such as insulin lispro, insulin aspart, and insulin glulisine provide a faster onset of action and a shorter duration of action than regular insulin.^{2,4} Because of their more rapid onset of action, rapid-acting analogs can be administered at mealtimes, unlike regular human insulin, which should be administered at least 30 minutes before a meal. Long-acting

insulin analogs such as insulin glargine and insulin detemir exhibit a relatively flat-action profile and longer duration of action compared with NPH.^{4,9,10,11} Perhaps most important, the insulin analogs, both the rapid-acting and long-acting, have more predictable insulin action profiles, allowing the use of more physiologic insulin regimens without the drawback of significant variability in insulin action.

5,7,10,12,13,14

WHY IS VARIATION IN INSULIN ACTION CLINICALLY IMPORTANT?

Variability in insulin action should be minimized because it has several adverse consequences (Table 1). One of the most important consequences of insulin variability is an increased risk of hypoglycemia, a primary barrier to effective and safe diabetes management.^{8,15} Variable rates of absorption, leading to variable and unpredictable peaks in insulin action, can cause unexpected hypoglycemia and hyperglycemia.^{5,7} For example, the combination of a peak in effect of NPH insulin and the unpredictability of the time and extent of this peak inevitably increases the risk of nocturnal hypoglycemia when NPH is dosed in the evening (when the peak in insulin action coincides with the period when insulin requirements are low).^{8,16} This variability limits the maximal tolerable dose, which can prevent patients from achieving their glycemic goals.¹⁵ Hypoglycemic episodes also may reduce patient quality of life and cause significant morbidity,¹⁷ including unpleasant symptoms of sweating, palpitations, tremor, and confusion. Severe episodes, although rare, can result in seizures and coma.⁸

Table 1: Potential Consequences of Variability in Insulin Action.^{7,9,15,16,18,19,20}

- Increased risk of hypoglycemia
- Increased weight gain associated with defensive eating to prevent hypoglycemia
- Changes in appetite due to fluctuations in glucose/insulin levels
- Reduced patient confidence in their treatment due to variability in glucose levels
- Increased risk of development and/or progression of diabetes complications
- Increased risk of mortality

Patients who experience hypoglycemia also have been

shown to gain more weight than patients without hypoglycemia.¹⁸ Both hypoglycemia and weight gain can negatively affect patient adherence and potentially long-term outcomes, particularly if patients try to avoid these adverse events by not maintaining tight glycemic control.^{15,21,22,23,24}

In addition, the unpredictability of insulin action can alter patients' confidence in their treatment.²⁵ Patients may not understand why their blood glucose levels vary so much despite their adherence to the treatment recommendations made by their health care providers, or they may become anxious due to concerns that they did not administer the correct dose.⁷

Perhaps most important, there is evidence that glycemic variability influences the progression of diabetes and its complications.⁹ For example, in the Diabetes Control and Complications Trial in patients with type 1 diabetes, the risk of retinopathy progression differed among patients who achieved the same mean glycated hemoglobin (A1c) level.¹⁹ At a given A1C level, participants who received intensive treatment (with 3 or more insulin injections or subcutaneous insulin infusion) had a significantly lower risk of retinopathy, nephropathy, and neuropathy compared with patients who received conventional insulin therapy (with 1 or 2 insulin injections).^{19,26,27} It has been speculated that the difference in risk is related to the greater frequency and magnitude of glycemic excursions in conventionally treated patients, who received fewer insulin injections compared with the intensively treated patients.⁹ An association between glycemic variability and an increased risk of mortality has also been reported in patients with type 2 diabetes.²⁰ Additional evidence suggests that large postprandial glycemic excursions are risk factors for diabetes complications, even when A1C levels are controlled.^{28,29}

WHAT CAUSES VARIABILITY IN INSULIN ACTION?

Several factors give rise to insulin variability (Table 2).^{5,7} Any factor that affects the delivery of insulin to or absorption of insulin from the subcutaneous tissue can affect the variability of insulin action. For example, variations in administration technique, including changes in the depth or site of injection, amount of subcutaneous blood flow, time lapse before needle withdrawal, and quality of the suspension (when crystallized insulins are used) all affect the predictability and intensity of insulin activity.⁷

Table 2: Causes of Intraindividual Variability in Insulin Action ^{5,7}

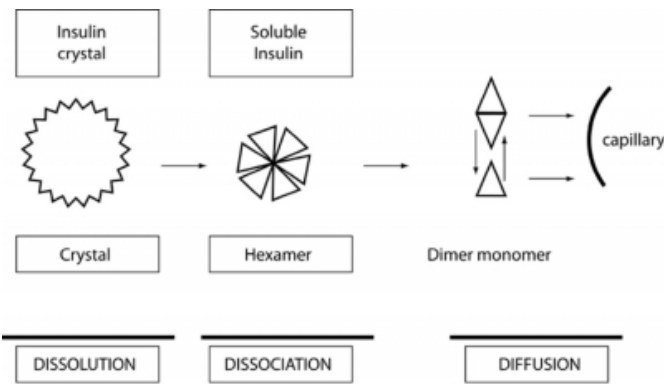
- Factors related to the insulin preparation/dose:
 - Physicochemical properties of the insulin preparation
 - Insulin concentration
 - Insulin dose
- Factors depending on the injection conditions:
 - Depth of injection
 - Anatomical site of injection
 - Delay before withdrawing the needle
 - Blood flow in the subcutaneous tissue
- Factors related to the individual:
 - Hypoglycemic effect
 - Physical activity
 - Diet

Other factors that affect insulin variability are patient-specific. Patients who experience hypoglycemia have also been shown to experience greater variability in insulin action ³⁰, largely because hypoglycemia triggers counter-regulation mechanisms that affect insulin sensitivity. ⁷ In other words, the injection of the same quantity of insulin can have a smaller effect than a similar amount of insulin administered before the hypoglycemic episode. ⁷ Variations in physical activity also modify the glycemic effects of a particular dose of insulin.

However, the greatest sources of variation in insulin action are frequently the differences in the physicochemical properties of insulin that affect its diffusion and its absorption in the subcutaneous tissue. In healthy individuals, insulin is produced in pancreatic beta cells, where it self-associates into hexamers for efficient storage. ³¹ After exiting the beta cells, insulin is diluted in interstitial fluid, where it immediately dissociates into biologically active monomers. ⁷ Insulin must be in the form of a monomer or a dimer to be able to diffuse in the interstitial fluid and cross into the blood (Figure 1). ⁵ The duration of insulin transit into the bloodstream also depends on its formulation and also

represents a significant source of variability in insulin action. ^{5,6,7,32} The concentration and the dose of the insulin preparation, both of which affect the absorption and diffusion time, can also influence insulin variability. ^{7,33,34}

Figure 1
Figure 1: Dissociation and Diffusion of Insulin Preparations



Adapted from Gin & Hanaire-Broutin, 2005 ⁷

HOW DOES INSULIN ABSORPTION AFFECT INSULIN VARIABILITY?

REGULAR HUMAN INSULIN AND RAPID-ACTING INSULIN ANALOGS

For many years, regular human insulin was the only option available for meeting the prandial insulin needs of patients with diabetes. Regular human insulin tends to form hexamers spontaneously when administered in a subcutaneous depot due to the high concentration of insulin in the depot. ¹⁶ The time lapse between hexamer formation and dissociation into dimers and monomers contributes to the delay in the effect of regular human insulin and is a source of intraindividual variability. ³⁵ Due to this delay, regular human insulin must be injected 30 minutes before meals so that the peak of insulin action corresponds to the peak in glycemic levels following the meal. However, because absorption of regular human insulin is slow, levels of regular human insulin remain elevated after the need for insulin is reduced, resulting in an increased risk of hypoglycemia. ³⁶ Regular human insulin also exhibits large day-to-day variations in insulin absorption. ³⁷

Rapid-acting insulin analogs were developed to provide a more physiologic approximation of the rapid increase in insulin following meals. These insulin preparations have a reduced tendency to aggregate into hexamers, which explains the faster rate of diffusion and the reduced variability of these formulations. ⁷ Because they are more rapidly absorbed, they can be injected closer to mealtimes

than regular human insulin.

NPH AND LONG-ACTING INSULIN ANALOGS

Ideally, a basal insulin should have a relatively long duration of action, a steady absorption rate to avoid peak plasma concentrations, and a reproducible absorption profile. The latter is particularly important with basal therapies because the opportunity for variable insulin absorption is greater due to their longer subcutaneous residence times.¹⁶

NPH

Early basal insulin therapies such as NPH were formulated with protamine to create suspensions of a precipitate that would slowly dissolve once injected. However, NPH is stored in crystalline form and requires thorough resuspension before injection or variability is introduced.^{16,38} Even if complete suspension is achieved, once injected the crystalline structure must be deconstructed to release the insulin complexes. The speed of dissociation varies from one patient to the next and varies within the same patient from one day to the next.⁷

LONG-ACTING INSULIN ANALOGS

The drawbacks of NPH and other early basal insulin formulations (eg, lente and ultralente, which are no longer available) prompted the development of the long-acting insulin analogs, insulin glargine and insulin detemir, both of which have a longer duration of action and a more constant time-action profile compared with NPH.^{10,11} These long-acting insulin analogs are completely soluble, making resuspension prior to injection unnecessary and eliminating one significant source of variability.

Insulin glargine. The protracted action of insulin glargine results from dissolution of microprecipitates formed after subcutaneous injection.³⁹ Once insulin glargine is injected into subcutaneous tissue that is at neutral pH, it produces a precipitate that subsequently dissociates into monomers.⁷ However, the processes of precipitation and redissolution of insulin glargine results in another source of variation.¹⁰

Insulin detemir. The prolonged duration of action of insulin detemir results from the addition of fatty acid side chains to native insulin, which stabilizes its self-association into hexamers and permits reversible insulin-albumin binding.¹⁶ The stabilization of insulin detemir into hexamers and reversible albumin binding allow insulin detemir to be formulated as a solute in a neutral liquid preparation that does not precipitate at any stage in the administration-

absorption process.⁷ Instead, when administered, insulin detemir aggregates into hexamers at the subcutaneous injection site and slowly dissociates into dimers and monomers, which are then absorbed into the bloodstream.⁴⁰ The absence of a crystalline or precipitate phase is believed to reduce intraindividual variability, as discussed below.⁷

The binding of insulin detemir to circulating albumin, via its fatty acid side chains, also delays its absorption into the circulation.^{41,42,43,44,45} Because insulin detemir is mostly albumin bound, its absorption rate is only slightly affected by variations in blood flow, limiting another source of variability.¹⁶ Once in the circulation, insulin detemir is 98% albumin bound, which also contributes to its protracted action.¹⁶ Binding of insulin glargine and other non-acylated insulin preparations to serum albumin is limited. Because of these mechanism of absorption and protraction, insulin detemir provides more constant and reliable basal insulin supply compared with NPH, and possibly other basal insulin preparations.^{10,25,46,47,48,49}

HOW CAN INSULIN VARIABILITY BE MINIMIZED?

Several steps can be taken to minimize insulin variability in patients with diabetes. Perhaps the most important method of minimizing insulin variability in patients using crystalline preparations is to adequately resuspend the preparation before administration. Proper use of insulin delivery devices can also help reduce insulin variability. For example, sufficient time (5 seconds) should be allowed before the needle is withdrawn⁵⁰, and the same anatomical site should be used at the same time each day.⁷

Using the most predictable insulin therapy can also minimize variability in insulin action. Several clinical trials have evaluated the variability of currently available insulin regimens, as summarized below.

VARIABILITY OF SHORT- AND RAPID-ACTING INSULIN THERAPIES

The primary advantages of rapid-acting insulin analogs compared with regular human insulin are their faster onset of action (which allows administration immediately before a meal and enhances their convenience) and their shorter duration of action (which reduces the risk of late hypoglycemia). Rapid-acting insulin analogs have also been shown to exhibit a more reproducible profile with less intraindividual variability than regular human insulin.⁵¹

VARIABILITY OF INTERMEDIATE- AND LONG-ACTING INSULIN THERAPIES

INSULIN GLARGINE

Insulin glargine, the first basal insulin analog, offers significant improvements over NPH, providing a relatively constant level of insulin and a longer duration of action. ² Insulin glargine has important clinical advantages, including a reduced incidence of hypoglycemia and greater convenience compared with NPH in patients with type 1 and type 2 diabetes. ^{52,53} In patients with type 1 diabetes, there is also evidence that insulin glargine provides greater improvements in fasting plasma glucose compared with NPH. ⁵⁴ Although some data suggest that interindividual variability is lower with insulin glargine than with NPH, other studies have reported no improvement in within-subject variability compared with NPH insulin. ⁵⁵ In addition, no improvement in the coefficient of variability of glargine compared with NPH insulin has been observed, even when injections are made under well-controlled conditions. ⁷

INSULIN DETEMIR

As noted earlier, glargine's ability to be injected without resuspension eliminates one of the sources of variability seen with NPH. ⁷ Because the absorption of insulin detemir does not depend on adequate resuspension or the dissolution of microprecipitates and exhibits a potential buffering effect from reversible albumin-binding, insulin detemir is able to provide more constant and consistent basal insulin coverage. Several studies of its pharmacokinetic and pharmacodynamic properties and trials of its long-term effects have confirmed this hypothesis. ^{10,11,56,57}

Insulin detemir has been shown to have a flatter, longer, and more predictable time-action profile than NPH insulin. ^{10,11} In a euglycemic glucose clamp study, insulin detemir was associated with significantly less within-subject variability than both NPH insulin and insulin glargine in patients with type 1 diabetes. ¹⁰ In another head-to-head study that compared the pharmacodynamic and pharmacokinetic properties of insulin detemir and insulin glargine in patients with type 2 diabetes day-to-day within-subject variability of self-measured fasting plasma glucose levels with insulin detemir compared with NPH insulin in patients with type 1 and type 2 diabetes (Table 3). ^{46,47,48,49,57,58,59,60,61,62} Another consistent finding in these studies was the reduced weight gain and risk of hypoglycemia with insulin detemir compared with NPH, despite a comparable improvement in

glycemic control.

Figure 2

Table 3: Within-patient variability of self-monitored pre-breakfast blood glucose levels.

Author, year	Standard Deviation (mmol/L) or Coefficient of Variation (%)		
	Detemir	NPH	P
Russell-Jones et al., 2004	2.8	3.6	<.001
Home, 2004*	3.0/2.9	3.5	<.001
Pieber et al., 2005*	2.5/2.6	3.1	<.001
Robertson et al., 2004†	3.3	4.3	<.001
Kolendorf et al., 2006‡	2.7	3.2	<.001
Haak et al., 2005§	1.3	1.4	.02
Hermansen et al., 2004¶	2.6	3.0	<.001
Raslova et al., 2004	1.2	1.5	<.001
Hermansen et al., 2006§§	0.9	0.9	NS**

From Home, 2006 ⁵⁸. Abstract data from Kolendorf, 2006 and Hermansen, 2006 have been updated based on published studies.

*Two detemir groups in the study.

†Study in children and adolescents.

‡Crossover study (other studies, parallel group).

§Type 2 diabetes (other studies, type 1 diabetes).

||Aspart with detemir, unmodified human insulin with NPH insulin.

¶Addition to oral glucose-lowering drugs (other studies, mealtime and basal regimens).

**Significant difference observed for standard deviation pre-supper blood glucose (1.4 vs 1.5 mmol/L; $P = .008$), and pooled pre-breakfast and pre-supper blood glucose (1.3 vs 1.4 mmol/L; $P < .001$).

WHAT ARE THE POTENTIAL CLINICAL BENEFITS OF REDUCED INSULIN VARIABILITY?

Insulin formulations associated with reduced variability provide several potential clinical benefits, including a more predictable time-action profile, a reduced risk of hypoglycemia, and greater convenience. ^{10,11,49,62} Because the opportunity for variable absorption is greater with basal insulin regimens, the use of long-acting insulin analogs may provide particular benefit. For example, insulin detemir has been shown to have a more predictable time-action profile, have a reduced risk of hypoglycemia, and cause less weight gain than NPH insulin. As noted above, it has been proposed that the reduced risk of hypoglycemia and weight gain with insulin detemir results from its more predictable time-action profile. ⁸

In a recent meta-analysis of 4 multinational, randomized, phase 3 trials of patients with type 1 diabetes treated with insulin detemir or NPH insulin, Heller and colleagues reported consistently lower mean coefficient of variation in self-measured FPG with insulin detemir (30.9% vs 33.6%; mean difference of 2.7%; $P = .001$). ³⁰ In addition, the incidence of hypoglycemia was reduced by 5.26 episodes per person per year for insulin detemir compared with NPH

($P = .033$). Of interest, the authors reported a clear positive correlation between the incidence of hypoglycemia and variation in fasting plasma glucose ($P < .0001$). This meta-analysis demonstrated that the reduction in within-subject variability of fasting plasma glucose accounts for about 53% of the reduced risk of hypoglycemia observed with insulin detemir compared with NPH insulin.^{8,30} Heller and colleagues concluded that a difference of 2.7% in the coefficient of variation results in approximately 3 fewer hypoglycemic episodes per year, a correlation that was independent of treatment.

Clinical trials have consistently reported that insulin detemir is associated with significantly less weight gain than NPH, and even insulin glargine.^{57,58,60,62,63} Although several hypotheses have been proposed to explain the reduced weight gain with insulin detemir, it is possible that the reduced within-subject variability of insulin detemir contributes to this beneficial effect.⁶⁴ Because variations in the duration of action or peak action of insulin likely increase the risk of hypoglycemia, patients may attempt “defensive eating” to avoid the possibility of hypoglycemia, which may result in weight gain. Therefore, it is possible that the improved predictability of the action of insulin detemir, which is associated with a reduced risk of hypoglycemia compared with NPH, also reduces the risk of weight gain.⁶⁴ The use of insulin detemir may also limit changes in appetite resulting from unnecessary fluxes in plasma insulin or glucose.¹⁶ Other mechanisms for the more favorable impact of insulin detemir on weight are being explored, such as increased insulin signaling in the brain, which can affect appetite, and the potential benefits of a more physiological insulin profile.^{65,66}

CONCLUSIONS

Because accumulating evidence suggests that limiting glycemic variability and long-term glucose instability may reduce the risk of diabetes complications^{9,67}, using more predictable insulin regimens may have additional clinical benefits. Perhaps most important, the lower day-to-day variation and more predictable glycemic responses may increase the confidence of clinicians and their patients in titrating insulin doses to achieve intensive glycemic control due to a reduced fear of hypoglycemia.⁶⁸ Insulin analogs provide effective therapy with greater predictability, and enhanced convenience, in addition to reduced risk of hypoglycemia. Together, these benefits may help improve glycemic control in today's patients, possibly by encouraging the earlier initiation of insulin therapy or more intensive

insulin titration in patients who are not at goal on insulin therapy. The development of even more predictable and convenient insulin formulations and easy-to-use and accurate delivery systems, as well as effective patient education, will continue to improve the care of patients with diabetes.

ACKNOWLEDGMENTS

The author would like to thank Nicole Cooper for writing and editorial assistance and Novo Nordisk for funding that helped support the preparation of this paper for publication.

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