EFFECTIVE USE OF INSULIN THERAPY IN TYPE 2 DIABETES*

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ABSTRACT

Type 2 diabetes is a progressive disease; an individual's ability to secrete insulin in increasing amounts to overcome insulin resistance progressively fails over time. As diabetes and beta cell failure progress, the increasing need for insulin becomes apparent. Thus, to improve metabolic outcomes and prevent complications, insulin must be used effectively and in a timely manner. The gold standard of insulin therapy today is to create physiologic insulin replacement with mealtime insulin spikes and continuous basal insulin replacement. Peak insulin concentration can vary by 39%, representing a significant intrasubject coefficient of variation.

The pharmaceutical industry has attempted to develop and produce more effective insulin formulations to meet varying patient needs. Efforts have been directed at developing both basal and premeal insulin analogs. Rapid-acting insulin analogs are superior premeal insulins. Several insulins can be used for basal replacement, including neutral protamine Hagedorn (NPH), lente, ultralente, and insulin glargine. There are also several premixed insulin formulations, including lispro/neutral protamine lispro, and regular/NPH; these premixed insulins are suitable only for type 2 diabetes. They are particularly valuable for patients who may have problems with mixing accuracy and compliance.

Patients must be educated early about the progressive nature of type 2 diabetes and the common requirement of insulin. The importance of glycemic control must be emphasized in order to avoid complications.


The first injection of insulin was given on January 11, 1922.1 By 1925, Macleod, one of the discoverers of insulin, and Campbell, who set up the first diabetes clinic, had perceived that the ideal treatment would involve an insulin substitute that could imitate natural insulin. They knew, even then, that continuous injection or “some method of delaying absorption” would be required.1 Could they have imagined continuous subcutaneous insulin infusion with insulin pump therapy to satisfy this need? Could they have imagined the development of insulin glargine? Perhaps not, but it is clear that they understood the physiologic needs of patients with diabetes and appreciated the deficiencies of the preparations they were using.

The gold standard today, much the same as Macleod and Campbell had proposed in 1925, is to create physiologic insulin replacement. We have learned that a healthy functioning pancreas can control glucose throughout the day and keep postprandial excursions to a minimum. We know that controlling hemoglobin A1c (HbA1c) can reduce the microvascular and macrovascular complications of type 2 diabetes mellitus. We also know that HbA1c is determined by both fasting and premeal glucose, as well as postpran-
dial values. Thus, insulin therapy must focus on physiologic replacement with mealtime insulin spikes and continuous basal insulin replacement.

Type 2 diabetes is a progressive disease. The United Kingdom Prospective Diabetes Study (UKPDS) has clearly demonstrated that diabetes worsens over time. The progression of the disease is not a function of worsening insulin resistance, but rather continuous beta cell failure. Insulin resistance and impaired glucose tolerance are established early in the sequence of metabolic events and are mostly driven by obesity. Indeed, what we have today in North America and other parts of the world is not only an epidemic of diabetes, but also an epidemic of insulin resistance resulting from a sedentary lifestyle and obesity. Type 2 diabetes is a progressive disease because a person’s ability to secrete insulin in increasing amounts to overcome insulin resistance progressively fails over time. As diabetes and beta cell failure progress, the increasing need for insulin becomes apparent. Thus, to improve metabolic outcomes and prevent complications, insulin must be used effectively and in a timely manner.

The UKPDS demonstrated that despite the therapy employed—insulin, sulfonylureas, or metformin—HbA1c progressively worsens over time. For type 2 diabetes to develop, both a decrease in insulin secretion and an increase in insulin resistance are required. If we wish to duplicate physiologic insulin secretion, we must stop thinking about the type of insulin previously used (e.g., fast-acting, short-acting, intermediate-acting, or long-acting), but rather focus on how to use it effectively. We should concentrate on replacing meal and basal insulin requirements.

There are 2 options for premeal insulin: rapid-acting insulin (analogs) and short-acting insulin (regular). Using regular insulin as a premeal insulin is inappropriate in the management of diabetes under most circumstances. Rapid-acting insulin analogs are superior premeal insulins. Several insulins can be used for basal replacement, including neutral protamine Hagedorn (NPH), lente, ultralente, and insulin glargine. The best basal insulin appears to be insulin glargine because it provides insulin in a manner that closely duplicates basal physiologic insulin secretion. There are also several premixed insulin formulations, including lispro/neutral protamine lispro (NPL), and regular/NPH; these premixed insulins are suitable only for type 2 diabetes. They are particularly valuable for patients who may have problems with mixing accuracy and compliance.

Physicians should review glucose clamp data for any new insulin preparation because these data provide a clear description of pharmacokinetics and biological action. Glucose clamp data document peak insulin concentrations, time to peak concentrations, area under the

| Table. Intrasubject Coefficient of Variation Observed During Glucose Clamp in 8 Normal Volunteers |
|-------------------------------|----------|
| Peak insulin concentration | 39.0     |
| Time to peak                 | 51.4     |
| Area under curve             | 44.1     |
| Total glucose infused        | 35.1     |

Data from Massey et al.

**Figure 1. Biological Action of Insulin Lispro vs Regular Insulin: Glucose Clamp Study in Healthy Subjects**

Data from Howey et al.
curve, and total glucose infused (biological action) when given to normal subjects. Euglycemia is maintained by infusing glucose. Massey et al injected NPH insulin (0.4 U/kg) in 8 normal volunteers using the euglycemic clamp (Table). It is interesting to note that peak insulin concentration can vary by 39%, representing a significant intrasubject coefficient of variation. Despite using the same person, environment, and injection site, peak insulin concentration varied by 39%, time to peak varied by 51%, and area under the curve varied by 44%. Most importantly, total glucose infused to maintain euglycemia, a measure of the biological action of that insulin, varied by 35%. It is a wonder that any of our patients have any semblance of control.

The pharmaceutical industry has long been aware of this deficiency and has responded by attempting to develop and produce more effective insulin formulations, referred to as insulin analogs. Efforts have been directed at developing both basal and premeal insulin analogs. Currently, 3 insulin analogs are clinically available. In 5 to 10 years, there will likely be an entire spectrum of insulin analogs.

**Premeal Insulin**

There are several advantages of rapid-acting insulin analogs. They modify the time-action of subcutaneous injected insulin, resulting in an insulin profile closely resembling the physiologic secretion of insulin by the beta cells of the pancreas. This insulin profile results in improved postprandial hyperglycemia, which has a significant impact on HbA1c levels and may reduce cardiovascular morbidity. If postprandial hyperglycemia and hypoglycemia are reduced, the need for between-meal snacks is reduced. This consideration is important in patients with type 2 diabetes. It is well known that insulin promotes weight gain; however, if between-meal snacks and caloric intake are reduced, patients may maintain their weight or even lose weight. When insulin is delivered in a physiologic manner, it is important to note that rapid-acting insulin analogs also reduce nocturnal hypoglycemia.

Glucose clamp studies in healthy subjects demonstrate the superiority of using insulin lispro rather than regular insulin before meals. Figure 1 demonstrates a significant shift in the amount of glucose required to control the response to an injection of insulin lispro compared with regular insulin. The peak biologic action and duration of insulin lispro closely duplicate physiologic insulin secretion in response to a meal.

Another major advantage of a rapid-acting premeal insulin analog is that it facilitates compliance with intensive diabetes management. The paradigm of empowering the patient to take responsibility for the

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**Figure 2. Direct Comparison of Insulin Lispro and Insulin Aspart**

A

![Graph A](image)

Plasma concentrations of free insulin in 13 patients with type 1 diabetes after a 10-U single subcutaneous injection of insulin lispro and insulin aspart at 7:30 AM immediately before breakfast. Values are means ± SEM. Adapted with permission from Hedman et al.

B

![Graph B](image)

Time from subcutaneous injection of 10 U of insulin lispro and insulin aspart from fasting levels to 50% of the peak free insulin concentration, peak concentration, and 50% decrease from peak concentration in 13 patients with type 1 diabetes. Values are means ± SEM. Adapted with permission from Hedman et al.
day-to-day management of diabetes is now well accepted. Consequently, it is important to give patients the necessary tools to make meaningful insulin dose adjustments for meals as well as for basal replacement. Thus, patients learn how to adjust their premeal-insulin doses in response to their premeal blood glucose levels and to the food (primarily carbohydrates) they will eat. If this approach is attempted with regular insulin, its peak action is delayed and its duration of action is lengthened, leading to inadequate postprandial glucose control and increased risk of hypoglycemia before the next meal. Using a rapid-acting premeal-insulin analog can avoid these problems. These analogs provide lifestyle flexibility—doses of insulin can be adjusted to suit individual nutrient choices.

In a direct comparison between the 2 meal-insulin analogs, insulin lispro and insulin aspart, there appears to be no clinically significant difference (Figure 2A). Upon further analysis, however, 50% of the peak value was reached faster with insulin lispro compared with insulin aspart (Figure 2B). The peak is reached earlier and declines faster with insulin lispro.

The impact of improving postprandial glucose control on HbA1c is illustrated in a study conducted by Bastyr et al. They examined the efficacy of combination therapy in patients whose glycemic levels were not adequately controlled with a sulfonylurea (glyburide). A total of 135 patients were randomly assigned for 3 months to 1 of 3 combination regimens with glyburide: insulin lispro plus glyburide, metformin plus glyburide, or bedtime NPH insulin plus glyburide. Not surprisingly, the highest fasting glucose value occurred with lispro plus glyburide in the morning (Figure 3). The addition of metformin improved the fasting glucose value; however, the best approach to reducing fasting glucose was achieved with bedtime NPH. It was also clear that the most effective way of reducing 2-hour postprandial glucose is to use something that specifically targets postprandial hyperglycemia. In this case, lispro was the best postprandial agent. The interesting and somewhat unexpected finding was seen in the HbA1c levels, which were lowered to the greatest extent when insulin lispro was added to glyburide in these patients (Figure 4). The message from these studies is that postprandial glucose contributes significantly to HbA1c, and both postprandial and fasting hyperglycemia should be targeted to achieve the best outcome.
**Basal Insulin**

The notion that NPH is a uniform basal insulin is incorrect. Either NPH or insulin glargine was injected into healthy subjects, and the biological actions were documented using the glucose clamp; each achieved different peaks. With NPH, the peak biological action occurred at about 6 to 7 hours and then declined in about 18 to 20 hours (Figure 5). There was no true basal action. Insulin glargine, on the other hand, reached a plateau of biologic action at 3 to 4 hours and then remained reasonably flat, consistent with the pattern seen in overnight physiologic insulin secretion.

Scholtz et al examined intrasubject variability with insulin glargine. In the majority of patients, there was very little variability with insulin glargine; however, there was significant variability in 2 patients. They concluded that compared with NPH or ultralente insulin, insulin glargine offered much less variability.

In a 28-week study conducted by Rosenstock et al, glargine was compared with NPH. The most significant difference was in the rate of nocturnal hypoglycemia (Figure 6). There was no major difference in either HbA1c or fasting glucose. It would appear that there was less nocturnal hypoglycemia in patients taking insulin glargine due to less variability in basal insulin replacement.

In one study of patients with type 2 diabetes, there was less nocturnal hypoglycemia and better postmeal glucose control with bedtime insulin glargine compared with bedtime NPH insulin (Figure 7). It is interesting to note that postmeal glucose excursions were improved when basal replacement was optimized. This study supports previous findings that glargine therapy is associated with a reduction in all hypoglycemic episodes, particularly nocturnal episodes. This is an important therapeutic advantage.

**Premixed Insulin**

Premixed insulins offer several advantages. They are convenient, provide accurate mixtures, and offer improved postprandial glucose control. Free mixing of insulin can be a difficult problem for the elderly, and errors in accuracy frequently occur. Using a premixed insulin containing a rapid-acting premeal-insulin analog offers rapid onset of action of insulin, thus allowing injection as close as 15 minutes before a meal. Thus, the rapid-acting formulation of premixed insulins is an important therapeutic advantage.
insulin promotes improved postprandial glucose control. With the lispro mixture (75 NPL/25 lispro), the separate responses to each component of the mix are maintained (Figure 8). Does premixed insulin actually change glycemic control and HbA1c level? Roach et al compared the insulin lispro mixture (75 NPL/25 lispro) and the human insulin combination (70 NPH/30 regular) in a randomized controlled trial. Postprandial glucose control improved with the lispro mix, but HbA1c did not improve, probably because the improvement in postprandial glucose control was accompanied by a reduction in hypoglycemia (Figure 9).

**EduCating Patients**

Patients must be educated early about the progressive nature of type 2 diabetes and the fact that insulin is commonly required. The importance of glycemic control must be emphasized, and physicians must do whatever it takes to avoid complications. Insulin should not be used as a threat. If patients understand that diabetes is a progressive disease with continued beta cell failure and that insulin can effectively control their glucose levels, they should not fear insulin therapy. Many patients think that insulin is “the end of the road.” This belief is not uncommon, particularly in certain minority populations in whom the only memory of insulin use is that a grandmother was fine until she started taking insulin. In such cases, insulin was likely introduced as a last resort to control glucose long after serious complications had developed.

It is important to review the new delivery systems, including pen therapy, and to point out that smaller more comfortable needles are now available. Physicians should use diabetes educators to provide instruction to patients. When patients begin insulin therapy, it should be explained that they have not met their glycemic targets and that glycemic control must be improved in order to avoid complications. Patients should be assured that they can continue to take their pills, but that the pills are not doing the job completely. Patients should begin with 1 injection of insulin at bedtime that can be done in the privacy of their homes. The single-dose regimen is very simple: 0.2 U/kg of body weight given as NPH or glargine. This regimen will target fasting glucose and, with appropriate adjustment in insulin dose, a satisfactory glycemic level can be achieved in the morning. The oral agent

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**Figure 7. Bedtime Insulin Glargine vs Bedtime NPH in Type 2 Diabetic Patients Taking Insulin Combination Therapy**

![Graph showing blood glucose levels over time for bedtime insulin glargine and NPH insulin groups.](image)

**Figure 8. Insulin Lispro Mixture: Pharmacodynamics**

![Graph showing pharmacodynamics of lispro and lispro mix.](image)

NPL = neutral protamine lispro.
Adapted with permission from Heise et al.11
will be sufficient to manage daytime glucose levels in approximately 40% to 50% of these patients. In the remainder of patients, a breakfast and dinner insulin should be selected, and bedtime insulin discontinued. The beta cell secretagogue can be discontinued, but metformin might be useful in reducing total daily insulin requirements. If satisfactory glycemic control is not achieved, more intensive insulin regimens should be considered. Using a rapid-acting insulin analog (lispro or aspart) with meals and a basal insulin (glargine) at bedtime provides an excellent insulin regimen.

**Summary**

Type 2 diabetes mellitus is a progressive disease with continued beta cell failure. Insulin therapy should be used early and effectively to achieve glycemic targets in order to avoid long-term complications.

**REFERENCES**