Effective use of insulin

A balancing act

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Preview

Day-to-day control of diabetes demands an ongoing balance of diet, exercise, and insulin dosage that can only be achieved with regular self blood glucose monitoring. Patients need to be familiar with factors that affect the action of insulin and to know that "less is sometimes more." In this article, Dr Bohannon explains the simple concepts that lead to the most effective use of insulin.

Modern diabetic management is based on self blood glucose monitoring, the results of which guide the patient in using insulin effectively. Proper education of the patient by the physician, dietitian, and nurse educator is essential to this end. The necessary instruction includes (1) the influence of diet and exercise on insulin needs, (2) the peak and duration of insulin action, (3) timing of insulin injections, and (4) proper adjustment of insulin dosage.

Types of insulin

The insulins primarily used for diabetes are the human insulins, because they do not stimulate antibody production. Insulin antibodies, which develop within about 2 weeks of using an animal insulin, are not desirable because they change the time of insulin action. They also bind human insulin.

Traditional charts giving the duration of insulin action are not accurate for human insulin. NPH and lente animal insulins acted for 22, 24, or 26 hours because they stimulated the production of antibodies, which then bound to the insulins and prolonged their action. With antibodies present, an insulin that should have a duration of action of 10 to 14 hours may have a duration of 24 hours or more. The length of action of human insulin in a person without antibodies is much shorter. If a person has never been exposed to animal insulin, the action of regular human insulin now available peaks at 1 to 2 hours and lasts about 6 hours.

Goals of conventional and intensive therapy

Insulin can be used effectively in either conventional or intensive management. For a young, healthy person with diabetes, conventional management (ie, two injections a day of a mixture of regular and NPH insulin, given before breakfast and dinner) aims for blood glucose levels of 70 to 130 mg/dL before meals and levels of less than 180 mg/dL at 1 to 2 hours after meals (remember that 180 mg/ dl is the upper limit for good white cell function and wound healing). This goal should be accomplished without nocturnal hypoglycemia. In older patients, blood glucose levels with conventional therapy may be somewhat higher.

With intensive management, the goal is a blood glucose level of 70 to 90 mg/dL before breakfast, 70 to 105 mg/dL before other meals, less than 160 mg/dL at 1 hour after meals, and less than 120 mg/dL at 2 hours after meals.

For a pregnant patient with either preexisting or gestational diabetes, fasting and premeal blood glucose values definitely should be less than 90 mg/ dl, and those at 1 to 2 hours after meals should be less than 130 mg/dL. The pregnant patient cannot achieve this degree of control if she injects a large

amount of regular insulin, eats breakfast, and then waits 4 to 5 hours before eating again at lunch; if she has a 1-hour postprandial blood glucose level of 120 mg/dL, she is likely to become hypoglycemic before she eats again. Obviously, she has to snack between meals to maintain blood glucose levels in a normal range.

Timing of insulin injections

Some patients who have had diabetes for as long as 20 years have never been told to take their regular insulin at least ½ hour before a meal. The rationale for this basic recommendation lies in the physiology of insulin, which is normally secreted by the pancreas in two phases. The first phase is a quick spurt of stored insulin, which is immediately released when the blood glucose level rises. The amount released is small but extremely important in controlling postprandial blood glucose levels. Early insulinization is important in priming the tissues to take up glucose.

The second phase of insulin release occurs over a period of 20 minutes or longer and is a result of synthesis of new insulin molecules.

At least 30 minutes is needed for regular insulin to be taken up into the circulation from subcutaneous tissues. If the patient smokes, the rate of uptake can be decreased by as much as 15%. Erratic uptake can also result from fibrosis or fat atrophy or hypertrophy at the injection site. Vigorous exercise of muscles underlying the injection site can speed insulin absorption, as can heat from, for example, a heating pad or a hot tub. Because of these variables, most adults should inject regular insulin 30 to 45 minutes before a meal to maximize control of postprandial blood glucose values. The effect of timing on these values is shown in figure 1.

Managing acute hyperglycemia

Some patients awake with a high blood glucose level, indicating that they are underinsulinized in the basal state. If they take insulin immediately before eating, their postprandial glucose levels show an extreme rise (figure 2); they did not have enough insulin for their fasting state, and they do not have enough to control a postprandial rise. Patients therefore should not eat when glucose levels before meals are above 150 mg/dL.

Some patients take extra insulin when they have a high fasting blood glucose level. This is not wrong; we teach patients how to supplement their insulin intake at such times. For an average sized adult, a typical recommendation might be 1 extra unit of insulin for every 30 mg/dL of glucose above 120 mg/dL, but no more than 3 extra units at one time. Thus, if the fasting blood glucose value is 150 mg/dL, the patient should take 1 extra unit of regular insulin, but not immediately before eating, which, unfortunately, is what many patients do. Taking more insulin does not make it work faster. When patients eat immediately, glucose levels still go sky-high after the meal because the insulin has not yet taken effect; when the extra insulin finally kicks in later, glucose levels fall.

If patients see that glucose levels are too high after meals, they may repeatedly increase the amount of insulin taken immediately before a meal; the effect of this is that glucose levels are still high after the meal, but hypoglycemia occurs later because of excessive insulin. The extra insulin does not work fast enough to prevent high glucose levels but leads to hypoglycemia when it finally does work.

Subsequently, patients may have rebound hyperglycemia because counterregulatory hormones (epinephrine, glucagon, cortisol, growth hormone) are released in response to hypoglycemia. If they then take as much supplementary insulin for the rebound hyperglycemia as they would for a similar blood glucose level caused by overeating, they are at great risk for another hypoglycemic episode.

Hyperglycemia due to rebound release of counterregulatory hormones does not require as much supplementary insulin to control as hyperglycemia due to other causes. Even if no supplementary insulin is given, the blood glucose level usually stabilizes in a more usual range after 8 to 12 hours. A person

with diabetes is at greatly increased risk (50%) for a second hypoglycemic episode within 24 hours after the first, so supplementation of insulin should be kept conservative for at least 24 to 48 hours.

The preceding scenarios may be responsible for a lot of "brittle diabetes." The problem is that too much insulin is being taken at the wrong time.

When regular insulin is taken ½ hour before eating, it starts to be absorbed and have some action when the person eats, even if the blood glucose level is high. But, if the premeal glucose level is high, insulin should be taken even earlie1; and the patient should wait until the level is starting to decrease before eating; the balance between insulin action and food absorption is then much better.

My routine advice is as follows: If the blood glucose value is over 150 mg/dL before a meal, insulin should be taken and the meal postponed until the blood glucose is below 150 mg/dL. The glucose level should be checked hourly until it is below 200 mg/dL and glucose levels to become acceptable, the patient can consume large amounts of raw lettuce, celery, cucumbers, jicama, and similar foods (with or without a vinegar dressing); gelatin, sodas, and Popsicles (all sugar-free); dill pickles; and other "free foods."

Correction of fasting hyperglycemia

Diet, activity, and insulin amounts have to be balanced. A regimen of regular plus NPH insulin before breakfast and again at dinner has been standard for a long time, but that may not be the best schedule for all diabetic patients who require insulin. Many patients routinely wake up with high fasting blood glucose levels because NPH insulin taken before dinner does not last through the night. The peak effect of intermediate-acting insulin (NPH or lente) given at 5 to 7 PM is often between midnight and 2 AM, which is the blood glucose nadir for most people (ie, when they are most sensitive to insulin and most prone to hypoglycemia). If, however, a patient takes NPH or lente insulin at 10 to 11 PM, he or she is less likely to be hypoglycemic at 2 to 3 AM because of the later peak insulin effect and partial protection by the dawn, or sunrise, phenomenon (insulin resistance that occurs between 3 and 8 AM). The bedtime dose of insulin should be sufficient to offset the phenomenon and promote a lower, more normal fasting blood glucose level.

If insulin taken before dinner is peaking in action between midnight and 2 AM but the fasting blood glucose level is high, it is tempting to keep increasing the amount of predinner NPH insulin; however, that can eventually lead to hypoglycemia in the middle of the night. Despite this, NPH insulin action usually does not last until morning, and taking more insulin does not make the action last much longer. Fasting hyperglycemia occurs in many cases when the patient or physician gives up and accepts a fasting glucose level of 150 mg/dL or higher because an increased amount of NPH or lente insulin before dinner leads to nocturnal hypoglycemia.

Dr Lois Jovanovic-Peterson, senior scientist at Sansum Medical Research Foundation, Santa Barbara, California, has a motto: "Fix the fasting first." The fasting blood glucose level should always be corrected first, regardless of whether the patient has insulin-dependent (type I), non-insulin-dependent (type II), or gestational diabetes. Often, as noted, insulin action is insufficient around the time of awakening in the morning because NPH or lente insulin was given too early the evening before. To correct this situation, only regular insulin is given before dinner to manage postprandial glycemia, and then NPH or lente is given at bedtime. The insulin taken at 10 or 11 PM peaks in action not between midnight and 2 AM but between 3 and 7 AM, which is when it is needed to control the dawn phenomenon. Growth hormone (which is probably the most important counterregulatory hormone) and cortisol are maximally secreted between 3 and 7 AM. These hormones cause relative insulin resistance, and even nondiabetic persons need secretion of more insulin between 3 and 7 AM than between midnight and 2 AM.

I prefer giving lente insulin at bedtime because (1) it has less of a peak action, so there is a smaller chance of

hypoglycemia, and (2) it has a little longer duration of action, so it may be helpful through breakfast and may even allow patients to sleep later on weekends while still controlling fasting glucose levels until midmorning. If the fasting blood glucose level is 80 mg/dL, the glucose level during the rest of the day is easier to control. The Somogyi effect (middle-of-the-night hypoglycemia leading to rebound hyperglycemia in response to counterregulatory hormones) is talked about more often than it actually occurs. To check for it, the patient should set the alarm for 2 to 3 AM and test the blood glucose level at that time.

Alternative insulin regimens

Other common insulin regimens include (1) regular insulin given three times a day before meals, with NPH or lente at bedtime, and (2) human ultralente insulin given as basal insulin, with regular insulin before meals. Animal ultralente lasts about 36 hours, but some preparations have been withdrawn from the market in the United States. Human ultralente insulin lasts about 22 hours and has its maximum effect (not really a peak) at about 11 hours. This is convenient for some patients (eg, thin patients with type II diabetes) who need a little background insulin throughout the day.

In patients with type II diabetes whose condition is not well controlled by oral hypoglycemic agents alone and who have fasting hyperglycemia, it does not make sense to add NPH or lente insulin to the regimen if it is given only in the morning. An intermediate-acting insulin given in the morning does not peak until afternoon. If the fasting blood glucose level is too high, insulin should be given at bedtime to control the glucose level the next morning. When fasting blood glucose levels are reliably less than 120 mg/dL, oral agents have a much better chance of working to stimulate endogenous insulin secretion, because the glucotoxicity effect (ie, suppression of first-phase insulin secretion by hyperglycemia [blood glucose >115 mg/dL]) on the beta cell is decreased. This regimen of bedtime insulin and daytime sulfonylurea is termed BIDS therapy.

When controlling fasting blood glucose levels by using insulin at bedtime, there is much less concern about inducing hypoglycemia than when using insulin during the day. Remember, as stated earlier, diet, exercise, and insulin amounts must balance. At bedtime, the only real variable is insulin dosage. No food is consumed during the night, and no bedtime snack is eaten unless regular insulin is given to cover the snack. Exercise during the night is virtually zero. It is thus very easy to determine the correct dose of insulin at bedtime by starting with a small dose (5 to 10 U of NPH or lente insulin in an average-sized adult) and slowly increasing the amount by 1 or 2 U every one to three nights, depending on fasting blood glucose values; the amount is increased more slowly as the desired fasting value of 70 to 120 mg/dL is approached. Checking glucose levels between 2 and 3 AM helps to reassure both patient and physician regarding nocturnal hypoglycemia during the adjustment period.

Summary

The effective use of insulin requires familiarity with how the hormone acts as well as appreciation of such modifying factors as insulin antibodies, exercise, and smoking. Optimal insulin use is facilitated by knowledge of the dawn phenomenon, which causes insulin resistance in early morning hours. Rebound hyperglycemia should be treated much more conservatively than comparable hyperglycemia due to other causes because of the greater likelihood of recurrent hypoglycemia. Diet, exercise, and insulin dosage must be balanced in order to attain good diabetes control, and this balance is possible only when it is guided by regular self blood glucose monitoring.

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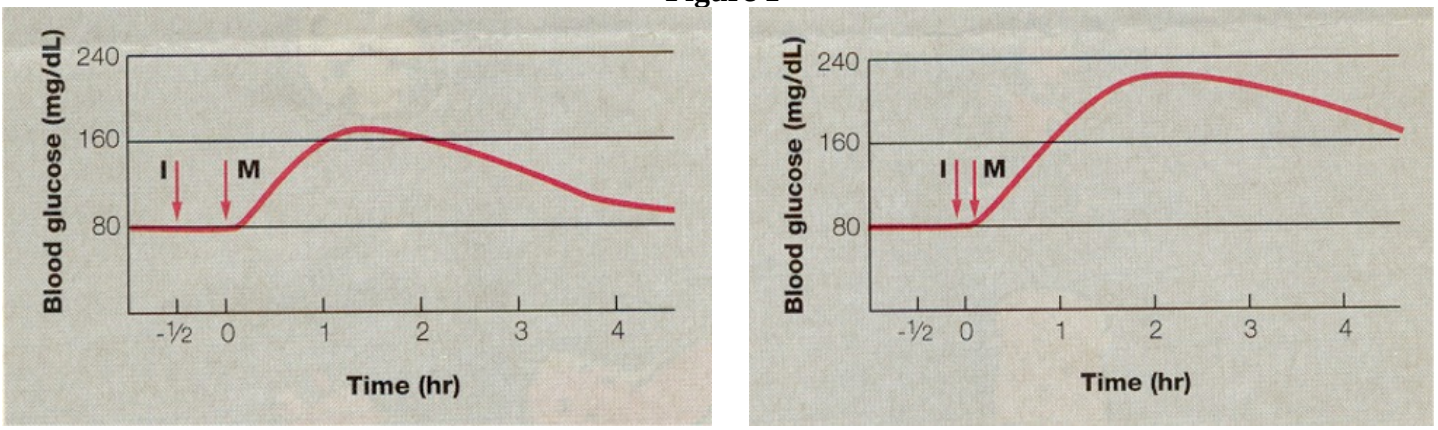
Figure 1



a. **b.**

Figure 1. Effect on blood glucose values of timing of prebreakfast regular insulin injection. **a.** Patient awakes with satisfactory blood glucose level, injects proper amount of insulin 1/2 hour before breakfast, eats appropriately, and has acceptable postprandial blood glucose level. By lunchtime, glucose levels are below 100 mg/dL. **b.** Patient awakes with identical blood glucose level, takes same amount of insulin immediately before breakfast, and eats identical meal. As a result of taking insulin too soon before meal, postprandial blood glucose levels rise too high, decrease too slowly, and remain unacceptably high at lunchtime. In these circumstances, patient may conclude that more insulin is needed before breakfast, when actually it should be taken earlier. I, insulin injection; M, meal.

Figure 2

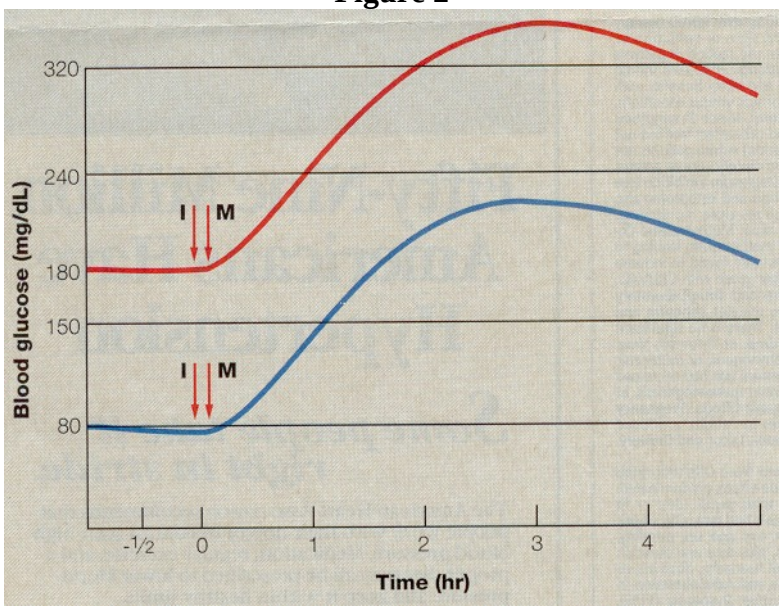


Figure 2. Acute hyperglycemia (red line) in patient with high fasting blood glucose level who took insulin immediately before breakfast. Patients should not eat when fasting blood glucose level is over 150 mg/dL (see text). Blue line shows hyperglycemia in patient with acceptable fasting blood glucose level who also took insulin too close to breakfast. I, insulin injection; M, meal.

BONUS ARTICLE – MANAGING HYPOGLYCEMIA: HOLD THE CHOCOLATE AND ICE CREAM

It is clear that, in general, the longer a patient has diabetes, the less obvious are the symptoms and signs of hypoglycemia. Patients who have had diabetes for 10 years or more may have quite different manifestations of hypoglycemia than they had at disease onset. Sweating, tachycardia, and tremulousness may decrease or disappear, and numbness or tingling (especially around the mouth), yawning, heaviness in the legs, or other subtle changes may become primary symptoms.

Patients should check their blood glucose level whenever signs or symptoms of hypoglycemia appear. They should also check the level immediately before driving or undertaking any other potentially dangerous activity that requires mental alertness or motor coordination. If the level is below 70 mg/dL and they are symptomatic (or below 60 mg/dL even if asymptomatic), they should consume 10 to 15 g of fast-acting carbohydrate, such as 4 oz of fruit juice, 6 or 7 pieces of hard candy (not sugar-free), 1 cup of milk, ½ cup of regular soda (not sugar-free), 5 small sugar cubes, or glucose tablets equivalent to 10 to 15 g of sugar. Glucose tablets are available commercially in various flavors and sizes.

If patients plan to drive or engage in other activity requiring alert coordination for more than 15 minutes, they should also have a glass of milk, a piece of bread, or a similar longer-lasting carbohydrate. The blood glucose level should be retested every 15 minutes until it stabilizes at normal or until the next meal is eaten.

Hypoglycemia should not be treated with chocolate or ice cream. The large fat content of these foods slows the absorption of the sugar so that the blood glucose level does not rise as rapidly, putting the patient in danger of more prolonged hypoglycemia. When the sugar finally is absorbed, the patient may have profound and prolonged hyperglycemia for a number of reasons. The patient may panic because of the slow absorption of sugar and longer period of hypoglycemia and keep eating more of the chocolate or ice cream in an effort to bring the glucose level up, thereby greatly overfeeding the reaction and leading to hyperglycemia from overconsumption of calories and carbohydrate. Also, because the blood glucose level is lower longer and may continue to fall before significant absorption of sugar takes place, the risk of stimulating counterregulatory hormones and rebound hyperglycemia is greater.

Unfortunately, many patients look forward to mild hypoglycemic reactions and use them as a "legitimate" excuse to eat chocolate or ice cream, not realizing that these are inappropriate. Patients need to be educated to eat "pure sugar," which will help raise the blood glucose level faster and also decrease the caloric load they ingest as a result of a hypoglycemic episode.

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