Advances in Insulin Therapy—Physiological Replacement with Insulin Analogs

a report by
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Since its discovery in 1921, insulin-replacement options have evolved substantially and now provide us with more physiological, more flexible, and safer alternatives to normalize glycemia and prevent diabetes-related morbidity and mortality. For patients with type 1 diabetes, insulin replacement is the only viable option for both glycemic control and survival. For those with type 2 diabetes, on the other hand, insulin therapy is an effective alternative when lifestyle intervention and oral antiglycemic therapies are not sufficient to maintain normoglycemia.[1] The newer insulin analogs, simplified insulin adjustment algorithms, and more user-friendly delivery devices have substantially facilitated the introduction of insulin in the management of type 2 diabetes.[2] The recent consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend considering insulin therapy early in the management of type 2 diabetes (as early as second-line therapy), based on its superior effectiveness, relative safety, and lower expense.[1]

All insulin currently manufactured for therapeutic purposes in the US is made through recombinant DNA technology. Alterations to the basic human insulin molecule are made to alter its absorption profile but not affect its effect on the insulin receptor once the insulin reaches its target cell.[2] This can be achieved by varying the amount of zinc or protamine in the insulin preparations, or by changing some of the amino acid sequences on sites of the insulin molecule that determine its pre-disposition to form hexamers. Rapid-acting insulin preparations are used to replace meal-related needs (prandial insulin replacement) and to correct hyperglycemia (corrective insulin replacement), while intermediate and long-acting insulin formulations are administered to keep blood glucose levels stable in between meals and overnight (basal insulin replacement). The rapid-acting insulin analogs (lispro, aspart, and glulisine) are absorbed more rapidly and have an earlier and higher insulin peak concentration and a shorter duration of action than their non-analog counterpart, soluble human insulin or regular insulin (refer to individual product package inserts). The more physiological absorption profile of rapid-acting insulin analogs should translate into greater patient adherence to proper timing of insulin to mealtimes, as well as fewer post-prandial glycemic excursions (within two hours of the meal) and a lower risk of late-prandial hypoglycemia (four to six hours after the meal).[3] On the other hand, basal insulin analogs (glargine and detemir) tend to be absorbed more slowly and consistently than their non-analog counterpart (NPH insulin), resulting in a longer duration of action and a flatter absorption profile,[4] possibly translating into better 24-hour basal insulin coverage and less risk of hypoglycemia, especially nocturnal hypoglycemia when basal insulin is administered at bedtime.[5,6] Although insulin analogs are increasingly preferred over their non-analog counterparts because of their more physiological absorption and action profile, cost may force the use of regular and NPH insulin in certain circumstances (for updated information visit www.drugstore.com).

Whereas individuals with type 1 diabetes are dependent on both basal and prandial insulin replacement to optimize glycemic control, in patients with type 2 diabetes insulin therapy is often implemented in a stepwise approach. The current paradigm for initiating insulin therapy in the patient with type 2 diabetes with elevated A_{1c} is to start with 10–20 units of basal insulin, usually at night, and gradually adjust the dose based on the morning blood glucose levels and goal.[2] Alternatively, instructing patients to test their blood glucose both fasting and one to two hours after their largest meal may reveal the source of glycemic burden (either fasting or post-prandial) and help better target insulin replacement therapy. Patients who are started on basal insulin can be empowered to make their own insulin dose adjustments if provided with simplified titration algorithms under their physician's supervision.[7] Properly applied insulin adjustment algorithms usually result in adequate basal insulin replacement (0.4–0.8 units/kg/day) within three to four months, as reflected by fasting blood glucose levels less than 130mg/dl and an A_{1c} under 7%. For patients on adequate basal insulin replacement, introduction of a rapid-acting insulin preparation should be considered if post-prandial glycemic targets are not being achieved (blood glucose <180mg/dl). This can be achieved by switching to a pre-mixed insulin preparation (human 70/30, lispro mix 75/25 or 50/50, aspart mix 70/30) or by adding a rapid-acting insulin before one or more meals. Although pre-mixed insulin preparations are usually dosed twice daily, they can also be started once daily before the culprit meal. As with basal insulin titration, pre-mixed insulin doses can be adjusted with simple algorithms based on fasting and pre-dinner blood glucose levels and goals.[8] If needed, adding a third injection of pre-mixed insulin before lunch may provide additional lowering of the pre-dinner blood glucose values. For subjects who might eventually make a transition to full

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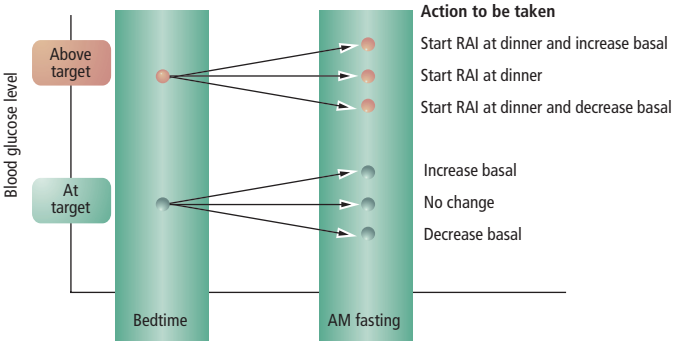
basal/prandial (or basal-bolus) insulin replacement, continuing the basal insulin preparation and adding one or more pre-prandial injections of rapid-acting insulin would make better clinical sense. One simple strategy to achieve this could be to start a dose of rapid-acting insulin representing 10% of the current basal dose prior to the culprit meal.[9] Blood glucose levels at bedtime and fasting can then be used to gradually adjust the doses of prandial and basal insulin, respectively (see *Figure 1*).

An increasing number of patients with long-standing type 2 diabetes may require full basal/prandial insulin replacement (basal insulin replacement plus rapid-acting insulin before every meal) to optimize blood glucose control and reduce the long-term risk of vascular complications associated with hyperglycemia. When switching patients to basal/prandial insulin therapy, the total daily insulin dose is usually redistributed into 50% basal insulin and 10–20% as fixed prandial doses before each meal.[10] For more sophisticated patients who are able and willing to learn how to estimate carbohydrate intake, an individualized insulin-to-carbohydrate ratio might provide greater flexibility and less weight gain.[11] A simple weight-based formula that can be used to derive basal and prandial insulin doses is the Miami 4/12 rule. Basically, divide the patient's weight in kilograms by four to estimate the basal insulin requirement and by 12 to calculate the fixed prandial insulin dose. The final step to proper basal-bolus insulin replacement is to set pre-prandial blood glucose targets and provide the patient with instructions to correct hyperglycemia (corrective insulin replacement). Dividing 1,700 by the patient's current total daily dose of insulin should yield a number that estimates the expected fall in blood glucose (in mg/dl) per one unit of injected rapid-acting insulin.[12] For example, a patient on 68 units of insulin a day would be given a corrective (supplemental) scale that adds one unit of rapid-acting insulin for every 25mg/dl that the pre-prandial blood glucose is above target (1,700÷68=25). Once basal/prandial insulin therapy is initiated, the treating physician should periodically review the patient's blood glucose profile (as reflected from the self-monitoring blood glucose log) to make the appropriate adjustments to the basal and prandial insulin components of the therapy. The fasting blood glucose value will continue to be used to make adjustments to the basal insulin component. The blood glucose levels before lunch, before dinner, and at bedtime can be used to adjust the morning, noon, and dinner prandial doses, respectively.

The same basal-bolus concepts used for outpatient management of insulin-requiring diabetes can effectively be implemented in the hospital setting. While basal and corrective insulin doses can usually be continued regardless of the patient's per os (PO) status, prandial insulin doses are held when the patient is fasting and reinstituted with regular food intake. Rapid-acting insulin analogs may even be dosed and administered within 20 minutes of starting the meal in patients who may have erratic or unpredictable PO intake due to loss of appetite, nausea or vomiting, or post-prandial bloating.[13] Glycemic goals for the hospitalized patient suggested by the American College of Endocrinology/American Association of Clinical Endocrinologists call for pre-prandial and fasting blood glucose level of ≤110mg/dl with maximum glucose levels of 180mg/dl in the non-critical setting and values of ≤110mg/dl in the critical care unit.[14,15] Although there exists ample evidence supporting tight control in the critical care setting, the recommendations for the non-critical patient are based mostly on expert opinion.[16-20] Nutritional coverage with insulin therapy will need to be adjusted to specific situations. For example, regular insulin may be placed in the hyper-alimentation bag to cover the daily dextrose content, usually using a ratio of one unit of insulin per 10–15g dextrose. Subjects receiving enteral alimentation through tube feedings can receive insulin therapy that matches the quantity and timing of the carbohydrate delivery, usually using a ratio of one unit of insulin for every 5–10g of carbohydrate received. For example, a patient receiving Deliver 2.0 enteral feeds (Novartis) at 40cc/hour would be receiving 8g carbohydrates/hour or 32g every four hours (Deliver 2.0 contains 0.2g carbohydrate for every 1cc of formula). Accordingly, three to six units of a rapid-acting insulin analog can be administered every four hours to match the carbohydrate load from the enteral feeds.[21] Prandial/nutritional insulin doses would then be adjusted based on glycemic response.

Insulin analogs currently provide a number of effective choices for physiological insulin replacement. Matching individual patient needs to appropriate insulin replacement strategies represents a safe and flexible alternative to optimize glycemic control in both the hospital and outpatient clinical settings. ■

Figure 1: Treatment Options in Subjects on Basal Insulin



If blood glucose levels are above target at bedtime, consider adding rapid-acting insulin at dinner. Use the change in blood glucose levels between bedtime and the next morning to adjust insulin dose.

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