VIEWPOINT

Human Insulin for Type 2 Diabetes
An Effective, Less-Expensive Option

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Affordability of insulin has become a major issue for patients with diabetes in the United States.[1] The price of insulin, particularly insulin analogues, has increased substantially over the past 2 decades.[1] Pharmacy prices for 1 vial of glargine or detemir (long-acting insulin analogues) or 1 vial of lispro or aspart (short-acting insulin analogues) now exceed $170 (**Table**). Prefilled pen injectors are even more expensive. Insurance may cover some of the cost, but the burden is increasingly shifting to patients in the form of higher premiums and copayments. As a result, insulin analogues are not feasible for many uninsured or underinsured patients.

Synthetic human insulin, once the mainstay of treatment, is much less expensive but is now prescribed less frequently.[2] A vial of neutral protamine Hagedorn (NPH), human regular (R) insulin, premixed 70/30 NPH, or regular (Novolin R, N, or 70/30) insulin can be obtained for as little as $25, approximately one-tenth of the list price of analogues. Although strategies for using human insulins were well understood 20 years ago, most training programs no longer emphasize the use of these agents. The advantages of insulin analogues over human insulins are less clear for type 2 diabetes than for type 1 diabetes. For patients with type 2 diabetes, insulin analogues do not improve glycemic control or reduce the risk of severe hypoglycemia compared with human insulin, but long-acting insulin analogues modestly reduce the risk of overall and nocturnal hypoglycemia.[3,4] In addition, insulin doses for type 2 diabetes, and thus costs, are generally higher. When used skillfully, human N, human R, and premixed human insulin formulas can be very effective for glycemic control in type 2 diabetes. This Viewpoint provides recommendations for the use of human insulin in this setting.

How Treatment With Human Insulins Differs

Some differing properties of human N insulin and human R insulin, compared with those of insulin analogues, require modest but important differences in therapeutic approaches (Table).

Duration of Action. The action of human N insulin does not reliably cover 24 hours so more than 1 daily injection is often required (Table). In contrast, the long-acting analogues have relatively constant plasma insulin levels and durations of action approaching or beyond 24 hours at doses common in type 2 diabetes (30-60 U/d).[5]

Hypoglycemia Risk. Among patients with type 2 diabetes, long-acting insulin analogues modestly reduce the rate of nocturnal hypoglycemia compared with human N insulin.[4] To limit the risk of hypoglycemia with human insulin, patient education, strategic snacking (eg, bedtime), self-measured plasma glucose targets, and when appropriate, less-aggressive hemoglobin A_{1c} (HbA_{1c}) targets may be advisable.

Timing With Meals. Human R insulin begins to act no sooner than 30 minutes after injection, while rapid-acting insulin analogues (lispro, aspart, and glulisine) have a shorter onset of action of 5 to 15 minutes. Based on these differences, human R insulin is typically injected 30 minutes before meals, whereas insulin analogues are injected right before meals. While this is common practice, one trial suggests that human R insulin can be injected immediately before meals without appreciable differences in glycemic control or hypoglycemia.[6]

Vial vs Pen. Insulin can be injected with a syringe (filled from a vial) or a pen. Prefilled pens are more convenient than syringes and may be more accurate when small doses of insulin are used or when patients have problems with dexterity or vision. However, the least-expensive human insulin products (ReliOn) are not available as prefilled pens and no human R product is available in a pen in the United States.

Injection Techniques. Human N insulin is a cloudy particulate suspension. To avoid inconsistent effects, it must be gently agitated before drawing into a syringe for injection. Absorption of human R insulin is fastest when injected from abdominal sites, followed by the upper arm and thigh; whereas absorption kinetics of rapid-acting insulin analogues seem less site dependent.[7]

Starting Human Insulin. Patients must be involved in the decision to start insulin and in the selection of the type of insulin to be used. The patient's cognitive and physical capacity, motivation, daily routines (including the timing and consistency of meals), and preferences about treatment are critically important in choosing an insulin regimen, whether human or analogue, that will fit each patient's individual context. Cost has to be considered (Table) because even the best plan cannot be realized if the patient cannot afford the treatment.

The purpose of bedtime basal insulin is to suppress overnight hepatic glucose production. The starting dose of bedtime human N insulin is typically 10 U (or 0.2 U/kg of body weight). The dose can be titrated up by 2 U every week (or 2 ×/wk if desired) until target fasting plasma glucose levels are achieved. When fasting target levels are achieved but glycemic control remains suboptimal at other times, advancing to a 2-injection regimen of human N insulin (at bedtime and before breakfast) can be considered. When a mealtime injection of human R insulin is added, 6 U injected into the abdomen is usually an appropriate starting dose.

Premixed 70/30 human insulin (70% N insulin with 30% R insulin) can be used as a 2-injection regimen, taken before breakfast and dinner. Although this regimen is simple, it is limited by higher risk of hypoglyce-

Table. Characteristics of Selected Synthetic Human Insulin and Analogue Insulin Products

	Time of Action					Price, $[a]	
	Onset	Peak	Duration	Use	Trade Name	per Vial	per Carton
Synthetic human insulin							
NPH (N)	2-4 h	4-10 h	12-18 h	Once at bedtime or twice daily	Novolin N Humulin N	25 100	NA 288
Regular (R)	30-60 min	2-3 h	8-10 h	0-30 min before meals	Novolin R Humulin R	25 100	NA NA
Premixed 70/30 N/R	30-60 min	2-6 h	12-18 h	Before breakfast and dinner	Novolin 70/30 Humulin 70/30	25 100	NA 288
Insulin analogues							
Degludec	1 h	No peak	>40 h	Once daily	Tresiba	NA	390-452
Detemir	3-4 h	3-9 h	6-24 h	Once or twice daily	Levemir	221-284	330-409
Glargine	2-6 h	No peak	20-24 h	Once or twice daily	Lantus Toujeo Basaglar	178 NA NA	266 275-347[b] 332
Aspart	5-15 min	30-90 min	4-6 h	0-15 min before meals	Novolog	210-290	403-538
Glulisine	5-15 min	30-90 min	4-6 h	0-15 min before meals	Apidra	185	400
Lispro	5-15 min	30-90 min	4-6 h	0-15 min before meals	Humalog	174	322
Premixed	5-15 min	2-4 h	14-24 h	0-15 min before breakfast and dinner	Novolog 70/30 Humalog 75/25 Humalog 50/50	218-300 179 179	403-538 322 322

Abbreviations: NA, not applicable; NPH, neutral protamine Hagedorn.

[a] Approximate prices are based on goodrx.com, which searches for the lowest local pharmacy prices (accessed June 7, 2017). Insurance co-pays are typically less. Prices may vary based on eligibility requirements so ranges are presented for some drugs. One vial contains 10 mL of insulin (1000 U). One carton contains five 3-mL pens of insulin (1500 U).

[b] Three 1.5-mL pens of 300 U per mL (1350 U).

mia in midday and near midnight, the times of its peaks of action. For patients with HbA_{1c} greater than 9% of total hemoglobin, this dose can be started (0.3 U/kg per day) in approximately equal doses before breakfast and dinner. With this approach, patients can typically attain HbA_{1c} levels in the 7.0% to 8.0% range before hypoglycemia limits further titration. The tendency to cause hypoglycemia is the main drawback of this approach, but overall glycemic control and risk of hypoglycemia do not greatly differ between human and analogue premixed insulins.[8]

Switching to Human Insulin

Patients can safely switch from insulin analogues to human insulins. Total daily insulin dose can be initially reduced by 20%, because of the different profiles of action and because some patients may have been taking less analogue insulin than had been prescribed.

For patients already treated with multiple insulin analogue injections, the number of injections and distribution of dosage can remain the same but with a 20% reduction of dosage for safety. Early contact between the physician and the patient by phone or in person is desirable to ensure that an unexpectedly large reduction of glucose has not occurred due to improved adherence.

In summary, many patients with type 2 diabetes can be treated with human insulin. Due to high costs of analogue insulins, use of human insulin may be the only practical option for some patients, and clinicians should be familiar with its use.

ARTICLE INFORMATION

Published Online: June 12, 2017. doi:10.1001/jama.2017.6939

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lipska reports receipt of a grant from the National Institutes of Health and working under contract to the Centers of Medicare & Medicaid Services. Dr Hirsch reports receipt of honoraria for consultancies with Abbott Diabetes Care, Roche, Intarcia, and Valeritas. Dr Riddle reports receipt of research grant support through Oregon Health & Science University (OHSU) from AstraZeneca, Eli Lilly, and NovoNordisk; honoraria for consulting from AstraZeneca, Elcelyx, Eli Lilly, GlaxoSmithKline, Sanofi, Theracos, Biodel, and Valeritas; honoraria for speaking from Sanofi; and personal fees for chairing an observational study monitoring board from the National Institute of Diabetes and Digestive and Kidney Diseases.

Funding/Support: National Institute on Aging and the American Federation of Aging Research through the Paul Beeson Career Development Award (K23AG048359) and the Yale Claude D. Pepper Older Americans Independence Center (P30AG021342) (Lipska). The Rose Hastings and Russell Standley Memorial Trusts (Riddle).

Role of the Funder/Sponsor: The funders did not have a role in the conception and design of this article; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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