The Future of Insulin Therapy for Patients With Type 2 Diabetes Mellitus

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Insulin therapy has been the mainstay of therapy for patients with type 2 diabetes mellitus for the past 90 years. This trend is likely to continue as new formulations are developed to more closely mimic physiologic insulin secretion and to provide patients who have diabetes with more convenient options for integrating this therapy into their lifestyle. The present article reviews how the role of insulin continues to evolve, from its earlier use in the treatment paradigm (even at first diagnosis) to its role in combination therapy with incretin-based therapies, as well as new formulations that provide more-convenient forms of insulin replacement therapy.

J Am Osteopath Assoc. 2013;113(4 suppl 2):S29-S39

From the Albert Einstein College of Medicine in Flushing, New York.

This article is based on a continuing medical education symposium held on October 10, 2012, during the American Osteopathic Association’s 2012 annual Osteopathic Medical Conference & Exposition in San Diego, California. This article was developed with assistance from Global Directions in Medicine.

The author has approved the article and all of its content.

Financial Disclosures:
Dr. Tibaldi is on the speakers’ bureaus for Daiichi Sankyo Company, Merck & Co., Inc., and Novo Nordisk Inc. He is also a consultant for Novo Nordisk Inc.


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The number of patients with type 2 diabetes mellitus (T2DM) far exceeds the number of endocrinologists and diabetes specialists available to treat them. The majority of patients are treated in primary care environments, and by virtue of the common comorbidities that “travel” with diabetes, including hypertension, dyslipidemia, and obesity or overweight, comprehensive and holistic approaches to care are required. Osteopathic physicians are likely to encounter more and more such patients in their practices. As a result of improvements in health care and increases in longevity, patients are more likely to require insulin therapy at some point during the progression of T2DM. With advances in insulin therapy still occurring, it is well worth keeping up to date on trends in the use of this powerful glucose-lowering agent.

Patients with T2DM are insulin resistant, have relatively low insulin production, or have both characteristics. Most patients with T2DM eventually require insulin if other medications fail to control their blood glucose levels adequately. Insulin replacement therapy lets patients know that a key component of their natural glucose-regulating system is being restored. When insulin replacement therapy was introduced more than 90 years ago, it was a lifesaving option for patients with type 1 diabetes mellitus (T1DM), even though the formulations used were relatively crude. During past decades, major advances in our ability to synthesize more reproducible and physiologic formulations have enabled the production of much more sophisticated and patient-friendly agents. The present review article discusses initiation of insulin replacement therapy at the time of diagnosis, basal insulin therapy used in combination with incretin therapy, and second-generation basal insulin analog therapy, using a case study to demonstrate clinical application. Other means of enhancing delivery of insulin to patients are also discussed.

Pathophysiologic Profile of T2DM Drives Treatment Choices

Insulin is instrumental in managing T2DM, which is a complex, multihormonal, and progressive chronic disease. Our approach to the treatment of patients with T2DM requires an understanding of the pathophysiologic profile of this condition to determine when and how to use the many pharmacologic agents available.

Type 2 diabetes mellitus results from the abnormal secretion or abnormal actions of key hormones that regulate glucose production by the liver and glucose uptake in the peripheral muscle and adipose tissue. In patients with established T2DM, insulin secretion is reduced because of progressive loss of pancreatic β-cell function. Plasma glucose levels increase as insulin deficiency and insulin resistance reduce normal insulin activity, leading to diminished stimulation of peripheral glucose uptake and decreased inhibition of hepatic glucose production.

Glucagon normally helps maintain fasting plasma glucose levels by stimulating hepatic glucose production. In patients with T2DM, the normal postprandial suppression of glucagon secretion is inadequate, leading to increased hepatic glucose output that worsens hyperglycemia. In turn, chronic hyperglycemia leads to glucose toxicity that paradoxically results in reduced synthesis and secretion of insulin. Native glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the gut that normally slows gastric emptying, acts on the pancreas to stimulate glucose-dependent insulin secretion, and suppresses the release of glucagon. Incretin deficits or incretin resistance may result in the abnormal regulation of insulin and glucagon secretion that characterizes T2DM. Like insulin, GLP-1 and glucagon are important targets of pharmacologic treatment strategies for improving glycemic control.

Use of Insulin Therapy Early in the T2DM Treatment Paradigm

Insulin remains integral to the treatment of patients with diabetes. For patients with T1DM, insulin therapy is essential and lifesaving. For patients with T2DM, use of insulin therapy was formerly relegated to use during later stages of the disease. This approach is being reexamined as more recent treatment paradigms encourage earlier use of insulin treatment algorithms for patients with T2DM. On the basis of guidelines from the American Association of Clinical Endocrinologists, insulin therapy clearly is recommended for patients with severe hyperglycemia and for pa-
tients receiving oral antidiabetic drugs who have glycated hemoglobin (HbA\(_1c\)) levels greater than 9%.\(^{12}\)

Of particular interest are data assessing the use of insulin as a first-line treatment option for T2DM, often in patients who initially have very high levels of glucose toxicity. This treatment option was reviewed by Rolla\(^{13}\) in 2009, and additional data have since been published. Several studies\(^ {14-16}\) have shown prolonged remission of T2DM in patients receiving intensive insulin therapy for 2 weeks. A 2- to 3-week course of intensive insulin therapy can lay the foundation for prolonged good glycemic control in patients with newly diagnosed T2DM who have elevated fasting glucose levels. Figure 1 shows an example of the effects of short-term intensive insulin therapy on glucose and insulin levels.\(^{14}\)

In a more recent study, the use of low-dose insulin therapy (given as premixed insulin in one study) for patients with newly diagnosed T2DM led to evidence of β-cell recovery, as documented by plasma insulin and C-peptide levels.\(^{17}\) It appears that reversing glucose toxicity may result in a rapid improvement in β-cell function, which then allows the β cell to start to function and to secrete adequate amounts of insulin for clinically significant periods of up to 1 year.\(^ {14-16}\) This series of events is also known as a “second-wind” phenomenon for the β cell.\(^ {13}\) After symptom relief occurs and glucose levels are normalized in such patients, oral agents often can be added to therapy, and it may be possible to withdraw insulin.

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**Figure 1.**
Glucose and insulin levels before insulin therapy, immediately after insulin therapy, and 1 year after insulin therapy, demonstrating the effects of short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes mellitus.\(^ {14}\) Reprinted with permission from the American Diabetes Association, from Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes mellitus. *Diabetes Care*. 2004;27(5):1028-1032; permission conveyed through Copyright Clearance Center, Inc.
Other recent data show that β-cell function can be preserved for at least 3.5 years with the use of early and intensive T2DM therapy involving administration of either insulin plus metformin or triple oral therapy after an initial 3-month period of insulin-based treatment. These data support the premise that insulin should not be relegated to use as a last-line therapy but, rather, could be used earlier in the disease paradigm, when some β-cell function remains intact. Insulin therapy can be discontinued in patients who have early disease, and it can be restarted when necessary or continued in conjunction with other oral agents or GLP-1 receptor agonists.

Case Study

Harry

Harry is a 52-year-old man who, for the past 6 months, has been struggling with a new job that has required his attention during most of his waking hours. His past medical history includes hypertension, for which he takes a diuretic, and mixed hyperlipidemia managed with a modest dose of a statin.

Harry has been fastidious in taking his medications, but his job keeps him at his desk most of the time. His only exercise is walking to the local fast food restaurant where he buys most of his meals. The owner of the restaurant noted that Harry was returning more frequently and buying more juice and soda. The owner’s wife had diabetes, so the owner gently questioned Harry about his thirst levels and weight loss, thinking that he might have diabetes. After talking with the owner, Harry realized that he had unquenchable thirst. He promptly made an appointment to see his primary care physician, even though he had been negligent in doing so for the past year.

The findings from Harry’s visit to his physician were notable. He had a weight loss of 15 lbs, a nonfasting glucose level of 430 mg/dL, an HbA1c level of 12%, and trace levels of ketone bodies in his urine sample. Insulin replacement therapy was recommended as initial treatment.

In Harry’s case, insulin therapy was clearly indicated. He had T2DM, clinically significant hyperglycemia, and signs of catabolism (weight loss), and no oral agent or other noninsulin agent would begin to bring him close to his goal HbA1c level. Pathophysiologic findings revealed that his liver was secreting excess glucose that was unable to enter the muscle. His problematic glucose levels occurred in part because Harry has diminished insulin levels. However, it also occurred because Harry has a GLP-1 deficit, and because, with that deficit, he was producing too much glucagon.

It is gratifying to treat a patient like Harry, who arrives at the office feeling poorly but who, after approximately 3 to 6 months, is in much better health and can have blood glucose levels that are close to normal. Chronic hyperglycemia leads to reduced insulin secretion (Figure 2). By reversing glucotoxicity, it is possible for the body to resume insulin secretory capacity.

Harry, 2-Year Follow-Up

Harry’s diabetes treatment regimen now includes basal insulin as well as metformin. During the 2 years since Harry was first seen in the physician’s office, he has been self-titrating his basal insulin and has generally been able to keep his HbA1c level at less than 7%. However, despite engaging in exercise on a relatively consistent basis, he has gained 11 lbs. For the past 6 months, however, his HbA1c level has been 8.3%, in spite of fasting blood glucose levels between 90 and 115 mg/dL. Harry’s goal is to once again attain an HbA1c level of less than 7%.

Many patients who receive basal insulin therapy will ultimately require treatment intensification. Notably, the HbA1c level reflects not only fasting blood glucose levels but also postprandial glucose levels. Adding a sulfonylurea to insulin-based therapy increases the risk of hypoglycemia without providing much benefit. Sulfonylureas also lower fasting glucose levels much more than postprandial glucose levels, so they may not be the best treatment option for Harry. At this point, the clinical decision traditionally is to switch to a premixed insulin or move toward a basal-bolus regimen (which is often done by sequentially adding prandial insulin before meals as needed and as tolerated).

This clinical decision is certainly a well-validated and effective treatment strategy, but there are drawbacks for some patients—namely, an increased risk of hypoglycemia, weight gain, and number of complications for patients in terms of the number...
of injections needed and the complexity of titrating both basal and prandial insulin doses.  

**Basal Insulin Therapy in Combination With Incretin-Based Therapy**

Another approach used to augment insulin therapy is to add incretin-based agents to the treatment regimens of patients who are receiving basal insulin therapy but who are no longer achieving treatment goals. Although these approaches are similar, they have important differences (Figure 3).  

Glucagon-like peptide-1 receptor agonists provide supraphysiologic levels of the incretin hormone and have greater efficacy in lowering glucose levels.  

The benefit of using these approaches is that incretin-based therapies work in a glucose-dependent manner (ie, only in the presence of hyperglycemia). They also are weight neutral (dipeptidyl peptidase-4 [DPP-4] inhibitors) or are associated with weight loss (GLP-1 receptor agonists).  

Currently, DPP-4 inhibitors, as well as both liraglutide and short-acting exenatide, are approved for use with long-acting basal insulin analogs in patients with T2DM who are not achieving their goals for glycemic control. Incretin-based therapies primarily target postprandial hyperglycemia (although longer-acting GLP-1 agonists also affect fasting plasma glucose levels) and lower postprandial glucose levels, with a low associated risk of hypoglycemia and without weight gain (an advantage over prandial insulin analogs). However, basal insulin doses may need to be adjusted downward or sulfonylureas may need to be discontinued.  

Table 1 provides a summary of some of the available published literature on DPP-4 inhibitors used in combination with insulin therapy.  

The use of GLP-1 agonists in combination with insulin therapy for postprandial glucose control also may result in some weight loss. Some clinicians prefer to start with a GLP-1 agonist or an incretin-based therapy early in the treatment paradigm, before initiating insulin.
Case Study Revisited

Harry Follow-Up

Harry was presented with options to help him return to his goal HbA1c level of 7%. A DPP-4 inhibitor would be a simple treatment option but would not allow him to attain this goal. A successful treatment option that could achieve this goal is the addition of prandial insulin injections at mealtimes.

Harry was also concerned about losing weight, so it was decided to use GLP-1 receptor agonists. Because Harry was traveling a great deal and eating at irregular times (usually at a restaurant), he wanted a simple treatment plan that involved the least number of injections and a medication that did not require strict dosing in relation to meals. Therefore, once-daily liraglutide was selected. Liraglutide is administered once daily, without regard to mealtimes, but it

<p>| Table 2. Comparison of Onset, Peak, and Duration of Longer-Acting Basal Insulins |</p>
<table>
<thead>
<tr>
<th>Basal Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral protamine Hagedorn</td>
<td>1-2 h</td>
<td>4-8 h</td>
<td>8-12 h</td>
</tr>
<tr>
<td>Glargine</td>
<td>30-60 min</td>
<td>Relatively peakless</td>
<td>16-24 h</td>
</tr>
<tr>
<td>Detemir</td>
<td>30-60 min</td>
<td>Relatively peakless</td>
<td>16-24 h</td>
</tr>
<tr>
<td>Degludec</td>
<td>30-90 min</td>
<td>Peakless</td>
<td>&gt;24 h</td>
</tr>
</tbody>
</table>

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Abbreviations: HbA1c, glycated hemoglobin; T2DM, type 2 diabetes mellitus.

<p>| Table 1. Outcomes of Select Studies of Dipeptidyl Peptidase-4 Inhibitors in Combination With Insulin Over 24 Weeks Duration |</p>
<table>
<thead>
<tr>
<th>Source</th>
<th>Agent</th>
<th>Comparison</th>
<th>Patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong et al, 201228</td>
<td>Sitagliptin</td>
<td>Add-on to insulin vs an insulin dose increase</td>
<td>Patients with T2DM (n=140); baseline HbA1c level, 9.2%</td>
<td>Compared with a 25% increase in the insulin dose, adding sitagliptin to an insulin-based regimen was more effective at lowering HbA1c levels and was associated with less hypoglycemia and weight gain</td>
</tr>
<tr>
<td>Barnett et al, 201223</td>
<td>Saxagliptin</td>
<td>Insulin alone or insulin plus metformin, addition of saxagliptin vs placebo</td>
<td>Patients with T2DM (n=455); baseline HbA1c level, 7.5% to 11%</td>
<td>Addition of saxagliptin improved glycemic control and was generally well tolerated</td>
</tr>
<tr>
<td>Vilsboll et al, 201029</td>
<td>Sitagliptin</td>
<td>Add-on to basal or premixed insulin vs placebo</td>
<td>Patients with T2DM (n=451); baseline HbA1c level, 7.5% to 11%</td>
<td>Addition of sitagliptin improved glycemic control and was generally well tolerated</td>
</tr>
</tbody>
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should be administered at approximately the same time each day, if possible. Short-acting exenatide is administered twice daily before meals. It should be noted that the once-weekly formulation of exenatide is not currently approved by the US Food and Drug Administration (FDA) for use with insulin.

The physician discussed the possibility of nausea occurring in association with initiation of GLP-1 receptor agonist therapy. The nausea tends to be mild to moderate and of a transient nature. Harry was told that if severe nausea or abdominal pain were to occur, he would need to call the physician’s office right away, because the presence of these symptoms might be a sign of a more serious condition, such as pancreatitis.

Harry’s basal insulin dose was reduced by 20%, from 40 U to 33 U, at night. When basal insulin is used with GLP-1 receptor agonists, the need for lower doses of insulin has been observed. There also is the possibility that patients may transiently eat less if nausea is problematic, which may increase the possibility of insulin-related hypoglycemia developing. Furthermore, by means of mechanisms independent of adverse gastrointestinal effects, patients treated with GLP-1 receptor agonists experience greater satiety than placebo-treated patients, and their food intake may decrease.

Harry already knew how to use an insulin pen delivery device, so he was told to start with a dose of 0.6 mg of insulin given subcutaneously daily. One week later, Harry increased the insulin dose to 1.2 mg given subcutaneously daily.

A follow-up appointment was scheduled for 6 weeks after Harry started using the insulin pen. At that visit, mild nausea had occurred; however, it abated 3 weeks later. Harry had a weight loss of 5 lbs, and he noted that his fasting blood glucose level was still between 80 and 120 mg/dL.

The next follow-up visit occurred after Harry had been receiving the new medication for 12 weeks. At that time, he had lost an additional 4 lbs, and his HbA1c level was 6.8%.

What Else Is New?

Ultra-Long-Acting Basal Insulin in Development

Current research efforts are focusing on improving the pharmacokinetics and pharmacodynamics of long-acting insulin analogs to make them even less variable and longer acting (ie, make them truly once-daily insulin analogs). These
Advances have been made in the clinical development of both insulin degludec (administered alone or in combination with insulin aspart) and pegylated insulin lispro. Insulin de-
gludec has been submitted to the FDA for review. This ultra-long-acting basal insulin has a flat and stable glucose-lowering effect, and it is associated with a much lower risk of nocturnal hypoglycemia than insulin glargine, as has been demonstrated in studies of patients with T1DM and T2DM. The pharmacodynamic variability of insulin degludec is much lower than that of insulin glargine. Insulin degludec has received an approvable status from an FDA regulatory panel and has been approved for use in Europe.

Because insulin degludec has a stable and prolonged time-action profile, coupled with low within-subject variability, it allows for more-flexible once-daily dosing. Insulin degludec has a flat and stable glucose-lowering effect that is not affected by dose. This concept was tested in patients with T2DM participating in a 26-week randomized trial in which insulin degludec (administered in variable dosing intervals in a flexible regimen) was compared with insulin glargine (administered at the same time each day). Both insulins were added to an existing regimen of oral glucose-lowering therapy, as in the case study described here, and study patients were titrated to achieve fasting plasma glucose levels of less than 90 mg/dL. The once-daily regimen of insulin degludec involved a compulsory, rotating morning-and-evening schedule of dosing that created 8- to 40-hour dosing intervals. From a baseline HbA1c level of 8.4%, HbA1c values were reduced by 1.28% and 1.26% with the use of insulin degludec and insulin glargine, respectively. Low rates of hypoglycemia were noted with both regimens. This trial showed that insulin degludec can be administered at varying times without resulting in either a loss of glycemic control or the development of hypoglycemia to accommodate changes in a patient’s daily schedule.

Another new agent, pegylated insulin lispro, is currently moving into phase 3 of clinical development. This agent appears to be associated with less variability, less nocturnal hypoglycemia, perhaps slightly more overall hypoglycemia (which may be related to some dosing and titration issues), and some interesting effects on weight. To my knowledge, few data on this compound have been published in the peer-reviewed literature to date.

A summary of available data from clinical trials is shown in Table 3. Overall, these exciting developments may be used by physicians to improve glycemic control and to increase patient acceptance of and adherence to insulin therapy.

Inhaled Insulin

Inhaled insulin has been under development for many years, but a product that actually reached market (Exubera, an insulin human [recombinant DNA origin] inhalation powder; Pfizer, New York, New York) was eventually withdrawn because of poor market uptake, perhaps because of the complex requirements for its administration. Other inhaled insulin agents that have been investigated have been found to produce nocturnal hypoglycemia.

Technosphere insulin (MannKind Corporation, Valencia, California), another inhaled insulin, was compared with subcutaneous regular human insulin in a randomized, open-label study of their efficacy and safety in covering prandial insulin needs. Technosphere insulin substantially improved postprandial glucose levels and had a more favorable pharmacodynamic profile than subcutaneous regular human insulin. The Technosphere insulin system is currently undergoing phase 3 trials.

All of these efforts illustrate the difficulty of working with complex proteins, such as hormones, and highlight the successes that have been achieved with current and emerging formulations as they continue through the approval process.

Oral Insulin

The physiologic barriers of the gastrointestinal tract pose a major challenge for the optimal delivery of any hormone, including insulin. Oral insulin would provide a convenient method of administration, potentially leading to improved glycemic control for patients with poor adherence to subcutaneous insulin regimens.

Conclusion

Development of insulin replacement therapy is ongoing. Physicians need to understand the central role of insulin in the pathophysiologic profile of diabetes, how it can be used early or late in the disease process, and how it complements other agents. As more insulin...
products become available, an understanding of the relative characteristics, benefits, and potential of these agents in helping us to improve glycemic control in patients currently coping with unsatisfactory glycemic control cannot be overstated.

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