Intensive Insulin Therapy as the Primary Treatment for Type 2 Diabetes

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Presentation
A 47-year-old obese, white man with a history of prediabetes and dyslipidemia presented to his primary care physician for a routine follow-up. He weighed 285.6 lb, and his BMI was 39.8 kg/m². He was a smoker with a 30-pack-year history and drank Mountain Dew soft drinks all through the day. He occasionally consumed alcohol, exercised rarely, and had no history of illicit drug use. His medications included Naproxen, 500 mg, and Flexeril, 10 mg, for use as needed. He had an extensive family history of type 2 diabetes and hypertension. He had a normal physical examination except for truncal obesity. His most recent laboratory values included a random glucose of 264 mg/dl, total cholesterol of 225 mg/dl, triglycerides of 459 mg/dl, HDL of 27 mg/dl, and LDL of 144 mg/dl. His A1C at this visit was too high to be recorded, and his C-peptide level was 2.6 ng/ml.

We informed him of the new findings and presented him with numerous treatment options. He agreed to initiate lifestyle modifications with diet and exercise but was not keen on taking two or three oral medications. Thus, he opted to initiate his treatment with intensive insulin therapy to get back in control. He completed diabetes education and was instructed on self-monitoring of blood glucose (SMBG), use of an insulin pen, and recognition of the signs and symptoms of hyper- and hypoglycemia.

He was started on basal-bolus analog insulin therapy, including glargine, 16 units daily, and aspart, fixed dose of 6 units/meal. He was also advised to stop drinking Mountain Dew. His initial glucose values are shown in Table 1. His recommended blood glucose targets were fasting 80–150 mg/dl and random 80–120 mg/dl. Any reading < 70 mg/dl was considered a mild hypoglycemic event, and those < 60 mg/dl were considered severe hypoglycemia.

For the first 12 days, he was globally hyperglycemic, with highest readings at bedtime. Glargine was increased to 20 units daily, and aspart was continued at 6 units/meal. His glucose values for the following 2 weeks are shown in Table 2. His bedtime glucose readings improved tremendously, with more fasting and random glucose readings within the target ranges. He had discontinued Mountain Dew. There was no change made in insulin dosage for the next 2 weeks. His blood glucose readings for weeks 4 and 5 are presented in Table 3.

At the end of week 5, we increased his insulin to 22 units of glargine daily and 8 units of aspart before dinner. Aspart was continued at 6 units before breakfast and lunch. Glucose values with this insulin regimen are shown in Table 4.

As evident from the blood glucose readings, all his fasting blood glucose results were < 150 mg/dl, most of his random glucose readings fit the target range of 80–120 mg/dl, and his bedtime readings showed remarkable improvement since his initial range of 250–350 mg/dl with intensive insulin therapy.

At the end of week 7, he was advised to discontinue aspart and

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**Table 1. Initial SMBG Results (mg/dl) With Intensive Insulin Regimen**

<table>
<thead>
<tr>
<th>Day</th>
<th>Fasting</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>204</td>
<td>225</td>
<td>293</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>203</td>
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<td>285</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>—</td>
<td>322</td>
<td>296</td>
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<td>182</td>
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<td>306</td>
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<td>174</td>
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<tr>
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<td>168</td>
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</table>
slowly down-titrate glargine by 4 units every week for 5 weeks. His total time on insulin was 12 weeks. He never experienced a hypoglycemic event throughout the treatment therapy.

His A1C after 15 weeks of intensive insulin therapy was 6.4%. At his annual follow-up, his A1C was 6.0%, and his C-peptide level increased to 3.4 ng/ml. Additionally, his laboratory values included total cholesterol of 186 mg/dl, triglycerides of 197 mg/dl, HDL of 30 mg/dl, and LDL of 116 mg/dl without the use of any lipid-lowering medications.

At his most recent visit, 27 months after completing intensive insulin therapy, his A1C was 6.7% without any additional exogenous insulin or oral diabetes medications. He had no complaints except for recent weight gain he attributed to stress related to being laid off from work.

Questions

1. What is the benefit of recommending intensive insulin therapy as primary treatment for type 2 diabetes?
2. Is there additional evidence supporting the use of insulin therapy as a primary treatment?
3. What determines insulin titration, and how does it affect A1C values over time?
4. What are the potential short-term and long-term benefits of early insulin therapy with disease progression?

Commentary

The natural history of type 2 diabetes demonstrates the relentless decline of β-cell function over time. The progressive defects in insulin secretion and action lead to uncontrolled hyperglycemia, further aggravating insulin resistance and impairing β-cell function.
The American Diabetes Association has historically recommended incorporating lifestyle modification followed by oral antidiabetic medications for diabetes treatment and supplementing insulin for those who fail initial therapy. By the time diabetes is diagnosed, β-cell function and mass have declined by 50%. With the progression of the disease, there is a continuous decrease in β-cell mass because of increased apoptosis that results in absolute insulin deficiency. When insulin is needed, < 10% of β-cells are functioning.

Thus, the objective of intervening with intensive insulin therapy early in the disease is to rest the β-cells and possibly preserve the retardation of cell function over time. This can potentially restore endogenous insulin production and induce remission (maintenance of normoglycemia using no medication) in diabetes. The exact effects of insulin treatment on β-cell function are not fully understood. It is believed to reduce glucotoxicity and prevent hyperstimulation of pancreatic insulin release and therefore lay the foundation for improved β-cell function.

In a study by Ryan et al., 16 newly diagnosed type 2 diabetic patients received 2–3 weeks of intensive insulin therapy and were followed for 1 year. All 16 patients presented with fasting serum glucose levels > 200 mg/dl at the time of initial diagnosis. Regular insulin was initiated at a dose of 5 units before meals, and NPH was given at 10–15 units at bedtime. Fasting serum glucose levels decreased to 125 ± 8 mg/dl after insulin therapy (P < 0.01) and remained improved at 1 year. After 1 year, all subjects had reasonable glycemic control with a mean A1C of 6.6 ± 0.3%. Seven patients remained off medication, six were on glyburide, two were on a combination of glyburide and metformin, and one was on insulin after the initial 3 weeks of therapy. These results demonstrate the success of rapidly correcting serum glucose levels in most patients with newly diagnosed diabetes.

In this case study, basal-bolus analog insulin therapy was used as the primary treatment for type 2 diabetes. Insulin was titrated based on SMBG results to gain tighter glucose control. This patient had a prolonged reduction in A1C for as long as 27 months after insulin therapy without any oral medications or exogenous insulin. This case study supports the use of aggressive insulin early in the disease process to gain tighter glucose control, possibly preserve β-cell function and mass, and potentially induce remission (even if only temporarily) over time. The potential short-term benefits are not limited to lowering hyperglycemia, but also include reducing free fatty acid levels, lipid levels, and endogenous glucose production. This case study is the first, so far, to use outpatient intensive insulin therapy as the primary treatment for type 2 diabetes.

Clinical Pearls
• Short-term insulin therapy as an initial treatment of type 2 diabetes can lead to significant improvement in A1C and lipid values.
• No severe hypoglycemia was observed throughout the course of this treatment.
• Primary treatment for type 2 diabetes using intensive insulin has the potential of quickly attaining and maintaining recommended A1C values of < 7% or < 6.5%.
• Sustained euglycemia over time without any oral antidiabetic medications or exogenous insulin after intensive insulin therapy is known as the “legacy effect.”
• Benefits of this approach include reducing hyperglycemia, preserving β-cell function, and possibly restoring normal insulin secretion for lasting glucose control.

REFERENCES
4 Shubrook JH, Jones SA: Basal-bolus analogue insulin therapy as initial treatment of type 2 diabetes mellitus: a case series. Insulin 5:100–105, 2010

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