

# Case Study: Treating New-Onset Catabolic Type 2 Diabetes With Gargine and Lispro

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## Presentation

N.D., a 38-year-old African-American woman, was admitted to the hospital with a plasma glucose level of 793 mg/dl and 2+ urine ketones. She had no history of diabetes and last saw her primary care provider 6 months ago for her annual examination. Her plasma glucose level was normal at that time. She had lost 30 lb in the past 8 weeks, and she reported having had polyuria and polydipsia for 2 weeks. She reported anorexia with very little oral intake for the past 2 days. Her weight was 220 lb (100 kg). Physical examination showed acanthosis nigricans and morbid obesity.

She had been given 10 units of regular insulin subcutaneously and 2 l of normal saline intravenously in the emergency department, resulting in a plasma blood glucose of 525 mg/dl. Results of a basic chemistry panel were:

- Sodium: 134 mg/dl
- Potassium: 3.9 mg/dl
- Bicarbonate: 20 mg/dl
- Chloride: 100 mg/dl
- Creatinine: 1.0 mg/dl

Overnight, she was given “sliding scale” insulin, 10 units every 6 hours, for glucose levels consistently > 400 mg/dl. The next morning, an insulin drip was started. During the next 24 hours, 100 units of intravenous lispro in a drip resulted in a fasting plasma glucose of 120 mg/dl. Her hemoglobin A<sub>1c</sub> (A1C) was 12.2%.

The next evening, she was given 50 units of gargine with premeal supplements of lispro to a total of 50 units (15 units at breakfast, 15 units at lunch, and 20 units at dinner). Her blood glucose

levels now were well controlled without initial hypoglycemia.

During the next 3 months, she lost 22 lb (10 kg), and her insulin requirements gradually decreased. She was eventually switched from insulin to metformin. However, she did not continue to limit her calorie intake, and as a result she regained the weight she had lost and required insulin again.

## Questions

1. Why does N.D. have type 2 diabetes when she has urine ketones?
2. Why didn't the “sliding scale” insulin bring her glucose levels down?
3. Why was this patient started on insulin instead of an oral agent, and how was the insulin regimen selected?
4. Why was N.D. eventually able to stop insulin therapy, at least for a while?

## Commentary

N.D. presented with classic catabolic symptoms of diabetes: weight loss, polydipsia, and polyuria with ketones in her urine. When this happens, even in an obese patient, type 1 diabetes should be considered. In this case, there was a combination of insulin resistance because of N.D.'s obesity and evidenced by her acanthosis nigricans (a sign of hyperinsulinism) and decreased insulin output because of a decrease in pancreatic secretion.

As demonstrated in the U.K. Prospective Diabetes Study (UKPDS),<sup>1</sup> virtually all patients have < 50% insulin secretion at the time of diagnosis. Her ketonuria was most likely caused by her

decreased oral intake for the previous 2 days. However, in patients who are less ill and for whom oral agents are being considered, antibody testing may be appropriate if there is a question about whether the patient could have autoimmune type 1 diabetes or latent autoimmune diabetes of adults (LADA).

Because oral agents only lower A1C by 1–2 percentage points as monotherapy or up to 3 percentage points when used in combination, and because N.D.'s A1C was > 12%, insulin was indicated. Initially, insulin was required to overcome her glucose toxicity. Clinically, this is evident because she did not respond to the “sliding scale” regimen of subcutaneous insulin. Additionally, even if she had been given the maximum allowed by the physician orders (i.e., 40 units of subcutaneous regular insulin per 24 hours), her insulin needs were clearly much higher.

In such a situation, a weight-based calculation can be helpful in predicting a patient's insulin needs. A general guideline for starting insulin is to use 0.4–1.0 units of insulin per kilogram of body weight, with up to 2.0 units per kilogram often needed for obese, insulin-resistant patients. Because N.D. weighed 220 lb (100 kg), 100 units of insulin per day was a reasonable dose and was, not coincidentally, what she required.

Once it becomes clear that insulin is needed, a regimen of bedtime gargine with premeal lispro offers clear advantages over more traditional regimens, such as bedtime NPH with mealtime supplements of regular or lispro or twice-daily pre-mix 70/30 insulin. In a trial comparing NPH to gargine,<sup>2</sup>

patients on glargine experienced better fasting glucose control, equivalent day-time control, and, most importantly, 25% less nocturnal hypoglycemia. The main disadvantages are multiple injections (four versus two with pre-mix 70/30), cost (glargine and lispro are about twice as expensive as NPH or pre-mix 70/30), and perhaps additional blood glucose testing.

In a basal (long-acting)/prandial (premeal) regimen, basal insulin (50% of total daily insulin) covers gluconeogenesis, and prandial insulin (50% of total insulin divided among meals) covers intake. Glargine is a clear, basal insulin that must be given separately because it cannot be mixed with other insulins. Rapid insulin analogs lispro, aspart, and glulisine are convenient for patients because they are administered right at mealtime instead of 30 minutes before eating, as with regular insulin. These analogs have an onset of 15 minutes, a peak at 60–90 minutes, and a duration of 3–5 hours. They are also easily adapted to meal content, using either carbohydrate counting (e.g., 1 unit of insulin per 10–15 g of carbohydrate) or an estimate of the percentage of total daily carbohydrate calories consumed at each meal.

N.D. required 100 units of insulin in 24 hours via insulin drip. To begin her basal/prandial regimen, this amount was divided into 50% basal (50 units of glargine at bedtime) and 50% prandial (50 units of lispro divided based on car-

bohydrate intake estimates as 15 units before breakfast, 15 units before lunch, and 20 units before dinner).

Glargine is adjusted based on fasting glucose, with a goal of 90–110 mg/dl; if the fasting glucose is > 110 mg/dl for 3 days, the glargine is increased by 2 units. Of note, because the onset of glargine is several hours, N.D.'s insulin drip was continued for 4 hours after her first dose of glargine was given. Her fasting plasma glucose of 129 mg/dl the next morning meant these dosing calculations resulted in control that was very close to optimal.

Finally, N.D.'s initial weight loss after dietary counseling reduced her insulin resistance, and the use of insulin to overcome her glucose toxicity probably "rested" her pancreas. Thus, she was gradually able to stop using insulin.

This is a common scenario in patients with type 2 diabetes. However, in the UKPDS,<sup>1</sup> insulin secretion continued to decline. This is the primary reason for secondary failure of oral agents in most patients with type 2 diabetes by 10 years into their disease. Unfortunately, N.D. was unable to maintain her initial weight loss after she decreased her dietary compliance, and she eventually needed insulin again. It is reasonable to counsel most type 2 diabetic patients that continued weight loss, dietary compliance, and exercise are cornerstones of diabetes therapy, and that they will likely need insulin in the long term.

### Clinical Pearls

- Obese patients with catabolic symptoms usually have type 2 diabetes, but autoimmune diabetes should be considered.
- Insulin drips and ongoing insulin therapy are the best treatment initially to overcome glucose toxicity.
- Basal/prandial insulin strategies are easy to initiate based on patients' insulin drip requirements (over 24 hours) and weight-based estimates of their insulin needs.
- Although oral agents, with weight loss, diet, and exercise, may be successful in the short term after initial insulin therapy, patients who have decreased insulin secretion will likely need insulin in the long term.

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# Case Study: Meal Provision as a Strategy for Supporting Weight Loss and Improving Metabolic Parameters in Type 2 Diabetes

Charlotte Hayes, MMSc, MS, RD, CDE

## Presentation

J.L. is a 65-year-old white woman diagnosed with type 2 diabetes at age 62 years. She has struggled with weight gain during her adult years and has repeatedly attempted to lose weight through various popular diets. Nevertheless, her weight continued to increase, and her glycemic control became increasingly erratic. She reports monitoring her blood glucose infrequently because seeing elevated glucose values causes her to feel “out of control” and depressed. She is generally not physically active and has recently been very inactive because of a leg injury resulting from a fall.

At her last physician visit, J.L.’s height was 5' 7", and her weight was 230 lb (BMI 36 kg/m<sup>2</sup>), her highest adult weight. Her hemoglobin A<sub>1c</sub> (A1C) was 7.2% on 1,000 mg of metformin twice daily taken with breakfast and with her evening meal, plus 8 mg of rosiglitazone once daily. Her blood pressure was 126/82 mmHg on 150 mg of irbesartan daily, and her lipid panel showed an LDL cholesterol of 107 mg/dl, HDL cholesterol of 42 mg/dl, and triglycerides 156 mg/dl on 20 mg of rosuvastatin daily.

J.L.’s physician referred her to a registered dietitian, who determined that J.L. was frustrated and overwhelmed with her attempts to follow multiple dietary recommendations and that meal planning was a considerable stressor for her. This contributed to dietary nonadherence. In addition, J.L.’s leg injury made meal preparation difficult.

The dietitian suggested that J.L. try a portion- and nutrient-controlled meal

plan that would provide a high degree of structure and support. This option could enable J.L. to experience success with weight loss and help improve her glycemic control and other metabolic parameters. Also, the meals could be used as a teaching tool to illustrate portion control and demonstrate how to translate dietary recommendations into healthy and appealing meals.

J.L. began a novel, home-delivered meal program that provides three portion- and nutrient-controlled meals each day. All the meals are freshly prepared and integrate nutrition guidelines advocated by various health care associations that link proper diet to disease management and prevention. With input from the dietitians, J.L. selected a 1,200-calorie daily meal plan option that provided a consistent amount of carbohydrate (~ 50 g) at each meal, < 10% of calories from saturated fat, and ≤ 2,300 mg of sodium per day. In addition to the meals, internet-based resources and telephone consultations with the dietitian were made available to J.L. to support her adherence with the meals and positive lifestyle changes.

J.L. closely followed the meal plan for 2 months and lost 11.25 lb. She felt positive about her weight loss success and began to feel more in control of her diabetes. She started monitoring her blood glucose four times per day, and 87% of the values on her meter were in the target ranges of 90–130 mg/dl before meals and < 180 mg/dl after meals. Her blood pressure also improved to 122/78 mmHg. Another A1C test and a repeat lipid panel were scheduled in her physician’s office.

J.L. also began physical therapy and was able to initiate a pedometer-based walking program. At this point, she felt ready to plan and prepare meals herself. J.L. said she was glad to know the option of portion-controlled meals was available should she need additional structure and support to maintain her weight loss and improve her diabetes control again in the future.

## Questions

1. Why should weight loss or prevention of weight gain be a primary goal for overweight individuals with diabetes?
2. What unique weight-loss challenges do people with diabetes face?
3. What strategies can be implemented to support success with weight management?

## Commentary

Weight gain during adulthood is directly correlated with an increased risk of developing type 2 diabetes.<sup>1</sup> Overweight or obesity typically precedes a diagnosis of diabetes, and as BMI increases, so does insulin resistance, glucose intolerance, and the likelihood of developing diabetes.<sup>1</sup> Eighty percent of individuals with type 2 diabetes have a BMI that classifies them as either overweight (25–29.9 kg/m<sup>2</sup>) or obese (≥ 30 kg/m<sup>2</sup>).<sup>2</sup>

Lifestyle interventions aimed at promoting a moderate weight loss of 5–10% of starting weight can improve insulin resistance and contribute to improved glucose, lipid, and blood pressure control.<sup>2–4</sup> Greater amounts of weight loss are associated with greater improvements in fasting glucose.<sup>5</sup>

Because considerable health risks are associated with obesity and diabetes, weight loss, or at least prevention of further weight gain, is essential for optimal diabetes management.

Although weight loss and maintenance are imperative for overweight individuals with diabetes, achieving significant reductions in weight can be challenging.<sup>2,6</sup> This, in part, is because of metabolic changes that influence energy expenditure. As individuals lose weight, their resting metabolic rate declines, and their nonresting energy expenditure decreases as the amount of body mass that must be moved through space becomes less.<sup>7</sup> When individuals with poorly controlled diabetes, which is characterized by high protein turnover, achieve improved glycemic control, thermogenesis of protein synthesis decreases, and energy expenditure drops. Calorie “wasting” from urinary excretion of glucose is diminished, and calories are retained. Hypothalamic signals that defend body weight amplify and increase the hunger signals that drive food intake. If this leads to an increase in caloric intake, additional weight loss is prevented.<sup>6</sup> Also, many of the medications that are aimed at reducing hyperglycemia, including insulin, sulfonylureas, meglitinides, and thiazolidinediones, increase anabolism and can contribute to weight gain.<sup>6</sup>

Beyond these biological and metabolic factors, environment and lifestyle behaviors contribute significantly to the development of overweight and obesity. Today’s societal environment limits physical activity and allows easy access to high-calorie, high-fat, nutrient-deficient foods. For many overweight people, poor food choices, overconsumption of calories, and a sedentary lifestyle set the stage for progressive weight gain and the onset of diabetes.

Although vitally important, changing established lifestyle behaviors and food preferences can be difficult. Lifestyle and behavioral approaches such as goal setting and self-monitoring; nutrition and physical activity education and counsel-

ing; reinforcement of healthy behaviors; stimulus control; modification of eating habits; and development of problem-solving and coping skills can help modify behaviors and lead to moderate weight loss.<sup>8,9</sup>

Food provision is a new trend in the management of overweight and obesity that focuses on directly changing the food environment by providing calorie-, portion-, and nutrient-controlled meals or meal replacements.<sup>8–10</sup> This approach, when combined with education and lifestyle coaching, may be especially effective for several reasons. It is a simple and effective strategy for meeting many complex nutrient recommendations.<sup>11</sup> The inherent structure of the meals may improve eating patterns and reduce snacking. The meals demonstrate appropriate portion sizes and illustrate how nutrition recommendations can be translated into healthy and appealing meals. And this strategy minimizes meal planning and preparation, which allows more time to focus on self-monitoring and improving overall self-care.<sup>9,11,12</sup>

Following are some resources for meal provision companies with menus that meet generally accepted, health-promoting nutrition guidelines or offer dietitian support.

- Diet Gourmet  
<http://www.dietgourmet.com>
- Fresh Cuisine  
<http://www.FreshCuisine.com>
- Good Measure Meals  
<http://www.GoodMeasureMeals.com>
- Susan’s Healthy Gourmet  
<http://susanshealthygourmet.com>

### Clinical Pearls

- Overweight and obese individuals with type 2 diabetes are at high absolute health risk. This is especially true for individuals who have multiple additional risk factors, such as hypertension, abnormal lipids, or cardiovascular disease.
- Moderate weight loss can improve insulin resistance, glycemic control, and cardiovascular risk factors. Greater amounts of weight loss tend

to result in greater improvements in glycemic control. For individuals with diabetes of long duration and impaired  $\beta$ -cell function, weight loss is imperative to lowering overall health risk, although it may not lead to significant improvements in glycemic control.<sup>4</sup>

- Standards of care indicate that lifestyle interventions aimed at diet and physical activity should be first-line treatments for diabetes and should remain essential components of diabetes management as the disease progresses.<sup>4,6</sup>
- Because multiple factors contribute to the development of overweight and obesity, multiple intervention strategies must be used to effectively treat the disorder. It is important for practitioners to develop a toolkit and to learn about clinical and community resources that can offer overweight or obese patients the guidance and support they need to successfully manage their disease.

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**Note of disclosure:** The author's employer, Project Open Hand/Atlanta owns Good Measure Meals, a program that sells home-delivered portion- and nutrient-controlled meals in the Atlanta, Ga., region.

# Case Study: The Meaning of Autoantibody Titers, Exercise, and Alcohol in a Thin 65-Year-Old Man Hospitalized for Cholangitis and Coincidental New Diabetes

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## Presentation

T.R. is a thin 65-year-old white man who was admitted for acute cholelithiasis and ascending cholangitis. The patient, who had not seen a physician for many years, also had symptoms of polyuria, polydipsia, and nocturia for 1 week before admission. While hospitalized, his blood glucose levels were 123–223 mg/dl. His weight was 154 lb (BMI 22.1 kg/m<sup>2</sup>). Inpatient blood pressure readings were 180–190/100–110 mmHg. He had no family history of diabetes, took no medications except occasional nonprescription analgesics, and exercised regularly. An eye examination 2 years previously was normal. He had no known kidney disease, peripheral neuropathy symptoms, or foot lesions.

Outpatient follow-up revealed random capillary blood glucose (CBG) levels of 227 and 139 mg/dl and a hemoglobin A<sub>1c</sub> (A1C) of 6.5%. His normal weight and regular exercise regimen suggested the possibility of type 1 diabetes. However, islet-cell antibodies (ICAs) and GAD antibodies were negative. He also had hypercholesterolemia, with an LDL of 154 mg/dl. To avoid having to

take diabetes medications, the patient increased his exercise and modified his diet by decreasing his carbohydrate intake.

T.R. monitored his CBG levels at home and returned to clinic after 2 weeks with a log and graph of his results. He noticed a significant increase in his blood glucose levels to > 200 mg/dl ~ 1.5 hours after breakfast. He varied his breakfast meal from carbohydrates to protein but observed no change in his CBG levels. He did not have substantial postprandial hyperglycemia after other meals. He noticed that exercising in the morning before breakfast lowered his CBG levels. Additionally, he reported that his CBG would consistently fall after he drank a glass of white wine.

The patient's symptoms resolved after he controlled his diabetes with diet and exercise. He has no evidence of retinopathy or neuropathy.

## Questions

1. Which type of diabetes is suspected in a thin older man with new-onset hyperglycemia in a metabolically stressful situation?

2. How would new-onset type 1 diabetes be ruled out in this patient?
3. What is the effect of cortisol on insulin resistance?
4. How does exercise affect hyperglycemia?
5. What effect does alcohol consumption have on blood glucose levels?

## Commentary

Diabetes is a metabolic disorder in which hyperglycemia is caused by abnormalities in insulin secretion or resistance. Insulin resistance in peripheral tissues and decreasing pancreatic  $\beta$ -cell insulin production characterizes type 2 diabetes. Autoimmune destruction of  $\beta$ -cells leads to complete absence of insulin secretion in type 1 diabetes and in latent autoimmune diabetes of adults (LADA), a slower autoimmune process.<sup>1</sup>

This patient clearly met the American Diabetes Association criteria for diabetes, with two separate fasting plasma blood glucose tests  $\geq$  126 mg/dl or one casual plasma glucose level  $\geq$  200 mg/dl plus symptoms.<sup>2</sup> However, it is difficult to distinguish between type 1 and type 2

diabetes in patients such as this.<sup>1</sup> Because T.R. is athletic and thin, he lacked the body habitus and lifestyle typically encountered in type 2 diabetes and had no specific risk factors for type 2 diabetes (race or family history).

In adult-onset type 1 diabetes, autoantibodies are directed against pancreatic  $\beta$ -cell antigens. Three clinically useful serum autoantibodies detected in type 1 diabetes are ICAs, insulin autoantibodies (IAAs), and antibodies to GAD. Patients may have any combination of ICAs, IAAs, and GAD antibodies. T.R. was negative for ICAs and GAD antibodies; he was not tested for IAAs.

Antibodies to GAD are predictive of progression to hyperglycemia in the absence of ICAs or IAAs and have been shown to have a positive predictive value of 50% and a negative predictive value of 97% for late insulin deficiency.<sup>3</sup> Moreover, the presence of two or more autoantibodies is highly predictive of the development of type 1 diabetes.<sup>4</sup> Nonetheless, some type 1 diabetic patients remain negative for all antibody types. In this case, because many adults with type 1 diabetes or LADA have a prolonged phase of declining  $\beta$ -cell function, only time will tell whether his disease progression will be more consistent with type 1 or type 2 diabetes. But in thin adults, clinicians should follow patients carefully, educate them about the symptoms of diabetic ketoacidosis, and be ready to start insulin if oral agents appear to be ineffective.<sup>5</sup>

The postbreakfast hyperglycemia reported by T.R. is probably related to increased insulin resistance in the morning (the “dawn phenomenon”). Cortisol is one of several counterregulatory hormones that increase glucose production and ultimately lead to a transient worsening of glycemic control.<sup>6</sup> Cortisol lev-

els are highest in the early morning and reach their lowest point in the late afternoon and evening. Growth hormone (also counterregulatory) also peaks in the early morning.

This patient found that exercising before breakfast decreased his hyperglycemia. Exercise improves insulin sensitivity in patients with insulin resistance. Increased insulin sensitivity associated with physical exercise was found to be especially beneficial for type 2 diabetic patients with impaired glucose tolerance.<sup>7</sup> Additionally, there is a cumulative effect of transient improvements in glucose tolerance associated with each individual period of exercise. These long-term benefits are maintained if patients exercise at least once every 2 or 3 days.<sup>8</sup>

T.R. consistently reported hypoglycemia after drinking wine. Alcohol intake has been associated with hypoglycemia in type 1 diabetes. A randomized controlled study investigating delayed hypoglycemia found that moderate consumption of alcohol in the evening may predispose patients with type 1 diabetes to hypoglycemia after breakfast the next morning.<sup>9</sup>

Finally, given his BMI and presentation, it is clinically likely that T.R. may still have LADA or type 1 diabetes in “honeymoon” phase. Patients such as this should have regular (every 3–6 months) evaluations for rapidly progressive insulin deficiency.

#### Clinical Pearls

- Autoantibody tests are helpful but not definitive methods of detecting type 1 diabetes.
- Early-morning insulin resistance (the “dawn phenomenon”) may affect blood glucose levels and is likely related to counterregulatory hormone secretion.

- Regular physical exercise is associated with increased insulin sensitivity and thus enhanced glycemic control in patients with type 2 diabetes.
- Moderate intake of alcohol may precipitate hypoglycemic episodes in patients with type 1 diabetes.

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# Case Study: A Unique Case of Basal-Bolus Therapy

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## Presentation

R.R. is a 60-year-old white man whom we were asked to evaluate for perioperative glycemic control. We met on his postoperative day 2 after repair of an abdominal aortoiliac aneurysm.

His medical history was significant for peripheral vascular disease status post-left lower extremity revascularization. His hypertension was controlled with metoprolol and amlodipine, and he took atorvastatin for mixed hyperlipidemia. Preoperative evaluation included a left heart catheterization, which demonstrated single-vessel disease and a depressed ejection fraction. His primary care physician had recently indicated that he may have "borderline diabetes." The patient reported nocturia and polydipsia. He had an allergy to sulfa drugs, although he did not know the exact nature of the allergy.

His father passed away in his 70s during his second coronary artery bypass. There was no immediate family history of diabetes. R.R. is now retired, having previously worked as a plumber. He reported a remote though significant history of tobacco use.

On physical exam, he was comfortably sitting up in his hospital bed. Pulse was 95 bpm, blood pressure 120/80 mmHg, and temperature 100.1°F. His weight was 81 kg, and his height was 1.8 m, yielding a BMI of 25 kg/m<sup>2</sup>. There were no xanthomas on the eyelids. His thyroid gland was not enlarged. Lungs were clear, and cardiovascular exam revealed the absence of jugular venous distension and a normal S1 and S2. There were no murmurs or gallops.

His abdomen was appropriately tender along the incision site, which appeared to be healing well without any drainage and only minimal erythema. His vascular exam revealed the absence of carotid bruits. Dorsalis pedis pulses were difficult to palpate on both right and left, although his feet were warm. He had a dime-sized, dry, nonerythematous ulcer on his right second toe. His neurological exam revealed intact ankle reflexes and decreased sensation to the 10-g monofilament exam on the soles of his feet bilaterally.

Hospital laboratory tests indicated fasting and postprandial blood glucose values ranging from 117 to 218 mg/dl. He had received ~ 44 units of regular insulin in the past 24 hours. Liver and renal function was normal; serum albumin was 4.2 g/dl. His hematocrit of 30% represented a decrease from his baseline. R.R. was to be discharged the next morning with plans for revascularization of his right lower extremity in the near future.

The patient was given a diagnosis of hyperglycemia, the etiology of which was believed to be from a variety of factors. His sulfa allergy precluded the use of sulfonylureas. He had recently received contrast, and though now eating and drinking, he would unquestionably receive contrast multiple times in the next year. He had impaired cardiac function and was scheduled to undergo another surgery in a few weeks. Thus, he was a poor candidate for metformin or thiazolidinedione therapy. We therefore opted for a trial of monotherapy with nateglinide, 120 mg three times daily with meals.

R.R. returned to see us in the outpatient setting 5 days after discharge. His fasting morning blood glucose levels remained in the mid-200 mg/dl range and decreased minimally throughout the day. He did not experience any hypoglycemia. His hemoglobin A<sub>1c</sub> (A1C) was 7.7%, and serum fructosamine was elevated at 286 umol/l. Thyroid function was normal. His spot albumin-to-creatinine ratio was mildly elevated at 32 µg/mg. The patient was started on ramipril, 2.5 mg daily, for renoprotection. Despite its being an "off label" use with nateglinide, glargine was started at a dose of 10 units nightly and titrated upward in the weeks that followed in an effort to control his fasting blood glucose levels.

One month later, R.R. was admitted for right lower extremity bypass in the setting of a gangrenous right foot. A computed tomography angiogram indicated the need for revascularization of his left lower extremity as well; this was undertaken 1 month later. He received intensive insulin therapy perioperatively, during which time his dose of glargine was increased to 21 units nightly based on fasting blood glucose values of ~ 120 mg/dl. His serum fructosamine was 231 umol/l.

Three months later, our patient underwent a left below-the-knee amputation for continued complications. Fasting blood glucose levels were between 99 and 140 mg/dl and ranged from 70 to 80 mg/dl during the remainder of the day. His serum fructosamine was 223 umol/l, and his A1C was 5.6%. Hematocrit was 27%. No changes were made to his regimen.



### Questions

1. What factors affect the accuracy of the A1C measurement? What alternatives exist for the assessment of long-term glycemic control?
2. What are the indications for nateglinide?
3. What prompted the addition of basal insulin therapy? How does this complement the use of nateglinide?

### Commentary

Our patient presented with hyperglycemia postoperatively, which was likely secondary to the progressive loss of  $\beta$ -cells in the setting of early type 2 diabetes, as well as stress hyperglycemia from raised levels of counter-regulatory hormones. These conditions were further exacerbated by the phenomenon of glucose toxicity, in which the hyperglycemia itself has a toxic effect on  $\beta$ -cell function.<sup>1,2</sup> When we met our patient, much of the stress surrounding surgery was resolving, and it was our hope that this treatment-naive patient may be a suitable candidate for oral therapy. He was initiated on therapy with nateglinide in an effort to primarily control his postprandial hyperglycemia, which had been prominent while hospitalized.

Postprandial hyperglycemia is caused primarily by an impairment in the early phase of insulin secretion after intake of a meal. This rise in blood glucose after a meal has been demonstrated physiologically to impair fibrinolysis, trigger the atherogenic process, and thus lead to increased cardiovascular risk in patients with type 2 diabetes. Indeed, studies have demonstrated that a 2-hour postprandial blood glucose is a better predictor of premature death than a fasting blood glucose.<sup>3,4</sup>

Early in the disease process, patients with type 2 diabetes exhibit impairment in their insulin secretory capacity, which is particularly challenged in the postprandial setting. Although oral agents such as metformin and thiazolidinediones effectively correct fasting blood glucose levels, they have less effect on

blood glucose excursions that occur after a meal. Nateglinide is a rapid-acting secretagogue that augments this early phase of insulin secretion after food intake. The agent competitively binds to sulfonylurea receptors within the pancreatic  $\beta$ -cells to stimulate insulin release in a manner that is dependent on existing glucose levels. This mechanism of action thereby precludes the use of these agents either with or after sulfonylureas.<sup>4</sup>

Nateglinide is indicated as monotherapy in patients with type 2 diabetes who are treatment naive or in the early stage of diabetes, as well as those with only moderately elevated plasma glucose levels. It additionally is used with success in the elderly, given its low incidence of hypoglycemia, as well as after a period of glucose toxicity in which insulin was administered. The administration of nateglinide before a meal in patients with type 2 diabetes induces insulin secretion comparable to that seen with a bolus dose of insulin therapy. Often, however, insulin secretory reserves become diminished to the extent that basal insulin secretion is inadequate.<sup>4</sup>

Adequate basal insulin is essential to regulate glucose production via suppression of hepatic gluconeogenesis and by the stimulation of glucose uptake within the muscle and adipose tissue. Thus, the normal physiological pattern of insulin secretion consists of a sustained phase in which short bursts of insulin are superimposed during the course of the day to maintain adequate glycemic control after periods of food intake.<sup>2</sup> Although metformin or thiazolidinediones may complement the use of nateglinide quite successfully by serving as a basal insulin component and thus controlling fasting blood glucose levels, the use of this medication was not possible in our patient. Although not officially indicated for use with nateglinide, the addition of the long-acting insulin glargine accomplished this goal quite effectively.

The treatment goal in all of our patients with diabetes is the prevention of short- and long-term complications.

The U.K. Prospective Diabetes Study demonstrated a 25% reduction in the development of microvascular complications with tight blood glucose control, defined as the maintenance of an A1C value  $< 7\%$ . Our aims for this patient were thus twofold: to control his postprandial glucose in an effort to decrease his cardiovascular risk profile and to lower his A1C in an effort to prevent microvascular complications.

The American Diabetes Association recommends the assessment of A1C values at least twice a year in patients who meet the A1C goal of  $< 7\%$ , and at least four times a year in patients with fluctuating therapy or in those who have not yet met this goal. Although A1C is accepted as the gold standard assessment of glycemic control, it must be noted that its accuracy is questioned in patients with disorders that either shorten the life span of erythrocytes or those with increased blood cell survival. In these situations, relying on the average serum blood glucose levels and obtaining a serum fructosamine level may yield a more accurate assessment of glycemic control.<sup>5</sup> Serum fructosamine, which represents primarily glycated albumin, yields an assessment of glycemic control over a period of 2–3 weeks. The assay is not standardized, and the measurement is inaccurate in patients with alterations in albumin secondary to nutritional status or liver or kidney disease.<sup>6</sup> Our patient demonstrated multiple episodes of acute blood loss requiring transfusions. The additional measurement of fructosamine thus served as a useful adjunct to the assessment of his glycemic control.

### Clinical Pearls

- Nateglinide is effective in controlling postprandial hyperglycemia. It may be used as monotherapy or in conjunction with metformin or a thiazolidinedione. Postprandial hyperglycemia has recently been demonstrated to contribute to increased cardiovascular risk in patients with type 2 diabetes.

- Progression of type 2 diabetes and subsequent loss of insulin secretory reserves necessitates intensified therapy. In this case, nateglinide provided adequate bolus coverage, whereas glargine was later added to provide basal coverage. Though effective in this case, this use of nateglinide is not currently approved by the U.S. Food and Drug Administration.
- Our current gold standard of glycemic control, the A1C test, has recognized limitations in its diagnostic accuracy that must be taken into consideration in certain subgroups of patients. The assessment of average serum blood glucose and serum fructosamine may

serve as a useful adjunct to the measurement of A1C.

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## Case Study: Dyslipidemia in a Patient With Type 2 Diabetes

John E. Anderson, MD

### Presentation

C.W. is a 51-year-old white man diagnosed with type 2 diabetes in March 2002. At the time of diagnosis, he had typical symptoms of weight loss, polyuria, and polydipsia. Examination revealed a healthy male with height of 6'1" and weight of 224 lb (BMI 29.6 kg/m<sup>2</sup>). Laboratory evaluation was remarkable for a random glucose of 580 mg/dl, triglycerides of 5,777 mg/dl, total cholesterol of 550 mg/dl, HDL cholesterol of 102 mg/dl, LDL cholesterol not calculable secondary to triglycerides, and a hemoglobin A<sub>1c</sub> (A1C) of 13.6%.

Over the next several months, he did remarkably well on combinations of sulfonylurea and metformin, with fenofibrate added to reduce the severe hypertriglyceridemia. His A1C was 5.9%,

LDL 97 mg/dl, HDL 39 mg/dl, and triglycerides 236 mg/dl by August 2002.

He has remained in good physical health but has continued to struggle with control of his dyslipidemia over the last year, despite the addition of a statin. His HDL has decreased to < 30 mg/dl with a gradual, steady increase in his triglycerides.

On 28 June 2006, he presented to the office, with examination revealing a weight of 250 lb. (BMI 33.0 kg/m<sup>2</sup>) and blood pressure of 110/76 mmHg. His medications were reviewed and are listed as follows:

- Fenofibrate, 145 mg daily
- Simvastatin, 40 mg at bedtime
- Glimepiride, 4 mg daily
- Metformin XL, 500 mg 2 tablets twice daily

- Aspirin, 81 mg daily

Laboratory studies revealed a fasting triglyceride level of 1,158 mg/dl, cholesterol of 204 mg/dl, HDL of 28 mg/dl, LDL not calculable, and A1C of 6.9%.

He has since been evaluated and undergone extensive counseling by a dietitian, revealing a diet high in saturated fats and red meat. He is continuing to exercise and attempt dietary modifications to improve control of both his dyslipidemia and his diabetes. He is scheduled for follow-up evaluation and assessment of his progress in the next 2 months.

### Questions

1. What are the goals of lipid management in patients with type 2 diabetes?

2. Which pharmacological agents are available for use with statins to help raise HDL cholesterol and lower triglycerides?
3. Is there evidence that use of a fenofibrate in combination with statins improves cardiovascular end points?

### Commentary

In patients with type 2 diabetes without overt cardiovascular disease (CVD), the primary goal of therapy is an LDL cholesterol of < 100 mg/dl. In addition, the use of statin therapy to achieve an LDL reduction of 30–40% is recommended for those > 40 years of age, regardless of their initial LDL levels. Given the proven reduction in coronary and cerebrovascular events with statin use, it should generally be considered as initial therapy for treatment of dyslipidemia in patients with diabetes. C.W.'s case is unique in that the severity of his hypertriglyceridemia necessitated treatment with fibrate therapy shortly after diagnosis.

A variety of pharmacological agents are available to address the secondary goals for lipid management in patients with diabetes: to lower triglycerides to 150 mg/dl and raise HDL cholesterol to 40 mg/dl in men and 50 mg/dl in women. Gemfibrozil is a fibric acid derivative proven to lower triglycerides and raise HDL and has been shown to achieve reductions in cardiovascular end points. Its limitations include the need to take the drug twice daily, which affects adherence, but more importantly its potential for significant interactions with statins. These may result in increased risk for abnormal transaminase levels, myositis, and life-threatening rhabdomyolysis. Conversely, fenofibrate is a once-daily medication shown to significantly reduce triglycerides and raise HDL and may have less potential for interaction with statins.

Niacin has also proven effective in treating the secondary goals of lipid

management in patients with diabetes, but the adverse effect of flushing limits its tolerability. Even with concomitant use of aspirin therapy or extended-release formulations to combat the flushing, many patients will not adhere to a prolonged course of therapy. In addition, niacin has been associated with worsening glycemic control and increased insulin resistance, limiting its use in some patients with diabetes.

Omega-3 fatty acids have been proven to raise HDL and lower triglycerides and are generally well tolerated. There are no known interactions with statin medications, but treatment in patients with very high triglycerides ( $\geq 500$  mg/dl) can result in significant elevations of LDL cholesterol, adversely affecting the overall lipid profile.

C.W.'s case is common among patients with type 2 diabetes and demonstrates that combination therapy for management of dyslipidemia is frequently required. Fenofibrate is a reasonable option among the alternatives to use in combination with a statin. The recent Fenofibrate Intervention and Event Lowering in Diabetes trial suggested the safety of fenofibrate/statin combination therapy in addition to showing effectiveness in primary prevention of total cardiovascular events in patients with type 2 diabetes.

Despite the use of combination therapy in patients with type 2 diabetes, achieving target goals for triglycerides and HDL cholesterol is often difficult. Clinicians should also remember that good glucose control is also crucial in controlling hypertriglyceridemia in the setting of diabetes. Development of newer statins have provided increased efficacy and potency, and LDL reductions associated with these drugs have enabled clinicians to better meet primary goals in their patients. In contrast, the other available pharmacological agents demonstrate only mild HDL-raising capacity and are often inadequate to lower

triglycerides to target levels when initial values are very high.

The pending arrival of new drugs to raise HDL, such as torcetrapib, may help clinicians better manage lipid disorders in their patients with diabetes. Until then, the prudent use of combination therapy for management of dyslipidemia, glucose control, intensive dietary modifications, and exercise remain the mainstays of therapy.

### Clinical Pearls

- Use of combination pharmacological therapy is common in treating hypertension and achieving glucose control in patients with diabetes. The same principle may be necessary to manage dyslipidemia.
- The use of a statin/fenofibrate combination is a reasonable option for many patients, with demonstrated safety and reduction in cardiovascular end points.
- Currently available pharmacological agents for lowering triglycerides and raising HDL cholesterol are frequently inadequate in patients with diabetes, and newer HDL-raising drugs should help in meeting secondary goals of therapy.

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