

# Case Study: Diabetes in a Patient With Cirrhosis

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## Presentation

J.T. is a 72-year-old man with chronic hepatitis C and Child-Pugh grade A (clinically well-compensated) cirrhosis. He takes propranolol for esophageal variceal bleeding prophylaxis. He had a blood transfusion 25 years ago.

Hepatitis C was diagnosed 10 years ago, and cirrhosis was diagnosed by liver biopsy 2 years ago. He does not drink alcohol. He has never been overweight. He has no personal or family history of diabetes. Over the past year, random plasma glucose levels have ranged from 110 to 180 mg/dl. The most recent random glucose was 210 mg/dl. The patient denies polydipsia, polyuria, nocturia, or any other symptoms of hyperglycemia.

He weighs 150 lb (BMI 22 kg/m<sup>2</sup>). Physical examination findings are normal except for mild palmar erythema, spider angiomas on the upper chest, and a palpable spleen tip.

Fasting blood glucose was 136 mg/dl, and a hemoglobin A1c (A1C) was 6.3%. Another fasting glucose several weeks later was 128 mg/dl.

## Questions

1. Does this patient have type 2 diabetes?
2. Should medication be started to treat hyperglycemia?
3. How does the diagnosis of diabetes affect this patient's prognosis?

## Commentary

At first glance, many clinicians might assume this patient has type 2 diabetes. The history is compatible with this diagnosis. However, the absence of classic risk factors for type 2 diabetes and the appearance of new hyperglycemia in the setting of known cirrhosis makes it more

likely he has "liver diabetes," also known as hepatogenous diabetes.<sup>1,2</sup>

Patients with cirrhosis have insulin resistance. Impaired glucose tolerance (IGT) is common, and about 20–40% have diabetes.<sup>1,3</sup> While there is no definitive test to distinguish type 2 diabetes from diabetes caused by liver disease, liver diabetes appears to be caused by hepatic dysfunction. It should be noted that the American Diabetes Association and the World Health Organization do not recognize liver diabetes as a specific type of diabetes. Regardless of whether the diagnosis is that of liver diabetes or type 2 diabetes, decisions about when and how to treat hyperglycemia should take into account comorbid conditions such as hepatic dysfunction.

This patient has only a minimal elevation in A1C, and the value is within standard treatment goals for diabetes. However, it should be noted that A1C reference ranges assume a normal erythrocyte life span. Older erythrocytes have higher A1C levels than younger cells. Any condition that reduces erythrocyte survival, such as cirrhosis<sup>4</sup> or hemolysis resulting from hypersplenism can cause spuriously low A1C levels. Therefore, in this patient, it would be desirable to institute home blood glucose monitoring in order to better assess the severity of his hyperglycemia.

The decision about whether to start treatment for any condition is based on a comparison of the risks and benefits of that treatment. First, a review is in order of the risks of each therapeutic option that should be considered for patients with hepatic dysfunction.

Diet and exercise are usually considered a very safe first-line of therapy for patients with mild hyperglycemia. How-

ever, many patients with cirrhosis are malnourished, and dietary restriction with a goal of weight loss may exacerbate hypoalbuminuria and worsen overall prognosis. If dietary restriction results in lower vitamin K intake, then a coagulopathy may result.

Every class of oral hypoglycemic medication currently available in the United States has been associated with at least a small risk of hepatotoxicity. For patients with marginal hepatic function at baseline, even mild hepatotoxicity can be fatal. Hepatic dysfunction can also cause an exaggerated response to a standard dose of medication and a higher risk of side effects if the drug is metabolized by the liver. Sulfonylureas, repaglinide, metformin, and thiazolidinediones are all extensively metabolized by the liver. It is generally advised that metformin and thiazolidinediones should not be used in patients with significant hepatic dysfunction.

For these reasons, many clinicians use insulin as a first-line agent to treat diabetes in cirrhotic patients. The main risk of insulin is severe hypoglycemia. Patients with cirrhosis have reduced hepatic glycogen stores. Glucagon may stimulate less hepatic glycogenolysis in cirrhotic patients than in patients without liver disease.<sup>1</sup> Also, many patients with severe hepatic dysfunction have hepatic encephalopathy, which may impair their ability to comply with instructions about therapy.

Patients with cirrhosis and diabetes have a shorter life expectancy than do nondiabetic patients with cirrhosis, but they typically die of complications of liver disease, such as gastrointestinal hemorrhage, rather than from complications of diabetes, such as cardiovascular

disease.<sup>2,3,5</sup> This suggests that in cirrhotic patients, the development of diabetes reflects a greater degree of liver failure.

No studies have been conducted to determine whether patients with cirrhosis benefit from diabetes treatment. However, there are several situations in which cirrhotic patients would be expected to benefit from glucose control. Treatment for symptomatic hyperglycemia should be used to reduce symptoms. Treatment of persistent hyperglycemia would be expected to lessen the risk of infection. Patients with A1C results  $\geq 7\%$  who are awaiting liver transplantation or whose life expectancy is expected to be several years might benefit from a lower risk of diabetes complications if their diabetes is treated.

In J.T.'s case, he was observed off therapy for about 6 months. He eventually started low-dose insulin for persistent hyperglycemia  $> 200$  mg/dl, A1C  $> 7.5\%$ , and patient preference. He did not have any episodes of severe hypoglycemia. He died of complications from liver disease 2 years after he was diagnosed with diabetes.

#### Clinical Pearls

- Severe hepatic dysfunction can cause IGT and diabetes. The clinical distinction between type 2 diabetes and liver diabetes is based on the onset of diabetes relative to the onset of cirrhosis and on whether the patient has typical risk factors for type 2 diabetes.
- A1C results may be spuriously low in patients with severe liver dysfunction.
- All currently available oral hypoglycemic agents pose some risk of hepatotoxicity. Metformin and thiazolidinediones should be avoided in patients with significant hepatic dysfunction. Many clinicians consider insulin to be the first-line agent for treating diabetes in patients with significant liver disease, although some clinicians advocate the cautious use of sulfonylureas in this situation.<sup>1</sup>
- Patients with cirrhosis are especially susceptible to hypoglycemia and may respond poorly to glucagon.
- Among patients with cirrhosis and diabetes, the main cause of death is hepatic failure rather than cardiovascular disease or other complications of diabetes.

- An individualized assessment of risks of benefits of diabetes treatment should be considered for each patient.

#### REFERENCES

<sup>1</sup>Petrides AS: Liver disease and diabetes mellitus. *Diabetes Revs* 2:2–18, 1994

<sup>2</sup>Holstein A, Hinze S, Thieben E, Plaschke A, Egberts E-H: Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol* 17:677–681, 2002

<sup>3</sup>Marchesini G, Ronchi M, Forlani G, Bugianesi E, Bianchi G, Fabbri A, Zoli M, Melchionda N: Cardiovascular disease in cirrhosis. *Am J Gastroenterol* 94:655–662, 1999

<sup>4</sup>Owens D, Jones EA, Carson ER: Studies on the kinetics of unconjugated [<sup>14</sup>C] bilirubin metabolism in normal subjects and patients with compensated cirrhosis. *Clin Sci Mol Med* 52:555–570, 1977

<sup>5</sup>Bianchi G, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E: Prognostic significance of diabetes in patients with cirrhosis. *Hepatology* 20:119–125, 1994

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## Case Study: Uncontrolled Type 2 Diabetes in a 48-Year-Old Woman on Interferon $\beta$ -1b Treatment for Multiple Sclerosis

Hema Padmanabhan, MD

#### Presentation

M.W. is a 48-year-old woman with a 15-year history of type 2 diabetes that has been treated with insulin for 13 years. She has a history of multiple sclerosis for 8 years, and had been relatively stable for 7 years on interferon (IFN)  $\beta$ -1b injections.

Recently she suffered from at least two exacerbations of the disease, requiring steroid therapy with intravenous methylprednisolone. She subsequently presented to the emergency room with uncontrolled diabetes (without acidosis). She also had a history of primary hypothyroidism (secondary to congenital

absence of thyroid), hyperlipidemia, peripheral neuropathy, and nephropathy, but no evidence of hypertension or coronary artery disease.

From the time diabetes was diagnosed, her insulin regimen and dosage were modified several times. She received a thiazolidinedione (TZD) for a

brief period, which was later discontinued because of bilateral lower extremity swelling. Her diabetes remained uncontrolled after the above hospitalization despite increases of her insulin dose to 52 units of glargine in the morning with 10–12 units of lispro with each meal.

The fasting, premeal, and bedtime blood glucose levels remained at 270–330 mg/dl. Therefore, twice-daily metformin (up to 1,000 mg twice daily) was added.

The dose of glargine was gradually increased based on her blood glucose profile up to 200 units in the morning and 240 units at bedtime, with 130 units of lispro with meals. Her blood glucose levels remained in the 400 mg/dl or higher range. The patient remained relatively asymptomatic except for dry mouth.

She was admitted to the hospital electively for planned intravenous insulin therapy in order to break the glucose toxicity. Her lab results were remarkable for normal carbon dioxide and a normal anion gap. Her blood glucose decreased temporarily to 150–180 mg/dl after up to 10 units/hour of regular insulin infusion. It remained in this range for only 48 hours and then increased again to 500–600 mg/dl.

Her medication list included levothyroxine, 100 µg daily; glargine and lispro insulins; metformin, 1,000 mg twice daily; neurontin, 600 mg three times daily; and daily IFN β-1b injections. Both an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker were previously discontinued because of dizziness and low blood pressure (in the range of 90/50–100/60 mmHg).

The Physician Drug Reference lists diabetes as one of the side effects of IFN β-1b treatment. Therefore, M.W.'s neurologist was consulted regarding switching the patient to an alternative, IFN β-1a, which does not list diabetes as a known side effect. IFN β-1b was discontinued, and IFN β-1a was introduced. Her blood glucose profile improved remarkably, with fasting and premeal levels in the 86–138 mg/dl range. Her insulin requirement dropped dramati-

cally to 45 units of glargine at bedtime and 3–4 units of lispro with meals. M.W.'s hemoglobin A<sub>1c</sub> while on IFN β-1b treatment was 12.7%. After 7 weeks of IFN β-1a treatment, it improved to 7.1%.

### Questions

1. Can worsening of glycemic control in type 2 diabetes be associated with IFN β-1b treatment?
2. Can substituting IFN β-1a for IFN β-1b result in better control of blood glucose?

### Commentary

Type 2 diabetes is the result of insulin resistance in the peripheral tissues, together with relative impairment of α-cell insulin secretion. Type 1 diabetes is an autoimmune disease resulting from destruction of α-cells. Cytokines, such as interleukin 2 and α-interferon (α-IFN), can enhance immune functions and initiate or augment an autoimmune process.<sup>1</sup>

Stimulation of immune responses may have deleterious consequences. Cytokine-induced exacerbation of underlying diseases or immune dysregulation are examples. α-IFN may enhance an ongoing autoimmune process directed against pancreatic α-cells and be involved in the development of type 1 diabetes in predisposed patients.<sup>2,3</sup>

α-IFN treatment has now been clearly linked to the exacerbation or occurrence of several types of autoimmune diseases (thyroiditis, systemic lupus erythematosus, hemolytic disease, as well as type 1 diabetes) and diseases involving altered cell-mediated immune functions (inflammatory dermatological diseases, nephritis, colitis, pneumonitis).<sup>4</sup> In contrast, immunological side effects of IFN β and IFN γ (another IFN) have been seldom reported, although a case of type 1 diabetes induced by administration of IFN β has been reported.<sup>5</sup>

Interferon β (both 1a and 1b) is now the most widely prescribed therapy for long-term immunomodulation of multiple sclerosis. The recombinant IFN β

requires continued administration to decrease disease activity.

IFN, produced in many viral infections, stimulates counter-regulatory hormone secretion, impairs glucose tolerance and insulin sensitivity, and increases insulin clearance.<sup>6</sup>

Flu-like symptoms, transient worsening of multiple sclerosis (especially spasticity), laboratory abnormalities, subcutaneous necrosis, and inflammation at the injection site are common side effects. Delayed occurrence of a severe cutaneous reaction has been reported in a multiple sclerosis patient taking IFN β-1b.<sup>7</sup>

The mechanism of the development of worsening glycemic control in this patient with type 2 diabetes is not clear. One may speculate based on the observed effects of IFN β-1b that one of two mechanisms occurred:

1. Worsening of peripheral insulin resistance
2. Transient damage to pancreatic β-cells via enhancement of an autoimmune process and temporary insulin deficiency.

Either of these phenomena could have resulted in her metabolic deterioration.

### Clinical Pearls

- IFN β-1b must be used with caution in patients with documented diabetes or known predisposition toward developing the disease.
- Therefore, in patients with preexisting diabetes, IFN β-1a may be desirable because it is less likely to cause worsening of diabetes control.

### REFERENCES

<sup>1</sup>Whitehead RP, Hauschild A, Christophers E, Figlin R: Diabetes mellitus in cancer patients treated with combination interleukin 2 and α-interferon. *Cancer Biother* 10:45–51, 1995

<sup>2</sup>Huang X, Yuang J, Goddard A, Foulis A, James RF, Lernmark A, Pujol-Borrell R, Rabinovitch A, Somoza N, Stewart TA: Interferon expression in the pancreases of patients with type 1 diabetes. *Diabetes* 44:658–664, 1995

<sup>3</sup>Fabris P, Betterle C, Greggio NA, Zanchetta

R, Bosi E, Biasin MR, de Lalla F: Insulin-dependent diabetes mellitus during  $\alpha$ -interferon therapy for chronic viral hepatitis. *J Hepatol* 28:514–517, 1998

<sup>4</sup>Vial T, Descotes J: Immune-mediated side-effects of cytokines in humans. *Toxicology* 105:31–57, 1995

<sup>5</sup>Kado S, Miyamoto J, Komatsu N, Iwaki Y, Ozaki H, Taguchi H, Kure M, Sarashina G,

Watanabe T, Katsura Y, Nemoto Y, Noritake M, Matsuoka T: Type 1 diabetes mellitus caused by treatment with interferon- $\beta$ . *Intern Med* 39:146–149, 2000

<sup>6</sup>Koivisto VA, Pelkonen R, Cantell K: Effect of interferon on glucose tolerance and insulin sensitivity. *Diabetes* 38:641–647, 1989

<sup>7</sup>Cohen BA, Greenberger PA, Saini S: Delayed occurrence of a severe cutaneous reac-

tion in a multiple sclerosis patient taking interferon  $\beta$ -1b. *Allergy Asthma Proc* 19:85–88, 1998

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## Case Study: The Prevention of Diabetes Through Diet and Intense Exercise

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### Presentation

L.H. is a 46-year-old married Hispanic man who sees his primary physician for scheduled diabetes screening. Although he is overweight (6 feet tall, 206 lb, BMI 27.8 kg/m<sup>2</sup>) and on medication to control his blood pressure, L.H. has no evidence of coronary heart disease or any family history of diabetes. However, last year his fasting glucose level was 122 mg/dl. Two weeks before his appointment, a random glucose test performed with a blood glucose meter at a local health fair revealed 180 mg/dl. At the time of his appointment, routine laboratory results indicate slightly elevated lipids: LDL cholesterol 142 mg/dl and total cholesterol 200 mg/dl. Fasting glucose is 154 mg/dl. Once an avid runner, L.H. has become less physically active in the past year, and his exercise consists of ~ 300 minutes of low-intensity physical activity per week.

L.H. typically eats 2 cups of cereal, 12 oz. of low-fat milk, and a large apple for breakfast. His lunch consists of one turkey or ham sandwich and one large apple. His main meal is a late dinner of large portions of Mexican food (such as enchiladas with rice), low-fat milk, and cookies. His average daily caloric intake

obtained from three different 24-hour recalls was 2,300 kcal.

After the evaluation, the primary physician explains the risks of diabetes and the importance of lifestyle modification to L.H. The physician also explains that an oral glucose tolerance test could be ordered to confirm a diagnosis of diabetes. The physician challenges L.H. to start an intense exercise program and make lifestyle modifications. L.H. is also referred to a registered dietitian for medical nutrition therapy. A 2-month follow-up appointment is scheduled.

### Questions

1. What type of lifestyle modification should be prescribed for L.H.?
2. What was the outcome after 2 months of treatment?
3. Can risk factors for diabetes be reversed in a short period of time with intense exercise and diet?

### Commentary

#### 1. What type of lifestyle modification should be effective for L. H.?

Because of his athletic history, L.H. was placed on an intense exercise program that consisted of running on a

treadmill 40 minutes/day, six days per week. After nutritional assessment and intervention, L.H. followed an 1,800 kcal/day meal plan. Food items such as flaxseeds, wheat germ, pecans, cinnamon powder, and skim milk were included with the morning cereal. Lunch remained the same as before. Dinner, now scheduled at 6:00 p.m., consisted mostly of baked fish fillet or salmon, steamed rice, and vegetables. A bedtime snack included low-fat milk and a granola bar. The intense exercise program and diet was composed of an average caloric deficit of 1,000 kcal/day (500 kcal from food intake and 500 kcal burned on the treadmill).

#### 2. What were the outcomes of the treatment after 2 months?

Aware of the adverse effects of diabetes, L.H. was committed to his treatment and was able to lose 7% of his body weight. The average weekly weight loss was 2 lb. His BMI after 2 months of exercise and diet was 25.8 kg/m<sup>2</sup>. Laboratory results for his follow-up appointment revealed a fasting glucose of 109 mg/dl, LDL cholesterol of 93 mg/dl, and total cholesterol of 146 mg/dl. During the second month of the treatment period,

his blood glucose was monitored and the 2-hour postprandial values were in the range of 97–102 mg/dl.

### 3. Can the risk factors for diabetes be reversed in a short period of time with diet and intense exercise?

In the 2-month period of treatment, an average of 1,000 kcal/day deficit allowed L.H. to lose 16 lb and to normalize his lipid profile, fasting glucose, and postprandial glucose levels. Motivation, diet, and intense exercise were crucial for L.H. in preventing a positive diabetes diagnosis by the time of his follow-up appointment. A weight loss of 16 lb could not have been achieved with the low-intensity exercise regimen L.H. was on during the previous year, and a positive diagnosis for diabetes could not have been prevented within the 2 months before the follow-up physician's appointment.

The patient was determined to make lifestyle changes, and motivation was a critical factor in preventing diabetes. For individuals at high risk, such as L.H., intensive lifestyle modification including a healthy diet and increased physical activity are crucial to prevent the onset of type 2 diabetes. The major dietary change in this case was decreasing caloric intake through portion control. For many patients, dietary intervention must also focus on reducing dietary fat intake, although for L.H., dietary fat intake was within recommended levels.

The major physical activity change for L.H. was a fairly intensive level of caloric expenditure, achieved by 40 minutes/day, six days per week of running on a treadmill. Many patients may not be able to achieve this level of physical activity, but this was reasonable for L.H. because of his athletic background. In addition to lifestyle changes, another treatment option for patients such as L.H. could be the use of a hypoglycemic agent such as metformin.

Extensive studies such as the Diabetes Prevention Program have compared lifestyle intervention with hypoglycemic agents and concluded that lifestyle changes are more effective than therapeutic agents. In order to potentially reverse diabetes risk factors, a 7% weight loss incentive and at least 150 minutes of physical activity per week has been recommended.

In a study conducted by Heled et al.,<sup>1</sup> three treatments were used to test the hypothesis that exercise training might prevent diabetes in *Psammomys obesus* (rodent animal models used to study diet-induced type 2 diabetes). The treatments included a high-energy diet, a high-energy diet plus exercise, and a low-energy diet, with protein kinase C- $\delta$  activity being measured. Conclusions from that study demonstrated for the first time that exercise training effectively prevented the progression of type 2 diabetes in *Psammomys obesus*. The study suggested that a mechanism involving protein kinase C- $\delta$ , a group of

enzymes that enhance glucose transport, may be involved in the adaptive effects of exercise in skeletal muscles that lead to the prevention of type 2 diabetes.

### Clinical Pearls

- Lifestyle modification including increased physical exercise and healthy diet can result in lower rates of diabetes.
- Patients' motivation is crucial to reversing diabetes risk factors.

### REFERENCE

<sup>1</sup>Heled Y, Shapiro Y, Shani Y, Moran DS, Langzam L, Braiman L, Sampson SR, Meyerovitch J: Physical exercise prevents the development of type 2 diabetes mellitus in *Psammomys obesus*. *Am J Physiol Endocrinol Metab* 282:E370–E375, 2002

### SUGGESTED READINGS

Hirsch IB: The prevention of type 2 diabetes: are we ready for the challenge? *Clin Diabetes* 20:106–108, 2002

Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, the Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002

Uusitupa M, Louheranta A, Lindstrom J, Valle T, Sundvall J, Eriksson Tuomilehto J: The Finnish Diabetes Prevention Study. *Br J Nutr* 83:S137–S142, 2000

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