

Case Study: A Patient with Diabetes, Hepatitis C Virus Infection, and Hemochromatosis Gene Mutation

Aidar R. Gosmanov, MD, PhD, DMSc, and Guillermo E. Umpierrez, MD

PRESENTATION

J.W., a 51-year-old African-American man, presented with fatigue, polyuria, and polydipsia. He was diagnosed with insulin-dependent diabetes mellitus 1 year ago when he presented with nonketotic hyperglycemic hyperosmolar syndrome. At the initial presentation, his blood glucose was 625 mg/dl, and his A1C was 18.9%. His adherence to a diabetes treatment, including basal and premeal insulin, was poor, which led to four different hospitalizations with hyperglycemic crises during the past year. His family history was unknown because he was adopted.

Physical examination was remarkable for sinus tachycardia and dry mucous membranes. He was afebrile, was hemodynamically stable, and had a BMI of 22.2 kg/m². Initial laboratory testing showed hemoglobin of 12.8 g/dl, sodium of 133 mmol/l, creatinine of 0.9 mg/dl, glucose of 590 mg/dl, bicarbonate of 29 mmol/l, normal anion gap, and negative urinary ketones. A chest X-ray and urinalysis did not indicate the presence of infection. He was treated with forced hydration and insulin therapy, with rapid resolution of hyperglycemia.

During this admission, his A1C was 12.1%; thyroid-stimulating hormone and total testosterone were within normal limits. A fasting lipid panel revealed total cholesterol of 129 mg/dl, triglycerides of 74 mg/dl, and HDL cholesterol of 32 mg/dl.

Subsequent laboratory studies done in the fasting condition revealed ferritin of 1,789 ng/ml, iron of 202 µg/dl, and transferrin of 276 µg/dl (calculated transferrin saturation of 73%); iron studies were repeated yielding similar results. Liver tests were significant for aspartate aminotransferase (AST) of 56 U/l and alanine aminotransferase (ALT) of 76 U/l, indicating mild elevation. Serological studies for chronic hepatitis demonstrated presence of hepatitis C (HCV), type 1b genotype. His C-peptide level was 0.7 ng/ml, and antibodies to GAD65 were not detected. Genetic testing for hereditary hemochromatosis (HH) showed that the patient was heterozygous for C282Y mutation (a carrier state). Hemoglobin electrophoresis did not reveal abnormal hemoglobin variants. Abdominal ultrasound demonstrated normal liver, spleen, and kidneys.

During the hospital stay, his condition improved, and his blood glucose significantly decreased after volume resuscitation and subcutaneous insulin therapy. He was discharged home with scheduled outpatient appointments.

QUESTIONS

1. What type of diabetes does this patient have?
2. What is the prevalence of diabetes in patients with chronic hepatitis C?
3. Does positive HH genotype

contribute to the development of diabetes?

COMMENTARY

The American Diabetes Association classifies diabetes into four categories: type 1 diabetes, characterized by absolute insulin deficiency caused by autoimmune β-cell destruction (type 1A) and, rarely, idiopathic (type 1B); type 2 diabetes, characterized by impaired insulin secretion and insulin resistance; gestational diabetes; and other specific types of diabetes.¹ The latter category of diabetes is broad and considers a variety of conditions, such as medications, endocrinopathies, infections, and genetic conditions affecting β-cells or insulin signaling.

This patient had several admissions with hyperglycemic crises and a low basal C-peptide concentration, suggesting type 1 diabetes. However, there was no evidence of autoimmune involvement given the absence of GAD65 antibodies. Diabetic subjects with a history of hyperglycemic crises, negative autoimmune markers, and low insulin secretion (defined as a basal C-peptide < 1 ng/dl) are classified as having type 1B, or atypical, diabetes.^{2,3} Despite the absence of autoimmunity, almost 100% of subjects with type 1B diabetes require lifelong insulin therapy and are at risk of

recurrent hyperglycemic crises and ketoacidosis.²

Both HCV infection and HH are associated with increased risk of developing diabetes. Diabetes is now recognized as one of the extra-hepatic manifestations of HCV infection.⁴⁻⁶ People with chronic HCV infection have a two- to four-fold higher likelihood of developing diabetes than nondiabetic control subjects. On the other hand, the prevalence of HCV infection is 2.5 times higher in patients with diabetes than in those without diabetes.⁷ Prevalence of HCV infection is disproportionate in U.S. minorities; non-Hispanic blacks are more prone to have HCV antibodies than whites or Hispanic whites.⁸

Advanced liver disease appears to potentiate the diabetogenic action of infection because as many as half of all patients with HCV cirrhosis develop diabetes. The clinical phenotype of a patient with HCV infection and diabetes is characterized by onset of diabetes in the fifth or sixth decade of life, BMI < 30 kg/m², lower cholesterol level, and advanced liver disease.

Multiple factors may contribute to the pathogenesis of diabetes in patients with HCV infection.^{5,6} Insulin resistance is a core defect in development of HCV-associated diabetes. Increasing evidence indicates that decreased insulin action in the liver is caused by hepatic steatosis/fibrosis and surge in proinflammatory cytokines tumor necrosis factor (TNF)- α and interleukin-6, as well as impaired insulin action in peripheral tissues, primarily muscle, largely underlined by TNF- α effects. Autoimmunity and α -cell cytopathic mechanism are unlikely to represent a primary mechanism in the pathogenesis of diabetes in HCV infection. Based on available clinical evidence, testing is recommended for HCV in individuals with diabetes

and elevated liver enzymes (AST and ALT).⁹

“Bronze diabetes” (diabetes related to iron-caused damage to the pancreas and characterized by a bronze skin tone caused by excess iron) has been considered a cardinal clinical manifestation of HH. Recent advances in genetic testing have elucidated that homozygosity of HFE gene mutation on single amino acid substitution in a certain position may lead to a severe tissue iron overload and the characteristic HH phenotype.¹⁰ It has been suggested that three key mechanisms could mediate iron-induced diabetes: insulin deficiency, insulin resistance, and hepatic dysfunction.¹¹ Iron overload can overwhelm antioxidant defense systems in pancreas and peripheral tissues, thereby promoting defects in insulin secretion and insulin effects, respectively.

Heterozygosity of HFE gene on C282Y or H63D mutation is unlikely to result in end-organ dysfunction, liver disease, or diabetes, but it may predispose to a significant iron overload in the presence of associated comorbidities, such as chronic HCV or alcohol use.¹² Recent population studies have demonstrated a frequency of HFE gene mutation in different racial cohorts. In the United States, C282Y homozygosity is present in 0.4% of whites, 0.01–0.03% of African Americans, and 0.027% in Mexican Americans; heterozygosity for C282Y mutation is identified in almost 10% of whites and 2% of African Americans.¹⁰⁻¹³

Progress in HH screening and genetics translates to an early diagnosis and therapy of this disease. Screening for HH is only initiated if there is high clinical suspicion for this condition. Fasting transferrin saturation > 45–50% and ferritin level > 200 μ g/l in women and > 300 μ g/l in men is an indication for HFE genotype testing.¹⁰ Recent

studies, however, have shown that the prevalence of diabetes in patients with HH may not differ from that in the general population.^{14,15} Thus, it has not been clear whether screening for HH should be performed in patients with diabetes.

Hahn et al.¹⁶ studied 3,500 white subjects with diabetes and found evidence of iron overload in 35 subjects, or 1% of the cohort, five of whom eventually were confirmed with having HH. The authors therefore emphasized the cost-effectiveness of screening of patients with diabetes for HH. Interestingly, it has also been suggested that C282Y genotype may predispose to higher risk of developing acute or chronic HCV infection.¹⁷ Our patient demonstrated the iron overload phenotype, which likely occurred in the presence of both HCV infection and HFE gene mutation.

No previous studies have reported on the prevalence of HCV infection or HH in patients with type 1B or idiopathic diabetes. HCV infection increases the risk of developing type 2 diabetes by two- to fourfold because of increased insulin resistance, both in the liver and in peripheral tissues. Similarly, iron overload and HH may also lead to end-organ damage and increased risk of type 2 diabetes because of hepatic and peripheral insulin resistance and impaired insulin secretion.

No retrospective or prospective clinical studies have investigated the presence of the coexisting HCV infection and HFE gene mutation in patients with idiopathic type 1B diabetes. However, given the high prevalence of these conditions, epidemiological studies are needed to elucidate a potential association between diabetes, chronic HCV infection, and HH gene mutation.

It is possible that longstanding hyperglycemia in our patient may have resulted in β -cell dysfunction.

This concept is known as glucose toxicity or glucose desensitization.^{18,19} Human studies have shown convincingly that β -cell function improves after chronic hyperglycemia is relieved by successful diabetes therapy.²⁰ Although the pathogenesis of glucose desensitization is not completely understood, it appears that chronic hyperglycemia induces a generalized downregulation of the glucose processing system that, at the level of the pancreas, may lead to impaired β -cell function and insulinopenia. The “blindness” of β -cells to glucose stimulation during sustained hyperglycemia may involve a reduction in the insulin and pancreatic duodenal homeobox factor-1 (PDX-1) gene expression.²¹ PDX-1 is a key transcriptional factor that regulates gene transcription in response to glucose. Thus, the putative role of glucose-induced β -cell desensitization has broad implications for the management of patients with decompensated diabetes and implies not only that hyperglycemia may be a consequence of altered β -cell function, but also, more importantly, that hyperglycemia might be an important etiological factor in the pathogenesis of metabolic decompensation.

CLINICAL PEARLS

- Diabetes is highly prevalent in patients with HCV infection and vice versa. In patients with diabetes who have abnormal serum transaminases, HCV infection should be considered and appropriate testing initiated.
- Iron overload manifested by elevated transferrin saturation and ferritin concentration in patients with diabetes may occur because of HFE gene mutation, and testing for HH in such a scenario may be indicated. In addition, other causes of iron overload, even in the presence of HH genotype, such as chronic

liver disease, hemoglobin variants, and transfusion history, should be considered.

- New-onset diabetes usually engages initiation of antidiabetic treatment. However, as in this case, diabetes can develop as a result of the interplay of different factors that are known to affect glucose metabolism. Therefore, guided by clinical judgment, a work-up for a presence of medical problems known to exert diabetogenic effects can be considered when diagnosis of diabetes is made.

REFERENCES

¹American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 31 (Suppl. 1):S55–S60, 2008

²Balasubramanyam A, Garza G, Rodriguez L, Hampe CS, Gaur L, Lernmark A, Maldonado MR: Accuracy and predictive value of classification schemes for ketosis-prone diabetes. *Diabetes Care* 29:2575–2579, 2006

³Umpierrez GE, Smiley D, Kitabchi AE: Narrative review: ketosis-prone type 2 diabetes mellitus. *Ann Intern Med* 144:350–357, 2006

⁴Antonelli A, Ferri C, Fallahi P, Pampana A, Ferrari SM, Goglia F, Ferrannini E: Hepatitis C virus infection: evidence for an association with type 2 diabetes. *Diabetes Care* 28:2548–2550, 2005

⁵Lecube A, Hernandez C, Genesca J, Simo R: Glucose abnormalities in patients with hepatitis C virus infection: epidemiology and pathogenesis. *Diabetes Care* 29:1140–1149, 2006

⁶Noto H, Raskin P: Hepatitis C infection and diabetes. *J Diabetes Complications* 20:113–120, 2006

⁷Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, Guo L, Jacob S, Regenstein FG, Zimmerman R, Everhart JE, Wasserfall C, Maclaren NK, Perrillo RP: Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 29:328–333, 1999

⁸Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ: The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 144:705–714, 2006

⁹Simo R, Hernandez C, Genesca J, Jardi R, Mesa J: High prevalence of hepatitis C virus infection in diabetic patients. *Diabetes Care* 19:998–1000, 1996

¹⁰Yen AW, Fancher TL, Bowlus CL: Revisiting hereditary hemochromatosis: current concepts and progress. *Am J Med* 119:391–399, 2006

¹¹Swaminathan S, Fonseca VA, Alam MG, Shah SV: The role of iron in diabetes and its complications. *Diabetes Care* 30:1926–1933, 2007

¹²Bulaj ZJ, Griffen LM, Jorde LB, Edwards CQ, Kushner JP: Clinical and biochemical abnormalities in people heterozygous for hemochromatosis. *N Engl J Med* 335:1799–1805, 1996

¹³Dawkins FW, Gordeuk VR, Snively BM, Lovato L, Barton JC, Acton RT, McLaren GD, Leiendecker-Foster C, McLaren CE, Adams PC, Speechley M, Harris EL, Jackson S, Thomson EJ: African Americans at risk for increased iron stores or liver disease. *Am J Med* 120:734.e1–734.e9, 2007

¹⁴Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, McLaren CE, Bahlo M, Nisselle AE, Vulpe CD, Anderson GJ, Southey MC, Giles GG, English DR, Hopper JL, Olynyk JK, Powell LW, Gertig DM: Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med* 358:221–230, 2008

¹⁵Ellervik C, Birgens H, Tybjaerg-Hansen A, Nordestgaard BG: Hemochromatosis genotypes and risk of 31 disease endpoints: meta-analyses including 66,000 cases and 226,000 controls. *Hepatology* 46:1071–1080, 2007

¹⁶Hahn JU, Steiner M, Bochnig S, Schmidt H, Schuff-Werner P, Kerner W: Evaluation of a diagnostic algorithm for hereditary hemochromatosis in 3,500 patients with diabetes. *Diabetes Care* 29:464–466, 2006

¹⁷Bonkovsky HL, Troy N, McNeal K, Banner BF, Sharma A, Obando J, Mehta S, Koff RS, Liu Q, Hsieh CC: Iron and HFE or TFR1 mutations as comorbid factors for development and progression of chronic hepatitis C. *J Hepatol* 37:848–854, 2002

¹⁸Robertson RP, Olson LK, Zhang HJ: Differentiating glucose toxicity from glucose desensitization: a new message from the insulin gene. *Diabetes* 43:1085–1089, 1994

¹⁹Yki-Jarvinen H: Glucose toxicity. *Endocr Rev* 13:415–431, 1992

²⁰Kahn SE: Clinical review 135: the importance of beta-cell failure in the development and progression of type 2 diabetes. *J Clin Endocrinol Metab* 86:4047–4058, 2001

²¹Robertson RP, Harmon JS: Diabetes, glucose toxicity, and oxidative stress: a case of double jeopardy for the pancreatic islet beta cell. *Free Radic Biol Med* 41:177–184, 2006

Aidar R. Gosmanov, MD, PhD, DMSc, is an endocrinology fellow, and Guillermo E. Umpierrez, MD, is a professor in the Department of Medicine, Division of Endocrinology, Metabolism, and Lipids at Emory University School of Medicine in Atlanta, Ga.