

Case Study: “Birds of a Feather Flock Together”: Type 1A Diabetes and Other Autoimmune Disease States

Russell D. White, MD, and George D. Harris, MD, MS

Presentation

W.E.W. is a 54-year-old white man who has type 1A diabetes, the most common form of type 1 diabetes. Type 1A diabetes is a cellular-mediated autoimmune disease characterized by the production of autoantibodies causing β -cell destruction and subsequent insulin deficiency.¹

At age 12 years, he was diagnosed with vitiligo. This autoimmune dermatological process involved mainly his neck, arms, and hands. After repeated medical consultations, he and his family received reassurance, but no treatment was recommended.

At age 14 years, W.E.W. was diagnosed with type 1 diabetes after the onset of polyuria, polydipsia, and weight loss. Because an older brother had been previously diagnosed at age 12 years with type 1 diabetes, his mother diagnosed his diabetes via home urine testing in 1964. Type 1 diabetes was subsequently confirmed via venous blood testing, W.E.W. was hospitalized, and insulin therapy was initiated.

In 1984, W.E.W. was diagnosed with Hashimoto's thyroiditis after experiencing fatigue, poor exercise tolerance, and weight gain. Thyroid peroxidase antibodies were positive, and he was begun on levothyroxine replacement therapy. His presenting symptoms resolved with this treatment. At age 34 years, W.E.W. now had three coexisting autoimmune diseases.

Pertinent family history includes:

- mother with Hashimoto's thyroiditis
- brother with type 1 diabetes
- paternal grandfather with Graves' disease

- suspicion of type 1 diabetes in a paternal great uncle. (This relative died without a definitive diagnosis at age 18 years in 1917, after a 2-month history of weight loss and frequent urination.)

Questions

1. How common are other autoimmune diseases in patients with type 1A diabetes?
2. In which patients should health care providers be more vigilant in testing for these other disease states?
3. What symptoms offer clues to other autoimmune disease entities?

Commentary

This case demonstrates the importance of both the patient's medical history and family history. Many autoimmune diseases have an insidious onset and rarely present as an acute medical problem. Primary care providers often are in the unique position to make the proper diagnosis in patients such as W.E.W. However, because of time constraints, providers may fail to collect all of the patient's medical history and family history or ignore this factual history after obtaining it.

Polyglandular autoimmune (PGA) syndromes are constellations of multiple endocrine gland insufficiencies. Three types are now recognized.^{2,3} Type I PGA is rare and presents in childhood. It is associated with candidiasis, hypoparathyroidism, and adrenal failure and is a rare disorder, having sporadic autosomal recessive inheritance. Type III PGA is the co-occurrence of autoimmune thyroid disease with two

other autoimmune disorders, including type 1A diabetes, pernicious anemia, or a nonendocrine, organ-specific, autoimmune disorder such as alopecia or vitiligo. Because it does not involve the adrenal cortex, Addison's disease is absent. Type II PGA is the most common and is defined as primary adrenal insufficiency (Addison's disease) with either autoimmune thyroid disease (Hashimoto's thyroiditis) or type 1A diabetes occurring in the same individual. Primary hypogonadism, Graves' disease, myasthenia gravis, pernicious anemia, Parkinson's disease, vitiligo, and celiac disease may also be observed in this syndrome. PGA II occurs primarily in adulthood, usually around the 3rd and 4th decades of life, and is associated with HLA-DR3 and/or HLA-DR4 haplotypes. Its pattern of inheritance is autosomal dominant with variable expressivity.^{3,4}

The pathophysiology of PGA II is thought to include an initial genetic susceptibility of the individual, allowing exposure to an autoimmune trigger (environmental or intrinsic factor), which initiates immunological change in specific proteins. These proteins mimic the molecular structure of a self-antigen and start the active production of organ-specific autoantibodies as well as the occurrence of autoimmune activity in the respective organ. This process leads to progressive glandular destruction. Unfortunately, the individual is asymptomatic during this process. Not until extensive organ damage has occurred does overt clinical disease ensue, as autoantibodies react to target tissue-specific antigens.^{2,3}

As mentioned above, type 1A diabetes is an autoimmune disease characterized by β -cell destruction and subsequent insulin deficiency. Approximately 85–90% of people with type 1 diabetes test positive for autoantibodies and are deemed to have type 1A. The remaining individuals test negative for autoantibodies and are classified as having idiopathic type 1 diabetes, sometimes called type 1B diabetes.¹ Many type 1A diabetic patients have a personal or family history of other autoimmune diseases, such as Hashimoto’s thyroiditis, Addison’s disease, pernicious anemia, or vitiligo.⁵

The insidious autoimmune process of type 1A diabetes begins long before clinical symptoms occur and a diagnosis is confirmed (Figure 1). More than 90% destruction of the components of the β -cells within the islets of Langerhans occurs before the onset of clinical symptoms. Autoantibodies that have been associated with type 1A diabetes and serve as markers of this process are listed in Table 1.

Because autoimmune diseases tend to occur in both the same person and within the same family, family members with type 1A diabetes are at risk for the following autoimmune disease states: Addison’s disease, celiac disease, Graves’ disease, Hashimoto’s thyroiditis, hypogonadism, myasthenia gravis, pernicious anemia, and vitiligo (Table 2).^{6–8}

In patients with autoimmune polyendocrine syndromes with a single disease such as type 1A diabetes or Addison’s disease, the prevalence of an additional autoimmune disorder is 30–50 times that in the general population.⁹ Screening should focus on the more common autoimmune disease states (Table 3). Because thyroid disease is the most common, some experts recommend that all patients with type 1A diabetes and their families be screened for autoimmune thyroid disease on a yearly basis. This is definitely indicated if the index case with type 1A diabetes has developed thyroid disease.^{10–14}

As noted, these autoimmune markers may precede overt disease states by

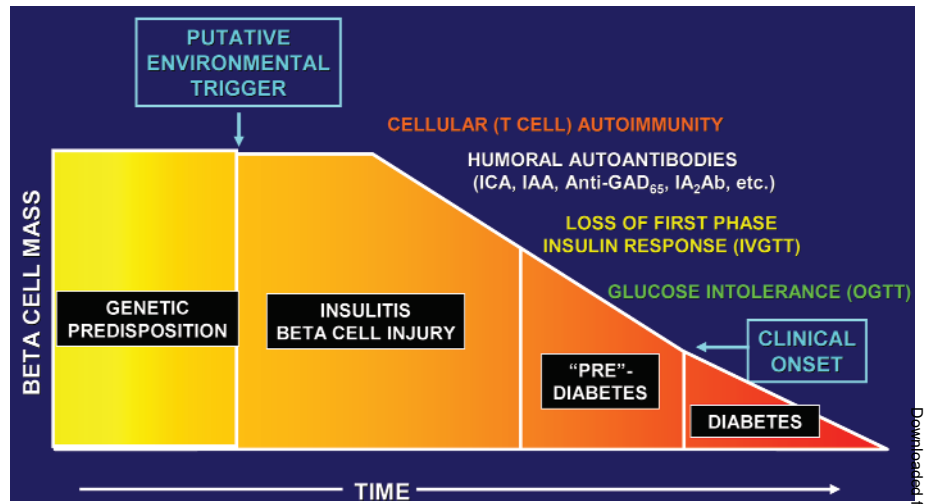


Figure 1. Natural history of type 1 diabetes. Adapted from Refs. 8, 9, and 17–19. IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

Table 1. Antibody Markers

Type 1A Diabetes	
• ICA ICA512, ICA512B	Islet cell autoantibodies (Antibodies formed against the antigen present in the cytoplasm of the endocrine cells in the pancreatic islets)
• IAA	Insulin autoantibodies
• GAD ₆₅	Autoantibodies against glutamic acid decarboxylase
• IA-2A	Insulinoma-associated 2 autoantibodies (Autoantibodies formed against the protein tyrosine phosphatase)
Addison’s disease	21-hydroxylase autoantibody
Hashimoto’s thyroiditis	Thyroid peroxidase autoantibody
Celiac disease	Transglutaminase IgG autoantibody
Graves’ disease	TSH receptor autoantibody
Pernicious anemia	Parietal cell autoantibodies

Table 2. Signs and Symptoms of Autoimmune Disease States

Addison’s disease	Fatigue, nausea, hypotension, hyperpigmentation, hypoglycemia (in type 1A receiving insulin) ¹⁴
Alopecia areata	Hair loss
Celiac disease	Anemia, osteopenia, abdominal pain, diarrhea
Hashimoto’s thyroiditis	Fatigue, weight gain, diastolic hypertension, anemia, hypercholesterolemia, bradycardia
Myasthenia gravis	Weakness, variable fatigue, ocular symptoms
Pernicious anemia	Neuropathic symptoms (balance, coordination difficulties), anemia
Type 1A diabetes	Polyuria, polydipsia, polyphagia, nausea, vomiting, weight loss, abdominal pain, weakness, hypotension
Vitiligo	Patchy loss of skin pigmentation

Table 3. Incidence, Prevalence, and Sex Distribution of Various Autoimmune Diseases

Disease	Incidence/100,000 person-years	Prevalence/100,000	% female
Addison's disease	0.6	14.0	93
Type 1 diabetes < 20 years	12.2	192.0	48
Graves' disease	13.9	1,151.5	88
Hashimoto's thyroiditis	21.8	791.7	95
Pernicious anemia	No data	150.9	67

Adapted from Ref. 16.

years and develop either 1) directly, be pathogenic, and cause damage; 2) serve as markers of disease; or 3) both. In T-cell mediated disorders, such as Hashimoto's thyroiditis, the autoantibodies serve as a marker of the disease state. These autoantibodies may be positive before thyroid-stimulating hormone (TSH) tests become abnormal.

The prevalence of these autoantibodies for other diseases varies. Twelve percent of patients with type 1A diabetes have transglutaminase autoantibodies. Thirty-three percent of patients with type 1A diabetes have thyroid antibodies.⁹ The prevalence depends on the age, race, and ethnic origin of the patient.

In addition, certain triggers are associated with the appearance of autoantibodies and specific autoimmune states. For example, one-third of women with type 1A diabetes will develop postpartum thyroiditis. These patients should be monitored closely for the development of autoimmune thyroid disease states. The administration of interferon- α for one medical condition can induce the formation of antibodies to 21-hydroxylase and islet cell and thyroid antibodies and lead to a new autoimmune state.⁹

Because the signs and symptoms can be subtle, one must be aware of these related disease states and their increased familial incidence (Table 2). Patients with type 1A diabetes and their family members have a 20% risk for developing autoimmune disease. Thyroid disease is the most common autoimmune disease encountered. Fifteen to twenty percent of patients with type 1A diabetes and their

parents or siblings have evidence of thyroid autoimmune disease. This is in contrast to 4.5% in the general population.¹⁵

Some authorities recommend the periodic screening for thyroid disease and pernicious anemia (intrinsic factor autoantibodies). However, no controlled trials have been published, and these recommendations are level C scientific evidence (expert opinion). In patients with type 1A diabetes whose control becomes unstable without obvious cause, one should consider evaluation for an associated autoimmune process.

These related diseases often coexist in the same patient or family. An awareness of these associations can provide clues in the index patient with type 1 diabetes. When diabetes control deteriorates or unexplained symptoms occur, consider a concomitant autoimmune disease process. Often birds of a feather do flock together.

Clinical Pearls

- A prominent family history of autoimmune disease raises the index of suspicion of an autoimmune process in the index patient.
- A previous autoimmune disease in a given patient increases the chances of another autoimmune disease in that same patient.
- When evaluating new presenting symptoms, one should always rule out an additional autoimmune disease process.
- Primary care providers should review patients' recorded medical history and family history when evaluating

patients with new presenting symptoms or complaints. History previously collected and documented in the chart may be overlooked years later.

REFERENCES

¹American Diabetes Association: Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 27 (Suppl. 1):S5-S10, 2004

²Baker JR Jr: Autoimmune endocrine disease. *JAMA* 278:1931-1937, 1997

³Eisenbarth G, Verge C: Immunoendocrinopathy syndromes. In *Williams Textbook of Endocrinology*, 9th ed. Wilson JD, Foster DW, Kronenberg HM, Larsen PR, Eds. Philadelphia, Pa., W.B. Saunders, 1998, p. 1651-1659

⁴Muir A, Katz D, McClaren N: Polyglandular failure syndromes. In *DeGroot Endocrinology*, 3rd ed. DeGroot LJ, Besser M, Burger HG, Jameson JL, Loriaux DL, Marshall JC, Odell WD, Potts JT Jr., Rubenstein AH, Eds. Philadelphia, Pa., W.B. Saunders, 1995, p. 3013-3022

⁵Betterle C, Zanett F, Pedini B, Presotto F, Rapp LB, Monciotti CM, Rigon F: Clinical and subclinical organ-specific autoimmune manifestations in type 1 (insulin-dependent) diabetic patients and their first-degree relatives. *Diabetologia* 26:431-436, 1984

⁶Hanukoglu A, Mizrahi A, Dalal I, Admoni O, Rakover Y, Bistrizter Z, Levine A, Somekh E, Lehmann D, Tuval M, Boaz M, Golander A: Extrapancratic autoimmune manifestations in type 1 diabetes patients and their first-degree relatives. *Diabetes Care* 26:1235-1240, 2003

⁷McAulay V, Fier BM: Addison's disease in type 1 diabetes presenting with recurrent hypoglycemia. *Postgrad Med J* 76:230-232, 2000

⁸Paronen J, Eisenbarth GS: Immunopathogenesis of type 1 diabetes in western society. In *International Textbook of Diabetes Mellitus*, 3rd ed. DeFronzo RA, Ferrannini E, Deen H, Zimmet P, Eds. Chichester, U.K., John Wiley & Sons, 2004, p. 495-513

⁹Eisenbarth GS, Gottlieb PA: Autoimmune polyendocrine syndromes. *N Engl J Med* 350:2068-2079, 2004

¹⁰Holl RW, Bohm B, Loos U, Grabert M, Heinze E, Homoki J: Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: effect of age, gender, and HLA type. *Horm Res* 52:113-118, 1999

¹¹Leong KS, Wilding J, et al.: Clinical presentation of thyroid dysfunction and Addison's disease in young adults with type 1 diabetes. *Postgrad Med J* 75:467-470, 1999

¹²Maugendre D, Massart C, Karacatsanis C, Guilhem I, Poirier JY, Sonnet E, Allanic H: Increased prevalence of thyroid autoantibodies and subclinical thyroid failure in relatives of patients with overt endocrine disease-associated diabetes but not type 1 diabetes alone. *Diabetes Metab* 23:302-307, 1997

¹³Umpierrez GE, Latif KA, Murphy MB,

Downloaded from http://diabetesjournals.org/clinical/article-pdf/24/1/45/321943/0040.pdf by guest on 29 May 2024

Lambeth HC, Stentz F, Kitabchi AE: Thyroid dysfunction in patients with type 1 diabetes. *Diabetes Care* 26:1181–1185, 2003

¹⁴Bhattacharyya A, Wiles PG: Diabetic ketoacidosis precipitated by thyrotoxicosis. *Postgrad Med J* 75:291–293, 1999

¹⁵What is diabetes? [article online]. Available from http://www.genetichealth.com/DBTS_What_Is_Type_1_Diabetes.shtml. Accessed 25 July 2005

¹⁶Cooper GS, Stroehla, BC: The epidemiology of autoimmune diseases. *Autoimmun Rev* 32:119–125, 2003

¹⁷Eisenbarth GS: Autoimmune beta cell insufficiency: diabetes mellitus type I. *Triangle* 23:111–124, 1984

¹⁸Eisenbarth GS: Type 1 diabetes mellitus: a chronic autoimmune disease. *N Engl J Med* 314:1360–1368, 1986

¹⁹Eisenbarth GS: The stages of type 1A diabetes: retrospective and prospective. *Diab Nutr Metab* 17:374–386, 2004

Russell D. White, MD, is a clinical associate professor at the University of South Florida in Tampa, Fla. George D. Harris, MD, MS, is an associate professor at the University of Missouri-Kansas City School of Medicine in Kansas City, Mo.

Case Study: A Patient With Type 2 Diabetes and Cirrhosis of the Liver

John E. Anderson, MD

Presentation

A.G. is a 47-year-old white man with a history of type 2 diabetes diagnosed at age 30. At his visit in July 1996, he weighed 275 lb with a height of 6'0" (BMI 37 kg/m²) and had measured A1C of 8.7%, mildly elevated triglycerides and LDL cholesterol, low HDL cholesterol, and normal transaminase levels. He had no signs or symptoms of complications from his disease and felt well.

Over the years, his history has been one of variable follow-up in the office with nonadherence to his diet and exercise regimen. His A1C results have fluctuated from 8.0 to 11.5%, his weight has remained > 250 lb, and his medical regimen has intensified to include an ACE inhibitor, a statin, aspirin, a sulfonylurea, and the maximum dose of metformin.

In February 2003, after 18 months of absence from follow-up, a bedtime dose of insulin glargine was added to A.G.'s regimen when he presented with thirst, polyuria, and weight loss to 221 lb. His A1C result was 10.6%, and liver function tests revealed aspartate aminotransferase (AST) of 67 units/l and alanine aminotransferase (ALT) of 78 units/l. He had early symptoms of sensory neuropathy

in the feet and retinopathy on dilated retinal exam.

Repeat assessment 3 months later, in May 2003, demonstrated resolution of leg cramps, urinary frequency, and blurred vision with an A1C of 8.3%. He was given parameters for continued titration of his bedtime insulin, yet he once again failed to return for reassessment until February 2005.

At his visit in February 2005, A.G.'s A1C was again elevated to 10.8% and a complete blood count revealed a white blood cell count of 3,200 and platelet count of 58,000. His liver function assessment revealed minimal ALT and AST elevations.

On 28 April 2005, A.G. presented to the hospital emergency department with hematemesis and anemia. Endoscopy revealed multiple bleeding esophageal varices, and banding procedures were performed. A computed tomography scan of the abdomen revealed diffuse fatty infiltration of the liver with evidence of portal hypertension. The patient was readmitted on 10 May 2005, for another episode of upper gastrointestinal bleeding requiring transfusion and repeat banding of bleeding esophageal varices.

Laboratory work-up including viral serologies, iron studies, and anti-nuclear antibody were negative, and a liver biopsy revealed stage 4 fibrosis with hepatitis and steatosis, confirming the diagnosis of nonalcoholic steatohepatitis (NASH).

A.G. has no history of drinking alcohol and is clinically stable at present, undergoing evaluation for possible future liver transplantation. He is maintained on a β -blocker and spironolactone, feels well, and has a weight of 207 lb and an A1C of 6.2%, with a renewed interest in his diet and exercise regimen.

Questions

1. What is the distinction between non-alcoholic fatty liver disease (NAFLD) and NASH?
2. What are the risk factors for NAFLD and NASH?
3. Are there proven effective therapies for NAFLD and NASH?

Commentary

NAFLD represents a spectrum of diseases from simple fatty liver (steatosis), to steatosis with inflammation, necrosis, and possible cirrhosis, that occurs in people who drink little or no alcohol.

NAFLD affects more women than men and can be found in all age groups, including children. NASH represents the more severe end of the spectrum and is associated with progressive liver disease, fibrosis, and cirrhosis.

The etiology of NASH is unclear, and the cellular basis for fat accumulation in the liver is not known. Like A.G., most patients with NASH are obese and have associated type 2 diabetes, hyperlipidemia, and insulin resistance. A study at the University of Virginia in 1999 examined 70 consecutive patients with cryptogenic cirrhosis to assess major risks for liver disease. Both diabetes and obesity were significantly more common in the cryptogenic cirrhotic patients compared with cirrhotic patients with primary biliary cirrhosis or hepatitis C. The prevalence of diabetes and obesity was similar to that in NASH patients, suggesting that NASH may play an underrecognized role in patients with cryptogenic cirrhosis.

A.G.'s case is typical in that patients with NASH generally feel well, with no overt signs or symptoms of liver disease. Some patients may come to diagnosis during the work-up of persistent, mild transaminase abnormalities or when imaging studies such as ultrasound or CT scan are performed for other reasons. Eliminating other possible causes for chronic liver disease must be undertaken, and the diagnosis must be confirmed by

liver biopsy.

Preferred treatments for NAFLD and NASH include weight loss, exercise, improved diabetes control, and the use of lipid-lowering medications. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) recently conducted a study of a 48-week course of pioglitazone in 21 nondiabetic patients with NASH. Serum aminotransferase levels and liver histology improved in most patients, and the improvements correlated with changes in insulin sensitivity.

Patients are currently being enrolled in another NIDDK study to treat 20 nondiabetic patients with NASH with metformin for 48 weeks. After an initial evaluation, patients will receive gradually increasing doses of metformin to a maximum of 2,000 mg daily. Primary end points of successful therapy will be improvement in hepatic histology, with secondary end points being improvement in insulin sensitivity, body fat distribution, and liver biochemistry.

Clinical Pearls

- Liver disease is rarely, if ever, mentioned as a potential complication from type 2 diabetes. With the increasing prevalence of obesity and patients with insulin resistance and type 2 diabetes, many experts believe that NAFLD and NASH will become increasingly common.

- Health care providers have yet another reason to continue to push for improvements in metabolic parameters in patients with type 2 diabetes, emphasizing weight loss, exercise, and control of both glucose and lipids.
- More research is needed to understand the cellular basis for fat accumulation in the liver and the progression to fibrosis and cirrhosis and for effective therapies to reverse the disease processes in NAFLD and NASH.

SUGGESTED READINGS

¹Ludwig J, Viggiano TR, McGill DB, Oh BJ: Nonalcoholic steatohepatitis: Mayo Clinic experiences with hitherto unnamed diseases. *Mayo Clin Proc* 55:434-438, 1980

²Caldwell SH, Delsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ: Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 29:664-669, 1999

³Mayo Clinic Staff: Nonalcoholic fatty liver disease. Mayo Foundation for Medical Education and Research (MFMER). 1998-2005 [article online]. Available from <http://www.mayoclinic.com/lookup/lookup?id=DS00577>.

⁴National Institute of Diabetes and Digestive and Kidney Diseases: Treating nonalcoholic steatohepatitis with metformin 2005 [article online]. Available from <http://www.clinicaltrials.gov/ct/gui/show/NCT00063232>.

John E. Anderson, MD, is a board certified internist at the Frist Clinic in Nashville, Tenn.

Case Study: If the Numbers Don't Fit . . . Discrepancies Between Glucose Meter Readings and Hemoglobin A_{1c} Reveal Stress of Living With Diabetes

Susan C. Conrad, MD, and Stephen E. Gitelman, MD

Presentation

C.S. is a 17-year-old girl who has had type 1 diabetes for 14 years. During early childhood, her hemoglobin A_{1c} (A1C) was usually < 8%, and her mother performed most of her diabetes care tasks. As she entered adolescence, C.S. took on more of the diabetes care herself and shared less of the management responsibilities with her mother. She used glargine once a day and lispro multiple times each day. She used a formula to calculate her insulin dose based on her carbohydrate intake (1 unit for each 10 g of carbohydrate eaten) and a correction factor for high glucose concentrations (1 unit for each 50 mg/dl above 100 mg/dl). She had been using this plan for 2 years.

At a recent diabetes clinic visit, she reported being satisfied with her glycemic control, and the average on her glucose meter memory was 147 mg/dl. In downloading her meter records, her providers noted at least 3–4 glucose tests each day, almost all within the 70–180 mg/dl range. Her A1C measured on the same day, however, was 9.4% (normal 4–6%).

After lengthy discussion with her about this discrepancy, C.S. admitted that she had used control solution in place of her own blood for most of the glucose meter checks. Control solution is part of the glucose meter kit and is used to confirm the accuracy of the machine and test strips. Results using control solution usually are close to the

normal range (the expected range is indicated on the control solution bottle) as long as the machine and test strips are working properly.

C.S. complained of being tired of dealing with her diabetes and said she found it “exhausting” to meet the expectations of her family and diabetes team. Her mother, who accompanied her to all the clinic visits, was surprised by C.S.’s use of control solution. The mother reported having little involvement in her daughter’s diabetes daily management in recent years since C.S. wanted to be independent and seemed to have things “under control.” Diabetes had become a source of tension between them, with C.S. feeling that her mother was nagging her, and her mother feeling excluded from the management decisions.

Questions

1. What are the causes of discrepancies between glucose meter numbers and the average reflected by A1C results?
2. Why would an adolescent manipulate the numbers on a glucose meter?
3. How can providers help with control and coping issues in adolescents with diabetes?

Commentary

This case exemplifies a number of issues that arise when dealing with adolescents with diabetes. A1C is an important tool for evaluating glycemic control and directly relates to risk for long-term microvascular complications.¹ When obtained in the office setting at the time

of a visit, as is possible with newer devices such as the DCA2000 (Bayer), A1C can be used to guide discussion at the visit. Alternatively, A1C can be drawn in a laboratory before the clinic visit, so that results are available at the time of the face-to-face meeting. In this case, the A1C was helpful in noting the discrepancy with numbers recorded on the glucose meter.

Such discrepancies may occur for a number of reasons. The glucose meter values are only individual points in time and may not detect fluctuations in glucose, especially postprandially and overnight. Checking glucose more frequently or using continuous glucose monitoring may help detect otherwise unnoticed hyperglycemia.² In addition, glucose meters need to be calibrated with a code from the test strip, and if the wrong code is entered, the numbers may be inaccurate. Test strips need to be protected from light and can become damaged, leading to unreliable measurements.

Hematological conditions can also affect the accuracy of the A1C measurement. A1C typically reflects the glucose concentration over the past 3 months, with ~ 50% determined by metabolic control during the past month. Conditions that shorten the lifespan of the red blood cell, such as hemolytic anemia, may falsely lower the A1C measurement.³ In beta-thalassemia, the presence of HbF may result in falsely elevated A1C measured by immunoassay, which is the method

used in most office A1C machines.⁴ The effect of these conditions on A1C measurement and the utility of the fructosamine measurement are reviewed in a recent issue of *Clinical Diabetes*.⁵

The discovery of a discrepancy between the A1C and glucose meter readings provides an opportunity to explore the patient's feelings about diabetes and the daily management routine. Most youth with diabetes experience worsening in their metabolic control during adolescence. This change is related in part to changes in the hormonal milieu, especially with an increase in growth hormone secretion serving to undermine insulin sensitivity. In addition, a number of psychosocial and developmental issues come into play: perceptions about body image develop, privacy and independence become important, and limit testing often challenges parent-adolescent relationships.

Adolescents cope with the stress of chronic illness in different ways. Emotion-focused coping strategies, such as behavioral and mental disengagement, are associated with poor metabolic control and reduced diabetes-related quality of life.⁶ In contrast, active coping strategies, such as seeking out more information about treatment and being involved in decision-making, are associated with lower A1C results.⁷ However, patients with poor glycemic control often experience negative feedback about their management, and this in and of itself may be the reason for disengagement. Parental concern can be expressed as anger and outrage, leading to a vicious cycle of deceit and shame for the patient. Not surprisingly, family conflict about diabetes is associated with poorer glycemic control.⁸

Although it is tempting to console families by telling them that their adolescent's difficulties with diabetes are likely to be temporary or just a passing phase, there is recent evidence that this is not the case. Bryden et al.⁹ reported worse-than-expected clinical and psychiatric outcomes in approximately one-third of

all young adult patients with diabetes. The authors suggested that much earlier identification of psychiatric and behavioral issues is needed, since symptoms in adolescence were predictive of later psychiatric disorders.

The negative cycle can be interrupted. Involving the family and discussing their concerns about the patient's diabetes can help dispel some of the fear and anxiety surrounding the numbers. Treating the numbers as information in a nonjudgmental manner can remove the negative emotional aspect of diabetes management. Identifying and treating psychiatric disorders is likely to affect long-term outcome. And, teaching coping skills to adolescents is effective, resulting in lower A1C results, better diabetes and medical self-efficacy, and less impact of diabetes on quality of life.¹⁰

While adolescents may desire independence from their parents, they likely do not have the maturity to handle every aspect of diabetes alone. Family-focused teamwork intervention is associated with improved A1C in children and adolescents with diabetes.^{11,12} In order to eliminate the perception of nagging on the part of the parent, some families have a set time in the evenings to review the glucose meter numbers. The parent's role may be recording the numbers in a logbook or helping the adolescent look for patterns in the logbook so that the insulin regimen can be modified if necessary. Some adolescents want a break from diabetes for a day, and the parent can take over the diabetes care for this period of time.

In this case, discussion during the clinic visit led to the patient's confession that she had falsified the glucose meter numbers. Although most patients likely would not readily admit to this, beginning the discussion about living with diabetes may uncover surprising revelations regarding coping skills and sense of personal control. Recognizing the issue is the first step, and a multidisciplinary approach is necessary to address the complicated issues that diabetes pres-

ents. Input from a psychologist, social worker, or psychiatrist consultant is often helpful. Removing the pressure of judgment about the glucose meter numbers while still involving the family in the diabetes care, involving the patient in diabetes management decisions, developing realistic treatment goals, and discussing coping methods are important strategies to help adolescents live successfully with diabetes.

Clinical Pearls

- Glucose meters can be manipulated to make it appear that numbers are in the target range.
- Hematological conditions can result in discrepancies between A1C results and glucose meter readings.
- Differences in glucose meter readings, written logbooks, and A1C results may be a sign of underlying stress and difficulty dealing with expectations about diabetes management.
- Worsening glycemic control during adolescence may reflect hormonal as well as psychosocial and developmental changes.
- Encourage interdependence rather than independence for adolescents with diabetes, and stress ongoing parental involvement.
- A multidisciplinary approach is essential for helping adolescents with diabetes.

REFERENCES

- ¹The DCCT Research Group: The effect of intensive treatment on the development and progression of long term complications in the diabetes control in insulin dependent diabetes mellitus. *N Engl J Med* 329:977-986, 1993
- ²Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV: Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. *Diabetes Care* 24:1858-1862, 2001
- ³Tack CJ, Wetzels JF: Decreased HbA1c levels due to sulfonamide-induced hemolysis in two IDDM patients. *Diabetes Care* 19:775-776, 1996
- ⁴Diem P, Walchli M, Mullis PE, Marti U: Agreement between HbA1c measured by DCA 2000 and by HPLC: effects of fetal hemoglobin concentrations. *Arch Med Res* 35:145-149, 2004

⁵Tran HA, Silva D, Petrovsky N: Case study: potential pitfalls of using hemoglobin A1c as the sole measure of glycemic control. *Clin Diabetes* 22:141–143, 2004

⁶Graue M, Wentzel-Larsen T, Bru E, Hanes-tad BR, Sovik O: The coping styles of adolescents with type 1 diabetes are associated with degree of metabolic control. *Diabetes Care* 27:1313–1317, 2004

⁷Rose M, Fliege H, Hildebrandt M, Schirop T, Klapp BF: The network of psychological variables in patients with diabetes and their importance for quality of life and metabolic control. *Diabetes Care* 25:35–42, 2002

⁸Anderson BJ, Vangsness L, Connel A, Butler D, Goebel-Fabri A, Laffel LMB: Family conflict, adherence, and glycaemic control in youth with

short duration type 1 diabetes. *Diabet Med* 19:635–642, 2002

⁹Bryden KS, Dunger DB, Mayou RA, Pevel-er, RC, Neil HAW: Poor prognosis of young adults with type 1 diabetes. *Diabetes Care* 26:1052–1057, 2003

¹⁰Grey M, Boland EA, Davidson M, Li J, Tamborlane WV: Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life. *J Pediatr* 137:107–113, 2000

¹¹Anderson BJ, Brackett J, Ho J, Laffel LM: An office-based intervention to maintain parent-adolescent teamwork in diabetes management: impact on parent involvement, family conflict, and subsequent glycemic control. *Diabetes Care* 22:713–721, 1999

¹²Laffel LM, Vangsness L, Connell A, Goebel-Fabbri A, Butler D, Anderson BJ: Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes. *J Pediatr* 142:409–416, 2003

Susan C. Conrad, MD, is a pediatric endocrinologist at Children's Hospital and Research Center at Oakland in Oakland, Calif. Stephen E. Gitelman, MD, is a professor of clinical pediatrics in the Department of Pediatric Endocrinology at the University of California, San Francisco.