



## Diabetes Educational Services

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On State-of-the-Art Diabetes Care



## Diabetes Detectives – Finding Uncommon Conditions

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### Another Downloadable Article from the Diabetes Educational Services Site

This article provides health care professionals with strategies to detect common, yet often underdiagnosed, complications associated with hyperglycemia and diabetes. It also describes how medications, organ transplants, and chronic illnesses can cause hyperglycemia.

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## ***Diabetes Detectives – Finding Uncommon Conditions***

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*Rebecca\* has Type 2 diabetes. Her diabetes and weight were stable, but over the last three weeks, her blood sugars have been consistently elevated, up to 300 mg/dL, and she has gained 10 pounds. Rebecca takes two diabetes oral medications plus insulin injections three times a day, thyroid replacement therapy, a cholesterol medication, and a new medication for “mood swings.” Frustrated and depressed, Rebecca wants to get her diabetes and weight back under control.*

Since people with diabetes are at greater risk for a long list of comorbidities, health care professionals often double as detectives while uncovering complications.<sup>1</sup> Several common, yet often underdiagnosed, complications are associated with diabetes.

People with diabetes can also experience weight gain or weight loss, or complain of something not feeling right because of a variety of factors that warrant investigation. By improving their “diabetes detective” skills, health care professionals can help patients improve the management of their diabetes — and their quality of life.

### **Unexplained weight gain**

If patients complain of sudden weight gain, more than overeating and skipping exercise may be to blame:

**Hypothyroidism:** People with diabetes are more likely to have thyroid disease.<sup>1</sup> Hashimoto’s thyroiditis, an autoimmune condition and common cause of hypothyroidism, is often associated with sluggish metabolism, weight gain, and dyslipidemia.<sup>1</sup> Because of this increased risk, people with diabetes should be screened annually for thyroid disease.<sup>2</sup>

Thyroid-stimulating hormone (TSH) levels higher than normal (normal levels are 0.3 to 3.0 mIU/mL) are indicators of hypothyroidism. Thyroid scans and measurement of free T4 and autoantibodies can help provide a clear diagnosis.<sup>1</sup> Thyroid hormone replacement therapy is critical to normalize metabolism and improve dyslipidemia. Health care professionals can evaluate TSH levels, and if above normal, discuss the possibility of thyroid dysfunction with the provider. If patients have established thyroid disease, health care professionals can check whether they are taking thyroid medications as directed.

**Depression:** People with diabetes are twice as likely to experience depression. About 30% of people with diabetes require treatment of depression, but most

patients receive none,<sup>3</sup> often because of inadequate health insurance or a reluctance to seek treatment.

Patients with diabetes and depression tend to have higher blood sugar levels and are at risk of being overweight. This may be due to unhealthy eating in response to depression combined with a lack of energy or ability to participate in exercise plus medication nonadherence. Since these patients also have higher glucose levels, they may be called “nonadherent” when, in reality, they are struggling with untreated depression.

Health care professionals can ask patients these questions as a quick depression assessment tool: During the last two weeks, have you felt down, depressed, or hopeless? During the last two weeks, have you felt little pleasure in doing things? If the answer to both questions is yes, further assessment and a mental health referral may be warranted.<sup>4</sup>

**Medications:** Certain medications increase the risk of weight gain in patients with or without diabetes. Patients may experience rapid weight gain and severe hyperglycemia with any atypical antipsychotic drug: olanzapine (Zyprexa), ziprisidone (Geodon), quetiapine (Seroquel), risperidone (Risperdal), clozapine (Clozaril), and aripiprazole (Abilify). The FDA has posted warnings and advised health professionals to closely monitor blood glucose levels in patients started on atypical antipsychotics.<sup>5</sup> If a person with diabetes is started on atypical antipsychotic drugs, increased blood sugar levels and weight may require an increase in diabetes medications or the addition of insulin. People without diabetes started on these agents should monitor their blood glucose regularly; know the signs of hyperglycemia (unusual thirst and hunger, blurry vision, infections, frequent urination); and report any signs to their provider.

Weight gain may also be associated with the thiazolidinediones class of diabetes medications (the “glitazones”), which include rosiglitazone (Avandia) and pioglitazone (Actos). They work by making the cells more sensitive to the body’s insulin. But fluid retention and weight gain are adverse effects. As such, these drugs are not indicated for patients with moderate (Class 3) or severe (Class 4) congestive heart failure as described by the New York Heart Association guidelines. Health care professionals can instruct patients taking this class of medications to inform their provider of weight gain.<sup>6</sup> In addition, the FDA has warned that patients taking rosiglitazone in clinical trials had an increased risk of heart attack and deaths related to heart failure.<sup>7</sup>

Glitazones are also found in combination medications. Rosiglitazone is combined with metformin (Glucophage) in Avandamet and with glimiperide (Amaryl) in Avandaryl. Pioglitazone is combined with metformin in Actosplus Met and with glimiperide in Duetact. These combination medications present the same fluid retention and cardiovascular risks as monotherapy and require monitoring.<sup>6,7</sup>

Insulin therapy and the diabetes oral agents that stimulate the pancreas to produce insulin — sulfonylureas, such as glipizide (Glucotrol) and glyburide (Micronase); nateglinide (Starlix); and repaglinide (Prandin) — can also induce weight gain. Since insulin is an anabolic hormone, it increases energy storage, and this can lead to weight gain, especially if the patient is receiving more insulin or oral medication than he or she needs (often called “overinsulinization”). Hypoglycemic episodes (blood glucose less than 70 mg/dL) are a sign that a patient is overinsulinized. Patients often overtreat hypoglycemia and end up eating more, or “feeding the insulin,” leading to a vicious cycle of weight gain, increased medication dosing, and further hypoglycemia.<sup>8</sup> If a patient on insulin or sulfonylureas is gaining weight, evaluating the frequency of hypoglycemia and talking with the provider about reducing the diabetes insulin or medication dosing can help stop the cycle and improve glucose control.

In Rebecca’s case, an atypical antipsychotic medication was causing weight gain. The provider decided to continue her on olanzapine since it was the best choice for her mental health. But he determined strategies to better manage her diabetes. He also made sure Rebecca was taking her thyroid medication and was not overinsulinized.

### **Weight loss without trying**

*John\* has managed his Type 1 diabetes well for 30 years. But over the past few months, his blood sugars have been erratic, and he is distressed at his ongoing severe weight loss. John keeps trying to adjust his insulin to get things under control, but nothing works.*

In addition to chronic hyperglycemia, patients who experience weight loss may be suffering from other associated undiagnosed diabetes complications:

**Celiac disease:** Generally occurring in youth and later age, celiac disease affects 4% to 6% of patients with Type 1 diabetes and is often underdiagnosed and misdiagnosed.<sup>9</sup> It involves a hypersensitivity to gluten, found in wheat, barley, and rye products. This hypersensitivity paralyzes the villi in the small intestine, and the lining of the intestine becomes inflamed. As a result, the person experiences chronic malabsorption of nutrients. Patients with chronic diarrhea, fatty stools, weight loss, and fluctuating glucose levels or with signs of malabsorption (including iron-deficiency anemia and bone disease) should be tested for antigliadin IgG, antigliadin IgA, and endomysial antibodies. If tests are positive, an intestinal biopsy is required to make a diagnosis.<sup>9</sup> If celiac disease is confirmed, the patient must follow a gluten-free diet for life. Health care professionals can help arrange a referral to a registered dietitian who has experience with celiac disease and provide other resources for patients.

**Hyperthyroidism:** The risk of Graves’ disease, the most common type of hyperthyroidism, is more than 0.5% to 2% in people with Type 1 diabetes.

Clinicians should rule out Graves' disease in a patient experiencing hypermetabolism, weight loss exophthalmus, tachycardia, and heat intolerance.<sup>9</sup> Patients with diabetes and an overactive thyroid often experience unexplained blood glucose elevations. A very low TSH is the first lab indicator that patients may have hyperthyroidism, but further testing is required to confirm the diagnosis. Treatment can include medications, radioactive iodine, and, rarely, surgery. After treatment, most patients will require lifelong thyroid hormone replacement.

**Addison's disease:** About 0.25% of patients with Type 1 diabetes have Addison's disease, a rare autoimmune condition.<sup>9</sup> It destroys the adrenal glands, which are responsible for releasing aldosterone, the hormone that regulates sodium and potassium and stores corticosteroids, generally known as the "stress hormones." In addition to weight loss, fatigue, and depression, patients with Addison's may have hypoglycemia unawareness, a condition in which people with diabetes don't experience the usual symptoms of low blood glucose levels, because their bodies do not release stress hormones in response to hypoglycemia. Potassium levels are often elevated, and sodium levels may be below normal, causing salt cravings. This, along with discoloration on the hands, face, and gums, may be the initial indicators of Addison's. Although rare, Addison's should be considered in patients with Type 1, especially if they have increasing problems with frequent and undetected hypoglycemia.

As for John, his healthcare provider thought he had gastroparesis (a condition associated with nerve damage causing gastric slowing and unpredictable absorption of food and erratic blood glucose levels). But test results were positive for celiac disease. John saw a dietitian and was counseled on avoiding foods containing gluten. A year later, he has regained all his weight, and his blood sugars are normal.

**Latent autoimmunity diabetes in adults:** During patient interviews, health care professionals may sense that something just doesn't feel right. Consider the case of a lean patient newly diagnosed with Type 2 diabetes and started on two types of oral diabetes medications. At his three-month checkup, the patient reports he has been exercising and following a healthy eating plan and has lost 4 pounds. Yet his blood glucose levels are still in the high 200s. This patient may have latent autoimmunity diabetes in adults (LADA), an autoimmune destruction of the pancreas that can occur over decades.<sup>10</sup> These patients may initially respond to oral agents, but usually need insulin within several years of diagnosis. Testing for antibodies — including islet cell autoantibodies and glutamic acid decarboxylase antibodies — can reveal LADA. Patients may benefit from early initiation of insulin therapy to preserve pancreatic function. If working with a lean older patient labeled as having Type 2 diabetes, consider suggesting an investigation into the possibility of LADA.

**Silent heart disease:** Over time, diabetes can damage and destroy the nerves that cause the typical pain associated with angina or an MI. This is called cardiac autonomic neuropathy and can lead to silent ischemia, putting patients with diabetes at greater risk of sudden death from acute coronary events. Health care professionals can help patients identify signs of coronary events and encourage them to report unusual symptoms. Tell patients with diabetes to immediately contact their provider if they experience any new or unexplained pain at the belt line or above. Explain cardiac autonomic neuropathy to patients and tell them that it can cause anginal pain to present in unusual ways in people with diabetes (e.g., fatigue, confusion, edema, hemoptysis, diaphoresis, or dyspnea). Heart disease is the leading cause of death for people with diabetes; paying close attention to symptoms of heart problems is critical.<sup>11</sup>

### **Vice versa**

Just as diabetes and hyperglycemia can put patients at risk for other medical conditions, a range of medications and medical conditions can put patients at risk for diabetes and hyperglycemia.

**Steroids:** Patients initiated on corticosteroid therapy, such as prednisone (Deltasone), may experience a sudden jump in blood glucose levels. But not all patients started on steroids become hyperglycemic. Those at greatest risk include patients with a history of glucose intolerance or a family history of diabetes. In some cases, steroids simply unmask previously undetected diabetes. If the steroid dose is tapered down or stopped, often the blood glucose normalizes. But the fact that the person had hyperglycemia on steroids is an indicator that he or she is at greater risk for expressing diabetes in the future.

Health care professionals can remind patients to have a blood glucose test at least yearly and make them aware of the signs of hyperglycemia. Patients on long-term steroid therapy with glucose elevations must receive tools to manage hyperglycemia. Untreated hyperglycemia puts these already immunocompromised patients at increased risk of secondary infections, weight loss, and fatigue. Health care professionals can help patients obtain a blood glucose meter and consults with a registered dietitian and certified diabetes educator. Usually, nutrition and exercise alone won't get blood glucose levels to target since steroids cause significant insulin resistance. Health care professionals can encourage patients to discuss diabetes medications with their provider.

Organ transplant patients also need close monitoring of blood glucose since they have a 20% risk of developing post-transplant diabetes mellitus because of steroid and antirejection therapy, physical stresses, and preexisting diabetes risk factors.<sup>12</sup> With unmanaged post-transplant hyperglycemia, patients are at increased risk of organ rejection and death from cardiovascular disease, making

this a complication that requires aggressive, ongoing management and self-care instruction.

**Cystic fibrosis:** CF can lead to hyperglycemia. In CF, abnormally thick mucus clogs the lungs and causes abnormalities in the beta cells (insulin-producing cells in the pancreas). Today, people with CF are living past early adulthood and as a result are experiencing increasing rates of hyperglycemia. About 40% of adults with CF develop diabetes, which decreases survival rates.<sup>13</sup> Since people with CF need extra calories to compensate for the work of breathing, caloric restriction to lower glucose levels is not recommended. Healthy eating and oral diabetes medications or low-dose insulin therapy are the best strategy, along with support and education to manage an additional chronic condition.

**Obstructive sleep apnea:** Researchers have discovered a link between OSA and diabetes. Over 20 million people in the United States have OSA,<sup>14</sup> and about half may have Type 2 diabetes. Patients tend to have coexisting cardiovascular risk factors, such as hypertension and heart disease.<sup>14</sup> Along with weight management and increased activity, treatment of sleep deprivation can result in improved glucose levels. Health care professionals can identify patients with OSA and review blood glucose levels to check for undetected diabetes.

#### **Don't forget the liver**

Liver disease affects glucose regulation. For example, after age 40, patients with hepatitis C have three times the risk of diabetes.<sup>14</sup> A link has been discovered between insulin resistance and fatty liver disease. Accumulation of triglycerides in the hepatocytes leads to fatty liver and can lead to liver damage if the condition isn't treated. People at risk of nonalcoholic steatohepatitis include those with hyperglycemia and obesity and those over 40. Signs and symptoms of nonalcoholic steatohepatitis include an enlarged liver with a soft, rounded edge easily felt on palpation, elevated liver enzymes, and conditions associated with insulin resistance, such as dyslipidemia and hypertension. Positive diagnosis can be made only with a liver biopsy; treatment includes exercise, weight loss, lipid correction, glucose control, and drugs to reduce insulin resistance.<sup>15</sup>

#### **In the hospital**

Patients hospitalized with acute illness should be evaluated for hyperglycemia. An estimated 30% to 40% of inpatients have diabetes,<sup>16</sup> but about 10% of them have undiagnosed diabetes. Physical stress, such as illness, can increase insulin resistance and provide a window into the health of the insulin-producing beta cells. During illness, most patients maintain normal blood glucose levels. If levels go higher than normal, patients can be diagnosed with diabetes.

Health care professionals have an opportunity to evaluate patients' levels and help identify patients with undiagnosed diabetes. An early diagnosis leads to early treatment and a reduced risk of complications. To start, health care professionals can provide inpatients with a record of their abnormal inpatient glucose levels and instruct them to follow up with their usual provider soon after discharge. Health care professionals can also arrange inpatient consults with a registered dietitian and diabetes educator.

A national movement based on scientific evidence is focusing attention on in-hospital glucose management.<sup>17</sup> Today, evidence-based protocols exist for diabetes and blood glucose management in the acute care setting.<sup>17</sup> Health care professionals can promote the protocols and make sure glucose levels are managed, even during acute illness.

### **Wanted: diabetes detectives**

By thinking outside the box when assessing patients with diabetes, health care professionals have a better chance of detecting less common, but serious, comorbidities. Careful listening and evaluation of lab results can help health care professionals identify complications and encourage follow-up treatment. Health care professionals can also be aware of conditions other than diabetes that are associated with hyperglycemia and be alert for undiagnosed hyperglycemia. By doing so, health care professionals improve quality of life and help reduce complications for millions of patients.

\*Patients' names have been changed.

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