# Case Study: Symptoms in a Diabetes Client: Type 1, Type 2, or Type 1.5?

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**Presentation**

W.G. is a 41-year-old white man who was diagnosed with diabetes 15 months ago. He is now beginning diabetes education and medical nutrition therapy (MNT) to gain weight upon referral from his primary care physician. His most recent hemoglobin A1c (A1C) was 5.0%. His current diabetes medication is metformin (Glucophage), 500 mg with breakfast, and he was started on pioglitazone (Actos) 2 weeks ago. He takes no other medications; denies smoking, alcohol, and drug use; and knows of no health problems other than diabetes.

His history revealed a blood glucose level >500 mg/dl at the time of diagnosis, with negative ketones. He checked ketones occasionally in the first year of diabetes, and all tests were negative. His mother had diabetes and was on insulin. He reports that he was on glimepiride (Amaryl) during the first year of diabetes, but that it was discontinued when he was started on metformin.

He complains of frequent urination, hunger, and thirst, which leads to drinking more than 1 gallon of water daily. He is very concerned because he is often agitated, anxious, and impatient to the point that it is affecting his family and work life. He was employed as a technician but is on leave until he feels better. His physician prescribed alprazolam (Xanax) for anxiety, but he did not fill the prescription.

Physical assessment reveals a height of 74 inches, weight of 174 lb, and body mass index of 22 kg/m$^2$. He reports a 35-lb weight loss over the past 15 months of diabetes, including a recent 10-lb weight loss resulting in the referral for MNT.

W.G. reports that his doctor has prescribed a 2,500-calorie daily meal plan. He includes no fruits and no sweets in his diet and has small snacks between meals. He eats a moderate breakfast and lunch and a bigger dinner before his exercise in the evening. He reports that he is not currently able to maintain his usual 1.5 hours per day of lifting weights and playing basketball because of fatigue and lack of energy. Instead, he is exercising in short intervals as he can tolerate. He also reports symptoms of hypoglycemia but has not checked his blood glucose.

**Questions**

1. Why is this patient losing weight?
2. Does this patient have type 1 or type 2 diabetes, and does it make a difference in his treatment?
3. Are other interventions needed considering his symptoms and most recent A1C?

**Commentary**

Nutrition assessment revealed that W.G. was eating ~1,800 calories daily rather than 2,500 calories, as prescribed. He had a good appetite but appeared to be controlling his blood glucose by exercising and eating less than his energy requirement. An 1,800-calorie meal plan would result in weight loss of 1 lb per week for a man of his height, weight, and activity level.

W.G.'s records from self-monitoring of blood glucose (SMBG) showed an average fasting blood glucose of 118 mg/dl, which is consistent with his A1C result of 5.0%. Previous A1Cs were 5.1 and 5.6%.

His classic diabetes symptoms of polyuria, polyphagia, and polydipsia indicated that diabetes education and MNT were not adequate diabetes care for this patient. His physician readily provided a referral to an endocrinologist/diabetologist. A new treatment plan would need to address nutrition, exercise, and medications.

MNT for W.G. began with an increase to 3,000 calories daily to gain weight and to observe the effect of adequate calories on his blood glucose before his appointment with the diabetologist. He was willing to increase his calories but needed education on meal planning. He was educated about calorie points for a 3,000-calorie daily meal plan. One calorie point equals 75 calories, so his 40 daily calorie points were distributed into meals and snacks and based on healthy eating guidelines for diabetes. The meal plan was individualized based on his usual food and eating habits.[1] His SMBG results with the 3,000-calorie meal plan showed a postprandial glucose average of 150 mg/dl and a fasting glucose average of 135 mg/dl.

Medication options included increasing the dosages of his current medications, adding new oral medications, or using a combination of oral agents and insulin. W.G. was quite willing to start insulin. Because of his marked symptoms and in light of this willingness, the diabetologist at his first visit discontinued his oral medications and initiated insulin therapy. Insulin was adjusted daily during the first week, and the regimen that allowed for normal blood glucose without hypoglycemia was 10 units of

glargine (Lantus) at 10:00 p.m. daily and 4 units of aspart (Novolog) with each meal.

W.G.'s education also included exercise recommendations, including safety issues such as how to recognize and treat hypoglycemia.

Laboratory tests were ordered during his first visit to the diabetologist. Because abnormal thyroid function can affect weight and anxiety, a thyroid-stimulating hormone reading TSH was ordered, with results in the normal range. A fructosamine measurement, which reflects glycemic control over the previous 3–4 weeks, was also in the normal range. Fasting C-peptide, which is a measure of insulin secretion, was 2.5 ng/ml (normal: 1.1–4.0 ng/ml) and islet cell antibodies were 10 JDF units (normal: 0–4.9 JDF units). The basic metabolic profile results were within normal range.

At a follow-up visit 4 months after insulin initiation, W.G. had gained 5 lb, felt more energetic and less anxious, was exercising, and had A1C results of 6.1%. Based on his SMBG results showing occasional hyperglycemia, his insulin was increased to 11 units of glargine at 10:00 p.m. daily and 5 units of aspart with each meal, which is 1/3 unit/kg of body weight. He was advised to continue following a 3,000-calorie daily meal plan, adjusted with exercise.

Recent research has identified a slowly progressive autoimmune diabetes in adult patients. Known as latent autoimmune diabetes of adulthood (LADA) or type 1.5 diabetes,[2] it is a slowly progressive form of type 1 diabetes.[3] After months to years, affected individuals become increasingly insulin-dependent. This type of diabetes could be the explanation for W.G.'s symptoms and progression of disease. He may have been preventing more severe hyperglycemia by exercising and restricting calories, but this also resulted in weight loss. His A1C and fructosamine results may have been surprisingly low because of his frequent hypoglycemic episodes.

**Clinical Pearls**

- Diabetes management should be based on more than A1C results if the results do not fit with the rest of the clinical picture. In this case, symptoms were the clue to the patient's actual condition and indicated the need for treatment.
- In the presence of frequent hypoglycemia, A1C levels may not accurately reflect the level of hyperglycemia present.
- Nutrition, medications, and exercise must each be assessed and addressed individually in diabetes management.
- Insulin initiation may be more acceptable to patients than some health professionals believe.[4]

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# Case Study: A 90-Year-Old Man With Confusion and Night Sweats

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**Presentation**

C.G. is a 90-year-old man with metastatic prostate cancer who was brought to the emergency room (ER) at midnight after being found confused and sweaty. In the ER, his blood glucose level was 44 mg/dl. He received one ampule of D50 and was started on intravenous D5NS. His confusion improved.

On transfer to the medical floor, his blood glucose level was 161 mg/dl. He denied nausea, vomiting, abdominal pain, diarrhea, constipation, chest pain, shortness of breath, palpitations, and weight loss. His last meal had been at 6:00 p.m. He recalled another episode of confusion 3 weeks ago in the middle of the night that was milder and did not require hospitalization.

His medical records revealed that his blood glucose levels had been elevated in 1996 (136–144 mg/dl) and that 1 month before admission, his blood glucose level was 50 mg/dl.

His medical history was remarkable for prostate cancer on leuprolide (Lupron) injection, colon cancer (status post hemi-colectomy) with recent negative colonoscopy, idiopathic thrombocytopenic purpura requiring splenectomy, and vitamin B12 deficiency. He did not smoke or drink alcohol and he had no allergies.

He took leuprolide via intramuscular injection every 3 months; vitamin B12, 1,000 μg via intramuscular injection monthly; and aspirin, 325 mg per day orally. There was no personal or family history of diabetes, occupation in an allied health profession, or past insulin treatment.

Physical examination showed a well-nourished man in no acute distress. He was alert and awake. His blood pressure was 120/80 mmHg, heart rate was 66 and regular, and temperature was 99.8°F. He was 68 inches tall and weighed 158 lb. His body mass index was 23.9 kg/m$^2$. Head, eyes, nose, and throat were normal. Lungs were clear, and cardiac exam was normal. Abdomen was soft, without tenderness, organomegaly, or masses. There was no edema in his extremities, and his skin was warm and dry.

Laboratory data on admission revealed macrocytic anemia. His chem 7 revealed glucose of 44 mg/dl, creatinine of 1.1 mg/dl, and blood urea nitrogen of 26 mg/dl. His calculated glomerular filtration rate was 60 ml/min. Liver function tests, creatine phosphokinase, urine analysis, chest X-ray, and electrocardiogram were unremarkable. Prostate specific antigen was 0.3 ng/ml (0–4 ng/ml) 6 months before admission.

**Questions**

1. What is the diagnosis?
2. How can the diagnosis be confirmed?
3. How should this patient be managed?

**Commentary**

C.G. was admitted with the diagnosis of spontaneous hypoglycemia. The differential diagnosis is broad and includes:[1]

- Fasting hypoglycemia (hypopituitarism, Addison's disease, myxedema, liver failure, renal failure, heart failure, hyperinsulinemia due to either pancreatic β-cell tumors or surreptitious administration of insulin or sulfonylureas, and non-insulin-producing extrapancreatic tumors)
- Postprandial (reactive) hypoglycemia: early (within 2–3 hours after a meal) or late (3–5 hours after eating)
- Alcohol-induced hypoglycemia: due to hepatic glycogen depletion combined with alcohol-mediated inhibition of gluconeogenesis
- Immunopathological hypoglycemia (antibodies to insulin receptor/antibodies to insulin)
- Factitious hypoglycemia (surreptitious administration of insulin or sulfonylureas)
- Drug-induced hypoglycemia (pentamidine [Pentam] due to lytic destruction of pancreatic β-cells, aspirin, propranolol [Inderal], disopyramide [Norpace], trimethoprim/sulfamethazole [Bactrim], etc).

He presented with Whipple's triad, characterized by hypoglycemic symptoms and blood glucose level ≤45 mg/dl, with recovery upon administration of glucose. During his stay, even with the infusion of D5NS, he had multiple episodes of hypoglycemia (blood glucose <45 mg/dl) between midnight and 8:00 a.m. and also throughout the day. He was treated with three low-carbohydrate meals, three snacks, and D10 to maintain his blood glucose levels at ~60 mg/dl.

His thyroid-stimulating hormone, free thyroxine, prolactin, cortisol, growth hormone, and calcium levels were within normal limits. Sulfonylurea in the urine was undetectable. With each episode of hypoglycemia, glucose, insulin, proinsulin, and C-peptide levels were measured.

With blood glucose levels of 30–37 mg/dl, his insulin levels were >400 μU/ml (normal: <22.7 μU/ml); proinsulin levels were 2,031, 2,385, and 4,524

pmol/l (normal: 1.7–12 pmol/l); and C-peptide levels were 4.5, 5.6, and 13.3 ng/ml (normal: 0.9–4.0 ng/ml). His insulin free was 388.5 μU/ml (normal: <22.7 μU/ml) and insulin bond was 392.1 μU/ml (normal: <3.5 μU/ml). Octreotide scan of the abdomen, computed tomography of the abdomen and pelvis, and transduodenal endoscopic ultrasound were negative for insulinoma.

Because of markedly elevated insulin, proinsulin, and C-peptide levels, we obtained antibodies to insulin that were 1,312 Kronus unit/ml (normal <1.0 Kronus unit/ml).

Therefore, the diagnosis of insulin autoimmune syndrome was made. C.G. was started on prednisone and was weaned off of intravenous D10. His glucose level remained within normal limits. He was discharged on prednisone, 60 mg daily by mouth, to be tapered over 3 weeks. He was also found to have another autoimmune disease: idiopathic thrombocytopenic purpura. His serum protein electrophoresis was negative. HLA analysis was not obtained.

At the 1.5-year follow-up, G.C. was now living in an assisted living home. The prednisone resolved his hypoglycemic episodes, but he could not be completely weaned from prednisone without hypoglycemia recurring.

Insulin autoimmune syndrome (IAS), or Hirata disease, is characterized by hypoglycemia without evidence of exogenous insulin administration, high levels of total immunoreactive insulin, and the presence of high titers of insulin autoantibodies.[2] The first case of a patient with insulin autoimmunity was reported by Hirata et al. in 1970.[3]

More than 200 IAS patients have been reported in Japan, where IAS is the third leading cause of spontaneous hypoglycemia.[3] In contrast, IAS is rare in Western countries, which can be explained by the rarity of HLA class II alleles that appear to be strongly associated with this autoimmune disorder.[4] There is a strong association of IAS with HLA-DR4. The insulin autoantibodies can be polyclonal or monoclonal.[4–6]

The mechanism of hypoglycemia in IAS is not completely understood. The most widely accepted theory invokes a buffering effect of antibodies on endogenous insulin levels. It is thought that insulin released from the pancreas in response to a meal and/or glucose loading is rapidly bound by antibody, leading to the diabetic pattern seen in the early stages of oral glucose tolerance testing in these patients. A subsequent spontaneous dissociation of insulin from antibody, perhaps in response to a decreasing level of free insulin in the patient's serum, is thought to occur several hours after eating, leading to hypoglycemia.[7,8]

Uchigata et al.[2] elucidated the following clinical characteristics of IAS:

- Peak age distribution 60–69 years
- Peak duration of hypoglycemia attacks >1 month and <3 months
- 82% (162 of 197 with IAS) of patients had spontaneous remission.
- 43% of patients had taken medication before the onset, e.g., methimazole (Tapazole), α-mercaptopropionyl glycine, glutathione, or captopril (Capoten), all of which are sulfhydryl compounds.

The clinical course of patients with IAS is generally favorable.[2] Some cases have evolved after exposure to penicillin,[5] hydralazine (Apresoline),[7] and imipenem (Primaxin).[9]

Patients with IAS may have a history of other autoimmune diseases, such as Graves' disease, rheumatoid arthritis, systemic lupus erythematous, or multiple myeloma.[3,7]

Therapy can be directed towards decreasing the hyperglycemia (medical nutrition therapy, acarbose [Precose]), the insulin secretion (diazoxide [Proglycem], octreotide [Sandostatin]), or the antibody concentration (corticosteroids, other immunosuppressants, plasmapheresis).[6]

**Clinical Pearls**

- Any fasting hypoglycemia is potentially serious and warrants evaluation.
- Timely diagnosis of IAS is important, both in order to discontinue any medication implicated in the pathogenesis of IAS and to avoid an unnecessary major surgical intervention in a vain search of insulinoma.[9]
- In IAS, fasting insulin levels are often >1,000 μU/ml, whereas in insulinoma, fasting insulin levels are usually <100 μU/ml.
- IAS is associated with high titers of insulin antibodies.

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