CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

# The After-Dinner Dip

Gertrud L.G. Haverkamp, M.D., Ph.D., Richard G. Ijzerman, M.D., Ph.D., Jos Kooter, M.D., and Yvonne H.M. Krul-Poel, M.D., Ph.D.

*In this* Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

From the Department of Internal Medicine and Endocrinology, Amsterdam University Medical Center, Amsterdam. Dr. Haverkamp can be contacted at g.haverkamp@amsterdamumc.nl or at the Department of Internal Medicine and Endocrinology, Amsterdam University Medical Center, Location VUMC, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands.

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**An 85-year-old woman was brought to the emergency department by emergency medical services (EMS) after losing consciousness. Her daughter reported that the patient had noted a sudden onset of sweating, palpitations, and feeling cold before she lost consciousness approximately 45 minutes after finishing her dinner. The patient had not reported chest pain or shortness of breath before she lost consciousness, and there was no urinary incontinence. She had had similar but milder symptoms three times in the previous 2 weeks, and each time she had recovered without assistance. She also reported having had headaches during the previous few days. In addition, she had unintentionally lost 2 to 3 kg of weight over the previous few months.**

The differential diagnosis of loss of consciousness includes syncope and nonsyncopal causes. Loss of consciousness in syncope is caused by a period of inadequate cerebral perfusion and can be divided into four major categories: orthostatic syncope, reflex syncope, cardiac arrhythmia, and structural cardiopulmonary disease. Nonsyncopal causes include seizure, intoxication, metabolic disturbance (including hypoglycemia), and psychiatric conditions that result in pseudosyncope.

**When EMS arrived at her location, the patient had not yet regained consciousness. Her temperature was 36.4 C, blood pressure 135/65 mm Hg, heart rate 78 beats per minute, and respiratory rate 12 breaths per minute. The patient s oxygen saturation was 99% while she was breathing ambient air. Her eyes were open, and her pupils were equal and reactive to light. The results of cardiovascular and pulmonary examinations were normal. Painful stimuli elicited a withdrawal response. She had incomprehensible speech and was unable to follow commands. An electrocardiogram showed no abnormalities. Her blood glucose level was 40 mg per deciliter (2.2 mmol per liter). She was immediately given 100 ml of intravenous glucose as a 10% infusion and promptly regained consciousness.**

**In the emergency department, the patient appeared well and was alert and oriented to person, place, and time. The vital signs remained within normal ranges. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 22. There were no skin abnormalities. There was no nuchal rigidity, and there were no motor or sensory deficits. The rest of the examination was normal. Her medical history was notable only for hypertension; she had no history of diabetes mellitus. Her only medication was triamterene hydrochlorothiazide for treatment of hypertension. She had never smoked and did not consume alcohol. The patient was of Eritrean descent and had emigrated 2 weeks previously to live near her daughters,**



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**who were already living in the Netherlands. There was no family history of cardiovascular, neurologic, or autoimmune disease.**

The low blood glucose level (<55 mg per deciliter [3.1 mmol per liter]), the associated symptoms, and the resolution of symptoms after correction of the glucose level comprise Whipple s triad, which indicates the presence of a hypoglycemic disorder. Medications are common causes of hypoglycemia, but the patient had no history of taking medications to treat diabetes or other drugs that can lower glucose levels (e.g., fluoroquinolones, lithium, or beta-blockers). No other clear clinical clues that might explain the hypoglycemia were present. The patient did not consume alcohol (although alcohol use is frequently misreported). The physical examination revealed no indications of critical illness (e.g., sepsis or hepatic failure). Hypocortisolism could explain both the hypoglycemia and unintentional weight loss; although the examination did not reveal other suggestive signs (e.g., hyperpigmentation or low blood pressure), such signs are not sensitive for the diagnosis. Paraneoplastic-induced hypoglycemia caused by a non islet-cell tumor mostly producing incompletely processed insulin-like growth factor (IGF) 2 or IGF-1 remains a possible diagnosis.

**The patient s complete blood count was within the normal range. The plasma glucose level was 176.4 mg per deciliter (9.8 mmol per liter), and the glycated hemoglobin level was 5.5%. The sodium level was 130 mmol per liter, potassium level 3.7 mmol per liter, creatinine level 0.51 mg per deciliter (45 μmol per liter), calcium level 9.1 mg per deciliter (2.28 mmol per liter), and C-reactive protein level 3 mg per liter (reference value, <8). The aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and total bilirubin levels were normal, as was the level of thyrotropin. The patient was admitted to the hospital for further evaluation.**

The laboratory results rule out hepatic or kidney failure as the cause of the patient s hypoglycemia. The hyponatremia might be explained by adrenal insufficiency; a morning cortisol concentration should be measured, or a short corticotropin stimulation test should be performed.

In this otherwise healthy-appearing patient, the most likely cause of the symptoms is factitious hypoglycemia or endogenous hyperinsulinism. Accidental, surreptitious, or malicious administration of insulin or insulin secretagogues (sulfonylurea and meglitinides) should always be considered. Inspection of the patient s medication and prescriptions can be helpful.

Endogenous hyperinsulinism is most commonly caused by an insulinoma, a usually benign neoplasm of the pancreas that produces inappropriately high amounts of insulin or insulin precursors. However, in contrast to the weight loss described by this patient, insulinoma is typically associated with weight gain. The absence of a history of bariatric surgery makes beta-cell hypertrophy (nesidioblastosis) as the cause of the patient s excessive insulin production unlikely. Insulin autoimmune hypoglycemia, which is caused by antibodies directed against endogenous insulin (insulin autoimmune syndrome) or against the insulin receptor (type B insulin resistance syndrome), should be considered, although the patient has no history of autoimmune diseases or use of medications commonly associated with insulin autoimmune syndrome (e.g., drugs containing a sulfhydryl group). Although hypoglycemia can occur in type B insulin resistance syndrome, hyperglycemia is much more common in patients with that syndrome, and there was no report on the physical examination of common associated findings, such as acanthosis nigricans or signs of hyperandrogenism.

Distinguishing between fasting and postprandial hypoglycemia can help guide the evaluation. Fasting hypoglycemia occurs predominantly in patients with an insulinoma, after the administration of long- or intermediate-acting insulin or the ingestion of long-acting sulfonylurea, and in those with type B insulin resistance syndrome. Postprandial hypoglycemia, as was present in this patient, is more typical of beta-cell hypertrophy and insulin autoimmune syndrome. However, in all these disorders, hypoglycemia can occur postprandially and during fasting.

If a hypoglycemic event does not occur spontaneously while the patient is in the hospital, provocative testing (with a 72-hour fast in the case of symptoms during fasting or a mixed-meal test if symptoms are predominantly post-



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prandial) can be performed to document hypoglycemia and to allow additional biochemical testing. During a mixed-meal test, a patient receives a meal containing a specified combination of fats, proteins, and carbohydrates and is monitored for hypoglycemia.

**In the 5 hours after admission, the patient s glucose level decreased to 35 mg per deciliter (1.9 mmol per liter) despite adequate food intake. She was sweating profusely and felt very weak but maintained normal consciousness. The glucose level was restored by administration of 120 ml of a 40% glucose infusion; 20 minutes later, the glucose level was 457 mg per deciliter (25.4 mmol per liter), which decreased spontaneously to 193 mg per deciliter (10.7 mmol per liter) within 1 hour. Continuous infusion of 5% glucose was started, but hypoglycemia recurred. The concentration of the basal glucose infusion was increased to 20% glucose administered at a rate of 2000 ml every 24 hours. A low-dose corticotropin stimulation test was performed, and the patient s cortisol level increased from 10.8 to 23.7 μg per deciliter (300 to 655 nmol per liter) after 30 minutes.**

The result of the corticotropin stimulation test rules out hypocortisolism. It is notable that the glucose levels decreased despite continuous administration of glucose infusion, an observation that makes either beta-cell hypertrophy or insulin autoimmune syndrome the most likely cause, but insulinoma, factitious insulin administration, or ingestion of insulin secretagogues still cannot be ruled out. Levels of insulin, C peptide, proinsulin, and β-hydroxybutyrate should be measured at the time of hypoglycemia to distinguish between endogenous insulin production (which is accompanied by elevated C-peptide and proinsulin levels, since proinsulin is cleaved into insulin and C peptide in equimolar amounts in the pancreatic beta cells) and exogenous administration (in which these levels are suppressed). Low levels of β-hydroxybutyrate indicate insulin activity, because insulin inhibits ketone production. In addition, testing is warranted for the presence of insulin secretagogues.

**The patient had another hypoglycemic episode (glucose level, 16.2 mg per deciliter [0.9 mmol per liter]) with loss of consciousness; a concomitant insulin level was 182 μU per milliliter (1264 pmol per liter) and the C-peptide level was 2.0 ng per milliliter (680 pmol per liter). A screening test for sulfonylureas was negative. Computed tomography (CT) of the abdomen showed no pancreatic mass or other intraabdominal abnormalities, but incidentally, a lesion arousing suspicion for cancer was found in the left breast. Subsequent magnetic resonance imaging (MRI) of the abdomen and endoscopic ultrasonography of the pancreas showed no abnormalities. A blood sample was sent for measurement of insulin antibodies.**

Both the plasma insulin level and C-peptide level are extremely high; an insulin level of at least 3 μU per milliliter (21 pmol per liter) and a C-peptide level of at least 0.6 ng per milliliter (200 pmol per liter) are considered to be elevated in the context of a glucose concentration that is less than 55 mg per deciliter. The increased C-peptide level indicates an endogenous source of insulin, which establishes a diagnosis of endogenous hyperinsulinemic hypoglycemia.

Imaging with CT, MRI, and endoscopic ultrasonography showed no pancreatic mass. However, insulinomas are often less than 1 cm in diameter, and false negative results of imaging are well recognized even if several methods are used. Possible next steps are a selective arterial calcium stimulation test (which measures hepatic venous insulin levels after selective injection of calcium gluconate into the supplying mesenteric arteries) or molecular imaging with a fluorine-18-L-dihydroxyphenylalanine ($^{18}$F-DOPA) positron-emission tomography (PET) scan, either of which can effectively localize insulinoma. The lesion that was identified in the left breast also needs further investigation but is unlikely to explain the hyperinsulinemia.

**In addition to the intravenous glucose already being administered, treatment with subcutaneous octreotide injections was started in order to inhibit insulin production, and the patient s glucose level stabilized. An $^{18}$F-DOPA PET scan was scheduled, but before it was performed, results of testing for insulin antibodies returned strongly positive, at a titer of more than 50 U per liter (reference range, 0 to 0.4).**

The presence of antibodies directed against endogenous insulin in a patient without a history of exogenous insulin use is diagnostic of insulin



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autoimmune syndrome. These antibodies bind to insulin that is secreted in response to a meal and make the insulin molecules ineffective. Hyperglycemia develops, leading to ongoing production of insulin, which causes hyperinsulinemia. Subsequently, the insulin autoantibodies disassociate in an unregulated fashion, which causes hypoglycemia, mostly in the postprandial state.

The patient should begin a diet consisting of frequent small, low-carbohydrate meals to prevent high postprandial insulin levels. Octreotide therapy should be continued. Glucocorticoids may lower the antibody titer and should be considered.

**Treatment with octreotide was continued, and a diet with small, frequent meals with low carbohydrate content was started. In addition, treatment with prednisone was initiated at a dose of 60 mg once daily.**

**Because insulin autoimmune syndrome can be associated with other autoimmune conditions, additional history that focused on symptoms and previous autoimmune disease was obtained, but it yielded no new information. A biopsy of the left breast revealed invasive ductal carcinoma. A mastectomy with sentinel-lymph-node biopsy was performed. Histologic examination confirmed invasive ductal carcinoma and revealed no neuroendocrine features.**

In the weeks after presentation, the continuous glucose infusion and octreotide injections were gradually discontinued, and the dose of prednisone was slowly tapered. The patient continued to follow the recommended diet and at follow-up more than 1 year after hospital discharge had had no further episodes of severe hypoglycemia. The insulin antibody titer was reassessed several times during the follow-up period and remained strongly positive.

## COMMENTARY

Spontaneous symptomatic hypoglycemia often poses a diagnostic challenge. In this patient, the identification of elevated insulin and C-peptide levels at the time of hypoglycemia initially aroused suspicion for insulinoma. The subsequent detection of a high titer of serum insulin antibodies ultimately led to the diagnosis of insulin autoimmune syndrome.

Insulin autoimmune syndrome, or Hirata disease, is a rare cause of hyperinsulinemic hypoglycemia.[1] This syndrome is characterized by the presence of autoantibodies directed against endogenous insulin in patients who have not had previous exposure to exogenous insulin and have no pathologic abnormalities of the pancreatic islet cells[2] and is one of the two identified causes of autoimmune hypoglycemia (the other being type B insulin resistance syndrome, which is caused by autoantibodies against the insulin receptor).[3] In type B insulin resistance syndrome, autoantibodies most commonly have an inhibitory effect on the insulin receptor, which causes insulin resistance and severe hyperglycemia, but in rare cases it may have a stimulatory effect. Levels of insulin, C peptide, and proinsulin are typically much higher in patients with insulin autoimmune syndrome than in those with type B insulin resistance syndrome.[3]

The prevalence of insulin autoimmune syndrome varies according to race. Higher rates are reported among Asians (with an estimated incidence among Japanese persons of 0.017 per 100)[4] than among persons of other races[2,5]; the HLA-DR4 allele, which is strongly associated with insulin autoimmune syndrome, is more common among Asians than among persons of other races.[2,6] Underdiagnosis is common, particularly among non-Asians, and in the past decade, the number of reported cases among Whites has increased.[2]

The presumed cause of hypoglycemia in insulin autoimmune syndrome is a disconnect between the glucose level and the free insulin concentration (Fig. 1), which results from the formation of insulin insulin autoantibody complexes after insulin is released postprandially.[5] Owing to this binding, the insulin is ineffective, which leads to transient postprandial hyperglycemia; hyperglycemia triggers the production of more insulin by the pancreatic beta cells, causing profound hyperinsulinemia. When the binding capacity of insulin autoantibodies is exceeded, the glucose level falls. The remaining insulin insulin autoantibody complexes form a reservoir of bound insulin, which is released randomly with respect to plasma glucose levels, resulting in spontaneous hypoglycemia. The insulin autoantibodies have both a high binding capacity and a low affinity for insulin, leading to a high spontaneous dissociation.[5]



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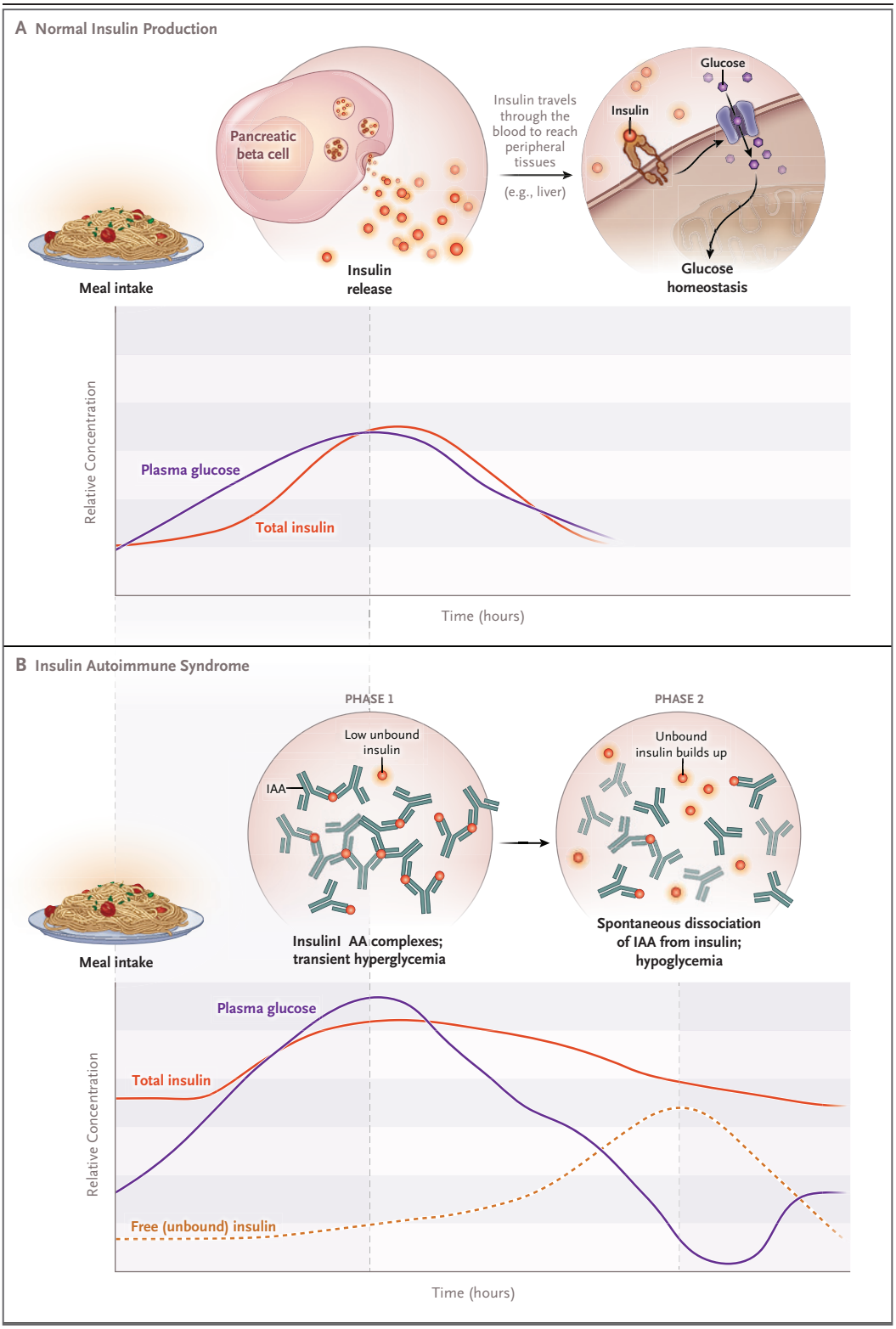




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**Figure 1 (facing page). Pathogenesis of Insulin Autoimmune Syndrome.**
After a meal, the blood glucose level rises, and in response, insulin is secreted by the pancreatic beta cells (Panel A). Normally, these insulin molecules bind to the insulin receptor on the cell membrane, which stimulates glucose uptake by the liver, skeletal muscles, and fat cells. In response, the glucose level in the blood normalizes, and a feedback loop reduces the release of additional insulin from the pancreatic beta cells. In insulin autoimmune syndrome (Panel B), the insulin molecules secreted after a meal by the pancreatic beta cells are bound by the insulin autoantibodies (IAAs), forming insulin IAA complexes. Owing to this binding, insulin is ineffective, which results in postprandial hyperglycemia (the free insulin concentration remains low). The production of insulin continues, causing hyperinsulinemia. Therefore, in insulin autoimmune syndrome, the baseline total insulin level (red line) is much higher than normal. When the binding capacity of the IAAs is exceeded, the glucose level will eventually decrease. The remaining insulin IAA complexes form a reservoir of insulin. The random release (regardless of the glucose level) of the IAAs from the insulin molecules causes episodes of spontaneous hypoglycemia, mostly in the postprandial state.

**Table 1. Patterns of Increase in Levels of Insulin, C Peptide, and Proinsulin and the Ratios of Insulin to C Peptide Typical during Hypoglycemic Events, According to Cause.***

| Cause | Insulin | C Peptide | Proinsulin | Ratio of Insulin to C Peptide |
|---|---|---|---|---|
| Insulin autoimmune syndrome | ↑↑ | ↑↑ | ↑↑ | >1 |
| Insulinoma | ↑ | ↑ | ↑ | <1 |
| Exogenous insulin | ↑ | Suppressed | Suppressed | >1 |
| Beta-cell hypertrophy | ↑ | ↑ | ↑ | <1 |
| Insulin secretagogues | ↑ | ↑ | ↑ | <1 |
| Type B insulin resistance syndrome | ↑↑ | ↑↑ | ↑↑ | <1 |

* An arrow indicates an increase; two arrows indicate a greater increase. The ratio of insulin to C peptide was calculated by dividing the concentration of insulin (pmol per liter) by the concentration of C peptide (pmol per liter).

Insulin autoimmune syndrome is often misdiagnosed as insulinoma or beta-cell hypertrophy, which can lead to unnecessary, invasive diagnostic procedures and, in some cases, unnecessary pancreatic surgery.[2,7] Insulinoma was initially the suspected cause of this patient s symptoms, although several features were atypical for this condition, including the history of weight loss, the postprandial symptoms, and the extremely high insulin concentration above 1000 pmol per liter, which is uncommon with insulinoma or beta-cell hypertrophy.[5] In retrospect, the ratio of insulin to C peptide (1.6) was an additional, unrecognized clue to the diagnosis. Insulin and C peptide are secreted from the pancreatic beta cells in equimolar amounts; because the half-life of C peptide is longer than that of insulin (30 to 35 minutes vs. 5 to 10 minutes), the ratio of insulin to C peptide is normally less than 1. In patients with insulin autoimmune syndrome, the binding of insulin autoantibodies to insulin prolongs the half-life of insulin, resulting in a ratio of insulin to C peptide greater than 1. Such a reversed ratio is only found in one other situation: hypoglycemia due to exogenous insulin administration (Table 1).[8,9] Had this elevated ratio been recognized, the extensive imaging to detect insulinoma could have been avoided.

In 60 to 80% of patients, remission of insulin autoimmune syndrome occurs spontaneously within 3 to 6 months or after treatment of the underlying cause (e.g., Graves disease or rheumatoid arthritis) or discontinuation of the medication that provoked the syndrome, with a concurrent decrease in autoantibody levels.[2,5] Therapy to manage symptoms is necessary during this period. The cornerstone of treatment is a diet consisting of frequent small, low-carbohydrate meals to prevent high insulin peaks.[8] Other empirical treatments aimed at reducing the release of insulin include somatostatin analogues (octreotide),[10] diazoxide,[11] or partial pancreatectomy. Case reports suggest that high-dose glucocorticoids can alleviate hypoglycemia, possibly by lowering the insulin autoantibody titer,[12]



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and that acarbose (an α-glucosidase inhibitor) in addition to glucocorticoid treatment can delay intestinal carbohydrate absorption and therefore lessen the postprandial rise in glucose and insulin in persons with insulin autoimmune syndrome.[13] In addition, reductions in antibody titers and in hypoglycemic episodes have been described in patients who were treated with plasmapheresis[14] or rituximab.[12,15]

This case indicates the importance of a structured diagnostic approach to spontaneous hypoglycemia[9] and of considering insulin autoimmune syndrome among the potential causes. Earlier recognition of the clinical significance of the extremely high insulin concentration and elevated ratio of insulin to C peptide in this patient might have led to earlier diagnosis and treatment and the avoidance of unnecessary testing.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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