Case Study: Screening and Treatment of Pre-Diabetes in Primary Care

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Presentation

J.M., a 48-year-old Hispanic man, was seen in the primary care clinic for routine follow-up of hypertension, for which he had been treated for the past 8 years. His only medication was lisinopril, 20 mg/day. Home blood pressure monitoring averaged 128/82 mmHg. He had a family history for hypertension, type 2 diabetes, and coronary artery disease. J.M. reported a 20-lb weight gain over the past year, along with a sedentary lifestyle with no regular exercise routine. Other medical history was negative, including symptoms of fatigue, polyuria, or polydipsia. He denied past or current tobacco use.

J.M. presented with a waist size of 42 inches, BMI of 34 kg/m^2, and blood pressure of 125/80 mmHg. A subsequent lipoprotein profile demonstrated the common pattern associated with pre-diabetes, including a low HDL cholesterol (30 mg/dl) and a high triglyceride level (185 mg/dl). The LDL was mildly elevated (132 mg/dl), and total cholesterol was 199 mg/dl. His fasting glucose was 111 mg/dl, with a repeat value of 115 mg/dl one week later.

Questions

1. Does this patient have pre-diabetes?
2. When should patients be screened for pre-diabetes?
3. How should pre-diabetes be treated in primary care settings?

Commentary

Type 2 diabetes is a significant cause of death, disability, and health care burden in the United States, affecting an estimated 16 million Americans. A prodromal phase of this disease, in which patients manifest impaired glucose metabolism, has recently been identified as "pre-diabetes" by the U.S. Secretary of Health and Human Services.[1] Pre-diabetes is also a major health care burden estimated to affect at least an additional 16 million Americans,[2] and possibly as many as 43 million with the new criteria for impaired fasting glucose (IFG) being reduced to 100 mg/dl.[3] Pre-diabetes is highly associated with concomitant cardiovascular risk factors and has been found to confer an increased risk of cardiovascular complications including myocardial infarction, stroke, and death.[1]

Pre-diabetes is clinically defined by either an IFG between 100 and 125 mg/dl or by a 2-hour oral glucose tolerance test (OGTT) result of 140–199 mg/dl, indicating impaired glucose tolerance (IGT), or both[4] (Table 1). The normal fasting glucose level was recently adjusted downward from 110 to 100 mg/dl, after analysis by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[5] (This report is reprinted in full in this issue starting on p. 71.) The committee recognized that IGT was more common in most populations by the older criteria. Lowering the impaired fasting level to 100 mg/dl should make the predictive value of future diabetes more concordant, regardless of whether IFG or IGT is used.

With the favorable results of the Diabetes Prevention Program for Type 2 Diabetes (DPP) published in 2002,[6] a recent position statement of the American Diabetes Association proposes screening recommendations for pre-diabetes to be done as part of a health care visit and suggests screening in individuals age ≥ 45 years, especially those who are overweight (BMI ≥ 25 kg/m^2)[1] (Table 2). Screening should also be considered in individuals who are < 45 years old and overweight in the presence of other risk factors, such as a first-degree relative with diabetes, history of gestational diabetes, high-risk ethnicity, hypertension, or dyslipidemia. Asian Americans may be screened at a lower BMI (≥ 23 kg/m^2).

Table 1. Definition of Pre-Diabetes

	Fasting Plasma Glucose (mg/dl)	2-hour Plasma Glucose (mg/dl)
Impaired fasting glucose (IFG)	100–125	
Impaired glucose tolerance (IGT)		140–199
Normal	< 100	< 140
Diabetes	≥ 126	≥ 200

The diagnosis of pre-diabetes is made by a positive finding of IFG or IGT or both, and test results should be confirmed on a different day.

Table 2. Routine Screening Recommendations for Pre-Diabetes

- Age ≥ 45 years, especially with a BMI ≥ 25 kg/m² (Asian Americans at BMI of ≥ 23 kg/m²)
- Age < 45 years with BMI ≥ 25 kg/m² plus additional risk factors for type 2 diabetes (hypertension, history of gestational diabetes, baby weighing > 9 lb, high-risk ethnic group, HDL < 35 mg/dl, triglycerides > 250 mg/dl, first-degree relative with diabetes, history of vascular disease, habitual inactivity, polycystic ovary syndrome)
- Either FPG or 2-hour OGTT can be used, with positive results confirmed on another day
- Done as part of a health care office visit
- Rescreening in 3 years

Based on these screening recommendations, J.M. was a candidate for screening with age, ethnicity, BMI, dyslipidemia, family history, sedentary lifestyle, and hypertension as prevailing risk factors. His low HDL, high triglyceride level, waist circumference, and hypertension made him a likely candidate for the diagnosis of pre-diabetes. These four risk factors, along with impairment of glucose tolerance, were established as clinical markers for insulin resistance by the National Cholesterol Education Program, Adult Treatment Panel III, and are used to confirm a diagnosis of the metabolic syndrome[7] (Table 3).

J.M.'s fasting glucose results of 111 and 115 mg/dl confirmed the diagnosis of pre-diabetes. To exclude a diagnosis of diabetes, a 2-hour OGTT was ordered. Its result of 173 mg/dl indicated that J.M. had IGT in addition to IFG. A recent analysis of glucose progression over several decades in the Baltimore Longitudinal Study of Aging suggests that IFG and IGT may represent different phenotypes in the natural history of progression to type 2 diabetes.[8] This suggestion, however, was based on the older definition of IFG.

The results of recent clinical trials to prevent or delay progression to type 2 diabetes demonstrate the benefit of identifying patients at risk and implementing early aggressive intervention. Although intensive lifestyle and selected pharmacological interventions have demonstrated effective outcomes in preventing or

delaying progression to diabetes, many questions, including that of cost-effectiveness, persist in the translation of these interventions into primary care settings. Based on the DPP and the Finnish study,[9] successful treatment of pre-diabetes requires thorough patient education, counseling, and support in lifestyle changes targeting a 5–7% reduction in total body weight and an exercise goal of 150 minutes/week. J.M. was provided with the necessary counseling for dietary intervention, and, following a pre-exercise treadmill stress test, a titrated exercise program was initiated.

Aggressive management of J.M.'s comorbidities may also help slow pro-

Table 3. Definition of Metabolic Syndrome from National Cholesterol Education Program Adult Treatment Panel III

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	> 102 cm (> 40 in)
Women	> 88 cm (> 35 in)
Triglycerides	≥ 150 mg/dl
HDL cholesterol	
Men	< 40 mg/dl
Women	< 50 mg/dl
Blood Pressure	≥ 130/≥ 85 mmHg
Fasting glucose	≥ 110 mg/dl

Diagnosis is made when three of the five criteria are present.

gression to diabetes. Studies of selected angiotensin-converting enzyme inhibitors (ramipril) and statins (pravastatin) have suggested that these drugs may delay the progression of pre-diabetes to diabetes.[10,11] Results of studies such as the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications (DREAM) trial are needed to confirm these findings. J.M.'s blood pressure was well controlled with lisinopril, 20 mg/day. A statin was added to treat his dyslipidemia. Both of these interventions may help to delay the progression to diabetes. Aspirin therapy was initiated to reduce cardiovascular risk.

The use of the insulin sensitizers—metformin and the thiazolidinediones (TZDs)—has been shown to be beneficial in delaying the progression from pre-diabetes to diabetes.[6,12] In the DPP, metformin, 850 mg twice daily, reduced the relative risk of progression to type 2 diabetes by 31%. Metformin may additionally improve outcomes by inducing weight loss. Although conducted in women with a history of gestational diabetes, the Troglitazone in the Prevention of Diabetes (TRIPOD) study demonstrated a 56% reduction in relative risk in progression of pre-diabetes to diabetes. Although treatment was discontinued because of the withdrawal of troglitazone from the U.S. market, persistent protective treatment effects were observed more than 8 months after discontinuation. Long-term clinical trial data are not yet available for the newer TZDs, but there is a reasonable expectation that the currently available medications in this drug class may provide similar benefits. Until further clinical trial data become available, clinician judgment–based individualized patient characteristics will determine the use of insulin sensitizers in pre-diabetes. However, lifestyle modifications are first-line treatment for pre-diabetes (Table 4).

J.M. met with a dietitian and a physical therapist for initial instruction. Brisk walking was the starting baseline exercise for 30 minutes each day, 5 days per week, with the use of a pedometer to

Table 4. Successful Treatment of Pre-Diabetes	
Method	**Reference**
Lifestyle Modification (first-line)	The Finnish Study[9]
• 5–7% loss body weight	DPP Trial[6]
• 150 min/week exercise	
Pharmacological Therapy	
Metformin	DPP Trial[6]
Troglitazone	TRIPOD Study[12]
Acarbose	STOP-NIDDM Trial[13]

measure distances. Calorie counting and knowledge of healthy choices from the food pyramid were discussed, but the intensive case management approach, as used in the DPP, was not possible because of insurance reimbursement issues and a lack of availability of individual case managers.

After a 6-month trial of diet and exercise, J.M. was only able to exercise for 20 minutes or less each week, had gained 7 lb, and had an increase in fasting glucose to 117 mg/dl. Although not approved by the Food and Drug Administration for this indication or recommended by the American Diabetes Association, metformin remains an alternative.

Clinical Pearls
• Pre-diabetes is diagnosed by a fasting glucose between 100 and 125 mg/dl (IFG) or a 2-hour OGTT result between 140 and 199 mg/dl (IGT), or both, confirmed.
• The onset of type 2 diabetes can be prevented or delayed.
• Screening for pre-diabetes should be considered for patients at age 45 years, especially for overweight or obese patients, and earlier for patients with a BMI of 25 kg/m^2 or more with

additional risk factors such as hypertension or dyslipidemia.
• A dyslipidemic pattern of low HDL cholesterol and high triglycerides, in addition to hypertension and large waist size, are clinical markers for insulin resistance and impaired glucose metabolism.
• Aggressive management of concomitant comorbidities, such as hypertension and dyslipidemia, may delay progression of pre-diabetes to diabetes.
• Aggressive lifestyle modification has delayed the progression of diabetes by about 60%, while medications such as metformin have reduced progression by about 30%.
• Efforts should be made to secure insurance reimbursement for intensive lifestyle modification, including classes and case managers such as those used in the DPP.

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Case Study: Hemachromatosis in Type 2 Diabetes

Peter Capell, MD

Presentation

G.O. is a 50-year-old white man referred for help in managing his diabetes. Two years before his visit, diabetes was diagnosed during a routine exam. He was started on oral hypoglycemic agents. He initially responded to this treatment, but over the ensuing 2 years, his medication doses were slowly raised until he was on 15 mg glyburide and 2,000 mg metformin. At the time of referral, his fasting blood glucose levels were in the range of 150 mg/dl and his hemoglobin A_{1c} (A1C) was 8%. He requested a consultation when he was advised to start on insulin therapy.

His medical history was significant for heavy alcohol intake and hepatitis B with full recovery. Family history was negative for diabetes and hemochromatosis. His review of systems was positive for joint discomfort in his hands and erectile dysfunction.

Physical exam revealed normal vital signs and no retinopathy or other signs of diabetic complications. His hand joints showed mild swelling and tenderness over the proximal interphalangeal joints, and his skin was slightly, diffusely hyperpigmented.

Lab data included a random glucose of 253 mg/dl, A1C of 7.9%, normal creatinine and electrolytes, aspartate aminotransferase (GOT) of 66 units/l (normal < 44), alanine aminotransferase (ALT) of 133 units/l (normal < 31 units/l), normal bilirubin and alkaline phosphatase levels, normal testosterone level, and negative hepatitis antigen screen. His iron level was 306 µg/dl (normal < 155) with an iron-binding capacity of 315 µg/dl (normal < 400) and percent saturation of 97% (normal < 50%). Serum ferritin was 2,920 µg/l (normal < 160). The poly-merase chain restriction assay demonstrated homozygosity for the C282Y chromosome. Referral to the hepatology clinic resulted in a liver biopsy, which identified increased iron stores and early periportal fibrosis.

Following confirmation of a diagnosis of hemochromatosis, he was started on phlebotomy therapy. Family screening was encouraged and resulted in the finding of asymptomatic diabetes associated with hemochromatosis in his brother. His medication doses have not changed, nor have his fasting glucose level or A1C results after 4 months of phlebotomies.

Questions

1. What is the prevalence of hemochromatosis in the general and diabetic population?
2. What is the effect of treatment on diabetic control in patients with hemochromatosis?
3. Should all people with diabetes over age 30 be screened for hemochromatosis?

Commentary

Hereditary hemochromatosis is an autosomal recessive genetic disorder caused by a mutation in the HFE gene located on the short arm of chromosome 6. This mutation results in increased intestinal absorption of iron and eventually to iron overload. About 10% of the white population in the United States is heterozygote, with the frequency for homozygosity at 0.2–0.5%. Heterozygote individuals are gene carriers but are not medically affected.

Onset of symptoms is seldom apparent before age 40 because it takes years to build up enough iron to cause tissue damage. Liver function abnormalities are the most frequent finding leading to a diagnosis. Other important organ systems usually involved include the pancreas (diabetes), skin (hyperpigmentation), joints (arthralgias and arthritis), heart (arrhythmias), and gonads (hypogonadism).

Approximately 50% of patients diagnosed with hemochromatosis will have either type 1 or type 2 diabetes. The likelihood of finding hemochromatosis in the adult population of diabetic patients is reportedly between 1–2%. Diabetes is not uncommonly the only apparent manifestation of hemochromatosis in unrecognized cases.

Early recognition of the presence of hemochromatosis is extremely important. Prompt therapy can prevent cirrhosis of the liver, development of a hepatoma, joint and gonadal damage, and the development of diabetes. In addition, as in this case, it can lead to early recognition of the disease in family members. Unrecognized, advanced hemochromatosis carries a high risk for premature death.

Development of diabetes in hemochromatosis is likely multifactorial. Selective β-cell damage, due to uptake of iron, leads to impaired insulin synthesis and release. α-Cell function is not impaired. In addition, liver fibrosis leads to insulin resistance and contributes to some patients requiring large amounts of insulin to obtain optimal blood glucose control. A family history of diabetes is observed in 25% of patients with hemochromatosis who develop diabetes. In contrast, only 4% of those with hemochromatosis who fail to develop diabetes have a positive family history. Therefore, it is likely that all three fac-

tors—β-cell damage, insulin resistance, and underlying genetic tendencies—play a causal role in patients with hemochromatosis developing diabetes.

Phlebotomy therapy has a variable impact on diabetes control. In a large study exploring the effect of therapy on diabetes control, 40% of 72 patients on insulin or oral agents showed improved glucose control following phlebotomy therapy. This same study reported that 6% of patients were able to stop insulin therapy during phlebotomy therapy, but 12% of the study group required increased medication to achieve good glycemic control. The majority of diabetic patients will experience no change or a progressive worsening in their diabetes management despite phlebotomy treatment.

The issue of screening all diabetic patients for hemochromatosis is currently debated. Screening by transferrin saturation using a level of > 50% is reasonably inexpensive. The dilemma is that some reports indicate no increased risk of hemochromatosis in an adult diabetic population. Furthermore, an elevated transferrin level is nonspecific, and a positive result will lead to many unnecessary evaluations being performed. Certainly type 2 diabetes and abnormal liver tests (as in this case), arthritis, or a family history of iron overload disease (as seen with this patient's brother) should trigger an order for a transferrin level.

Clinical Pearls

- Hemochromatosis is present in 1–2% of all diabetic patients, and diabetes is often the first clinical manifestation of the disease.
- Early recognition and treatment is imperative to prevent fatal liver or heart abnormalities and can prevent the onset of diabetes or improve diabetes control.
- Screening all diabetic patients for hemochromatosis may not be cost-effective. However, screening patients with a family history of iron overload disease, abnormal liver enzymes, or arthritis seems prudent.

SUGGESTED READINGS

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Case Study: An 82-Year-Old Woman Presents With Severe Hypoglycemia Induced by an Insulinoma

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Presentation

I.H. is an 82-year-old white woman who presented to her primary care physician with a 10-year history of episodic confusion and somnolence. The episodes occurred about twice a year, typically in the morning, just after waking. They lasted minutes and were relieved when she ate her breakfast or had juice. Over the 8–10 months before presentation, the patient noted that the episodes were increasing in frequency as well as occurring throughout the day.

When I.H. presented to her primary care doctor with the above complaints, the patient was reassured. As she was waiting for check-out, she developed confusion, a capillary blood glucose test was performed, and she was noted to have a plasma glucose level of 28 mg/dl. She was given juice and her symptoms resolved after a few moments.

The patient was subsequently admitted to the hospital for further work up.

On exam, I.H. was found to be a well-nourished woman in no apparent distress. Her vital signs were significant only for mild hypertension. Her physical and neurological exams were unremarkable. Her admission lab values were significant for a glucose level of 36 mg/dl. She was completely asymptomatic upon presentation and was thus placed on a fasting protocol. Subsequent laboratory results are listed in Table 1.

In this case (as is true in most centers), the serum insulin, serum C-peptide, and sulfonylurea levels were not readily available. Therefore, the fasting protocol was continued until she became symptomatic. The subsequent lab results were consistent with the suspected diagnosis of an insulin secreting tumor. To localize the tumor, I.H. had an abdominal CT with contrast, which revealed an

Table 1. Laboratory Results for Patient I.H. on Fasting Protocol				
Time	Serum Glucose (mg/dl)	Serum Insulin (μU/ml)	Serum C-peptide (ng/dl)	Sulfonylurea
0957	36	13.6	2.3	NEG
1150	50	20.6	2.6	NEG
1330	34	10.7	2.0	NEG
1430	34	6.9	1.3	NEG

enhancing mass in the pancreatic head suggestive of an insulinoma (Figure 1).

Questions
1. What are the clinical signs and symptoms of insulinomas?
2. How is the diagnosis of insulinoma made?
3. What imaging studies are best for localizing insulinomas?
4. What are the treatment options for insulinoma?

Commentary
Insulinomas are almost always islet cell tumors of the pancreas and occur as single or multiple tumors. They are typically benign, although malignant tumors have been reported as well.[1] Insulinomas present with the neuroglycopenic and sympathoadrenal symptoms induced by hypoglycemia.[2] I.H. presented with confusion, which is typical of insulinoma. Other symptoms include visual changes, unusual behavior, palpitations, diaphoresis, and tremulousness.[3]

Interestingly, I.H. had none of the sympathoadrenal symptoms. This phenomenon is known as "hypoglycemia unawareness" and is seen most often in type 1 diabetic patients who experience frequent episodes of hypoglycemia. This occurs because the set point for catecholamine secretion in response to hypoglycemia is lowered. I.H. did not have weight gain, which is noted in about 18% of insulinoma cases according to one study.[4]

Misdiagnosis of insulinoma is common. In one study, as many as 20% of patients had been misdiagnosed with a psychiatric, seizure, or other neurological disorder before the true diagnosis of insulinoma was made.[4]

Diagnosis of insulinoma is established by demonstrating inappropriately high serum levels of endogenous insulin in the setting of hypoglycemia.[5] Decrease in plasma glucose level occurs during fasting under normal physiological conditions. However, the fall in plasma glucose is accompanied by a concurrent fall in plasma insulin levels.[6] In cases where the diagnosis of insulinoma is suspected and the patient is observed with symptoms of hypoglycemia, the serum blood glucose, C-peptide, insulin, and sulfonylurea levels should be drawn immediately before intervention.

In patients who present for diagnostic work-up, a brief, observed fast should be performed in which the above lab values are measured every 4–6 hours initially and then every 1–2 hours after the patient's serum blood glucose level falls to < 60 mg/dl. The fast should be discontinued once the patient becomes symptomatic and the serum glucose falls below 45 mg/dl. A final set of labs should be drawn. The patient should then be given juice and monitored for resolution of symptoms. (Of note in patient I.H., the finding of a serum glucose of 36 mg/dl and evidence of insulin secretion probably would have sufficed.) The fast should be continued for 72 hours if symptomatic hypoglycemia does not occur.

Insulinoma patients have a tendency to develop hypoglycemia early during a fasting period, typically in the first 10–12 hours.[7] The change of insulin relative to glucose is inappropriate; thus, the insulin-to-glucose ratio increases rather than decreases as it does in normal subjects.[7] A serum insulin concentration of ≥ 6 μU/ml when the serum glucose concentration is < 45 mg/dl indicates inappropriate secretion of insulin, consistent with insulinoma.[8]

It is also very important to measure C-peptide concentrations, which should be inappropriately normal or high in the case of insulinoma. Proinsulin is the immediate precursor to insulin and is stored in the β-cell. Insulin is formed when the connecting peptide (C-peptide) is cleaved from the proinsulin molecule. This occurs at the time of insulin secretion, and thus both insulin
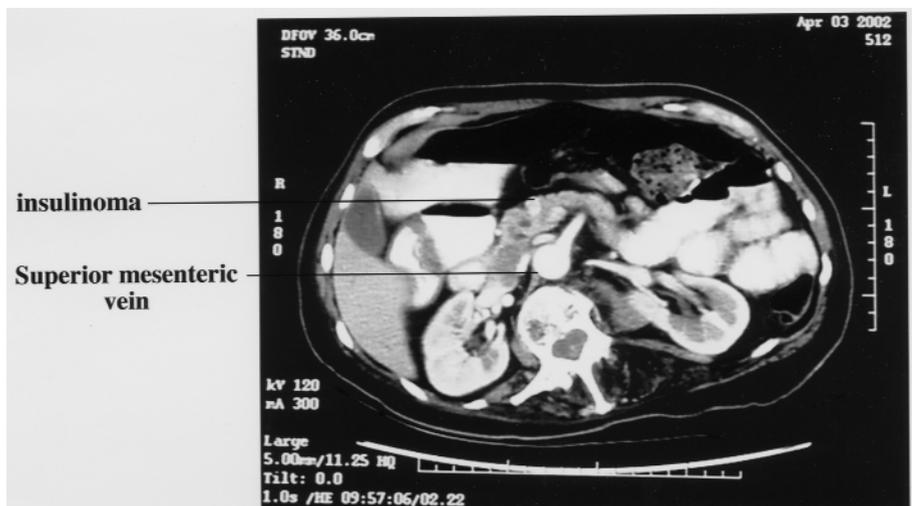

Figure 1. Contrasted abdominal CT scan illustrating enhancing mass at the head of the pancreas.

and C-peptide are released into the circulation.[9]

In a patient with a low or undetectable level of serum C-peptide in the setting of hyperinsulinemia, self-induced hypoglycemia secondary to the administration of insulin should be suspected and evaluated. Self-induced hypoglycemia may present in a similar way to that of insulinoma and is typically achieved by administering insulin or oral secretagogues such as sulfonylurea. Findings, however, in these cases do not typically correlate with food ingestion, because the agent is administered irregularly.[9] Patients presenting with self-induced hypoglycemia typically have access to hypoglycemic agents either through their work or through relatives. Factitious hypoglycemia induced by sulfonylurea administration has a laboratory presentation similar to that of insulinoma. The insulin and C-peptide levels will both be elevated; thus, it is imperative that the sulfonylurea level is measured as well.

Imaging and localization of insulinomas may be done by spiral CT, arteriography, ultrasonography (transabdominal, endoscopic, and intraoperative), or 111-In-penteotreotide or octreotide scintigraphy.[10] I.H., in addition to a CT scan, had an octreotide scan, which aided in characterizing the tumor's secretory nature and function. It illustrated a small focus of mildly increased activity in the upper abdominal region between the upper portion of the kidney just to the right of midline, placing it in the region of the pancreas. Self-induced hypoglycemia is often seen in patients seeking the attention of family and medical professionals or some other form of secondary gain.

I.H. had an open laparotomy with intraoperative ultrasound and enucleation of a 1.1-by-1.2 cm discrete, firm nodule in the center of the pancreatic head identified by palpation and ultrasound. Pancreatojejunostomy in Roux-en-Y fashion was performed in case of operative pancreatic ductal injury. Surgical resection is the treatment of choice for insulinoma. Enucleation of the insulinoma, partial distal pancreatectomy, enucleation of the insulinoma and partial pancreatectomy, a Whipple procedure (removal of the head of the pancreas, gastrectomy, duodenectomy, and splenectomy), and total pancreatectomy have all been reported. Enucleation of the tumor is the most common surgical procedure. Pathology revealed a 1.3-cm insulin-secreting endocrine neoplasm that was likely benign.

For patients who are not good surgical candidates, who refuse surgery, or whose insulinoma was missed during surgery, as well as for patients with metastatic disease, medical therapy should be attempted. The goal of medical therapy is to prevent symptomatic hypoglycemia. Medications that have been used for this purpose include diazoxide, verapamil, phenytoin, and octreotide. Diazoxide diminishes insulin secretion and is the most effective drug for controlling hypoglycemia. Octreotide, the somatostatin analog, is also a common treatment for patients with unresectable tumors.[1]

Postoperatively, I.H.'s glucose levels stabilized to the low 100s after an initial short period of hyperglycemia. Her postoperative course was complicated only by an ileus that resolved on postoperative day 11. The patient was discharged on a regular diet and has done well.

Clinical Pearls

- Insulinoma should be suspected in patients who present with symptoms of neuroglycopenic and sympathoadrenal symptoms induced by hypoglycemia.
- If the patient is symptomatic, a capillary blood glucose level should be measured immediately. If noted to be low, then serum glucose, serum insulin, C-peptide, and sulfonylurea levels should be measured before intervention.
- Factitious hypoglycemia should be suspected in patients who have access to insulin or antidiabetic secretagogue drugs through work or relatives.

- Imaging and localization of insulinoma is typically obtained by CT scan. If undetected and the clinical suspicion is still high, then arteriography, ultrasonography (transabdominal, endoscopic, and intraoperative), or 111-In-penteotreotide or octreotide scintigraphy may be pursued.
- First-line treatment of insulinoma is surgical resection. However, medical therapy may be initiated if the patient is not a good surgical candidate or the tumor is unresectable.

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