

Be Sure to Look for Secondary Diabetes

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A 63-year-old Hispanic woman was referred to endocrinology by her primary care provider for uncontrolled type 2 diabetes mellitus (T2DM), which was diagnosed 16 years ago. Her antidiabetic medications included insulin glargine (55 U bid), metformin (1,000 mg bid), and glipizide (10 mg bid). She also had known dyslipidemia, hypertension, and depression. There was a history of poorly controlled glucose (A1C between 9% and 13% in the past three years).

This was a relatively common new patient consult in our endocrine clinic. Upon entering the room, I was greeted by the patient and two family members. I quickly noticed the patient's facial plethora and central obesity with comparatively thin extremities. Further inquiry revealed that the greatest challenge for the patient and her family was her bouts of severe depression, during which she would stop caring and cease to take her medications.

During the physical exam, mild but not significant supraclavicular and dorsocervical fat pads were appreciated. The exam was otherwise unremarkable, with no purple striae on the torso, abdomen, breasts, and extremities.

In addition to routine diabetes lab tests (ie, A1C, chemistry panel, lipid panel, urine microalbumin-to-creatinine ratio), an over-

night 1-mg oral dexamethasone suppression test was ordered. Results of the latter were abnormal, and further workup confirmed Cushing disease (see Table 1 for results). The patient was referred for neurosurgery.

DISCUSSION: SECONDARY DIABETES

It is well known that the prevalence of diabetes is skyrocketing, and medical offices are filled with affected patients. According to a 2011 report from the CDC, 90% to 95% of all diabetes cases are type 2, 5% are type 1 (autoimmune), and the rest (about 1% to 5%) are "other types" of diabetes.³ Due to these disproportionate statistics, clinicians often overlook the possibility of uncommon etiologies and assume all patients with

diabetes have type 2—especially when the patient is overweight or obese.

Table 2 lists conditions and medications that may contribute to significant hyperglycemia.⁴ Some contributors are rather obvious (eg, status post pancreatectomy) or have no impact on treatment strategy (eg, chromosomal defects such as Down or Turner syndrome). However, certain conditions, such as Cushing syndrome, acromegaly, and hemochromatosis, can be relatively hard to recognize due to the variable rate of clinical manifestation, especially in the earlier stages of the disease. Experts have raised concerns that the prevalence of secondary diabetes (1% to 5%) may actually be underestimated due to "misdiagnosis" as T2DM.

TABLE 1
Results of Patient Workup

1-mg overnight dexamethasone suppression test

Total serum cortisol, 17 (< 1.8 µg/dL¹)
 Random serum ACTH, 88 (9-52 pg/mL)
 Cortisol, 32 (8-20 µg/dL)

24-h urinary free cortisol, 312 (< 50 µg)

8-mg overnight high-dose dexamethasone suppression test

ACTH, 13*
 Cortisol, 3[†]

Pituitary MRI with gadolinium, 6-mm microadenoma without sellar extension or optic chiasmopathy

Abbreviations: ACTH, adrenocorticotropic hormone

* Suppressible with Cushing disease and nonsuppressible with ectopic-ACTH secretion²

[†] < 5 µg/dL for most Cushing disease and > 5 µg/dL for ectopic-ACTH secretion²

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TABLE 2**Possible Contributors to Significant Hyperglycemia****Potentially modifiable**

- Hemochromatosis
- Growth hormone excess (acromegaly) and deficiency state
- Glucocorticoid excess (Cushing syndrome)
- Catecholamine excess (pheochromocytoma)
- Primary hyperaldosteronism
- Hyperthyroidism
- Tumors of endocrine pancreas or gut (glucagonoma, somatostatinoma, carcinoid syndrome, multiple endocrine neoplasia syndrome)
- Medications (glucocorticoids, growth hormone, glucagon, streptozotocin)
- Monogenic diabetes: neonatal and maturity-onset diabetes of the young (MODY)*

Usually not modifiable

- Pancreatic disorders (pancreatectomy, malignancy, chronic pancreatitis, cystic fibrosis)
- Lipodystrophic syndromes
- Prader-Willi syndrome (obesity related)

* Not modifiable, but recognition can significantly alter treatment strategy
Adapted from Ganda. 1995.⁴

Early detection of the underlying disorder, followed by initiation of appropriate treatment, is critical. It will not only improve but also may resolve the patient's hyperglycemia, and it may also reverse or stop the damage to other vital organs.

The case patient had an unfortunate situation in which her Cushing syndrome was masked by commonly encountered diagnoses of hypertension, T2DM, obesity, and depression. Cushing is an easy diagnosis to miss, since it has an insidious onset and it can take more than five years for some of the physical findings to become evident.

Pancreatic cancer is another

uncommon but critical disease worth mentioning. Pancreatic cancer should be in the differential diagnosis for previously euglycemic patients who experience abrupt elevation of glucose or previously well-managed patients whose glucose values quickly get out of control without obvious cause (eg, medication cessation, addition of glucocorticoid therapy, uncontrolled diet).

In our practice, we have encountered three patients with pancreatic cancer in this setting. The only sign was a sudden rise in glucose (300 to 500 mg/dL throughout the day) in patients whose A1C had been low (in the 6% range) with one or two oral

medications. Thorough history taking did not reveal any potential causes for sudden hyperglycemia. Only one patient had a palpable mass on abdominal exam and elevated liver enzymes and bilirubin. Unfortunately, that patient died eight months later. The other two had favorable outcomes from surgery and chemotherapy. Early detection was the key for those two patients.

CONCLUSION

Since the majority of patients with diabetes have T2DM, it is easy to “default” and start treating all patients as such, especially if they are overweight or obese. However, up to 5% of patients actually have underlying disease that may cause or worsen their diabetic status. Overlooking these rare conditions can be detrimental to the patient, as it will adversely affect not only glycemic control but more importantly, overall health. Identifying the underlying disease will allow the patient to receive appropriate treatment, which may offload a significant burden on glycemic control and in some cases, cure the hyperglycemia. **CR**

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