

# Diabetes and Primary Infertility in Young Males: Do Not Forget Cystic Fibrosis

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Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Defects in the *CFTR* gene cause abnormal chloride transport along the apical membrane of epithelial cells, resulting in progressive lung disease, pancreatic dysfunction, elevated sweat chloride, and male infertility. Atypical forms of CF are increasingly being recognized in older children and adults, posing a diagnostic challenge to clinicians. It is a diverse disorder affecting different organ systems of the body to varying degrees and combinations. Instead of having the classic symptoms, individuals with atypical CF might have involvement of only one organ system, and symptoms might not develop until adolescence or adulthood. We describe here two young men with diabetes who presented with primary infertility. Medical work up for evaluation of infertility led to a diagnosis of CF in both.

## Presentation 1

A 32-year-old married man, diagnosed with diabetes 3 years ago, consulted us for primary infertility. There was no history suggestive of erectile dysfunction, and he had preserved libido. He had been diagnosed with diabetes during an evaluation for leg cramps. He denied abdominal pain or steatorrhea and had no past acute metabolic decompensation. There was no family history of diabetes in any first- or second-degree relatives. On

physical examination, there was no acanthosis. His height was 158 cm, and his weight was 56 kg (BMI 22.4 kg/m<sup>2</sup>). He had normal testicular volume (25 mL) bilaterally, with normal consistency.

The patient was initially diagnosed with fasting and postprandial hyperglycemia, as evidenced from his initial blood glucose reports (fasting plasma glucose [FPG] 168 mg/dL, postprandial glucose [PPG] 240 mg/dL). Baseline biochemical parameters were within normal limits, including normal morning testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels. An abdominal ultrasound showed apparently normal liver, pancreas, and kidneys.

He had been taking glipizide (5 mg) and metformin (1.5 g) since his diabetes diagnosis, and his current glycemic status was satisfactory (FPG 92 mg/dL, PPG 132 mg/dL, A1C 6.6%). A recent postmeal serum C-peptide level was 1.97 ng/mL (cutoff 1.8 ng/mL). Pancreatic autoantibodies (anti-GAD65 and anti-IA2 antibodies) were negative. Repeated seminal fluid analysis showed low ejaculate volume (<1 cc), low pH (<6.7), absent fructose, and azoospermia.

Because of persistent azoospermia and evidence suggestive of distal duct obstruction (low ejaculate pH, volume, and fructose), a transrectal ultrasound (TRUS) was performed. It showed normal prostate with non-visualization of seminal vesicles and

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vas deferentia bilaterally. Given the absence of bilateral vas deferentia, a diagnosis of CF was entertained. We ordered a sweat chloride test. Sweat was collected by pilocarpine iontophoresis, and sweat chloride was estimated by titration with mercuric nitrate using diphenylcarbazone as an indicator. The chloride level was >60 mEq/L on two occasions (77.7 and 65.4 mEq/L, respectively).

### Presentation 2

A 27-year-old, nonobese (BMI 23.2 kg/m<sup>2</sup>) man presented to us for evaluation of primary infertility. He had normal testicular volume, and biochemical tests showed normal FSH, LH, and testosterone levels. Repeated seminal fluid analyses done earlier revealed low ejaculate volume (<1 cc), low pH (<6.9), and azoospermia. There was no history suggestive of erectile dysfunction or decreased libido.

He had been diagnosed with diabetes in the recent past during a routine check-up, and his blood glucose levels were fairly well controlled with oral agents. Since diagnosis, he had been taking gliclazide modified release (30 mg) and metformin (1,000 mg). He had no history of abdominal pain, steatorrhea, or acute metabolic decompensation. There was no family history of diabetes. Systemic examination was unremarkable, and there was an absence of acanthosis nigricans.

Considering the possibility of obstructive azoospermia in this patient, a seminal fluid fructose level was ordered, and, as in Case 1, seminal fluid fructose was absent. Bilateral absence of vas deferens and seminal vesicles was detected on TRUS. The sweat chloride test (performed twice) revealed sweat chloride levels of 63.7 and 69.8 mEq/L (normal <60 mEq/L). Subsequent investigation revealed a postmeal serum C-peptide level of 3.34 ng/mL (cutoff 1.8 ng/mL). Pancreatic autoantibodies (anti-GAD65 and anti-IA2 antibodies) were negative. Abdominal

ultrasound showed normal liver, pancreas, and kidneys.

### Questions

1. How might atypical CF pose diagnostic challenge?
2. What are the characteristics of CF-related diabetes (CFRD)?
3. When should you suspect CF in a patient with diabetes?
4. What is the pathogenesis of CFRD?
5. What type of screening should be performed for early diagnosis of CFRD?
6. What treatment options are available for CFRD?

### Commentary

Atypical CF, a milder form of the CF disorder, is a result of unusual mutations of the *CFTR* gene. Since the 1960s, a milder form of CF with atypical features has been known to exist; however, it is often not diagnosed until adolescence or adulthood (1). Individuals with mild or atypical symptoms of CF pose a significant diagnostic challenge to clinicians and can suffer substantial morbidity as a result of not receiving appropriate diagnosis and treatment (1,2). Over time, individuals with atypical CF can develop additional symptoms (3) or discover other preexisting health-related issues that were not properly identified in the beginning (4).

Atypical CF is a diverse disorder, affecting multiple systems to varying degrees and combinations. However, certain clinical signs and symptoms affecting the respiratory, gastrointestinal, endocrine, metabolic, and genitourinary systems should alert treating physicians to the possibility of CF. The patients in this report had CFRD and presented with primary infertility.

The genitourinary manifestations of CF are primarily related to fertility and are often not apparent until an individual is trying to conceive. For men, suspicion of CF might arise after finding azoospermia on semen analysis as a result of congenital bilateral absence of the vas deferens

(CBAVD) (3,5,6). CBAVD is also commonly associated with absence of the seminal vesicles. Both of our patients had similar findings on seminal fluid analysis and TRUS. Some male patients presenting with isolated CBAVD only may have *CFTR* mutations without overt symptoms of cystic fibrosis (7,8). These mutations could cause *CFTR* levels below the minimum 12%, which is necessary for normal protein function and could cause damage to organs most sensitive to *CFTR* dysfunction, such as the vas deferens.

The *IVS8* (5T) allele is the most common *CFTR* defect in patients with obstructive azoospermia due to CBAVD (9,10). Our patients were positive for sweat chloride tests. Patients with CBAVD with a positive sweat test are compound heterozygotes for two *CFTR* mutations or one *CFTR* mutation and the *IVS8* (5T) allele and probably warrant clinical follow-up for potential late complications of CF.

It is estimated that approximately half of adult CF patients develop CFRD, although the prevalence varies based on several factors. Although CFRD can occur at any age, the mean age of diabetes onset has been reported to be 18–21 years (11). Prevalence rates of CFRD increase with advancing age, and as many as 45–50% of adults >30 years of age may be affected (12,13).

Endocrine pancreatic dysfunction can be the primary presentation of CF. CFRD is considered a separate entity because of the mix of pathophysiological features it possesses that are typically seen in type 1, type 2, and pancreatogenic diabetes (14). The clinical evolution is insidious, and ketoacidosis is uncommon. Increasing evidence has demonstrated that CFRD primarily results from an insulin-insufficient state related to partial fibrotic destruction of the islet mass, which is exacerbated by worsening insulin resistance (15). More recently, it has been proposed that a combination of increased oxi-

ductive stress and an accumulation of malformed *CFTR* proteins in the endoplasmic reticulum (ER) of the pancreatic  $\beta$ -cell may lead to ER stress and eventual apoptosis of the cells (16).

CFRD is, in fact, the final period in a spectrum of progressive abnormalities in glucose tolerance. The first alterations may start with intermittent postprandial hyperglycemia, followed by impaired glucose intolerance, and then diabetes, with or without fasting hyperglycemia (17).

Early CFRD diagnosis is important because this complication is associated with a series of negative effects on the course of CF. In CFRD patients, frequency of infections, decline of pulmonary function, weight loss and growth impairment, occurrence of microvascular complications, and mortality are higher compared to CF patients without diabetes (17).

However, diabetes in CF is generally asymptomatic and clinically difficult to detect. Currently, a standardized routine is advocated with annual screening for early detection of CFRD with an oral glucose tolerance test for all CF patients, beginning at 10 years of age (18). In the CF population, A1C cannot be used as a screening tool because levels are often falsely low (19). During a period of stable health, the diagnosis of CFRD can be made in CF patients according to usual glucose criteria.

Our patients were at the late third and early fourth decade, and both had noninsulin-requiring diabetes, although their pancreatic  $\beta$ -cell reserve was not good. We switched both patients to insulin therapy. Interestingly, they had no abdominal or respiratory complaints, and there were no features of poor nutritional status. A CFRD diagnosis should not alter the usual CF dietary recommendations. Maintenance of an adequate caloric balance to preserve BMI is essential for the health and survival of CF patients.

Currently, insulin is the only medical therapy recommended for CFRD (18). Because of the variables, which are extremely dependent on the type of CF progression (degree of insulin deficiency, utilization of enteral nutrition, pulmonary function impairment, use of associated medications), insulin therapy regimens should always follow a patient's needs. Approximately 15% of all patients with CFRD have fasting hyperglycemia. In this population, insulin therapy is indicated to reverse morbid conditions, including weight loss and deterioration in lung function (20).

The oral agents for diabetes are not recommended in CFRD (20), but there are some data in the literature on their use in this situation. Glinides, which also stimulate insulin secretion, can be a better choice than sulfonylureas for patients without significant fasting hyperglycemia (14). Because the onset of the disease is often insidious, it is important to note symptoms suggestive of CFRD, such as significant weight loss and worsening of overall health status or worsening of pulmonary function.

### Clinical Pearls

- Atypical CF is a milder form of the CF disorder. Subtle clinical signs and symptoms affecting the respiratory, gastrointestinal, endocrine, metabolic, and genitourinary systems should alert physicians to the possibility of CF.
- Suspicion of CF should arise after the finding of azoospermia and absent fructose on semen analysis, as a result of CBAVD, even in the absence of major respiratory symptoms.
- Patients with CBAVD may have *CFTR* mutations without overt symptoms of CF but warrant clinical follow-up for potential late complications of CF.
- CFRD is an insidious complication of CF that may present with weight loss or poor weight gain and typically develops in older children and adults with CF.

- Not all people with noninsulin-requiring diabetes have type 2 diabetes. CF-induced diabetes can occur in absence of clinical risk factors. Early treatment with insulin should be instituted and individualized as soon as the diagnosis is confirmed, which will result in an important improvement in clinical conditions.
- The high frequency of CFRD, the absence of signs and symptoms in its initial phases, and its associated risk of clinical deterioration warrant new studies of the diagnosis and treatment of this disorder.

### Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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