Glycemic Control During Gender-Affirming Therapy in a Patient With Type 1 Diabetes

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Case Presentation

A 20-year-old transgender woman (natal male with feminine gender identity) with a 15-year history of type 1 diabetes presented to the clinic to begin gender-affirming hormone therapy. The patient was diagnosed with type 1 diabetes at the age of 5 years. Around the time of diagnosis of type 1 diabetes, she experienced two episodes of diabetic ketoacidosis but has had no additional episodes since adolescence. At initial presentation to the endocrinology clinic, her A1C was 6.8% (51 mmol/mol) on therapy with insulin detemir 33 units each night and mealtime insulin lispro at a 1:8 insulin-to-carbohydrate ratio. At this time, she was experiencing approximately one episode of hypoglycemia per week.

The patient reported gender dysphoria since the age of 15 or 16 years but had no prior gender-affirming hormonal therapy or surgery. She had a history of post-traumatic stress disorder, anxiety, suicidal ideation, and suicide attempt. The patient's family history was unknown because she was raised in the foster care system.

On social history, she had no history of tobacco use. She had a history of being abused by her biological father and foster parents. At the time of presentation, she had had two sexual partners and no history of sexually transmitted infections.

Baseline laboratory test values before starting gender-affirming therapy included thyroid-stimulating hormone 3.301 units/mL, prolactin 7.0 ng/mL, estradiol <20 pg/mL (<73.4 pmol/L), and testosterone 473.9 ng/dL (16.4 nmol/L). Her total cholesterol was 145 mg/dL (3.75 mmol/L), triglycerides were 44 mg/dL (0.50 mmol/l), LDL cholesterol was 73 mg/dL (1.89 mmol/L), and HDL cholesterol was 63 mg/dL (1.63 mmol/L). Point-of-care (POC) glucose was 112 mg/dL (6.2 mmol/L) (Table 1).

Gender-affirming hormonal treatment was initiated with 10 mg intramuscular estradiol valerate every 14 days and 50 mg spironolactone twice daily.

At follow-up 9 months later, the patient reported decreased terminal facial hair, fewer spontaneous erections, and breast growth. The patient did not experience any adverse side effects from the estrogen.

On physical exam, her weight had increased by 1.4 kg, and her BMI had increased from 27.8 to 28.5 kg/m^2. She had Tanner IV breasts bilaterally. Her laboratory test values showed an increase in estradiol to 73 pg/mL (268.0 pmol/L) and a decrease in testosterone to 32.5 ng/dL (1.1 nmol/L). However, her A1C had increased to 7.3% (56 mmol/mol), and her mealtime insulin requirements had increased to a 1:5 insulin-to-carbohydrate ratio. Her POC glucose was 270 mg/dL (15.0 mmol/l). Her total cholesterol increased to 206 mg/dL (5.33 mmol/L), triglycerides increased to 195 mg/dL (2.20 mmol/L), LDL cholesterol increased to 92 mg/dL (2.38 mmol/L), and

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TABLE 1. Baseline and Follow-Up Laboratory Test Values

Laboratory Tests	Baseline	9 Months After Initiation of Hormone Treatment
Weight, kg	75.7	77.1
BMI, kg/m^2	27.79	28.5
Mealtime insulin lispro insulin-to-carbohydrate ratio	1:8	1:5
Estradiol, pg/mL (pmol/L)	<20 (<73.4)	73 (268.0)
Testosterone, ng/dL (nmol/L)	473.9 (16.4)	32.5 (1.1)
A1C, % (mmol/mol)	6.8 (51)	7.3 (56)
POC glucose, mg/dL (mmol/L)	112 (6.2)	270 (15.0)
Total cholesterol, mg/dL (mmol/L)	145 (3.75)	206 (5.33)
Triglycerides, mg/dL (mmol/L)	44 (0.50)	195 (2.20)
LDL cholesterol, mg/dL (mmol/L)	73 (1.89)	92 (2.38)
HDL cholesterol, mg/dL (mmol/L)	63 (1.63)	75 (1.94)

HDL cholesterol increased to 75 mg/dL (1.95 mmol/L). Because her estrogen level was below the target range and the patient desired further feminization with her transition, her estradiol valerate dosage was increased to 15 mg every 14 days.

At her next follow-up 3 months later (12 months after initiation of gender-affirming therapy), she reported more breast growth. Her estradiol had increased to 518 pg/mL (1901.6 pmol/L), and her estradiol valerate dosage was decreased to 5 mg weekly in response.

Question

- How does gender-affirming hormone therapy affect glycemic control and clinical care of diabetes?

Commentary

This case demonstrates increased insulin needs and loss of glycemic control in a transgender woman with type 1 diabetes after initiation of gender-affirming hormone therapy with estrogen and spironolactone. The standard of care in gender-affirming therapy in a transgender woman is to lower testosterone and replace it with estradiol to levels that are within the reference range for cisgender women (natal female with feminine gender identity) (1). The factors contributing to increased insulin needs and loss of glycemic control in this transgender woman could be the result of decreased androgen levels or increased estrogen levels.

The relationship between sex hormones and insulin resistance is well established. In natal males, decreased testosterone levels due to hypogonadism or androgen deprivation therapy leads to increased insulin resistance (2,3). One study showed that replacement of androgens in hypogonadal cisgender men (natal male with masculine gender identity) with type 2 diabetes leads to decreased insulin resistance (4). In another study, there were no changes in insulin sensitivity due to testosterone replacement (5). Conversely, in cisgender females, the postmenopausal state is associated with increased insulin resistance and diabetes risk (6–8). Estrogen replacement decreases insulin resistance in healthy postmenopausal cisgender women (9) and improves glycemic control in postmenopausal cisgender women with diabetes (10,11). However, the effect of estrogen treatment on glycemic control in transgender women is unknown.

To our knowledge, there are no studies in transgender patients with diabetes investigating the effect of gender-affirming therapy on glycemic control. Several studies in male-to-female transgender patients without diabetes undergoing gender-affirming therapy have shown increased insulin resistance (12–14). Polderman et al. (13) hypothesized that administration of exogenous forms of estrogen may interfere with the interaction of insulin with its receptor, causing a decrease in insulin sensitivity. Auer et al. (12) found that transgender women undergoing gender-affirming hormone therapy experienced an increase in markers of insulin resistance and first-phase insulin secretion. There is little evidence on how this increase in insulin resistance seen in healthy transgender women translates to patients with diabetes. Given the increased insulin needs seen in our patient, it is possible that our patient became more insulin resistant.

We did not measure sex hormone–binding globulin (SHBG), free testosterone, or free estradiol levels. In healthy transgender women, SHBG increases with estrogen treatment (15). Lower SHBG levels are associated with a higher incidence of diabetes in cisgender men (16). In another study of cisgender men using data from the National Health and Nutrition Examination Survey, higher free estradiol and lower free testosterone and SHBG levels were associated with prediabetes (17). Because testosterone lowering is initiated at the same time as estrogen therapy, it is not possible to distinguish whether the change in insulin resistance is due to lower androgen levels or increased estradiol

levels. The increased insulin needs for this patient may be the result of weight gain. Transgender women have increased subcutaneous and visceral fat deposition (18) with increased body fat (19), which could in turn contribute to increased insulin needs. Although we did not ask whether our patient had a previous eating disorder, many transgender patients have a history of eating disorders relieved by gender-affirming therapy (20).

In this case report, we describe how the administration of estradiol affects glycemic control in a male-to-female transgender woman with type 1 diabetes. Further physiological studies using gold-standard methods to assess insulin resistance should be done to attain a better understanding of how feminizing and masculinizing gender-affirming hormone therapy affect the management of diabetes.

Clinical Pearl

- Gender-affirming hormone therapy for transgender women aimed at lowering endogenous testosterone and increasing estrogen may result in increasing insulin needs and challenges to glycemic control in transgender patients with diabetes.

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Duality of Interest

P.V. has received consulting fees from Boehringer Ingelheim and Merck. No other potential conflicts of interest relevant to this article were reported.

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S.H.C., K.L.F., and P.V. researched the data. All authors wrote and edited the manuscript. P.V is the guarantor of this work and, as such, had full access to all of the data and takes responsibility for the accuracy and integrity of the case presentation.

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