Physiology or Pathology? Elevated Serum Creatinine in a Female-to-Male Transgender Patient

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Clinical Presentation

A 36-year-old female-to-male (FTM) transgender patient was referred to our nephrology clinic for evaluation of an elevation in serum creatinine (Scr) level. He had a history of transient ischemic attack secondary to patent foramen ovale, as well as attention deficit disorder.

A review of records shows that the patient’s Scr level was 0.94 mg/dL before initiation of testosterone treatment (2 years before presentation). He denied acute changes in health, illicit drug use, recent or remote nonsteroidal anti-inflammatory drug use, or lower urinary tract symptoms. Home medications included clopidogrel, 75 mg, daily; dextroamphetamine, 10 mg, twice daily; and testosterone, 60 mg, injected intramuscularly weekly.

On physical examination, the patient’s temperature was 36.4°C (97.6°F), heart rate was 76 beats/min, blood pressure was 114/65 mm Hg, respiration rate was 18 breaths/min, and oxygen saturation was 98% while breathing room air. Cardiac examination findings were unremarkable. Lungs were clear bilaterally. His abdomen was soft with no visceromegaly or tenderness. There was no edema. There were no focal neurologic findings. A basic metabolic panel was done, showing the following values: Scr, 1.3 mg/dL; serum urea nitrogen, 18 mg/dL; serum sodium, 140 mmol/L; serum potassium, 4.8 mmol/L; and bicarbonate, 29 mmol/L. Urinalysis was negative for crystals and cellular elements, and urinary albumin-creatinine ratio was 4.2 mg/g.

What is the differential diagnosis of elevated Scr level during testosterone treatment?

In a case series of 4 body builders on testosterone therapy and creatine supplements who presented with acute kidney injury (AKI), kidney biopsy revealed acute tubular necrosis without evidence of rhabdomyolysis or crystal deposition. Two of the 4 patients in this case series had evidence of chronicity, with interstitial fibrosis and tubular atrophy. All 4 patients had resolution of AKI at 4 weeks after stopping supplementation.

Herlitz et al reported a case series of 10 men with AKI associated with testosterone used for participation in body-building competition. At the time of biopsy, mean Scr level was 3 mg/dL and mean proteinuria showed protein excretion of 10 g/d; 3 patients had nephrotic syndrome. Nine of 10 patients in the cohort had focal segmental glomerulosclerosis on biopsy, and most had more than 50% to 95% foot-process effacement on electron microscopy. Seven of the patients experienced stabilization or decrease in Scr levels (mean, 2.34 to 1.61 mg/dL) and 24-hour proteinuria (mean protein excretion, 9.47 to 1.83 g/d) after discontinuation of testosterone treatment. The possible mechanisms for focal segmental glomerulosclerosis associated with testosterone use include adaptive changes secondary to glomerular stress from increased muscle mass, as well as direct podocyte injury, as shown in animal models.

Doublier et al demonstrated the presence of sex hormone receptors on glomerular podocytes in a mouse model. Stimulation of these receptors by androgen leads to podocyte injury, whereas estrogen seems to offer protection against this injury pattern. Although we expect Scr levels to increase in FTM transgender patients, the potential of podocyte injury warrants surveillance for proteinuria.

What is the natural evolution of Scr levels in FTM transgender patients?

There is an expected increase in Scr levels in FTM transgender patients during hormonal therapy with testosterone. Fernandez and Tannock demonstrated this trend in a retrospective analysis of 19 transgender patients on hormonal replacement therapy during the transition process with laboratory measurements at baseline before initiation of testosterone treatment and subsequently at 3-6 months and 6-18 months after hormone treatment initiation. There was a statistically significant increase in Scr levels from baseline to 3-6 months (0.73 to 0.87 mg/dL), and this increase remained significant at 6-18 months (0.82 mg/dL). The effect is hypothesized to occur from increased creatinine release from the enhancement in muscle

Discussion

What is the differential diagnosis of elevated Scr level during testosterone treatment?

The differential diagnosis of elevated Scr level during testosterone therapy includes both physiologic and pathologic causes. Testosterone treatment increases total-body muscle mass, leading to an increase in release of creatinine into the circulation, as demonstrated by Brodsky et al in men with low testosterone levels on androgen replacement therapy.

What additional diagnostic study should be obtained?

Quiz
induced by testosterone. Body mass index in these patients also increased after testosterone therapy initiation, which may also be explained by increased muscle mass.

Vita et al conducted a similar retrospective analysis of 11 FTM transgender patients receiving testosterone for hormone replacement. Again, there was a statistically significant increase in Scr levels after initiation of testosterone treatment (0.7 mg/dL at baseline compared to 1.0 mg/dL at follow-up).

**What additional diagnostic study should be obtained?**

A direct measurement of glomerular filtration rate is warranted. Gold-standard measurements such as urinary inulin, iohexol, or iothalamate clearance would be ideal, but typically are reserved for research settings. Measurement of a 24-hour collection of urine for creatinine is used clinically. When measured, our patient's calculated creatinine clearance was 92 mL/min. Notably, the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation to estimate glomerular filtration rate yielded a value of 61 mL/min/1.73 m² with a female sex input and 81 mL/min/1.73 m² with a male sex input.

**Final Diagnosis**

Hypercreatininemia from testosterone effects on muscle.

**Article Information**

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**References**


