CLINICAL VIGNETTE

Spontaneous Fracture Linked to Aromatase Inhibitor Use in Older Male

Erin A. Cook, MD and Grace I. Chen, MD

Case Report

A 76-year-old male awoke with acute left hip pain and difficulty walking. He denied recent falls, trauma, or injury. He presented to the emergency department (ED) where x-ray and Computed Tomography (CT) imaging of his hip and pelvis, were both negative for a fracture or other obvious pathology. He was given pain medications for a presumed diagnosis of bursitis, referral to physical therapy, and discharged home. The patient has a history of squamous cell carcinoma of the tongue and underwent resection, chemotherapy, and radiation 4 years prior. He has been in and has a chronic gastrostomy tube. His history also includes GERD, recurrent oral herpes simplex virus (HSV), hypogonadism, and major depression in remission. He remains independent in all of his basic and instrumental activities of daily living. Prior to this event he walked without an assistive device and exercised regularly on a stationary bike. His medications include sertraline, trazodone, temazepam, testosterone, and acyclovir as needed.

He returned home and continued to have debilitating pain when bearing weight. Rheumatologist evaluation five days included additional imaging. The MRI showed a left subcapital femoral neck fracture. He was placed on non-weight bearing status, and scheduled for hip surgery. At his pre-operative visit, it was noted that anastrozole was on his medication list. He reported taking this medication for at least one year. It was prescribed by his naturopathic physician after he developed mild gynecomastia from his testosterone therapy. He was started on testosterone two years earlier for hypogonadism. His testosterone level prior to testosterone initiation was 9ng/dl (normal range 264-916ng/dl) and he was experiencing fatigue and sexual dysfunction. His clinical symptoms vastly improved after initiation of testosterone and his last testosterone level was 817 ng/dl. He underwent a successful hip surgery and returned home after a short rehab. His anastrozole was stopped and he was advised to consult with his medical doctor before starting any naturopathic prescribed treatments.

Discussion

Testosterone treatment in the older male adult is controversial. Testosterone naturally declines with age.[1] Sexual function, bone mineral density, muscle mass, strength, and hemoglobin also decline with age. These changes along with higher rates of depression and metabolic syndrome that occur in older males may be related to a decrease in testosterone. This has been referred to as “andropause”. Although it has not been proven that replacing testosterone in older males will reverse these age-related changes, testosterone is commonly prescribed.

Testosterone therapy in older men does not come without risk. The Endocrine Society recommends against routinely prescribing testosterone to men 65 years or older with low serum testosterone levels. Physicians may offer testosterone therapy on an individual basis in those with unequivocal symptomatic hypogonadism after an explicit discussion of the potential risks and benefits.[2] The patient must truly be deficient in testosterone based on two separate fasting morning total testosterone concentrations and pituitary-hypothalamic and testicular diseases must be excluded. Additionally, the patient needs to have symptoms of hypogonadism, specifically fatigue, depression, osteoporosis, sexual dysfunction, or unexplained anemia. Before initiating therapy, the clinician and patient should decide on a well-defined clinical outcome they hope will improve. If this clinical outcome is not achieved despite therapeutic testosterone levels, then replacement therapy should be discontinued. In older men, the target serum testosterone level on treatment should be 300-400ng/dl. Risks of testosterone therapy include erythrocytosis, gynecomastia, and increased prostate specific antigen (PSA). Recent studies suggest there may be additional risks including prostate cancer, sleep apnea, and cardiovascular disease. The physician and patient need to engage in shared decision making regarding prostate cancer risk and prostate cancer monitoring before starting treatment. PSA and digital rectal exam (DRE) monitoring should be done at baseline and 3-12 months after the start of testosterone therapy. After one year the physician may follow standard prostate cancer screening guidelines. Hematocrit should also be monitored when on therapy.[2]

The benefit of testosterone therapy in older adults with hypogonadism is still under investigation. The “testosterone trials” are a collection of 7 placebo controlled clinical trials looking at older men with low testosterone (average level <275ng/dl) and symptoms of hypogonadism.[3] These men received one year of testosterone therapy and seven primary outcomes were evaluated, including sexual function, physical function, vitality, cognitive function, anemia, bone density and cardiovascular risk. Sexual function, anemia, and bone density improved with testosterone therapy.[3-5] Physical function, vitality, and cognitive function remained unchanged.[3,6] Cardiovascular risk was felt to be increased as evidenced by an increase in coronary artery plaque on coronary computed tomography angiography

(CCTA) though major adverse cardiac events were not evaluated.[7]

Estradiol, not testosterone, is the major hormone responsible for bone health in men. Testosterone is converted into estradiol via the enzyme aromatase. Estradiol is made via testicular and adrenal androgen conversion. Men are at an increased risk of fracture when their serum estradiol level and testosterone level are low compared with low testosterone levels alone[8] and studies in elderly men show that low serum estradiol is more associated with low bone mineral density then a hypogonad state.[9] Aromatase inhibitors block the conversion of testosterone to estradiol. They are typically used in estrogen-receptor positive breast cancer. Studies have examined the use of aromatase inhibitors as an alternative way to increase testosterone levels in men given the complexity of testosterone administration, side effects, and cost. Aromatase inhibitors increase circulating levels of testosterone but have failed to show any clinical benefits perhaps because of small study size and short duration of use.[10] The main concern with aromatase inhibitors is bone loss. Post-menopausal women on aromatase inhibitors for prolonged periods experience decreased bone mineral density.[11] Studies on aromatase inhibitor use in men are not as robust and have conflicting findings on bone metabolism.[12,13] The use of aromatase inhibitors is common among body builders to prevent gynecomastia but this is not considered first line therapy as there is not strong evidence to support this use. Aromatase inhibitors to prevent bicalutamide-induced gynecomastia have failed to demonstrate benefit and are not recommended.[14] Aromatase inhibitors have a valuable role in younger men who experience constitutional delay of puberty, idiopathic short stature, or in gonadotropin-independent precocious puberty.[10]

This patient's fracture was likely a direct result of low estradiol levels caused by use of an aromatase inhibitor. He was already at risk for osteoporosis secondary to his hypogonadism and the use of the aromatase inhibitor compounded the problem by increasing bone resorption. Aromatase inhibitors are not recommended to increase testosterone levels. Additionally, testosterone replacement therapy should only be used in select clinical scenarios. This patient was an ideal candidate for testosterone therapy given his low serum testosterone and symptoms of fatigue and sexual dysfunction. However, a lower target serum testosterone level would have been more appropriate and may have prevented this unfortunate outcome.

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