Bone Mineral Density and Response to Treatment in Men Younger Than 50 Years with Testosterone Deficiency and Sexual Dysfunction or Infertility

Ravi Kacker, William Conners,* John Zade and Abraham Morgentaler†

From Men's Health Boston, Brookline, Massachusetts, and New York Medical College (JZ), Valhalla, New York

Abbreviations and Acronyms

BMD = bone mineral density
BMI = body mass index
DXA = dual energy x-ray absorptiometry
E2 = estradiol
FT = free T
T = testosterone
TT = total T

Accepted for publication October 18, 2013.
Study received Beth Israel Deaconess Medical Center institutional review board approval.

* Financial interest and/or other relationship with Eli Lilly.

† Financial interest and/or other relationship with Bayer.

Purpose: Testosterone deficiency is a known risk factor for osteopenia and osteoporosis in older men. Less is known about the impact of testosterone deficiency on bone mineral density in younger men.

Materials and Methods: We retrospectively reviewed the charts at an andrology/infertility clinic and identified 399 men younger than 50 years who underwent baseline dual energy x-ray absorptiometry and had total testosterone less than 350 ng/dl or free testosterone less than 1.5 ng/dl. Additional analysis was done in a subgroup of 75 men (18.8%) in whom dual energy x-ray absorptiometry was repeated after treatment at a mean ± SD of 30.4 ± 16.2 months. The determination of osteoporosis or osteopenia was based on T-scores (osteopenia less than −1.0 and osteoporosis less than −2.5) of the lumbar spine and left hip.

Results: Of all 399 men 141 (35.3%) had bone mineral density consistent with osteopenia at the lumbar spine (137) and/or the total hip (19). In 11 men (2.75%) bone mineral density was consistent with osteoporosis at the lumbar spine. On multivariate analysis higher body mass index was independently associated with increased bone mineral density at the spine ($p < 0.0001$) as well as the hip ($p < 0.001$). Testosterone treatment in 43 men increased spine bone mineral density ($p < 0.001$). Significant decreases in spine bone mineral density developed in 21 men treated with clomiphene citrate or anastrazole ($p = 0.003$). No significant change was noted in hip bone mineral density for any treatment.

Conclusions: More than a third of men younger than 50 years with testosterone deficiency and infertility or sexual dysfunction had decreased bone mineral density. Testosterone treatment increased bone mineral density while estrogen modulators such as clomiphene citrate or aromatase inhibitors decreased bone mineral density. These results suggest that dual energy x-ray absorptiometry may be warranted in young men with testosterone deficiency.

Key Words: testis; testosterone; infertility, male; bone density; age groups

Osteoporosis is characterized by decreased bone mass and increased bone fragility, leading to an increased risk of fracture.[1] While medical attention has historically emphasized the risk of osteoporosis in postmenopausal women, there is growing awareness that men are also at risk for decreased BMD and osteoporotic fracture.[2] Men account for 39% of new osteoporotic fractures and 15% of men older than 50 years experience an osteoporotic fracture in their lifetime.[3] These men may be at higher

0022-5347/14/1914-1072/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.10.070
Vol. 191, 1072-1076, April 2014
Printed in U.S.A.

risk for mortality than women but less likely to receive treatment for osteoporosis.[4]

The impact of sex steroids on BMD is well established. In men E2, which is primarily obtained through T aromatization, appears to be needed for normal bone development and the maintenance of healthy BMD.[5] T may also have a direct effect on bone[6] and possibly indirect effects through its influence on muscle mass. The negative effect of T and E2 suppression on BMD is clinically apparent in men on androgen deprivation therapy for prostate cancer, who have an annual 13% decrease in BMD.[7] Low E2 and decreased BMD are also common in elderly men with T deficiency and there is an increased risk of fracture in those with E2 below a threshold of 40 pmol/l.[8]

The risk of decreased BMD in T deficient young men and its clinical implications are less clear. The general consensus is that young men with profound hypogonadism due to specific endocrine disorders, eg Kallman syndrome, may have impaired bone formation and be at increased risk for fracture.[9] However, to our knowledge the impact of T deficiency on BMD in the larger set of young men who present with sexual dysfunction or infertility remains unexplored. Beyond the potential for fractures later in life decreased BMD may be clinically important in these men, who are often treated with medications that alter estrogenic effects on tissues, such as aromatase inhibitors or clomiphene citrate.

We hypothesized that T deficiency in men younger than 50 years would be associated with decreased BMD. We characterized BMD in this population and determined how treatments for T deficiency may impact BMD.

MATERIALS AND METHODS

We retrospectively reviewed the charts at Men's Health Boston, an ambulatory medical center specializing in andrology/infertility. The study was performed with approval from the Beth Israel Deaconess Medical Center institutional review board. The chart review identified 399 men who presented between January 2006 and July 2013 who were between 20 and 50 years old, were diagnosed with T deficiency and underwent DXA.

DXA was performed using the QDR® Discovery W system and analyzed using QDR System Software, version 12.5 to determine the T-score, Z-score and BMD for anteroposterior projections of the lumbar spine (L1 through L4) and total hip (BMD coefficient of variation 1 gm/cm^2). The left hip was used for measurement unless there were site specific issues such as prior hip replacement, in which case DXA of the right hip was done. The system was calibrated daily against an anthropometric quality control spine phantom (Hologic™). Reference curves were derived from NHANES (National Health and Nutrition Examination Survey) studies,[10] and additional data on male subjects collected by the manufacturer. In accordance with published guidelines a T-score of less than −2.5 at the lumbar spine or hip was categorized as osteoporosis and a T-score of between −1.0 and −2.5 was categorized as osteopenia.[11]

The medical record was reviewed to determine the race, reason for clinic presentation, age at DXA, comorbidities and laboratory values of each patient. T levels were based on a single blood sample obtained during normal clinic hours. Biochemical criteria for T deficiency were TT less than 350 ng/dl or FT less than 1.5 ng/dl.[12] Serum TT, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, sex hormone-binding globulin and E2 were measured using an electrochemiluminescence immunoassay (Tosoh Bioscience, Tessendero, Belgium). When E2 was below the assay range, the lower limit of the assay was chosen as a representative value. FT was determined using a radioimmunoassay (Siemens, Munich, Germany). The range of the intra-assay coefficient of variation was 2.4% to 2.8% for TT, 3.5% to 5.0% for E2 and 2.6% to 3.1% for FT.

In patients who underwent more than 1 DXA scan we determined the type of hormonal treatment during the period between scans. Testosterone cypionate was offered at an initial dose of 100 mg weekly or 200 mg biweekly. Clomiphene citrate was given at 25 mg daily or at 50 mg 3 times weekly. The initial dose of T 75 mg pellets was 10 to 12 pellets every 3 months. The dose was adjusted based on biochemical and symptomatic responses.

Statistical analysis was done with StatCrunch™. The chi-square test was used to compare osteopenia and osteoporosis rates with rates in the standard, healthy reference population used by the QDR system software. Univariate and multivariate linear and logistic regression models were used to determine predictors of decreased BMD and of BMD in the osteopenia range. With the Student t-test we determined whether BMD increased or decreased in men with 2 DXA scans who were treated with T, clomiphene citrate and an aromatase inhibitor.

RESULTS

Table 1 lists baseline demographics and hormonal laboratory values. Of the 399 men 141 (35.3%) had BMD consistent with osteopenia at the lumbar

Table 1. *Baseline demographics of all 399 men*

Mean ± SD age	36.9 ± 5.5
No. race (%):	
White	351 (88.0)
Black	19 (4.8)
Asian	19 (4.8)
Hispanic	10 (2.5)
No. referral reason (%):	
Sexual dysfunction/low T	237 (59.4)
Infertility	149 (37.3)
Other	13 (3.3)
Mean ± SD T (ng/dl):	
Baseline	308.9 ± 127.9
Free	1.26 ± 2.85
Mean ± SD baseline E2 (pmol/l)	37.8 ± 14.1
Mean ± SD baseline sex hormone-binding globulin (nmol/l)	22.8 ± 12.4
Mean ± SD BMI (kg/m^2)	29.0 ± 5.58