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

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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

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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

spine (137) and/or the total hip (19). Of the men 11 (2.5%) had BMD consistent with osteoporosis at the lumbar spine. The patient population was predominantly white and most men presented with sexual dysfunction (59.4%) or infertility (37.3%). In men who presented with infertility vs sexual dysfunction BMD did not differ in the spine ($p = 0.479$) or hip ($p = 0.498$). BMD was unrelated to diabetes ($p = 0.652$). Mean TT was 308 ng/dl and mean FT was 1.26 ng/dl. Only 10 patients (2.51%) had T less than 100 ng/dl due to a known or suspected endocrine abnormality. No patient had untreated hypothyroidism, none sought care for known or suspected low BMD and none was treated for T deficiency based on BMD alone.

Table 2 shows baseline BMD results. The prevalence of osteopenia was significantly higher than expected in a young, healthy male reference population. Compared to the young, healthy male reference population used by the QDR system software to calculate T-scores[10] the study population was at substantially increased risk for osteopenia (OR 3.79, $p < 0.001$) and osteoporosis (OR 7.64, $p < 0.001$). The mean T-score in this population was significantly less than 0 for the lumbar spine ($p < 0.0001$) but greater than 0 at the hip ($p < 0.0001$).

Age was not related to BMD for the spine ($p = 0.944$) or hip ($p = 0.7195$). Of the 32 men younger than 30 years 11 (34.4%) had osteopenia at either site. TT and FT were not related to BMD at the spine ($p = 0.315$ and 0.805) or hip ($p = 0.461$ and 0.262, respectively). There was no difference in spinal BMD in men with TT less vs greater than 300 ng/dl ($p = 0.291$). Mean BMD did not differ in the 10 men with TT less than 100 ng/dl compared to the remaining men ($p = 0.158$).

Mean BMI in all 399 men was 29.0 kg/m^2. Increased BMI was associated with increased BMD at the spine ($p = 0.0003$) and hip ($p < 0.0001$) independent of age and hormonal levels. Higher E2 was independently associated with higher BMD at the hip ($p = 0.00341$). Baseline E2 was not associated with spinal BMD ($p = 0.136$). However, low serum E2 was associated with osteopenia at the spine (OR 0.978, 95% CI 0.961–0.996, $p = 0.0139$) but not at the hip ($p = 0.523$). Men with E2 less than 40 pmol/l had a higher rate of osteopenia at the spine than men with E2 greater than 40 pmol/l (OR 3.013, 95% CI 1.871–4.852, $p = 0.0001$).

Baseline and followup DXA scans were available for review for 75 men (18.8%). The mean ± SD interval between initial and followup scans was 30.4 ± 16.2 months. Table 3 lists mean changes in spine and hip BMD, and mean posttreatment serum TT and E2. Significant increases in spinal BMD developed in the entire population ($p = 0.007$). The change in spinal BMD was unrelated to the change in T ($p = 0.986$) or E2 ($p = 0.823$). Spinal BMD increased in men treated with T ($p < 0.001$) but decreased in 21 treated with the estrogen modulators clomiphene citrate (17), anastrazole (3) or clomiphene citrate plus anastrazole (1). No significant change was noted in hip BMD with any treatment.

Table 2. *Study population BMD, T-scores and Z-scores*

	Lumbar Spine	Total Hip	Lumbar Spine or Total Hip
Mean ± SD BMD (gm/cm^2)	1.036 ± 0.131	1.064 ± 0.131	—
Mean ± SD T-score	−0.529 ± 1.181	0.173 ± 0.858	—
Mean ± SD Z-score	−0.447 ± 1.180	0.337 ± 0.868	—
No. osteopenia (%)	137 (34.3)	19 (4.76)	141 (35.3)
No. osteoporosis (%)	11 (2.75)	1 (0.25)	11 (2.75)

DISCUSSION

In recent years increasing attention has been given to T deficiency in aging men and the potential health consequences.[12] In particular, older men with T deficiency are at increased risk for decreased BMD and osteoporotic fracture.[9] Studies using DXA showed that these men benefit from T therapy, which consistently produces improvement in spinal BMD[13–15] and could possibly also prevent deterioration of hip BMD.[16] In contrast to the growing acceptance of the importance of androgens for bone health in older men, much less is known about T deficiency and BMD in younger men.

Previous reports of BMD in young hypogonadal men were about a small number of patients[17] or focused on young men with castrate levels of T.[9] Two previous groups found decreased lumbar and spine BMD using DXA in young infertile men, including men with and without T deficiency.[18,19] To our knowledge no large studies have been done to examine BMD in young, T deficient men and their response to treatment.

In our series of generally healthy men we found a high prevalence of decreased BMD in the lumbar spine but not at the hip. Spinal bone is primarily trabecular while the hip is predominantly cortical. The hip was unaffected by T therapy in trials in older men.[20] Vertebral fractures may result in less acute morbidity than hip fractures but the significance cannot be minimized since they may contribute to chronic back pain, osteoarthritis, kyphosis and reduced stature.[21]

Use of the terms osteopenia and osteoporosis currently remains somewhat controversial when applied to young men without a history of fracture.[2] While to our knowledge the risk of fracture in young men with osteopenia is not known, results in older men in the Rotterdam study demonstrated that

Table 3. *Hormonal levels and change in BMD T-score after treatment in 75 men with 2 DXA scans*

	Mean ± SD Overall	Mean ± SD T Only	Mean ± SD Clomiphene Citrate Only	Mean ± SD Anastrazole Only	Mean ± SD Any Regimen*
No. pts	75	43	17	3	8
TT (ng/dl)	635.6 ± 234.6	624.2 ± 226.2	667.2 ± 269.6	440.5 ± 324.5	659.3 ± 269.4
E2 (pmol/l)	46.2 ± 21.7	44.4 ± 15.0	63.1 ± 25.7	14.5 ± 0.707	22.8 ± 7.18
BMD change (gm/cm^2):					
Lumbar spine	0.0129 ± 0.0439	0.0306 ± 0.0392	−0.0144 ± 0.0199	−0.058 ± 0.0331	−0.027 ± 0.0408
p Value	0.0138	<0.001	0.0089	0.094	0.0805
Total hip	0.0117 ± 0.0551	0.0139 ± 0.0552	0.0145 ± 0.0504	−0.0093 ± 0.0462	−0.014 ± 0.0368
p Value	0.0695	0.105	0.252	0.76	0.287

* Including anastrazole.

each SD decrease in BMD doubles the risk of fracture.[22] Since BMD decreases progressively with age, it seems likely that young men with decreased BMD will eventually comprise a population at risk for osteoporotic fracture and its attendant sequelae. Young men with decreased spine BMD may be at risk for fracture at other trabecular sites, such as the rib or proximal humerus, which are common sites of fracture associated with low trauma in elderly men.[2,23]

The high incidence of BMD in the osteopenia range in our study suggests that routine DXA may be clinically indicated in young hypogonadal men. Men with low E2 and low BMI may be at particularly increased risk. The protective influence of obesity on BMD was previously reported in older men and it may be related to increased weight bearing.[24] Multiple cross-sectional and longitudinal studies show that low E2 is a risk factor for low BMD and continued loss of BMD in older men.[8,25] Based on our results BMI and serum E2 appear to have effects on BMD in young men similar to those in older men.

There was significant improvement in spine BMD in men who underwent followup testing after the initiation of T therapy, similar to previous findings in older men.[20] T therapy may be offered as treatment for decreased BMD in hypogonadal men along with calcium and vitamin D supplementation, as indicated. T appears to have positive benefits on bone formation via direct effects as well as via conversion to E2.[5,6] A possible additional indirect mechanism by which T therapy may aid bone density is by increasing energy. This may translate into increased physical activity, which in turn has a positive effect on BMD in young men.[26]

There are several limitations to this single center, retrospective chart review and results must be confirmed in future studies. BMD is affected by many factors, including vitamin D status and other factors that we did not measure. The study was not blinded and men informed of low BMD may have sought to improve it by increasing calcium intake or engaging in weight bearing exercise. Changes in posttreatment hormonal levels may not accurately reflect the androgen or estrogen exposure experienced by men in this series. Further studies are needed to better define if, how and for how long T therapy may be used to treat low BMD in young men.

Importantly, many younger men who wish to maintain or improve fertility are not candidates for T therapy due to its suppressive effect on spermatogenesis. In our practice young men are only treated with T if they do not desire further biological children. In men who desire fertility a frequently used, off label treatment strategy is to prescribe estrogen modulators, such as clomiphene citrate and aromatase inhibitors. These medications increase serum T by inhibiting negative feedback at the hypothalamic and pituitary levels, resulting in increased gonadotropin secretion and increased endogenous testicular production of T.

Given the importance of E2 on BMD, the safety of estrogen modulators on bone health is an important area that deserves investigation. Aromatase inhibitors suppress E2 and can harm BMD in older men.[27] In our study young men treated with estrogen modulators, including clomiphene citrate, showed decreased spinal BMD, including those with low BMD at baseline and those with normal BMD.

To our knowledge there is only 1 previous report of the BMD response to clomiphene citrate in young men.[17] In that study femoral neck and lumbar spine BMD increased significantly in 46 hypogonadal men in response to treatment with clomiphene citrate. The baseline osteoporosis or osteopenia rate was 72%. However, results in those men may not be applicable to most young men with T deficiency. Little is known about the effects of clomiphene citrate on estrogen receptors on bone and clomiphene citrate may possibly have an antagonistic effect at some sites. The cumulative effects of clomiphene citrate may be related to E2 and T2 levels along with baseline BMD.

The use of estrogen modulators is currently increasing along with T therapy. Based on our

results young men with T deficiency may already have decreased BMD. They may also have further BMD deterioration if treated with estrogen modulators. Until and unless the safety of these medications for bone health is established, estrogen modulators should be given with caution. DXA should be done to screen young men for low BMD before starting therapy as well as to monitor the effect of therapy on BMD.

CONCLUSIONS

More than a third of men younger than 50 years with testosterone deficiency and infertility or sexual dysfunction had decreased BMD. Testosterone therapy in this population increased BMD at a mean followup of 2.5 years. Men treated with estrogen modulators showed a significant reduction in BMD. Results suggest that routine DXA screening may be warranted in young men with T deficiency.

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