Osteopenia and Male Hypogonadism

Kendall Dupree, MD, Adrian Dobs, MD, MHS

The Johns Hopkins University School of Medicine, Baltimore, MD

A 34-year-old male, with a history of chronic myelogenous lymphoma (CML) previously successfully treated 20 years earlier with chemotherapy, bone marrow transplants, and donor lymphocyte infusion therapy, presented with fatigue and low serum testosterone level. Evaluation revealed male hypogonadism from primary testicular failure due to prior CML therapy in addition to osteopenia. The patient received supplementary calcium, vitamin D, and testosterone; improvement in serum testosterone level was noted in 6 weeks, along with increased energy level and good libido and erectile function. Dual-energy x-ray absorptiometry (DEXA) scan showed improvement in bone status. Male hypogonadism is associated with increased risk for osteopenia and osteoporosis. Supplemental testosterone therapy, because of its direct effect and its aromatization to estrogen, can improve bone density in these patients.

[Rev Urol. *2004;6(suppl 6):S30-S34*]

Key words: Bone mineral density • Hypogonadism • Osteoporosis • Testosterone

Osteoporosis is a frequently underestimated disease in men. There are several etiologies, including vitamin D deficiency, hyperparathyroidism, immobility, and low serum sex hormone levels. Male hypogonadism is an important and treatable cause of osteoporosis. One of the primary treatment regimens for hypogonadism is testosterone replacement therapy, which helps not only to ameliorate the symptoms of hypogonadism, but to increase bone mineral density (BMD) as well. Here we present the case of a young man with primary testicular failure and osteopenia.

Clinical Case

A 34-year-old man presented with a history of chronic myelogenous lymphoma (CML) initially diagnosed in 1982. The patient received chemotherapy and subsequently 2 bone marrow transplants in 1984. The first bone marrow transplant required full-body irradiation as a conditioning regimen; the second required a chemotherapeutic regimen. The bone marrow transplantation was successful, and the patient remained in remission until 1997, when he had a relapse. The patient required donor lymphocyte infusion therapy in 1997 and 1998. He is doing well and via donor sperm welcomed a new child into the family. Two months before the present endocrine referral, the patient had an oncologic visit, during which he complained of fatigue and was found to have a total testosterone of 181 ng/dL. The patient reported having undergone normal puberty with normal libido, erections, and ejaculation. His family history was notable only for diabetes mellitus on his father's side. He stated that his height was as expected based on his parent's stature. His past surgical history included an appendectomy. Artificial tears were his only medication. Findings on physical examination included normal male pattern baldness. The patient had a normal-sized thyroid, with no obvious mass. His skin was notable for terminal hair growth on his face and chest. There was no gynecomastia or galactorrhea. The genital examination showed small, firm testes, 6 mL bilaterally. Rectal examination revealed a small, nontender prostate, without nodules. His evaluation in the endocrine clinic revealed a total testosterone of 220 ng/dL (normal, 300-800 ng/dL), thyroxine (T4) of 8.8 μg/dL (normal 4.5-11.5 μg/dL), thyroid-stimulating hormone of 1.01 μU/mL (normal, 0.5-4.5 μU/mL), follicle-stimulating hormone (FSH) of 35.5 μU/mL (normal, < 10 μU/mL), luteinizing hormone of 10.0 μU/mL (normal, < 10 μU/mL), and prolactin of 3.8 ng/mL (normal, < 20 ng/mL). Dual-energy x-ray absorptiometry (DEXA) scan showed osteopenia with a T-score of +1.68 at L1–L4, −1.24 at the femoral neck, +0.54 at the trochanter, and +0.46 at the hip.

Repeat DEXA scan after 1 year of testosterone therapy revealed bone mineral density T-score at L1–L4 of −1.53, femoral neck −1.22, trochanter −0.41, and total hip −0.42: a 9%, 2%, 24%, and 9% improvement, respectively, from the previous year.

The patient was given a diagnosis of male hypogonadism from primary testicular failure due to total-body irradiation, chemotherapy, or graft-versus-host disease. He was started on calcium 1500 mg daily, vitamin D 400 mg daily, and Testim® (Auxilium Pharmaceuticals, Inc., Norristown, PA) testosterone gel 5 g daily. After 6 weeks, repeat laboratory testing showed a total testosterone of 872 ng/dL and prostate-specific antigen of 0.4 ng/mL. The patient stated an increased energy level with a good libido and erectile function. Repeat DEXA scan after 1 year of testosterone therapy revealed a BMD T-score at L1-L4 of −1.53, femoral neck −1.22, trochanter −0.41, and total hip −0.42: a 9%, 2%, 24%, and 9% improvement, respectively, from the previous year.

Table 1
Etiologies of Osteoporosis in Men

Social Factors	Chronic Diseases	Endocrinopathies	Malignancies	Genetic Disorders
Low weight	Liver	Hyperthyroidism	Multiple myeloma	Hemophilia
Lack of exercise	Kidneys	Hyperparathyroidism	Lymphoma	Hemochromatosis
Diet low in calcium and vitamin D	Gastrointestinal tract	Cortisol excess	Leukemia	Idiopathic scoliosis
Alcohol use	Pulmonary system	Type 1 diabetes mellitus		Osteogenesis imperfecta
Smoking	Autoimmune system	Primary or secondary gonadal insufficiency		Thalassemia

Epidemiology of Osteoporosis

According to the third National Health and Nutrition Examination Survey (NHANES III), between 3% and 6% of US men have osteoporosis in the hip while 28% to 47% have osteopenia.[1] Prior to the age of 50 years, most fractures are traumatic in origin and are not caused by osteoporosis. Fractures caused by osteoporotic fragility gradually increase in men from 60 to 80 years of age when testosterone levels are significantly reduced. The location of osteoporotic fragility fractures is most commonly at the femoral neck (30% of hip fractures worldwide) and vertebra. Vertebral fractures in men may be found along the entire vertebral spine. However, the majority are in the lower thoracic vertebrae, and are either anterior or compression fractures. Racial differences

have been notable as well. African-American men have significantly less incidence of hip fractures compared with white men.

Pathophysiology of Osteoporosis

A number of systemic diseases are associated with decreased bone mass (Table 1). These include 1) genetic disorders such as hemochromatosis, hemophilia, idiopathic scoliosis, osteogenesis imperfecta, thalassemia, and hypophosphatemia; 2) endocrine disorders such as primary and secondary hypogonadism (Klinefelter's syndrome, idiopathic hypogonadotropic hypogonadism), hyperprolactinemia, hyperthyroidism, and type I diabetes mellitus; 3) malignancies that may result in bone loss, including leukemia, lymphoma, and multiple myeloma; 4) chronic diseases such as chronic renal failure, hepatobiliary disease, gastrointestinal disorders, and sickle cell anemia, which are also associated with osteoporosis, as are autoimmune diseases; and 5) social factors such as alcohol drinking, which impairs osteoblastic function, and cigarette smoking.[2,3]

Osteoporosis and Hypogonadism

More than 95% of circulating testosterone is bound to albumin and sex hormone-binding globulin (SHBG), leaving only a small amount of biologically active free testosterone to mediate androgen effects. Although total testosterone does not always decrease in older men, there is commonly an increase in concentration of SHBG, resulting in a decline of free, biologically active testosterone. Testosterone is locally converted to 5 α-dihydrotestosterone, which more aggressively binds to the androgen receptors, or aromatized to estradiol.[4] An important cause of osteoporosis in men is reduced serum testosterone. The incidence of osteoporosis in men is indirectly correlated to the reduction in circulating testosterone. Because androgens may promote the proliferation and differentiation of osteoblasts, as well as inhibit osteoclast activity (recruitment and signaling), decreased bone density may ensue.

When discussing male osteoporosis secondary to hypogonadism, the direct effect of testosterone is likely 25% of its effectiveness whereas its aromatization to estrogen contributes to the remaining 75%. This became clear with the published study of a virilized man with tall stature and osteoporosis who was found to have a mutation in the estrogen receptor gene.[5] Falahati-Nini and colleagues[1] showed how estrogen may have regulatory effects on bone turnover in functional hypogonadal men and women. In this study, endogenous estrogen and testosterone were suppressed with gonadotropin-releasing hormone agonists while exogenous estrogen and testosterone were administered. Markers of bone turnover were measured to determine which sex hormones were dominant in regulating bone resorption. The markers used were urinary deoxypyridinoline (Dpd) and N-telopeptide of type I collagen (NTx), bone-specific alkaline phosphate (BSAP), and osteocalcin. In the patients with suppressed testosterone and estrogen, but no replacement, there was an increase in urinary excretion of Dpd and NTx, suggesting increased bone turnover in the absence of sex hormones. When estrogen alone was suppressed, there was still a high level of bone turnover marker excretion, but not as significant as when both androgens were suppressed. The changes seen when testosterone alone was suppressed and estrogen was not replaced indicate the crucial role of estrogen on BMD. Estrogen and testosterone were determined to have an additive effect on maintaining serum osteocalcin, which is produced by both osteoclasts and osteocytes. Estrogen was shown to be important in thickening bone cortices and in maintaining BMD, not only by enhancing bone mass during growth and maturation, but also by retarding bone loss.

In vitro studies showed that androgens inhibit the activity of isolated osteoclasts.[6,7] In addition, androgens inhibit the production of interleukin (IL)-6, which is a cytokine that promotes resorption in bone marrow stromal and mature osteoblastic cells.[8,9]

When discussing male osteoporosis secondary to hypogonadism, the direct effect of testosterone is likely 25% of its effectiveness whereas its aromatization to estrogen contributes to the remaining 75%.

Hypogonadism Secondary to Chemotherapeutic Agents

Chemotherapeutic agents commonly induce infertility by damaging the seminiferous tubules in men. Alkylating agents in particular may cause depletion of the germinal epithelium. The effects of alkylating agents on spermatocytes may cause complete disappearance of these cells, leaving only Sertoli cells lining the tubular lumen and germinal cell aplasia.[10] Combination chemotherapeutic agents can have an even greater effect on spermatogenesis. MOPP (mechlorethamine hydrochloride, vincristine, procarbazin, and prednisone) causes azoospermia, testicular atrophy, germinal aplasia, and elevated FSH levels.[10] The use of radiation therapy may cause infertility as well by damaging spermatogonia at very low levels, for example, 0.15 Gy (15 rad). When

higher levels of radiation are used—for example, at 1 Gy—extreme oligospermia or azoospermia develops; spermatids are damaged at this dose as well, resulting in a decreased sperm count. In addition to radiation's effects on spermatogenesis, Leydig cell function may be impaired, reflected by a decreased serum T level. Approximately 10% of patients receiving radiation of about 8 Gy will have permanently low plasma testosterone.[10] The decrease in testosterone is thought to be secondary to the direct effects of radiation and reduced blood flow.

Treatment Options for Osteoporosis

There are 2 primary mechanisms by which therapies for osteoporosis work: they can either inhibit bone resorption or stimulate new bone formation. Calcitonin may increase total body calcium. Although calcitonin has not been proven to prevent osteoporosis in men, it may be effective in reducing osteoclastic activity and continuing bone loss. Bisphosphonates (alendronate/etidronate) also work by reducing bone resorption and inhibiting osteoclastic activity. Testosterone replacement therapy may be beneficial because of its action on osteoblast proliferation and osteoclast inhibition.

Testosterone and BMD

Long-term treatment with testosterone replacement therapy has been shown to be well tolerated in men with osteoporosis. According to a study by Snyder and colleagues,[8] testosterone treatment in hypogonadal men increased bone mineral density approximately 7.5% in the lumbar region (L2-L4) and by 5% in the femoral trochanter region. As described in this study, testosterone inhibits osteoclastic activity and promotes osteoblast proliferation.

The benefits of using testosterone gels in treating osteoporosis were also demonstrated in a study done by Wang and associates.[11] The BMD in patients increased by 2% in the vertebrae over a 6-month period, and dihydrotestosterone levels were higher and persisted for as long as 6 months. Using testosterone replacement for 18–30 months resulted in a 3.1% increase in BMD. Mean estrogen levels were also higher after treatment with testosterone. Serum markers of bone turnover (serum parathyroid hormone, osteocalcin, serum skeletal-specific alkaline phosphatase, procollagen) were all decreased.[1]

Table 2
Testosterone Therapy Replacement Options

Dosage Form	Usual Dosage
Injectable enanthate, cyprionate	200 mg q 2 weeks
Transdermal patch	5 mg nightly
Transdermal gel	5 g gel daily
Buccal system	30 mg bid

Treatment Options

There are now multiple options available for testosterone replacement therapy in hypogonadal men (Table 2).[12] Although injectable esterified testosterone has been used for more than 50 years, its pharmacokinetics often result in wide swings in serum testosterone levels, with extremely elevated concentrations. Nonscrotal patch therapy (Androderm®; Watson Pharma, Inc., Morristown, NJ) is an option. When the patch is placed in the evening, it results in mimicking the

Main Points

- This report discusses the case of a young man with primary testicular failure due to chemotherapy and radiation therapy for chronic myelogenous lymphoma who presented 20 years later with infertility, fatigue, and osteopenia. Testosterone treatment, because of its direct effect plus its aromatization to estrogen, resulted in improved bone density.
- Male hypogonadism is an important and treatable cause of osteoporosis. One of the primary treatment regimens for hypogonadism is testosterone replacement therapy, which helps to not only ameliorate the symptoms of hypogonadism but to increase bone mineral density as well.
- According to the third National Health and Nutrition Examination Survey, between 3% and 6% of US men have osteoporosis in the hip and 28% to 47% have osteopenia.
- Although total testosterone does not always decrease in older men, there commonly is an increase in concentration of sex hormone-binding globulin, resulting in a decline of free, biologically active testosterone.
- Chemotherapeutic agents commonly induce infertility by damaging the seminiferous tubules in men. Radiation therapy may cause infertility as well by damaging spermatogonia.
- Osteoporosis therapies work either by inhibiting bone resorption or by stimulating new bone formation. Testosterone replacement therapy may be beneficial because of its action on osteoblast proliferation and osteoclast inhibition.

circadian rhythm noted in young men. Gels, either AndroGel® (Solvay Pharmaceuticals, Inc., Marietta, GA) or Testim, are good options, providing consistent hormone levels.[13] Testim has been shown to improve sexual function overall and bone density in a placebo-controlled study.[14] A buccal preparation (Striant®; Columbia Laboratories, Inc., Livingston, NJ) is available as well but requires twice-daily dosing.

Oral therapy with a methyl testosterone is not advised because of its potential liver toxicity. Testosterone implants are not available in the United States. When determining the route of administration of testosterone therapy, consider one that has minimum adverse effects of treatment, is convenient, and achieves physiologic levels of testosterone and its metabolites.

Summary

An important complication of male hypogonadism is the increased risk for osteopenia and osteoporosis. This report discusses the case of a young man with primary testicular failure due to chemotherapy and radiation therapy for CML who presented 20 years later with infertility, fatigue, and osteopenia. Testosterone treatment, because of its direct effect plus its aromatization to estrogen, resulted in improved bone density. ■

When determining the route of administration of testosterone therapy, consider a route that has minimum adverse effects of treatment, is convenient, and achieves physiologic levels of testosterone and its metabolites.

References

1. Falahati-Nini A, Riggs BL, Atkinson EJ, et al. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *J Clin Invest.* 2000;106:1553-1560.
2. Orwoll E. *Osteoporosis in Men: A Growing Challenge.* Beachwood, OH: Current Therapeutics Inc.; 2000;1-22.
3. Bain J. Andropause: testosterone replacement therapy for aging men. *Can Fam Physician.* 2001;47:91-97.
4. Howell S, Shalet S. Testosterone deficiency and replacement. *Horm Res.* 2001;56:86-92.
5. Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N Engl J Med.* 1994; 331:1056-1061.
6. Frances RM. The effects of testosterone on osteoporosis in men. *Clin Endocrinol.* 1999; 50:411-414.
7. Pederson L, Kremer M, Judd J, et al. Androgens regulated bone resorption activity of isolated osteoclasts in vitro. *Proc Natl Acad Sci USA.* 1999;96:505-510.
8. Snyder P, Peachey H, Berlin JA, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab.* 1999;84:2647-2653.
9. Hofbauer LC, Ten RM, Khosla S. The anti-androgen hydroxyflutamide and androgens inhibit interleukin-6 production by an androgen-responsive human osteoblastic cell line. *J Bone Miner Res.* 1999;14:1330-1337.
10. Wilson JD, Foster DW, Kronenberg HM, Larsen PR. *Williams Textbook of Endocrinology,* 9th ed. Philadelphia, PA: WB Saunders Company; 1998:844-845.
11. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab.* 2004;89:2085-2098.
12. Herman MB, von Eckardstein S, Kliesch S, Nieschlag E. Long-term substitution therapy of hypogonadal men with transscrotal testosterone over 7-10 years. *Clin Endocrinol.* 1999;50:629-635.
13. Steidle C, Schwartz S, Jacoby K, et al. and the North American AA2500 T Gel Study Group. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab.* 2003;88:2673-2681.
14. McNicholas TA, Dean JD, Mulder H, et al. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. *BJU Int.* 2003;91:69-74.