Testosterone Replacement Therapy and Bone Mineral Density in Men with Hypogonadism

Se Hwa Kim

Department of Internal Medicine, Kwandong University College of Medicine, Incheon, Korea

Osteoporosis is a skeletal disorder characterized by reduced bone strength and consequent increased fracture risk [1]; such fractures can be associated with increased morbidity and mortality. Men with hip fractures have a mortality rate two to three times higher than that of women [2,3]. In epidemiologic data on Korean subjects, the prevalence of osteoporosis was reported to be 7.8% in men and 37.0% in women aged 50 years or over [4]. The incidence of hip fractures in Koreans over 50 years of age was 146.4 per 100,000 women and 61.7 per 100,000 men in a recent report [5]. Nevertheless, the risk of mortality one year postfracture has been shown to be approximately 1.4 to 2.1 times higher in men than it is in women.

Previous reports found that osteoporosis was underdiagnosed and undertreated in men. Also, a secondary cause of osteoporosis is common in men, such as glucocorticoid excess, hypogonadism, or alcohol excess [6].

Sex steroids are major determinants of bone turnover and modelling from adolescence into old age. Therefore, hypogonadism prior to puberty is associated with low bone mineral density due to inadequate bone accretion. Meanwhile, adult-onset hypogonadism leads to increased bone resorption and accelerated bone loss. For example, Kallmann and Klinefelter syndromes, pituitary and hypothalamic tumors, and androgen deprivation therapy for prostate cancer can all lead to hypogonadism, and are associated with low bone mineral density (BMD) and an increased risk of fractures [7-10].

A number of studies have demonstrated the effect of testosterone on BMD in men with acquired hypogonadism or in aging men with low testosterone levels, although no data are available on fracture prevention. Behre et al. [11] showed that testosterone therapy significantly increased BMD in 72 hypogonadal men regardless of age. They also found that BMD can be normalized and maintained within normal range by continuous, long-term testosterone replacement. In aging men with low or borderline testosterone levels, the effect of testosterone therapy on BMD appears to be related to baseline testosterone levels; testosterone treatment increased BMD only in men whose baseline levels were below the reference range. Basurto et al. [12] found that 12 months of testosterone administration increased spine and total hip BMD in men aged 60 or older with serum testosterone levels <320 ng/dL. Recently, Aversa et al. [13] reported that long-acting testosterone undecanoate in middle-aged men with late-onset hypogonadism (testosterone <320 ng/dL) significantly increased spine and femoral BMD after 3 years. Another study showed that spine BMD increased to a similar extent in a testosterone-treated group compared to a placebo group after 3 years (4.2%±0.8% vs. 2.5%± 0.6%, P=not significant); however, among men with pretreatment testosterone levels below 200 ng/dL, testosterone therapy significantly increased spine BMD (5.9%±2.2%) compared to placebo-treated patients [14].

The Endocrine Society guidelines recommend testosterone therapy for symptomatic men with classical androgen deficiency syndromes to improve sexual function, sense of well-

Corresponding author: Se Hwa Kim
Division of Endocrinology, Department of Internal Medicine, Kwandong University College of Medicine, 306 Anagi-ro, Gyeyang-gu, Incheon 407-060, Korea
Tel: +82-32-553-5384, **Fax:** +82-32-545-0975, **E-mail:** bonesh88@gmail.com

being, and BMD [15]. Also, Endocrine Society guidelines on osteoporosis in men also recommend testosterone therapy alone for hypogonadal men (serum testosterone levels <200 ng/dL) at modest or borderline risk of fracture [16]. Several studies found that men whose serum testosterone level is 200 to 300 ng/dL or below are at higher risk for bone loss and fracture and have a favorable response to testosterone treatment [14,17,18]. In addition, the Endocrine Society guidelines recommend combination treatment with an agent with proven antifracture efficacy (e.g., bisphosphonate or teriparatide) for men who need testosterone therapy for hypogonadism and who have a high fracture risk [16].

Recently, Lee et al. [19] investigated the effect of testosterone replacement therapy on BMD in 21 men with hypogonadotropic hypogonadism due to pituitary tumor surgery. They reported that the mean serum testosterone concentration increased from 157 ± 126 ng/dL at baseline to 337 ± 243 ng/dL after 56 months of treatment. Also, there was significant improvement in lumbar spine BMD after 56 months compared with baseline values (from 1.067 ± 0.155 to 1.116 ± 0.177 g/m^2, $P = 0.028$). A nonsignificant decrease in femoral neck BMD (from 0.908 ± 0.148 to 0.875 ± 0.212 g/m^2, $P = 0.677$) was also observed. They did not find any significant correlation between change in serum testosterone levels and lumbar spine BMD. This study had several limitations, it was retrospective in nature, only a small number of patients were included, and they had no placebo control group. Nevertheless, the results were meaningful because the authors examined the long-term effects of testosterone treatment on BMD (up to 99 months) in Korean men with acquired hypogonadism. Also, this study suggested testosterone treatment was an effective method of increasing lumbar spine BMD in hypogonadal middle-aged men whose BMD was normal to within mild osteopenic range. Further studies are needed to investigate the effects of testosterone therapy on fracture prevention in acquired hypogonadism or aging men with low serum testosterone concentration.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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