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Short Communication

Does Testosterone Replacement Therapy Prevent Bone Fractures in Hypogonadal Men?

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Abstract

Bone fractures due to decreased Bone Mineral Density (BMD) in men with hypogonadism are an important issue in decreasing quality of life. Moreover, Testosterone (TT) plays a crucial role in maintaining BMD, but the relationship between TT levels and osteoporosis development has been conflicting. Nonetheless, Testosterone Replacement Therapy (TRT) seems to be beneficial, especially in men with hypogonadism and osteopenia or osteoporosis.

Serum Testosterone (TT) levels decline by 1% annually with age in elderly men [1], which may lead to clinical symptoms associated with late-onset hypogonadism (LOH) syndrome [2]. This syndrome is characterized by irritability, depression, sexual dysfunction, decreased muscle mass, and strength, decreased Bone Mineral Density (BMD), and metabolic syndrome [3].

Testosterone Replacement Therapy (TRT) has emerged as a crucial intervention for men with symptomatic hypogonadism, particularly those affected by pituitary or testicular disorders. Current evidence indicates that testosterone treatment significantly enhances bone structure and quality, increasing areal bone density as assessed by Dual-Energy X-ray Absorptiometry (DEXA) and volumetric bone density via quantitative Computed Tomography (CT). Furthermore, advanced imaging techniques such as magnetic resonance microimaging have revealed beneficial changes in trabecular architecture, highlighting the therapy's positive effects on bone health [4,5].

BMD is closely correlated with serum testosterone levels in men. Androgen Deprivation Therapy (ADT), commonly used in treating prostate cancer, leads to an immediate decline in TT levels, which in turn contributes to a reduction in BMD and an increased risk of osteoporosis. Additionally, estradiol (E2), derived from testosterone through aromatase conversion, plays a vital role in preserving BMD. The relative decrease in E2 levels resulting from ADT further heightens the risk of BMD loss [6,7].

Typically, BMD decreases by approximately 2% - 8% within the first year of initiating ADT. Moreover, ADT increases the risk of BMD decline by five to tenfold compared to prostate cancer patients with normal TT levels. A meta-analysis found that ADT is responsible for 9%–53% of osteoporosis cases. Hence, patients undergoing ADT face a significantly higher risk of fractures, particularly proximal femur fractures, which are 1.5- to 1.8-fold more likely. The decline in BMD in these patients is primarily attributed to the reductions in serum TT and estrogen levels induced by ADT [8,9].

In older men with symptomatic hypogonadism, TT treatment for three years has been linked to increased areal bone mineral density in the spine. The Bone Trial, part of the larger Testosterone Trials, found that just one year of therapy

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in older hypogonadal men resulted in improved volumetric bone mineral density and enhanced estimated strength in both the spine and hip [10].

In the current sub-trial of the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE), 5,200 middle-aged and older men (mean age 63 years) with TT levels below 300 ng/dL (median level of 227 ng/dL) were randomized to receive either TT gel or a placebo. Over a median follow-up period of approximately three years, the overall incidence of fractures (excluding those of the sternum, fingers, toes, skull, and face) was significantly higher in the treated group compared to the placebo group (3.5% *vs.* 2.5%). However, the low number of fractures limited the ability to draw meaningful conclusions regarding specific fracture sites. For instance, major osteoporotic fractures—defined as those of the hip, spine, humerus, or wrist—occurred in only 36 recipients of TT and 30 recipients of the placebo [11].

TRT for hypogonadal men can significantly alleviate a variety of symptoms, including those related to metabolic syndrome, and is recognized globally for its role in enhancing the overall Quality of Life (QOL) [12]. Furthermore, TT is closely related to bone health and BMD in men, suggesting that TRT may play a role in the prevention and management of osteoporosis in hypogonadal men. However, current evidence has not yet demonstrated a significant impact on bone-related outcomes.

Although evidence supports the benefits of TRT on bone health in patients with LOH and decreased BMD, most studies have focused on TRT for LOH. Further research is needed to identify the population that would benefit the most from targeted management of BMD decline itself. Consequently, active screening for BMD loss in hypogonadal patients may be advantageous for men's health.

Conclusion

Testosterone plays an important role in maintaining BMD and bone health among older men. Current evidence suggests that this therapy is not recommended as a tool to enhance and maintain BMD for hypogonadal men. Nonetheless, TRT could be a tool to improve both LOH symptoms and BMD simultaneously.

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