Osteoporosis and Low Bone Mineral Density in Men with Testosterone Deficiency Syndrome

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ABSTRACT

Introduction. Testosterone deficiency syndrome (TDS) is a risk factor for low bone mineral density (BMD) and osteoporosis. Knowledge of the relationship between TDS and bone health, as well as the practical aspects of how to diagnose and treat low BMD, is therefore of practical importance to sexual medicine practitioners.
Aim. The aim of this study was to review the physiologic basis and clinical evidence of the relationship between TDS and bone health; and to provide a practical, evidence-based algorithm for the diagnosis and management of low BMD in men with TDS.
Methods. Method used was a review of relevant publications in PubMed.
Main Outcome Measures. Pathophysiology of low BMD in TDS, morbidity, and mortality of osteoporosis in men, association between TDS and osteoporosis, indications for dual X-ray absorptiometry (DXA) scanning in TDS, evidence for testosterone replacement therapy (TRT) in men with osteoporosis, treatment for osteoporosis in the setting of TDS.
Results. Sex hormones play a pleomorphic role in maintenance of BMD. TDS is associated with increased risk of osteoporosis and osteopenia, both of which contribute to morbidity and mortality in men. DXA scanning is indicated in men older than 50 years with TDS, and in younger men with longstanding TDS. Men with TDS and osteoporosis should be treated with anti-osteoporotic agents and TRT should be highly considered. Men with osteopenia should be stratified by fracture risk. Those at high risk should be treated with anti-osteoporotic agents with strong consideration of TRT; while those at low risk should be strongly considered for TRT, which has a beneficial effect on BMD.
Conclusion. Low BMD is a prevalent and treatable cause of morbidity and mortality in men with TDS. Utilization of a practical, evidence-based approach to diagnosis and treatment of low BMD in men with TDS enables sexual medicine practitioners to make a meaningful impact on patient quality of life and longevity. **Gaffney CD, Pagano MJ, Kuker AP, Stember DS, and Stahl PJ. Osteoporosis and low bone mineral density in men with testosterone deficiency syndrome. Sex Med Rev 2015;3:298–315.**

Key Words. Osteoporosis; Bone Mineral Density; Testosterone Deficiency; Hypogonadism; Men

Introduction

Rising awareness of the associations between sexual dysfunction and health-relevant disease processes has enabled healthcare providers who specialize in male sexual dysfunction to play increasingly broad roles in men's overall health. This paradigm has been most pronounced in men with erectile dysfunction (ED), a condition that independently predicts cardiovascular events, cerebrovascular events, and all-cause mortality [1]. However, the association of male sexual

dysfunction with other men's health issues has received somewhat less attention. In particular, ED, low sexual desire, and decreased spontaneous and/or nocturnal erections each effectively double the risk of testosterone deficiency syndrome (TDS) [2]; and TDS is associated with osteoporosis.

Osteoporosis is a progressive disorder of bone remodeling in which bone loss exceeds bone formation, resulting in micro-architectural defects and skeletal fragility. It is associated with fractures and increased mortality [3–6]. The overall risk of fracture in men with osteoporosis is correlated with loss of bone mineral density (BMD) [7], although other factors related to testosterone such as fragility and fall risk may also contribute to fracture risk in men [8,9]. In this review, we focus on the relationship between TDS and osteoporosis, which represents a critical opportunity for sexual medicine practitioners to diagnose and treat a medically important disorder in its early stages when intervention can make an important clinical difference.

Sex Hormones and Bone Pathophysiology

In healthy adults, there is a balance between osteoblasts that create new bone and osteoclasts that resorb bone. This balance exists primarily to continuously repair and replace existing bone mass, and plays a prominent role in calcium and phosphate homeostasis. Cytokines (interleukin [IL]-6 and transforming growth factor-beta), hormones (parathyroid hormone, vitamin D3, calcitonin, sex hormones, glucocorticoids, and thyroid hormone), and lifestyle factors (alcohol and cigarette use) affect the dynamic balance between osteoblasts and osteoclasts. Dysregulation in any of these domains can adversely affect bone health [3].

Sex hormones have a pleomorphic effect on bone physiology. Androgens and estrogen both block IL-6, a cytokine important in activating bone resorption. Androgens increase periosteal bone formation and promote osteoblast proliferation, differentiation, and lifespan [10]. Estrogen decreases cytokines that activate bone resorption (IL-1, IL-7, tumor necrosis factor [TNF] α, and macrophage colony-stimulating factor), favor osteoclast apoptosis (TNF-β), and inhibit the receptor activator of nuclear factor kappa-B ligand (RANKL), an osteoclast activator produced by osteoblasts in response to parathyroid hormone [10].

Variation in the androgen receptors (AR), sex hormone-binding globulin (SHBG) levels, and androgen metabolites influences the role of sex hormones on bone physiology. The number of CAG repeats in the AR is an independent predictor of bone density in men [11,12], and men with shorter CAG repeats have a greater BMD response to testosterone [13]. SHBG, a protein that influences sex hormone levels in the serum, has been associated with decreased BMD in older men [14,15]. There may also be a role for androgen metabolites such as dihydrotestosterone (DHT) in bone health. Mice with a 5alpha-reductase deletion, normal androgen levels, and no DHT had reduced bone and muscle mass. However, this relationship has not been observed in humans [16].

Knowledge of the pathophysiological interplay between testosterone and bone is expanding through active research on the bone–testis axis. This research shows that osteocalcin, a protein produced by osteoblasts that requires osteoclast activation, increases serum testosterone independently of luteinizing hormone. Therefore, it appears that bone may actually directly regulate levels of serum testosterone in men [10,17,18].

Association between Sex Hormones, BMD, and Bone Health

Evidence from one large, multicenter prospective study, and several smaller retrospective and prospective studies supports an association between TDS and the diagnosis of osteoporosis and/or a history of fracture (Table 1). One large study that examined 2447 men over the age of 65 showed an increased odds ratio (OR) of osteoporosis in men with TDS (OR 2.6) when adjusted for weight, age, and estradiol levels [19]. In the only study that has specifically addressed men under 50 years of age, men with TDS (defined as total testosterone [TT] less than 350 ng/dL or free testosterone [FT] less than 1.5 ng/dL) seen at an andrology clinic had greater odds of osteopenia (OR 3.79) and osteoporosis (OR 7.64) as compared with age-matched reference data [20].

The associations between sex hormones and quantitative BMD have been very clearly delineated by large, well-designed studies (Table 2). It is important to note that these associations could be affected by the methodological variability in the assays that were utilized in each particular study to measure serum sex hormone levels. Immunoassays are generally less reliable than mass spectrometry (see table footnotes for assay methodologies used