Restoration of bone mass in male hypogonadal osteopenic subjects by androgens


SUMMARY

Seventy-two adult male hypogonadal patients aged 18–74 years received androgen replacement therapy and underwent serial measurements of lumbar spine bone mineral density (BMD) by single energy quantitative computed tomography (QCT). Thirty-seven patients with primary hypogonadism [Klinefelter’s syndrome (21), and anorchia, previous orchitis, or idiopathic (16)] and 35 with secondary hypogonadism [Kallman’s syndrome or idiopathic hypogonadotropic hypogonadism (14) and pituitary tumours (21)] were enrolled in the study. Other causes of osteoporosis, e.g. constitutional delay of puberty, Cushing’s syndrome, vitamin D or calcium deficiency or heritable disorder of connective tissue were excluded. BMD measurements were performed in 32 patients (primary hypogonadism 17, secondary hypogonadism 15) before androgen replacement therapy was started and in 40 patients after having received androgens for 3.4 years (range 1–11 years).

Androgen replacement therapy was instituted either by exogenous testosterone [testosterone enanthate (TE) 250 mg intramuscularly every 3 weeks (n=52, range 2–4 weeks); transdermal scrotal testosterone patch (TTP) 4–6 mg/day (n=1)]; oral testosterone undecanoate (TD) 40 mg t.i.d. (n=2) or gonadotropins [human menopausal gonadotropin (hMG) and human chorionic gonadotropin (hCG)] or pulsatile gonadotropin-releasing hormone (GnRH) (n=1).

Serum testosterone and oestriadiol measurements were made before start of treatment, at yearly intervals while on androgen substitution therapy and at the end of the study. Adequacy of androgen substitution was assessed by measurement of serum testosterone at the second week of TE injections, 3–6 hours after application of testosterone patch or oral administration of TD, or on day 2 after hCG injection. QCT was performed for measurement of trabecular BMD of lumbar vertebra L2, L3, L4 at baseline and thereafter at yearly intervals. The results were analysed by ANOVA for repeated measures, multiple linear regression and partial correlation analysis. Subjects receiving TD, hCG and hMG or GnRH were excluded from comparative analysis due to small numbers.

Thirty-two patients underwent QCT before start of androgen substitution therapy. Before treatment, patients with secondary hypogonadism had significantly lower BMD, serum testosterone and serum E2 levels as compared to those with primary hypogonadism. Multiple regression analysis revealed significant association of BMD with serum testosterone levels and age, whereas E2 levels showed no independent association with BMD.

Androgen substitution therapy resulted in normalization of serum testosterone levels in all 72 patients. In all previously untreated patients, androgen replacement resulted in significant increase in
BMD from baseline [mean (SD) 95.2 (5.9) mg/cm²] to first year [120.0 (6.1) mg/cm²; p<0.001]. BMD further increased to 125.8 (6.1) mg/cm² after 2.7 (0.3) years (range: 1–7 years) of therapy (p=0.0001). In patients who had prior treatment for one year before QCT, BMD increased significantly from 136.6 (4.8) mg/cm² to 150.9 (5.4) mg/cm² during an average treatment period of 4.0 (0.4) years (p<0.001). However, the increase in BMD in patients previously treated with androgens was significantly smaller as compared with previously untreated patients. No significant association could be detected between the age of the patients at initiation of therapy and increase in BMD during replacement therapy.

Multiple regression analysis in all 72 patients revealed a significant association between serum testosterone levels and BMD at first QCT measurement (r=0.58, p=0.0001) and a weaker relationship between age and BMD. Serum oestradiol had no significant correlation with BMD and age. Regression analysis revealed a strong negative association between the initial BMD and the relative increase in BMD during androgen therapy, indicating that patients with low BMD at initial QCT measurement had the largest increase in BMD by testosterone therapy.

In all hypogonadal men, effective testosterone substitution therapy of more than 3 years increased BMD to a previously described normal reference range. There was no significant difference in BMD at last QCT measurements in both treatment groups: testosterone enanthate (n=52) and transdermal preparation (n=11).

COMMENT

The present study demonstrates a lower BMD in all hypogonadal men and the beneficial effect of adequate androgen substitution therapy in restoring BMD to a normal reference range.

Osteoporosis is a disease characterized by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility and an increase in fracture risk. This risk corresponds with the degree of reduced bone mass. Bone density is determined by the amount of bone gained during growth (peak bone mass) and the amount of bone lost during advancing years. A low peak bone density, excessive bone loss, or both may contribute to the pathogenesis of reduced bone density in patients with fractures.

Osteoporosis is not a diagnosis but a description. Bone remodelling is normally regulated by various systemic and locally produced agents. Hence, osteoporosis can be the result of diverse aetiological factors such as endocrine abnormalities, myeloproliferative disorders, drugs, genetic abnormalities in bone collagen synthesis, or deficiency of calcium or vitamin D. It may also be idiopathic. Amongst the endocrine causes, hypogonadism is a leading cause of osteoporosis. Hormonal replacement in post-menopausal women is a well-established therapy in the prevention and treatment of osteoporosis. However, hypogonadism-induced osteoporosis is a less appreciated entity in men. Testosterone deficiency in men can lead to a significant decline in BMD. Osteoporosis is less common in men than in women, presumably because men have a greater peak bone mass at all ages, lose less bone during ageing, have a shorter life-span, and no distinct equivalent of menopause. The prevalence of hypogonadism increases significantly in elderly men and exceeds 20% in men over 60 years. The evolution of hypogonadism is insidious and non-skeletal features of hypogonadism may not be clinically apparent in up to 50% of patients. Osteopenia is sometimes the presenting symptom of androgen deficiency particularly in elderly men, who may fail to seek medical advice for impotence and other classic symptoms of androgen deficiency. Almost one-quarter of elderly men with hip or vertebral fractures have biochemical evidence of androgen deficiency. With ageing, the level of testosterone falls due to decreased number of Leydig cells, changes in hypothalamic–pituitary functions, and co-existent illness.

There are certain differences between bone metabolism and osteoporosis in men and women. The peak bone mass of the appendicular and vertebral skeleton is greater in men than in women. The rate of bone loss in the spine and femur neck is also slower in men. Vertebral fractures, the most common osteoporotic fracture in women, are unusual in men <70 years of age. The male spine shows greater subperiosteal cortical bone formation and less endocortical resorption than that in women; this results in larger cross-sectional vertebral and long bone diameter in men and may contribute to the relatively greater breaking strength of the male vertebral body. Further, men sustain significantly less falls contributing to fracture risk than women (19% vs. 34%).

Androgens have an important effect on skeletal development, attainment of peak bone mass, and rate of bone turnover. The peak bone mass during adulthood is reduced in men who had androgen deficiency during adolescence. Androgen deficiency developing in adulthood, after attaining peak bone mass, results in loss of cortical and trabecular bone. Androgens also influence bone mass in women. Young women with hyperandrogenism have increased trabecular (not cortical) bone density, the magnitude of which correlates with their androstenedione levels. Perimenopausal androgen deficiency has also been reported to be an independent risk factor for osteoporosis.

The cellular mechanisms by which androgen influences bone resorption and formation are poorly defined. Osteoblast and osteoblast-like lines have high-affinity androgen receptors. Androgen increases gene expression and cellular secretion of transforming growth factor β (TGF-β) and decreases secretion of PGE2 by mixed bone cells in vitro. These cytokines have potent effects on osteoblasts and osteoclasts. The recent report of a young man with osteoporosis and an oestrogen receptor mutation suggests that androgen indirectly affects the skeleton. Androgens can therefore influence bone remodelling directly or indirectly; the relative importance of these pathways is presently not clear.

Previous studies on the effect of androgen substitution therapy on BMD have been few and included only few subjects, used different methods of BMD measurement, different duration of treatment with different preparations, and showed discrepant results. Androgen replacement therapy in hypogonadal men improved trabecular BMD in young patients with open epiphyses while older patients with closed epiphyses showed no significant change. However, replacement therapy in patients with hyperprolactinaemic hypogonadism increased trabecular and not cortical BMD.

The present study is important in view of the large number of patients, long follow up, and the use of the volumetric methods of BMD measurement at the same site using single energy QCT to improve long term precision. BMD is restored to normal reference range with prolonged androgen substitution therapy. This study further suggests the comparative efficacy of transdermal testosterone patch to parenteral testosterone enanthate in increasing BMD. The results are similar to those obtained in post-menopausal women receiving oestrogen replacement therapy where therapy is most effective during the first year of treatment and the magnitude of increase in BMD is greatest in those women with lower initial BMD.
Osteoporosis is still an unexplored area in our country with no published prevalence of osteoporosis, or normal reference range of BMD for our population. It is partly due to non-availability of facilities for investigations of metabolic bone disorders and precise measurement of bone density even at the majority of tertiary health care centres. The age-specific incidence of hip fractures is increasing all over the world and the burden of care will be seen particularly in Asia. This is partly because of chronic malnutrition, vitamin D and/or calcium deficiency. Hormone replacement therapy in postmenopausal women is gradually gaining acceptance in the urban population. Males, particularly the elderly, presenting with osteopenia and osteoporotic fractures, should be investigated to identify the cause of osteo-porosis and, if hypogonadal, receive substitution with testosterone on a long term basis.

REFERENCES