Androgens and bone metabolism

Joel S. Finkelstein

6.1 Introduction

Osteoporosis is one of the leading causes of morbidity and mortality in the elderly. Osteoporosis affects 20 million Americans and leads to approximately 1.5 million fractures each year (Finkelstein 1996). The annual cost of health care and lost productivity attributed to osteoporosis exceeds $13 billion in the Unit-
ed States. Even though osteoporosis is less common in men than in women, men lose about 30% of their trabecular bone and 20% of their cortical bone during their lifetime. Thirty percent of all hip fractures occur in men (Cooper et al. 1992) and the incidence of hip fractures in men over the age of 65 is 4 to 5 per 1000 (Jacobsen et al. 1990). By the age of 90 one of every six men will have fractured their hip. Hypogonadism has been identified as a probable risk factor for hip fractures in men (Jackson et al. 1992). Case series of men with osteoporotic fractures suggest that hypogonadism is present in between 7 and 30% of such individuals (Jackson et al. 1992; Jackson and Kleerekoper 1990; Kelepouri et al. 1995; Seeman et al. 1983; Stanley et al. 1991). This review will examine the roles of androgen in bone metabolism.

6.2 Mechanism of action of androgens on bone

6.2.1 Effects of androgens on osteoblasts in vitro

The mechanism(s) whereby androgens affect bone density is still unclear. Some data suggest that androgens may affect osteoblast function directly. Several observations are consistent with this notion. First, androgen receptors have been found on normal human osteoblasts (Colvard et al. 1989), in human osteosarcoma cell lines (Orwoll et al. 1991) and in bone marrow-derived stromal cells (Bellido et al. 1995). Second, both aromatizable and non-aromatizable androgens stimulate proliferation of human osteoblasts in vitro (Gray et al. 1992; Kasperk et al. 1989; Kasperk et al. 1997; Vaishnav et al. 1988), a process that appears to require adequate stores of vitamin D (Somjen et al. 1989). Third, dihydrotestosterone (DHT), a non-aromatizable androgen, and DHEA stimulate differentiation of human osteoblasts in vitro (Kasperk et al. 1989, 1997) although this effect has not been seen consistently in all studies. The ability of 1,25-dihydroxyvitamin D to stimulate alkaline phosphatase activity in vitro is enhanced by DHT (Gray et al. 1992). DHT also stimulates collagen production in vitro (Gray et al. 1992). The effects of androgens on osteoblast proliferation and differentiation might be due to increased local production of TGF-β or increased sensitivity to the mitogenic effects of fibroblast growth factor and IGF-II (Kasperk et al. 1990, 1997).

6.2.2 Effects of androgens on osteoclasts in vitro

Although it appears likely that androgens stimulate osteoblast activity, it also appears that androgens inhibit osteoclast activity. Because androgen receptors are not expressed on osteoclasts, effects of androgens on osteoclastic activity are likely indirect and may involve local production or action of cytokines in bone. Both testosterone and DHT inhibit the production of interleukin-6 (IL-6) by bone marrow-derived stromal cells by inhibiting expression