Bone Biology and Growth

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Bone biology has always been of great interest to growth and development investigators.

During the last decade, new physical and biochemical techniques have been devised in order to understand the biochemical and structural changes occurring in the bone during growth, pubertal development, diseases, and hormone therapy.

Osteoblast and osteoclast activity, used to assess bone formation and resorption rates, can be measured using biochemical markers, including: (1) osteocalcin; (2) pro-collagen type I C-terminal propeptide (PICP); (3) the crosslinked telopeptide of type I collagen (ICTP), and (4) bone alkaline phosphatase (BALP).

Dr. Crofton presents the results of three studies in which the markers PICP, ICTP, and BALP were used to assess growth and bone turnover in children. In short normal children treated with growth hormone, BALP gives the best correlation with height velocity after 3 months of therapy. Cytotoxic chemotherapy in children with acute lymphoblastic leukaemia induces significant changes in collagen peptides and BALP during the first 6 months of treatment. In babies with bronchopulmonary dysplasia treated with high-dose dexamethasone, both PICP and ICTP decrease dramatically.

Dr. Mohan reviews the effects of the insulin-like growth factor (IGF) system on the dynamics of bone formation and resorption in vivo and in vitro. This complex system involves a number of components, including IGF-I, IGF-II, type I and type II IGF receptors, IGF binding proteins (IGFBPs) and IGFBP proteases. IGFBPs can either potentiate (e.g. IGFBP-5) or completely inhibit (IGFBP-4) the mitogenic actions of IGFs.

Techniques used to date to evaluate bone mineral density have been criticized, as they do not take into account the bone volume, or differentiate cortical and spongiosa bone density. Nor do they take into account the influence of the muscle system on bone. Dr. Schönau analyses spongiosa bone mineral density and a bone strength index (BSI) using peripheral quantitative computer tomography, in children and adults. In addition, muscle (grip) strength is analysed. The spongiosa density is similar in children and adults, whereas the BSI increases with age, as does the muscle strength. There is a strong correlation between BSI and muscle strength. Thus combined analysis of BSI and muscle strength can be used to evaluate the functional muscle-bone unit.

The effect of growth hormone therapy on bone growth and development is discussed by both Prof. Saggese and Prof. Shalet. Bone mineral density increases in children deficient in growth hormone during therapy and biochemical parameters of bone formation and bone resorption

increase markedly, particularly during the first year of therapy. Prof. Saggese reports that, after having reached final height, these patients have a lower than normal radial and lumbar spine bone mineral density. This suggests that therapy with recombinant human growth hormone should be continued during late adolescence. Moreover, the incidence of bone fractures is higher in adults deficient in growth hormone.

The reduced bone mineral density of patients with childhood-onset growth hormone deficiency is confirmed by Prof. Shalet. However, the heterogeneity of patients makes evaluation of the causes of the reduction in bone mineral density difficult to assess. During growth hor-

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more therapy in adults with childhood-onset growth hormone deficiency, there is either no change or a reduction in the cortical and integral bone mass, whereas there is an increase in the vertebral trabecular bone mineral density during the first 6 months of therapy.

Subsequently, there is a steady increase in bone mineral density at all sites during the next 12-18 months of therapy. However, there is much variation, probably due to genetic factors.

In patients with adult-onset growth hormone deficiency there is a definite increase in vertebral trabecular bone and bone mineral density with therapy. However, it is too early to say whether growth hormone therapy modifies the risk of fracture.

The state-of-the-art techniques and exciting results described at this symposium are at the very forefront of this challenging research area. However, many questions remain unanswered. Although biochemical markers represent some aspects of bone mineral metabolism, the contribution of growth factors and their binding proteins, vitamin D, parathormone, calcitonin and diet, remains to be clearly determined. The various techniques used to evaluate bone density and strength produce different results that are not yet fully understood. Finally, the duration and doses for growth hormone therapy remain to be settled.