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SESSION TIME: 1500 - 1640, Monday 23 Oct 2006

Invited Plenary Abstracts
Plenary Lectures 2 - Growth

P5

Growth related origins of bone disease

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Growth is important process to attain healthy adult bone. Throughout childhood, bone mineral acquisition and longitudinal bone growth take place. Although the bone mass increases through childhood, from the first half of adolescent to the middle, increasing most comes out and when postpuberty comes, the increase speed decreases. According to the longitudinal study, in a girl, the increase speed in the bone mass reaches a peak at the age of 11 to 14, and this corresponds about two years after the peak of the increase in height. Then, 16 years old or about two years after menarche, the increase speed in the amount of bone mineral shows a fall remarkably, and will become zero mostly at the age of around 18. Since adolescent in a boy delayed for about two to three years, the peak of the increase in the amount of bone mineral becomes around 16 years old.

Bone mineral density and bone strength cannot catch up with the longitudinal growth. Thus early through middle puberty can be considered to be a relative bone fragile term. The bone metabolism of a cortical bone increases, the porosity of a cortical bone increases at this stage, and a bone becomes fragile. In a male, a junior high school term corresponds at this stage, and the incidence of fracture is high. Junior high school student's fracture frequency is increasing in Japan in recent years. The annual incidence of the fracture in junior high school students increased about 2 twice for 20 years. One of the causes of this increment is decrease in exercises during schoolchild period and decreased basic physical strength. A sport opportunity increases abruptly at junior high school term, and it increases the opportunity of the trauma leading to fracture.

The problem of nutrition is also important. In Japan, the intakes of calcium are an average of 550 mg/day remarkably low. We should be careful of the nutritional problem with the intake of vitamin D during adolescent.

Glucocorticoid induced osteoporosis (GIO) is the major form of the childhood osteoporosis. Other than the decreased bone mass and increased bone fragilities, glucocorticoid induced growth failure should be taken into account for the management of GIO. The actual condition in Japan of the GIO during childhood will be also discussed.

P6

Growth – choosing the right parents

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Osteoporosis is a skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The cumulative incidence of fracture from age 50 years is estimated at around 50% among white women and 20% among white men. Preventive strategies against osteoporotic fracture can be targeted throughout the life course. Thus, modification of physical activity and dietary calcium/vitamin D nutrition in the elderly and during midlife, should complement high risk approaches entailing appropriate measurement of bone mineral density and targeting of anti-resorptive and formation stimulating drugs. Prevention of osteoporotic fracture can also be directed earlier in the life course. Although most effort in fracture prevention has been directed at retarding the rate of age-related bone loss, and reducing the frequency and severity of trauma among elderly people, evidence is growing that peak bone mass is an important contributor to bone strength during later life. The normal patterns of skeletal growth have been well characterised in cross-sectional and longitudinal studies. It has been confirmed that boys have higher bone mineral content, but not volumetric bone density, than girls. Furthermore, there is a dissociation between the peak velocities for height gain and bone mineral accrual, in both genders. Puberty is the period during which volumetric density appears to increase in both axial and appendicular sites. Many factors influence the accumulation of bone mineral during childhood and adolescence, including heredity, gender, diet, physical activity, endocrine status and sporadic risk factors such as cigarette smoking. Measures to maximise bone mineral acquisition, particularly through encouraging physical activity and adequate dietary calcium intake, are likely to impact upon fracture risk in later generations.

Although there is evidence to suggest that peak bone mass is inherited, current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk. Evidence has also begun to accrue that fracture risk might be modified by environmental influences during intrauterine or early postnatal life, which modify the trajectory of skeletal growth and mineral accrual. The relatively rapid rate of mineral gain during this period, coupled with the plasticity of skeletal development in utero, offer the possibility of profound interactions between the genome and early environment in this stage of the life course. There is a strong biological basis for such a model of disease pathogenesis. Experimentalists have repeatedly demonstrated that minor alterations to the diet of pregnant animals can produce lasting changes in the body build, physiology and metabolism of the offspring. This is one example of a ubiquitous phenomenon (developmental plasticity), which enables one genotype to give rise to a range of different physiological or morphological states in response to different prevailing environmental conditions during development. Its essence lies in the critical period during which a system is plastic and sensitive to the environment, followed by a loss of that plasticity and a fixed functional capacity.

The evidence that osteoporosis risk might be modified in this way stems from four groups of studies: (1) Epidemiological studies which confirm that subjects who are born light and whose growth falters in the first year of postnatal life, have significantly lower bone size and mineral content, at age 60 to 75 years; (2) Cohort studies demonstrating that subsequent lower trajectories of childhood growth are associated with an increased risk of hip fracture among such men and women; (3) Detailed physiological studies of candidate endocrine systems which might be programmed have shown that birthweight and growth in infancy alter the functional settings of the GH/IGF-1, and hypothalamic pituitary adrenal axes; (4) Studies characterising the nutrition, body build and lifestyle of pregnant women which relate these to the bone mass of their newborn offspring, have identified a number of important determinants of reduced fetal mineral accrual (maternal smoking, low maternal fat stores and maternal vitamin D deficiency, intense levels of weight-bearing physical activity in late pregnancy). Follow-up studies of randomised controlled trials of vitamin D supplementation in infancy suggest persisting benefits in adolescence and young adulthood. These data suggest that undernutrition and other adverse influences arising in fetal life or immediately after birth have a permanent effect on body structure, physiology and metabolism, which might independently influence the later risk of osteoporotic fracture.

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Signalling for cartilage differentiation

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Sox9 is an essential transcription factor for mesenchymal condensation in the formation of cartilage anlagen, and Sox9, 5, and 6 are required for acquiring chondrocyte phenotype. After acquiring the phenotype of chondrocytes, the immature chondrocytes further differentiate to hypertrophic chondrocytes in the process of endochondral ossification. Many factors, including PTHrP, FGFs, and BMPs, regulate chondrocyte differentiation at the late stage. Runx2 and Runx3 are essential transcription factors in the late stage of chondrocyte differentiation.

Runx2 and Runx3 are transcription factors that belong to Runx family (Runx1, Runx2, and Runx3). Each of the Runx family genes encodes a DNA-binding domain, runt that is homologous with the Drosophila pair-rule gene runt. Runx2 is induced by BMPs, FGFs, retinoic acid, and TGFβ, and Runx2 interacts with many other transcription factors and co-regulators in the transcriptional regulation of its target genes. Cbfb forms heterodimers with Runx2 and is required for Runx2-dependent transcriptional regulation.

Runx2 regulates bone formation by regulating osteoblast differentiation as well as chondrocyte maturation. Runx2 is essential for the commitment of multipotent mesenchymal cells into the osteoblastic lineage. Runx2 triggers the gene expression of bone matrix proteins, while keeping the osteoblastic cells in an immature stage. Runx2 and Runx3 have redundant functions in chondrocytes, and they are essential for chondrocyte maturation. They prevent chondrocytes from acquiring the phenotype of permanent cartilage. Runx2 directly induces Ihh, which plays an important role in chondrocyte proliferation. Further, PTHrP, which is induced by Ihh, inhibits Runx2 expression. Therefore, the Runx2-Ihh-PTHrP cascade coordinates the proliferation and differentiation of chondrocytes. The regulation of chondrocyte differentiation by Runx family transcription factors will be discussed in detail.

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Bone health in chronic disease: evaluation and treatment – a paediatric perspective

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During childhood, musculoskeletal development is characterized by sex- and maturation- specific increases in trabecular bone mineral density (BMD), cortical dimensions and lean mass. Children with chronic diseases have multiple risk factors for impaired bone accrual, including malnutrition, decreased muscle mass and biomechanical loading, delayed pubertal maturation, alterations in the growth hormone axis, inflammatory cytokines, and bone-active medications such as glucocorticoids. The assessment of glucocorticoid induced osteoporosis is confounded by the effect of the underlying inflammatory disease and by glucocorticoid effects on growth and body composition. Furthermore, conventional DXA measures of areal-BMD (g/cm2) result in an underestimate of volumetric BMD (g/cm3) in children with decreased height for age, and fail to adequately distinguish between alterations in trabecular and cortical bone. The comparison of two childhood diseases treated with high-dose chronic glucocorticoids illustrates the impact of the underlying disease. Childhood Crohn disease (CD) is associated with significant reductions in DXA whole body bone mineral content (BMC) and femoral shaft cortical dimensions (adjusted for age and height), as well as quantitative computed tomography (QCT) tibia trabecular volumetric BMD and cortical thickness, compared with controls. The cortical deficits are characterized by both a smaller periosteal circumference and loss of bone on the endosteal surface, with a consequent reduction in bone strength (cross-sectional moment of inertia), relative to tibia length. In contrast, steroid-dependent nephrotic syndrome (NS) is associated with increased DXA whole body bone mineral content, DXA femoral shaft cortical dimensions, and pQCT cortical thickness and strength, with minimal deficits in trabecular volumetric BMD. We propose that the markedly and persistently elevated cytokines observed in childhood CD result in direct detrimental effects on bone modeling, as well as catabolic effects on muscle. In contrast, SSNS is not associated with sustained elevations in inflammatory cytokines, and the glucocorticoid-induced obesity results in preserved lean mass and linear growth. In CD, adjustment for the lower lean mass explains the cortical bone deficits observed by DXA and QCT. Similarly, in NS,

adjustment for the greater lean mass explains the greater cortical bone strength observed by DXA and QCT. Ongoing studies will address the impact of targeted anti-cytokine therapy (e.g. infliximab) and daily therapy with low magnitude mechanical stimuli as potential anabolic therapies in children with CD.