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EFFECT OF GROWTH HORMONE (GH) TREATMENT ON BONE METABOLISM IN ULLRICH-TURNER-SYNDROME (UTS)

Background and Methods. The cause of decreased bone mineralization in UTS and the effect of different doses of GH on bone turnover are unknown. We therefore measured total (AP) and bone (BAP) alkaline phosphatase and osteocalcin (Oc) as markers of osteoblastic bone formation and the hydroxyproline-creatinine-ratio (OH-P/Cr) in fasting morning urine as an index of osteoclastic bone degradation, as well as IGF-I as an index of the effect of exogenous GH on its receptor.

Patients and Study Protocol. 80 untreated prepuberal girls with UTS (bone age 3 - 11yr) were studied prior to and most of them after a 21-33 months-therapy with 3 different doses of GH (Humatrope, Lilly), given subcutaneously: 2U/sqm/day (UTS-2U, n = 27), 3 U/sqm/day (UTS-3U, n = 24) and 4 U/sqm/day (UTS-4U, n = 19). The results were compared to 8 patients with growth hormone deficiency (GHD) prior and during GH therapy with 2 U/sqm/day and 25 healthy age-matched controls (basal levels of bone metabol.)

Results. IGF-I was normal in UTS-groups and GHD. AP, BAP and Oc were decreased prior to GH treatment and showed a lower response than in the patients with GHD (receiving only 2 U), even at a dose of 4 U in patients with UTS. In contrast, OHP/Cr was normal before treatment and showed a dose-dependent increase in the 3 UTS-groups.

Conclusions. Our study indicates that children with UTS have reduced osteoblastic bone formation but unimpaired osteoclastic bone degradation and that this imbalance may worsen during treatment with high doses of GH.

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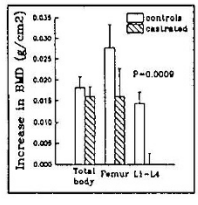
EFFECT OF TESTOSTERONE ON BONE MINERAL DENSITY (BMD) IN GROWTH HORMONE (GH) DEFICIENT RATS. P.W. Lu, C.T. Cowell, J. Briody, R. Howman-Giles. Robert Vines Growth Research Centre & Department of Nuclear Medicine, Royal Alexandra Hospital for Children, Sydney, NSW 2050, Australia

The contribution of GH and sex steroids to attainment of peak bone mass are not clear and require longitudinal studies. We are examining the interactions between testosterone and GH on BMD using the GH deficient and GH sufficient rat models (Lewis strain). In the first part of study, forty male GH deficient rats were included with half the rats castrated at age 4 weeks and half remained as controls. All rats received identical diet and housing. BMD of total body, femur and lumbar spine (L1-L4) were measured from early adulthood at age 12 and 36 weeks, using Dual Energy X-ray Absorptiometry (DEXA, LUNAR) equipped with special software for small animals.

This DEXA software was validated for small animals prior to the study. There was strong agreement between bone mineral content and ash weight for total body (r^2=0.90) and femur (r^2=0.83) in 17 rats with weight ranging from 146 to 212 grams.

At age 12 weeks, there was no difference in total body, femur and L1-L4 BMD between two groups. However at 36 weeks, the castrated rats had significantly lower L1-L4 BMD compared to the controls (data not shown). From age 12 to 36 weeks, rats of both groups had significant increase in total body and femur BMD (left). The castrated group had no increase in L1-L4 BMD, which is significantly different from the control rats.



We conclude that testosterone, even in the presence of GH deficiency, is critical for maintaining BMD of lumbar spine, which is predominantly trabecular bone. The impact of GH deficiency on BMD will be examined in the second part of study with GH deficient and sufficient models.

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INCREASED BONE MINERAL DENSITY IN CONGENITAL ADRENAL HYPERPLASIA (CAH). Phyllis W. Speiser, Maria I. New, Joseph M. Gertner. Dept. of Pediatrics, The New York Hospital-Cornell University Medical Center, New York, NY 10021 USA.

To examine the influence of sex steroids on bone accretion, we studied bone mineral density (BMD) by dual energy x-ray absorptiometry (DEXA) of the lumbar spine, L2-L4, in 6 patients with CAH-21-hydroxylase deficiency who had been exposed to age-discordant levels of adrenal hormones. 3/6 patients had been treated since infancy with low doses of glucocorticoids. Children (mean age 7.8 ± 4 y) had advanced height age and bone ages (9.0 ± 3.4y and 10.3 ± 3.0y, respectively). Irrespective of treatment status, BMD (L2-L4;g/cm^2) was increased in CAH compared with mean BMD for age-matched population norms (J Bone & Min Res 6:507,1991; patients 0.83 ± 0.25 vs. controls 0.63 ± 0.34; p = 0.01). Adjustment for bone age again showed increased BMD in patients (0.76 ± 0.19 vs. 0.62 ± 0.18; p = 0.02). Since DEXA measurements are dependent on body size, we corrected for height age, again finding increased BMD in patients (0.76 ± 0.19 vs. 0.56 ± 0.15; p = 0.007).

CONCLUSIONS: 1. Treated and untreated children with CAH show an increase in BMD. 2. This early increase in BMD may protect against later osteoporosis and may represent the converse of the observation that pubertally delayed subjects have reduced BMD, even as adults.

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LOW DOSES OF VITAMIN D_3 ARE TO REQUIRE FOR RICKETS PROPHYLAXIS. V.Hesse[1], A.E.Kapuths[2], E.Radecke[2], H.Vogel[3] and the Germany rickets study group
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The effects of prophylactic administration of 400 IU containing vitamin D_3 tablets were tested in 2707 newborn to 15-month-old infants. Only Vitamin D free formula milks were used in formula-fed infants. Vitamin D_3 prophylaxis was started in the 2nd week of life. 57 out of 89 (64%!) one-week- old newborns had 25 OH-D serum conc. below 20! nmol/l (range 20-130 nmol/l, method Aksnes et al. Clin. Chem. Acta 104, 1980:133,147). Under 400 IU of vit.D_3/day 25 OH-D increased from 22.6 ± 13.8 to 83.1 ± 36.1 nmol/l from the 2nd week to the 3rd month (n = 163, p < 0.0001) and to 93.9 ± 36.6 nmol/l between 4-6 months (n = 182, p > 0.0001). Elevated 25 OH-D conc. (>130 nmol/l) were found in 35/345 (10.1%) in the first half year and 4/149 (2.6 %) in the second one. Elevated calcium serum conc. (> 2.8 mmol/l) were observed in 28 of 439, infants (6.4 %) in the first 6 months. Anorg. phosphate conc. above > 2.4 mmol/l were measured in 143 of 616 (23.2 %). (Ca values < 2.0 mmol/l = 2).One of 2707 infants had rickets. Slightly elevated alk. phosph. conc. (> 12.5 umol/l.s were found in 87 of 676 infants (12.9 %) in spite of normal Ca, P and 25 OH-D conc. Concl.: Daily applic. of 400 IE Vit.D_3 day leads to increased 25 OH-D and calc. conc. in the first 6 months of life. 300 IE vit. D_3/day are recommended as prophylactic dose for the first and 400 IE/day for the second half year of life.

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ULTRASOUND VELOCITY IN THE OS CALCIS, THUMB AND PATELLA DURING CHILDHOOD AS INDICATOR OF BONE DENSITY

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The morbidity and mortality associated with postmenopausal osteoporotic fracture is becoming increasingly recognized as a major health problem in the elderly. Maximising the accumulation of bone tissue during growth and puberty is one of the most important aims in the prevention of osteoporosis. For prevention studies in children it is necessary to develop methods for bone densitometry without radiation. Ultrasonic velocity (speed of sound = SOS) has been proposed as an alternative method for evaluating skeletal status. Using a new ultrasonic system (Osteoson K4, MTO, F.R.G.), we investigated reproducibility and age-dependency of SOS at several peripherial bones.

Results: 1. Intra-Observer reproducibility (day to day): calcaneus CV = 0.64; patella CV = 1.18 and thumb CV = 0.43 (n = 25). Inter-Observer reproducibility: calcaneus CV = 1.1, patella CV = 2.48 and thumb CV = 0.62 (n = 16).

Age-Dependency (n = 207 healthy probands; age:1-30 years) of SOS indicated as range:

Age (years)	SOS-Calcaneus (m/sec)	SOS-Patella (m/sec)	SOS-Thumb (m/sec)
1-6	1615-1832	1567-1827	1587-1707
6-11	1754-2014	1701-1980	1592-1707
11-17	1805-2132	1928-2123	1614-1758
21-30	1952-2156	1976-2297	1605-1778

The reproducibility of SOS measurements especially through the thumb is comparable with those of radiation methods. The SOS age-dependency curves of our study are similar to those of bone mineral density and content in lumbar spine and femoral neck measured by dual X-ray absorptiometry (DXA). DXA and our SOS data showed a dramatic reduction in "bone mass" growth during the first years after puberty.

Further studies in well defined bone diseases have to demonstrate whether SOS allows to differentiate between normal and pathological conditions and whether this method facilitates prevention studies of osteoporosis to optimize peak bone mass during childhood.

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URINARY GALACTOSYL-HYDROXYLYSINE - A MARKER OF HEIGHT VELOCITY

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In practical pediatric endocrinology assessment of current height velocity (HV) plays an important role for diagnosis and treatment of growth disorders. However, to date, there is no quick and simple method to determine HV. Urinary excretion of Galactosyl-hydroxylysine (GHLy), a marker of osteoclast activity, has been shown to closely reflect the activity of bone metabolism in adults. In this study we tested the hypothesis that GHLy can also be used to evaluate skeletal growth in children.

GHLy was measured in 24h-urines of 74 healthy children, 21 girls with Turner's syndrome (TU) and 15 children with growth hormone deficiency (GHD). HV was calculated from two measurements of body height 6 to 12 months apart. When related to body weight, the 24h excretion of GHLy showed a highly significant correlation to HV in normal children ($r = 0.75$, $p < 0.001$) and GHD ($r = 0.69$, $p = 0.004$) but not in TU ($p > 0.05$). Data for weight-adjusted daily excretion of GHLy were transformed to standard deviation scores (SDS) to allow for comparison in different age groups. The mean SDS of both GHD and TU were significantly below zero (-1.31 and -1.83 respectively; $p < 0.05$). None of the values in these two disorders was above the mean for healthy children of the same age.

Thus, GHLy might be a useful indicator of HV for the evaluation of growth disorders. Further studies are needed to test if GHLy excretion can be used to predict the changes of HV during growth-promoting therapies.