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BONE MINERAL DENSITY (BMD) IN ADOLESCENT FEMALES PREVIOUSLY TREATED WITH GONADOTROPIN RELEASING HORMONE ANALOGUE (GnRH-a) FOR CENTRAL PRECOCIOUS PUBERTY (CPP). R.Baens-Bailon, S.F.Siegel, F.Mimouni, J.Sumkin, P.A.Lee. Children's Hospital of Pittsburgh and Magee Women's Hospital, Pittsburgh, PA 15213 USA.

Long-acting GnRH analogues effectively and safely suppress pituitary-gonadal function in children with CPP. However, the effects of long term therapy with GnRH-a on the bone mineral density of these children has not been studied. Using dual energy X-ray absorptiometry (Hologic QDR-1000), we evaluated the spinal (L1-L4) BMD of 9 girls with CPP who were previously treated with the GnRH-a, Leuprolide® compared to control girls matched for bone age, body mass index (BMI), and Tanner stage. Patients were treated with daily or depot injections of leuprolide acetate for 2.3 ± 1.7 years (mean ± SD). At BMD determination, GnRH-a had been discontinued for 0.5-2 years and pituitary-gonadal axis recovery documented by responses to GnRH stimulation. No significant differences in spinal BMD were observed between CPP and controls.

	CPP (n=9)	CONTROLS (n=8)
Age(y)	12.7 ± 1.35	15.8 ± 1.2*
Bone Age(y)	14.4 ± 1.02	15.7 ± 1.4
Height(cm)	151.2 ± 10.4	164.7 ± 4.7*
Weight(kg)	57.7 ± 10.4	58.9 ± 4.7
Body mass index(kg/m^2)	25.5 ± 5.1	21.9 ± 1.9
Tanner stage	4.4 ± 0.5	4.4 ± 0.5
Bone density(gms/cm^2)	0.86 ± 0.16	0.995 ± 0.13
Bone density SDS(vs age)	0.55 ± 1.4	0.09 ± 1.3

* p value < 0.005

These preliminary findings suggest that chronic treatment with GnRH-a in girls with CPP does not significantly affect the acquisition of peak bone mass during midadolescence.

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DETERMINATION OF 24 HOUR URINARY ESTROGENS DURING PUBERTY. E Norjavaara and K Albertsson-Wikland, Dep of Physiology and Pediatrics, Int Growth Research Centre, University of Göteborg, Sweden.

The first sign of puberty in girls can be observed by either clinical examination or the LH and FSH response to GnRH. However, serum estradiol levels can not be detected. The aim of the study was to develop a method for determine the early increase in estrogens and therefor we focused our work on metabolites in the urine.

24h urine was collected from healthy girls with breast development of stage B_1 or B_2. The volume of urine was measured, albumin added (0.1% final concentration) in the samples for analysis. Sorbent solid extraction technology was used for extraction of the steroids. BondElut extraction cartridges C18 1211-3027 were used. The estrogen content was determined with bioMériux Estradiol enzymatic U kit (nr 6.1483), using β-glucuronidase G7771 from sigma for hydrolyzing estrogens from glucuroconjugates.
Total urinary estrogens (estradiol and estrone) varied between 0.01-0.04 µg per 24h for girls in Tanner stage B_1 (n=3) and between 0.23-3.45 µg per 24h for girls in Tanner stage B_2 (n=4).

Determination of urinary estrogens seems to be a method to determine whether puberty has started or not. This could be used both in diagnosis and treatment of precocious puberty.

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DIFFERENCES IN INHIBIN AND GONADOTROPIN SECRETION BETWEEN PREPUBERTAL AND LATE PUBERTAL FEMALES. P.K. Manasco, S.M. Muly, D.C. Godwin, M.D. Culler, Lab.of Molecular and Integrative Neurosciences, NIEHS, NIH, Res. Tri. Pk, NC 27709, USA and Div. of Ped. Endo., Univ. of North Carolina, Chapel Hill, NC 27599, USA.

To determine whether inhibin secretion differs between prepubertal and late pubertal females, we measured inhibin and gonadotropins in venous samples drawn every 10 minutes from 9pm-7am in 9 prepubertal and 20 late pubertal (Tanner stages IV and V) females. Mean luteinizing hormone (LH), follicle stimulating hormone (FSH) and inhibin concentrations were significantly greater in the late pubertal girls when compared with the prepubertal girls (0.61±.5 vs 4.25±.6 IU/L LH, 1.54±.5 vs 3.0±.3 IU/L FSH, and 161.0± 32.9 vs 375.5 ± 41.1 pg/ml inhibin, mean ± SEM, P<0.05 in prepubertal vs fully pubesced girls respectively). The mean number of LH, FSH and inhibin peaks did not increase significantly as the girls progressed throughout puberty (2.4±.6 vs 4.9±.9 LH peaks/10 hours , 3.2±.7 vs 5.0±.2 FSH peaks/10hours, and 1.4±.7 vs 3.4±.4 inhibin peaks/10 hours). LH and inhibin peak heights were significantly greater in the late pubertal girls when compared to the prepubertal girls (1.14±.8 vs 5.6±.7 IU/L LH, 273±66 vs 479±111 pg/ml inhibin, p<0.05); although no changes were observed in FSH peak height. These data suggest that inhibin secretion is pulsatile in the human female with increases in mean concentration and peak height as puberty progresses. These data show that mean concentrations of inhibin are lower in prepubertal and late pubertal females when compared to males at comparable stages of puberty studied previously in our lab.

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CAN GNRH AND TRH TEST DURING PREPUBERTAL PERIOD PREDICT THE OCCURRENCE OF PUBERTY IN SHORT CHILDREN? T. Yamamoto, S.Nukina, S. Matsuo, Z. Kizaki, F. Inoue, A. Kinugasa and T. Sawada, Department of Pediatrics, Kyoto Prefectural University of Medicine, Kamikyo-ku, Kyoto, 602, JAPAN

To investigate whether GnRH and TRH test during prepubertal period is useful for the diagnosis of gonadotropin deficiency in short children, 20 children (12 boys, 15.7±0.6 years old and 8 girls, 17.9±1.0 years old) were evaluated. All have received GH replacement according to the Japanese standard of assessment of short stature. Seven (4 boys and 3 girls) of the 20 children have multiple pituitary hormone deficiencies (MPHD) without the occurrence of puberty, who had been treated with thyroxine, cortisol and so on. Other 13 (8 boys and 5 girls) presumed to be isolated GH deficiency (IGHD) show normal pubertal development. The levels of LH, FSH and prolactin (PRL) on GnRH (2µg/kg) and TRH (10µg/kg) test during prepubertal period were compared between the MPHD and the IGHD. The chronological age when the tests were performed was at 9.8±0.9 years old in both groups. In boys, ΔFSH levels were decreased and basal PRL levels were increased in the MPHD as compared with those of the IGHD (0.9±0.4 vs 10.7±1.9 mIU/ml, 24.7±4.2 vs 12.5±2.5 ng/ml, respectively). In girls, basal LH and FSH, peak FSH and ΔFSH were decreased and basal PRL levels were increased in the MPHD as compared with those of the IGHD (3.6±0.9 vs 1.0±0.4 mIU/ml, 2.0±0.0 vs 3.8±0.3 mIU/ml, 5.2±2.5 vs 19.5±2.8 mIU/ml, 3.2±6.1 vs 15.7±2.5 mIU/ml, 19.0±3.0 vs 3.5±1.4 ng/ml, respectively). These results suggest that the subnormal response of gonadotropins to GnRH and the increased level of basal PRL might be an available index for the prediction of the absence of puberty in short children at adolescent age.

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INSULIN RESISTANCE (IR) OF PUBERTY IS MEDIATED BY GROWTH HORMONE (GH) AND NOT BY SEX STEROIDS (SS): STUDIES IN BOYS WITH DELAYED PUBERTY. C.A. Bloch, G. J. Klingensmith, F. Papanti. Division of Pediatric Endocrinology, University of Colorado School of Medicine and Children's Hospital, Denver, CO, 80218, USA.

Many factors have been invoked for the cause of pubertal IR, including GH, SS, and increasing adiposity. To determine the respective roles of GH and SS in mediating IR, we studied 24 boys with delayed puberty before and after random assignment to one of 4 research groups: Control (Ctrl), Testosterone (T) Rx, GH Rx, GH + T Rx. We quantitated the insulin sensitivity index (IS) via the minimal model approach. GH was measured Q 20 min from 2000 through 0600 via the Hybritech assay.

BEFORE	IGF I (ng/mL)	GH (pool)	GH (peak)	T (ng/dL)	Free T (pg/mL)	IS (x 10^{-4})
Ctrl n=4	294.3	1.88	5.68	22.35	0.56	7.15
T n=8	188.0	1.81	9.56	20.65	0.38	8.10
GH n=5	208.0	3.30	11.98	31.00	0.44	12.90
GH+T n=7	135.7	1.53	7.60	50.67	0.63	5.73

AFTER	IGF I	GH	GH	T	Free T	IS
Ctrl	339.8	2.70	9.30	89.3	1.70	8.10
T	445.3	7.49	21.21	1128	32.35	5.24
GH	559.0	19.66	33.34	48.8	0.30	5.84
GH + T	627.3	21.27	41.80	1108.5	31.26	3.97

Body mass index did not change with GH, but increased significantly with T, and T + GH. Paired ANOVA, and analysis of covariance of the data indicate that IR is highly correlated with GH, but not with T. GH is stimulated by T. We conclude that GH is the predominant factor responsible for the IR of puberty. (Funded by Genentech, Inc., and NIH CRC Grant #RR-69).

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EFFECTS OF SEX STEROIDS ON PROTEIN AND CALCIUM METABOLISM IN THE PREPUBERTAL HUMAN N Mauras, AD Yergey, MW Haymond. Nemours Children's Clinic, Jacksonville, FL (NM,MWH) and NIH (ADY)

Androgenic steroids participate in the acceleration of linear growth and increase in muscle mass during the transformation from the prepubertal to the pubertal man. To determine the acute changes in whole body protein and calcium (Ca) metabolism in the prepubertal human, we studied 6 healthy prepubertal boys (mean age:13±1 yrs) in the post absorptive state using a primed 4 hour infusion of [1-13C]leucine and the reciprocal pool model. Concomitantly, bone turnover was assessed by administering dual tracers of Ca, 42Ca iv, 44Ca P.O., and measuring the Ca isotopic enrichments in blood & urine samples. Testosterone (T) enanthate (100 mg IM) was given 2 wks apart and patients studied again within 4 days of last injection. Mean [T] rose from 11±6 ng/dL to 843±125 and weight from 36.8±6.0 kg to 39.1±6.2 after T therapy. The rate of appearance of leucine (an indicator of proteolysis) was 1.66±.24 µMol/kg.min and increased to 1.98±.29 after T therapy, p=.08. Leucine oxidation decreased from 0.25±.04 µMol/kg.min to 0.13±.02, p=.017; thus the non oxidative leucine disappearance, which estimates protein synthesis, also increased significantly from 1.41±.21 µMol/kg.min to 1.85±.27, p=.033. Kinetic studies on 2 subjects showed that all indicators of bone turnover (Vt), accretion (Vo+) and resorption (Vo-) showed an increase by approximately 30% after T therapy. These results demonstrate for the first time that short term acute administration of testosterone increases whole body estimates of protein turnover and anabolism and concomitantly increases Ca and bone turnover in the prepubertal human.