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**ABSORPTION KINETICS AND METABOLIC EFFECTS OF GH FOLLOWING SUBCUTANEOUS INJECTIONS IN THE ABDOMEN VERSUS THE THIGH.**

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The significance of changing the site of injection on the absorption and metabolic effects of human growth hormone (GH) was studied. In a cross-over design nine GH-deficient patients were randomized to subcutaneous (s.c.) injections of GH in the thigh or abdomen. After each treatment period (four weeks), serum profiles of GH, IGF-I, IGFBP-3, glucose, insulin and glucagon were measured for 37 hours after GH injection (3 IU/m²) (19.00 h). Mean (± SEM) integrated levels (AUC) of GH (μg/l) were similar: 2.63 ± 0.38 (thigh) versus 2.67 ± 0.31 (abdomen)(NS). AUC (μg/l) for the initial six hours were significantly different: 1.11 ± 0.23 (thigh) and 1.50 ± 0.27 (abdomen)($p < 0.05$). $C_{max}$ (μg/l) [11.59 ± 1.93 (thigh) and 14.83 ± 2.39 (abdomen) ($p = 0.19$)] was achieved faster following s.c. injection in the abdomen. $T_{max}$ (hours) was 5.89 ± 0.41 (thigh) and 4.26 ± 0.49 (abdomen) ($p < 0.002$). IGF-I levels were similar. AUC's (± SEM) were 345.6 ± 62.0 (thigh) and 355.7 ± 65.1 (abdomen)(NS). Levels of IGFBP-3 were however different [AUC's (± SEM) (μg/l) were 2044.3 ± 147.7 (thigh) and 2287.9 ± 181.5 (abdomen)($p = 0.05$)]. Insulin, glucose and glucagon levels were not significantly different. We conclude that subcutaneously injected human GH is absorbed faster when injected in the abdomen as compared with the thigh. Metabolic effects of GH were similar. Levels of IGFBP-3 however were higher after s.c. injections in the abdomen.

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GH THERAPY IN TURNER GIRLS: FASTING AND STIMULATED INSULIN DURING AND AFTER TREATMENT.

GH treatment in Turner syndrome (TS) represents a risk factor for further rise of frequently increased insulin levels. Data about the reversibility of this phenomenon are missing. The aim of our study was to investigate reversibility of changes in insulin secretion in TS during and after GH treatment. 9 prepubertal girls, age (mean±SD) 8.7±1.8 yr, were treated with GH, 1 IU/kg bw/week in daily sc injections for 12 months. Then the treatment was stopped. Glucose tolerance and insulin response were measured by an iv GTT (0.5 g glucose/kg bw) before and after 3,6,9 and 12 months of GH treatment and 3 months after its cessation. Glucose tolerance remained unchanged during the treatment period. Fasting insulin increased from (mean±SD) 13.0±3.8 mIU/l to 22.9±11.1 (9 mo,p=0.02) to 14.7±5.0 (12 mo) and to 13.5±8.2 (3 mo after treatment). Integrated insulin secretion (AUC 1st phase) was increasing from 555±154 $mIU/l.min^{-1}$ to 9 months (1024±377, p=0.01) and decreased at 12 months (824±268, p=0.005) and at 3 months after therapy (685±184, p=0.01). Peak insulin response to treatment was predicted by pretreatment fasting insulin (r=0.74, p=0.006). In conclusion, patients with TS exhibit an increase in fasting and stimulated insulin secretion during the first year of GH therapy. A decrease follows by the end of the first year and after therapy.

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METHODS FOR EVALUATION OF GROWTH IN ULLRICH TURNER SYNDROME (UTS)

Patients with UTS are now increasingly treated with GH to improve growth velocity and final height. For evaluation of the effectiveness of this treatment different methods have been applied and we demonstrate that the results depend to some extend on the specific method that has been used for analysis. We have reviewed height ad growth velocity data as well as the applied methodology from 13 studies on spontaneous growth in UTS. Most studies were based on calculations of annual means or medians of data collected in a longitudinal/cross sectional manner, others used mathematical models. Growth velocities were calculated longitudinally in individual patients or were derived from height curves graphically or mathematically. Individual height data for a given age varied between 2.6 and 7.7 cm when annual means were applied and between 0.4 and 5.8 cm when mathematical models were used. Data on growth velocity were nearly identical in all studies except for the age of expected puberty, when some authors found a minor pubertal growth spurt. Standard deviations for growth velocity increased at the time of pubertal age and amounted in up to 70% of the respective growth velocity. When various UTS height standards were applied for evaluation of treatment effects we found a difference up to 100% of the SD score due to the different SD values of reference data. Results expressed as height SDS may be biased by relatively low mean heights of reference data at adolescent ages.

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BIRTH DATA OF PATIENTS WITH GROWTH HORMONE DEFICIENCY

The pathogenesis of idiopathic GH deficiency (GHD) is not clear and it was presumed that GH is not essential for prenatal growth. We have therefore analysed in the clinical and auxological data of patients with GHD. History of pregnancy, birth history and birth data as well as postpartal data were evaluated. 48 unselected patients (boys:girls=2:1) with complete GHD had isolated (IGHD,n=24) or multiple pituitary hormone deficiencies (MPHD,n=24). 25% of the patients were born prematurely. Complications during pregnancy (impending abortion, gestosis) were observed in 27% of patients. Abnormal birth occured in 40% (breech and footling presentation, assisted delivery). Birth length of boys (-1.0±1.3SDS;p<0.01) and of girls (-0.4±1.0SDS;ns) was reduced when compared to local reference data. The data for IGHD and MPHD patients (-0.9±1.3SDS vs. -0.8± 1.2SDS) were not different. Birth weight was reduced in boys (-0.8± 1.2SDS;p<0.05) but not in girls (+0.06±1.3SDS). No difference in birth weight was found between IGHD and MPHD (-0.4±1.5SDS and -0.6± 1.5SDS), respectively. This indicates relative overweight already at birth. 50% of patients had various complications during the postpartal period (prolonged jaundice, hypoglycemia etc.). Maternal height was -0.5±1.2SDS and did not correlate with patients length at birth. In conclusion, we have shown that children with idiopathic GHD as a group are short at birth and have relative overweight. This may indicate the importance of GH for prenatal growth. In a high proportion of patients with idiopathic GHD perinatal complications were observed.

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A COMPARISON BETWEEN THE PLASMA GHBP-3 AND IGF-1 LEVELS AS INDICATORS OF A GH DEFICIENCY IN PRESCHOOL CHILDREN. N.Sasaki, S.Miyamoto, Y.Hasegawa, T.Hasegawa, Y.Tuchiya, and H.Niimi.

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The clinical usefulness of the GHBP-3 and IGF-1 plasma levels as indicators of GH deficiency has been evaluated in preschool children of short stature under the age of 6 (n=72), and the results compared with results seen in prepubertal children of short stature 6 years or older (n=65). The subjects were placed in to 1 of 3 groups based on GH responses to insulin and arginine: normal children of short stature (NS) with more than 10ng/ml value in one of the two testings; children with a partial GH deficiency (pGHD) with less than a 10ng/ml in both and more than 5ng/ml in one of two tests; children with a complete GHD (cGHD) with less than 5ng/ml in both tests.

The GHBP-3 sensitivity for detecting cGHD in preschool children (n=6) was 83.3% and its specificity for NS was 72.7%. Whereas the IGF-1 sensitivity was 42.9% (n=7). Their sensitivity for detecting pGHD was 11.8( (n=17) and 10% (n=20), respectively. But in the prepubertal children, the sensitivity of GHBP-3 and IGF-1 for pGHD was 88.9% (n=9) and 100% (n=9), respectively.

It thus appears that when screening preschool children of a short stature, the plasma GHBP-3 value is a good indicator of a possible cGHD.

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EFFECT OF GROWTH HORMONE ADMINISTRATION OF NEUROTENSIN RELEASE

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The aim of our study was to investigate the effects of GH on neurotensine (NT) levels. Plasma samples were obtained from 7 GH-deficient children (5 boys, 2 girls), are range 1.1-14.5 years (11.23±1.75 mean ±SEM) to evaluate NT and GH values, before treatment and 12 and 24 hours after a subcutaneous rhGH injection (0.15 IU/kg). NT concentrations were measured by RIA and expressed as fmol/ml; GH values were evaluated by RIA using commercial kits and expressed as ng/ml. NT levels in our pts before GH administration (3.20±1.72 fmol/ml) were significantly lower ($p<0.01$) than those in controls (17±2.5 fmol/ml). A significant increase in NT values were found 12 h (39.57±10.42 fmol /ml, $p<0.01$) and 24 h (13.64±5.28 fmol/ml, $p<0.05$) after GH injection. Circulating GH concentrations significantly increased ($p<0.005$) 12 h (2.02±1.23 vs 12.56±2.18 ng/ml), but not 24 h after GH administration (0.74±0.17 ng/ml). We observed a close correlation between NT and GH values before treatment ($p<0.005$) and at the 24th h after GH injection ($p<0.05$), but not at the 12th h. Our preliminary results point to a stimulating effect of GH on NT release by mechanisms still unknow. The GH-induced NT release could be due to an increase in NEFA concentrations.