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GROWTH HORMONE SECRETION IN HEALTHY CHILDREN IS NOT A MAJOR DETERMINANT OF BODY COMPOSITION MEASURED AS BIOELECTRICAL IMPEDANCE.

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Bioelectric Impedance (BIA) correlates with anthropometric methods as well as other methods to estimate body composition in humans. In children BIA has mainly been used in nutritional studies, whereas hormonal influences have not been studied. In adults excess and deficiency of GH markedly change the body composition.

**Aim:** The aim of this study was to find out if the variation of GH secretion in children influences their body composition measured as BIA.

**Material and methods:** BIA measurements (n=221) were performed at standardized conditions in 189 children (140 male, 87 prepub/53 pub, 81 female, 31/50) with a mean age of 11.8 (SD 3.5) and range 2.0-19.9 years; mean height SDS of -1.09, range -4.3 to 4.4 and with a mean spontaneous 24h-GH secretion expressed as peak secretion ($AUC_s$) of GH mU/L/24h (range 25-268 mU/L/24h). The children were investigated due to short or tall stature or were normal controls. Only children with severe GH deficiency ($AUC_s$< 25 mU/L) were excluded. The technical error of the BIA measurement was 2%. The BIA measure is expressed as Height$^2$/Resistance ($H^2/R$) or as fat free mass (FFM) calculated by formulas by Deurenberg et al, for prepubertal (Eur-J-Clin-Nutr. 1989:43,623-9) and pubertal children (Eur-J-Clin-Nutr. 1990:44. 261-8).

**Results:** In a multiple regression model, weight followed by sex and pubertal stage were the main determinants of $H^2/R$ (r=0.97) and FFM (r=0.99). Baseline-GH(*) and $AUC_s$(***) add a significant but minor part to the model. All GH parameters where significant for prepubertal boys ($GH_i$(***), $AUC_s$(*), baseline(*)) but not for the other subgroups (pre/pub girls and pub boys).

**Conclusion:** Body composition measured by BIA in healthy children varies with weight, sex and pubertal stage, but only to a minor degree with GH secretion. Therefore the dose response curves of GH are different for growth and metabolic effect, measured by BIA. The relationship in severely GH deficient or hypersecreting children remains to be studied.

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**INSULIN-LIKE GROWTH FACTOR I (IGF-I) INDUCES ACUTE INTRACELLULAR POTASSIUM SHIFT IN PATIENTS WITH LARON DWARFISM.**

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Transient falls in plasma potassium (K) concentration following IGF-I injection have previously been reported. However, the precise mechanism of this effect has never been investigated. To adress this point, 4 prepubertal patients (2 girls, 2 boys, aged 5 to 14 yrs) with Laron dwarfism have been studied. In all patients, treatment with IGF-I had been withdrawn for at least 3 weeks. After an overnight fast, a 30-min urine collection period was performed. Venous blood was drawn (through an indwelling catheter, without a tourniquet) at the mid-point of the period. After subcutaneous injection of IGF-I (provided by KABI Pharmacia, 40µg/kg B.W.), a 3-hr urine collection period was performed during which blood was sampled every 60 min.

| | T-15 | IGF-I | T60 | T120 | T180 |
|---|---|---|---|---|---|
| Plasma K(mM) | 4.47±0.25 | injection | 4.20±0.09 | 3.79±0.13* | 3.72±0.29* |
| UrineK/Urine Cr (mM/mM) | 22.2±8.5 | | | | 14.9±5.2 |
| IGF-1 (ng/ml) | 21.3±3.0 | | | | 229.5±61.9** |

* p<0.05, **p<0.01

There was no significant change in venous pH, plasma bicarbonate, plasma cortisol, plasma glucose, plasma insulin, and plasma glucagon concentrations. Plasma norepinephrine concentration remained stable all over the study, whereas plasma epinephrine and plasma aldosterone concentrations increased in 2 patients but remained stable in the 2 others. We conclude that: 1) IGF-I induces a steep decrease in plasma K concentration in patients with Laron dwarfism 2) the decrease in plasma K concentration is due to an acute intracellular K shift, since urinary K excretion did not increase 3) the IGF-I induced K shift occurs despite no significant change in the known determinants of transcellular K movements, suggesting that intracellular K shift is a direct effect of IGF-I.

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PREDICTORS OF FINAL HEIGHT (FH) AFTER GROWTH HORMONE (GH) THERAPY IN PERIPUBERTAL SHORT CHILDREN.

Seventy three peripubertal children (49 M, 24F) were studied. Height was <2 SD for age and gender, growth velocity was <4.5 cm/year, bone age was more than 2 SD below mean for age and GH response to provocative tests (PT) was <10 mcg/L in 12 children (group GHD). PT was >10 mcg/L in 61 children of which 31 subjects (group T) were treated with GH 0.75 u/kg/week for 2-5 years, until FH was attained. 20 (group C) were untreated children who were followed until cessation of growth and served as controls. The Tanner-Whitehouse (TW) and the Bayley-Pinneau (BP) predictions (in SDS) were highly correlated with FH in treated groups (r=0.747 and r=0.646, p<0.02). The TW and BP methods over estimated FH in treated groups by 3.6 and 3 cm. The untreated group was shorter by 0.7 SDS than the treated groups. Neither pretreatment height velocity nor GH measurements by physiologic or pharmacologic tests were correlated with FH. The main effect of GH was observed during the first year of treatment in group T when height velocity was significantly higher in the than in the untreated (9.3±2.1 vs 5.3±1.1 respectively, p<0.001) FH of group G and T were similar. The high cost of the treatment in group T should be weighted against the results.

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COMPARATIVE STUDY OF GROWTH HORMONE (GH) IMMUNOGENICITY IN NORMAL VARIANT SHORT CHILDREN.

The immunogenicity of 3 recombinant GH preparations used to treat 117 children have been compared. Children were 4-12 years of age, 70 M, 47 F. Height <2 SD for age and gender, height velocity <4.5 cm/year and bone age delay > 2 SD for age. Fifteen children were with chronic renal failure, and 102 with growth failure without known etiology. GH response to provoc-ative tests in all children were > 10 mcg/L. The children were treated with Bio-Tropin (Bio-Technology General, Israel ;n=55, 6 years), Norditropin (Novo-Nordisk, Denmark; n=62 ,3-4 yrs) and Saizen (serono; n=8, 0.9-1 year). For the detection of anti GH anti-bodies (ab), a double antibody immunoassay was utilized. Thirty of the samples were analyzed by two different laboratories. Non of the patients developed anti GH ab. It is concluded that in contrast to the past experience where the detection of anti GH ab in children treated with different brands of authentic GH was frequent, the degree of purity of contemporary preparations prevents development of anti GH ab.

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ARE HEIGHTS AND WEIGHTS NORMALLY DISTRIBUTED ?

We measured heights and weights of 5056 children, from birth to 18 years of age, in the vicinity served by our hospital. On all children body mass index (BMI) was calculated (Kg/m$^2$) . Children younger than 3 years of age were measured in the recumbent position, older children were measured by an upright portable harpenden stadiometer. All children were measured barefoot with light under-wear. Ages in children younger than 2 years were calculated in 3 months intervals, in older children the age was calculated in yearly intervals. Heights were normally distributed in both sexes in all age groups. Weights were normally distributed up to the age of 6. In children older than 6, skewness to the right in weights was noted in both sexes. Log transformation of weight data in children older than 6 years of age gave a normal distribution. BMI best fitted with a 4th degree polynom, were BMI decreased progressively up to the age of 6 and increased progressively thereafter. It is possible that the skewness to the right of weight measurements can be explained by environmental factors like food consumption habits in a society in which under-nutrition is rare and overfeeding is a problem. This can also explain the progressive increase in BMI which can be as a result of a greater increase in weight gain as compared to height gain.

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**PRETREATMENT $^{15}$N-RETENTION TEST ($^{15}$N-T), BUT NOT IGF 1-GENERATION TEST (IGF 1-GT) DIFFERENTIATES BETWEEN COMPLETE AND PARTIAL GROWTH HORMONE DEFICIENCY.**

$^{15}$N-T and IGF 1-GT were studied by correlating shortterm effects to subsequent growth velocity (GV) during therapy. **Methods:** Nitrogen excretion using the stable isotope $^{15}$N and IGF 1 were measured before and after 2 IU rHGH/m$^2$ BW s.c. on 3 consecutive days in patients with complete growth hormone deficiency (cGHD, n=17), partial GHD (pGHD,n=16) and normal variant short stature (NVSS,n=18). Only cGHD and pGHD patients were treated for 1 year with rHGH (12 IU/m$^2$xwk). Before treatment there were no significant differences in auxological data between the 3 groups; $^{15}$N-T, IGF 1-GT and growth velocity (GV) were compared with GV in the subsequent year either with rHGH-therapy (cGHD and pGHD) or without (NVSS). $^{15}$N-excretion was measured by isotope masspectrometry. IGF 1 was determined by a RIA after extraction. **Results:** The effect of rHGH-administration on the $^{15}$N-T differed significantly between the 3 groups. The best response (143±6,9% $^{15}$N-retention) was seen in the cGHD group, while 130,1±16,4% (p<0,001) in the pGHD and 108,9±6,4% (p<0,001)in the NVSS group were reached. The IGF 1-GT did not show any differences between the three groups of patients. After 1 year of rHGH therapy GV was 11,3±3 cm/a in the cGHD and 7,6±2,2 cm/a in the pHGH group. The GV in the untreated NVSS patients was significantly lower (4,2±1,7 cm/a) compared to the cGHD (p<0,001) and the pGHD (p<0,001) patients. The $^{15}$N-T can discriminate between patients with complete and partial GHD and patients with short stature after only 3 injections of rHGH. A correlation between $^{15}$N-T and GV after 1 year of rHGH treatment was seen in the pGHD group (r=0,87). IGF 1-GT as well GV before treatment were not suitable to predict growth hormone response in any group. **Conclusions:** In this study the $^{15}$N-T was reliable in differentiating the 3 groups of patients and in predicting the response to growth hormone treatment in patients with pGHD.