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Effects of Growth Hormone and Nutritional Therapy in Boys with Constitutional Growth Delay: A Randomized Controlled Trial

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Abstract

Objective—To examine whether supplemental nutrition augments the anabolic actions of growth hormone (GH) in boys with constitutional delay of growth and maturation (CDGM).

Study design—We conducted a randomized, controlled trial at an outpatient clinical research center. Subjects were 20 prepubertal boys (age 9.3 ± 1.3 y) with CDGM (height-SDS -2.0 ± 0.5 , bone age delay 1.8 ± 0.8 y, BMI-SDS -1.2 ± 1.0 , peak stimulated GH 15.7 ± 7.7 ng/mL), who were randomized (N=10/group) to 6 months observation or daily nutritional supplementation, followed by additional daily GH therapy in all for another 12 months. T-tests and repeated measures ANOVAs compared energy intake, total energy expenditure (TEE), growth, hormones and nutrition markers.

Results—Energy intake was increased at 6 months within the Nutrition ($p=0.04$) but not the Observation group, and TEE was not statistically different within either group at 6 months. Addition of 6 months GH resulted in higher energy intake and TEE in the GH/Nutrition group at 12 months ($p<0.01$), but not in the GH group vs. baseline. Height, weight, lean body mass, hormones and nutrition markers increased comparably in both groups throughout 18 months.

Conclusions—Boys with CDGM utilize energy at an accelerated rate, an imbalance not overcome with added nutrition. GH therapy increases growth comparably with or without added nutrition in these patients.

Keywords

growth hormone; nutrition; short stature; constitutional delay of growth and maturation; delayed puberty; energy expenditure; doubly-labeled water method; body composition; pediatrics

Constitutional delay of growth and maturation (CDGM) is a condition of short stature and delayed skeletal maturation in an otherwise healthy child. Idiopathic short stature, on the other hand, represents a heterogeneous group of disorders of significant shortness where no underlying etiology has been found, although many may end up having defects in the GH/

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IGF-I/IGF-I receptor cascade yet to be identified [1]. The underlying mechanism of CDGM is likely multifactorial, but several observations point to an intrinsic imbalance between energy intake and expenditure as a possible contributing factor. Youngsters with CDGM are typically thin, often have delayed onset of puberty, and exhibit a growth pattern that is similar to that of malnourished children in impoverished environments [2-5]. Using doubly labeled water, we have reported that boys with CDGM display increased total energy expenditure (TEE) per kg fat-free mass (FFM) compared with age-matched, taller boys and height-matched, younger boys, suggesting a state of hypermetabolism which may be hindering growth [6].

CDGM is generally considered a variant of normal development, frequently accompanied by a family history of other “late bloomers,” and therefore, routine care typically consists of reassurance and observation. However, some potential adverse associations that have been observed with CDGM include diminution in adult height that is often shorter than the mid-parental target [7-9], negative psychosocial effects (though true psychopathology is rare) [10-11], and reduction in peak bone mass [12-14]. Androgens, growth hormone, and aromatase inhibitors can be used to accelerate growth and pubertal development in boys with CDGM [15-16], and can potentially improve final adult height. However, none of these therapies specifically address the underlying etiology for the poor linear and ponderal growth of CDGM, and it should be noted that only GH is FDA-approved for the treatment of short stature; the use of androgens and aromatase inhibitors to augment adult height is still considered investigational.

Based on our previous findings of a significantly increased rate of TEE in boys with CDGM [6], we conducted a randomized clinical trial to investigate whether dietary supplementation in boys with CDGM improves growth better than GH alone. We also studied whether dietary supplementation in boys with CDGM alters biochemical mediators of satiety and glucose metabolism. This was a considered secondary outcome. We hypothesized the nutritional supplementation would improve linear and ponderal growth compared with observation, and that nutrition would augment the anabolic effects of GH compared with GH alone.

Methods

The protocol was approved by the Nemours Clinical Research Review Committee and the Institutional Review Board of Baptist Medical Center/Wolfson Children's Hospital. Informed written consent from the parents/guardians and assent from the boys were obtained. The study was registered in Clinicaltrials.gov (NCT00102258).

We enrolled 20 boys from among patients seen at the Pediatric Endocrine Clinics in Jacksonville, Florida who met the following inclusion criteria: age 7-11y, genital Tanner stage 1, significant short stature (height ≤ -2 SDS or predicted adult height (PAH) > 2 SD below mid-parental target height), bone age ≤ 10 years and delayed by ≥ 1 year, with an otherwise normal physical exam. Our study was limited to males because of the higher prevalence of boys referred to our clinic for evaluation of short stature, a reflection of referral bias, similar to other pediatric endocrine centers.[2] Height criterion of short current stature or short predicted adult stature was used because of intention to treat all subjects with GH. To ensure that subjects did not have GH deficiency, all subjects had to have normal GH responses to stimulation with standard secretagogues (arginine/L-DOPA). All other forms of endocrinopathies and other disorders impairing growth were excluded, including chronic illnesses, and skeletal dysplasias. We also excluded children participating in highly competitive endurance sports activities. Subjects who were receiving medications for

attention deficit hyperactivity disorder (ADHD) were required to maintain the same dosages in the 6 months prior to the study and for the entire 18-month duration of the study.

Each boy was randomized to either observation or aggressive nutritional supplementation for 6 months. After 6 months, GH therapy was initiated in all subjects in both arms of the study and continued for a total of 12 months. Subjects who had been randomized to the nutrition group, continued nutritional supplementation for the full 18 months.

Interventions

Nutritional Supplementation—Liquid nutrition supplement (PediaSure[®], provided by Ross Laboratories, 237 kcal and 7g protein/8 oz can) was dosed to achieve a total daily energy intake of 110% recommended daily allowance (RDA) adjusted for catch-up growth based on the subject's ideal body weight (50th percentile weight-for-height) [17]. This dose of nutritional supplementation was empirically chosen based on typical nutritional counseling at our institution; the dose of the liquid supplement was subsequently adjusted for each subject based on weight measurements in the clinic at 2 and 4wk, and monthly thereafter, and repeated dietary intake assessment at 6 and 12 months to maintain total intake of regular diet plus additional liquid supplement at 110% RDA. Subjects in the observation group were monitored with equal frequency but received no extra nutritional intervention. Compliance was monitored by empty cans reports and review of 3-day dietary records.

GH Therapy—GH was dosed at 0.3mg/kg/wk administered subcutaneously once daily (Nutropin AQ[®], kindly provided by Genentech, So. San Francisco).

Anthropometric and body composition measures

Weight was measured in subjects wearing light clothing using a digital scale at baseline, 2wk, 4wk, and monthly thereafter for 18 months. Height was measured in triplicate between 08:00 and 10:00 using the same Harpenden stadiometer in all subjects at baseline, 3, 6, 9, 12, 15, and 18 months. Short-term height velocity was calculated as change in height over a 3-month interval. Skeletal age was interpreted [18] by a single blinded pediatric endocrinologist and predicted adult height calculated [19] at baseline, 6, 12, and 18 months. Body composition was assessed by dual energy X-ray absorptiometry (DEXA) using a Hologic Discovery A (S/N 45903) instrument (Waltham, MA).

Assays

At baseline, 6, 12, and 18 months, blood samples were obtained for measurement of IGF-1, IGFBP-3, pre-albumin, transferrin, acylated (active) ghrelin, fasting insulin, glucose, and lipid profile. Hormones and growth factors were measured by RIA, using commercial kits; pre-albumin, lipids, and transferrin were measured commercially using automated analyzers. All samples were assayed in triplicate at the Nemours Biomedical Research Laboratory in Jacksonville, Florida. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as $[\text{glucose (mmol/L)} \times \text{insulin (mU/L)}] \div 22.5$ [20].

Doubly-labeled water (DLW) for total energy expenditure (TEE) assessment

TEE was measured at baseline, 6, and 12 months using DLW as previously described [6]. Stable isotopes were purchased through Cambridge Isotope Laboratories, Andover, MA, and were orally administered at a dose of 0.15g/kg body weight of H₂¹⁸O, containing 10% atoms percent excess of ¹⁸O, and 0.3g/kg of ²H₂O (99.9% enriched). Periodic urine samples were collected by subjects at home over the next 10 days. Samples were stored at -20°C in sealed vacutainer tubes until analysis. Isotope enrichment was determined by isotope ratio mass spectrometry (IRMS, Europa) and TEE calculated as previously described [6].

Dietary records

Nutritional intake was assessed at baseline, 6, and 12 months using 3-day dietary records. Total energy intake and macro- and micronutrient compositions were analyzed by a research dietician using nutrition software (Food Processor 7.8, Esha Research, Salem, Oregon). The average of all three days of the dietary log was used for calculations.

Statistical Analyses

Our primary outcome was to measure the changes in linear growth and lean body mass (LBM) accrual at 6 and 12 months. A secondary outcome was the change in these same measures at 18 months. Changes in TEE, ghrelin, insulin, and IGF-1 concentrations were also secondary outcomes.

Based on estimated expected changes in height-SDS and growth velocity in previous studies [21] a sample size of 10 subjects in each group was calculated to have >90% power to detect differences between the groups in height-SDS and LBM. Nonparametric tests were performed if skewed data could not be normalized by log-transformation. The Observation and Nutrition groups were compared using independent samples T-test or Mann-Whitney U-test for differences in baseline characteristics, and using repeated measures analysis of variance (ANOVA) for differences in outcome measures over time. Within each group, changes in outcome measures over time were assessed with repeated measures ANOVA or associated samples Friedman test, followed by post-hoc paired T-test or Wilcoxon signed ranks for comparison with baseline values. Energy intake and TEE were adjusted for LBM for all analyses. When Bonferroni correction for multiple comparisons was applied, p-values of <0.006 are considered for statistical significance, and p-values <0.05 are considered only for nominal significance. Data are shown as mean $\pm$ SEM with nominal p-values unless otherwise indicated.

Results

We enrolled twenty subjects, all of whom completed the full 18 months study. Baseline characteristics were similar between the Observation and Nutrition groups (Table I). Two subjects in the Nutrition group were receiving stimulant medication for ADHD at a constant dose throughout the study. All remained Tanner stage 1 throughout the study.

At baseline, the boys in the Nutrition group were prescribed, on average, 10.4 ± 2.5 oz nutritional supplement daily (i.e., energy 13.4 kcal/kg-d and protein 0.4 g/kg-d), with subsequent adjustments based on individual weight and energy needs (6 months: 16.8 ± 2.0 oz/day; 12 months: 20.0 ± 1.9 oz/day; 18 months: 22.0 ± 2.1 oz/day). Overall compliance, as estimated by counting empty cans, was $94 \pm 4\%$, $87 \pm 6\%$, and $79 \pm 5\%$ consumption of prescribed nutritional supplement at 6, 12, and 18 months, respectively, with 18-month average of $87 \pm 5\%$. The Nutrition group had increased daily energy intake at 6 and 12 months as compared with baseline (baseline: 1584 ± 107 kcal; 6 months: 1913 ± 125 kcal, $p=0.02$ vs. baseline; 12 months: 2212 ± 122 kcal, $p<0.001$ vs. baseline), whereas the Observation group had no significant change over time (baseline: 1732 ± 137 kcal; 6 months: 1748 ± 125 kcal, $p=0.93$ vs. baseline; 12 months: 2036 ± 111 kcal, $p<0.09$ vs. baseline). Daily energy intake adjusted for LBM increased over time within the Nutrition group but not the Observation group (Figure 1, A).

Doubly labeled water was given and isotopic enrichments in the urine for ^{18}O and ^2H were measured and used to calculate TEE at baseline, 6 and 12 months. The Nutrition group had increased TEE at 6 and 12 months as compared with baseline when expressed as total kcal (baseline: 2064 ± 64 kcal; 6 months: 2304 ± 88 kcal, $p<0.01$ vs. baseline; 12 months: 2555 ± 161 kcal, $p<0.01$ vs. baseline). TEE adjusted for LBM was not significantly higher at 6

months in the Nutrition group; the difference reached statistical significance at 12 months (Figure 1, B). The Observation group had higher TEE at 12 months compared with baseline (baseline 2341 ± 157 kcal; 6 months: 2384 ± 167 kcal, $p=0.78$ vs. baseline; 12 months: 2623 ± 115 kcal, $p=0.03$ vs. baseline), but no significant change in TEE adjusted for LBM at any time points (Figure 1, B).

There were no consistent differences between the groups in the hormonal and nutritional data gathered. IGF-1 concentration was higher compared with baseline at 12 months and 18 months within both groups in response to GH therapy ($p<0.05$, Table II), with no difference between groups over time ($p=0.94$), indicating no additional increase in IGF-1 due to nutritional supplementation. Transferrin was higher compared with baseline at 12 months within only the Observation group ($p<0.01$), and there was no significant difference between groups over time ($p=0.38$). HOMA-IR was significantly higher at 12 months within the Observation group ($p<0.05$), but there was no significant difference between groups over time ($p=0.46$). IGFBP-3, pre-albumin, and ghrelin (Table II), and lipid concentrations (data not shown) were unchanged within groups and not different between groups over time.

Height-SDS and weight-SDS were similar to baseline at 6 months within both groups and significantly higher compared with baseline at 12 months and 18 months within both groups, with no difference between groups (Figure 2). Growth velocity increased comparably in both groups after 6 months of either nutrition or observation [Observation vs. Nutrition (change in growth velocity compared with baseline): $+1.30 \pm 1.15$ vs. $+1.22 \pm 0.58$ cm/yr ($p=0.95$)] and after additional treatment with 12 months of GH therapy [$+4.13 \pm 0.83$ vs. $+4.92 \pm 0.90$ cm/yr ($p=0.52$)]. Lean body mass accrual was also comparable between both groups after 6 months of either nutrition or observation [Observation vs. Nutrition (change in LBM compared with baseline): $+0.86 \pm 0.22$ vs. $+0.96 \pm 0.20$ kg ($p=0.73$)], and after additional treatment with 12 months of GH therapy [$+5.68 \pm 0.43$ vs. $+5.34 \pm 0.65$ kg ($p=0.67$)].

Discussion

In this study, in subjects who received supplements, total daily energy intake increased, but total energy expenditure with time increased also. Thus, nutritional supplementation alone was not associated with greater benefits in height-SDS, weight-SDS, lean body mass accrual, or growth velocity compared with the observation group. Furthermore, combining nutritional supplementation with GH therapy was not associated with improved linear or ponderal growth compared with GH therapy alone.

Children with CDGM are short, grow poorly (particularly prior to puberty), tend to be thin, and seem to utilize energy at an accelerated pace. The use of the doubly labeled water method allows the calculation of total energy expenditure under free-living conditions with minimal intrusion to daily activities, making it ideally suited for studies in children. Using this technique and indirect calorimetry to assess resting energy expenditure, we had previously reported similar resting metabolic rate in boys with CDGM compared with age- and size-matched controls, but much higher TEE in those with CDGM [6]. Underlying differences in metabolic pathways of substrate utilization (e.g., mitochondrial uncoupling proteins and homologues [22-24] or increase in non-exercise activity thermogenesis (NEAT) [25], may explain these differences in TEE. We hypothesize that a similar increase in TEE may have occurred in the subjects reported here who received added nutrition, essentially canceling any putative benefit of the added nutrition on growth. We had previously studied the effects of combined nutritional supplements (glutamine – a non-essential amino acid) alone and in combination with GH in another condition of relative under nutrition, children with cystic fibrosis, on rates of whole body protein synthesis [26]. Although the metabolic

tools used were different, we also observed in this previous study that the combination of supplemental nutrition and GH was not any better at enhancing protein synthesis rates than GH alone. It is possible that the potent anabolic actions of GH override any added benefit from nutrition supplementation, although a dose effect of much higher nutrition supplementation cannot be excluded.

Compliance among our subjects was very good with estimated intake of 87% of prescribed supplemental calories. However, it is possible that the subjects may have compensated for the additional calories by downregulating intake at other times during the day, a phenomenon that would reflect energy homeostatic mechanisms observed in normal children and adults [27-31]. An imbalance between energy intake and utilization likely contributes to the spectrum of failure-to-thrive [32] and obesity [29]. Although energy intake increased within the Nutrition group, there was no difference between the group Nutrition and Observation groups with regard to energy intake over time, suggesting that the frequent clinical visits with weight assessments in the Observation group and the subsequent initiation of GH therapy may have diminished differences between the groups. Still, the findings of this study are clinically meaningful, as the subjects had high compliance with aggressive nutritional therapy (on average, >2 cans of nutritional supplement each day for 18 months) – whether this failed due to lack of increased total intake or because increased nutrition does not affect growth in boys with CDGM may not be ascertainable from this study. Inpatient admission to a metabolic unit to ensure increased total daily intake would be the only way to address this question, but such an approach would not be practical from either a research or clinical standpoint. Because only prepubertal boys were studied, the diagnosis of CDGM was based on delayed skeletal maturation rather than delayed puberty; we would anticipate, but cannot be certain, that their entry into puberty will be delayed. Furthermore, whether supplemental nutrition might promote peripubertal growth in contrast with prepubertal growth was not addressed by this study. However, the findings of this study would suggest that in the absence of true nutritional deficiency, supplemental nutrition would not be expected to be a particularly effective strategy to promote linear growth.

There were no quantifiable differences in a host of nutritional and hormonal measures over time between the 2 groups, despite the additional nutrition supplements, suggestive that at least at this level of extra supplement, these excess calories were not enough to alter these markers significantly, especially IGF-1, the ultimate mediator of linear growth, which is both GH- and nutrition-dependent. Of note, this is a preliminary study and the original study design was powered to assess the primary outcome measures, height-SDS and lean body mass accrual. However, examination of our findings indicates that our sample size permitted 80% power to detect an increase in IGF-1 of 150 ng/mL at a one-tailed significance of 5%. Such a difference is the equivalent of less than half the effect observed with GH therapy in our study. Thus, although our study may have not been designed to detect small differences in IGF-1 in response to nutrition, it was adequately powered to detect clinically significant changes in IGF-1, *i.e.*, increases typically associated with improved growth.

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Abbreviations

GH	growth hormone
CDGM	constitutional delay of growth and maturation
SDS	standard deviation score
BMI	body mass index
TEE	total energy expenditure
ANOVA	analysis of variance
LBM	lean body mass
FFM	fat-free mass
y	year
wk	week
d	day
PAH	predicted adult height
ADHD	attention deficit hyperactivity disorder
L-DOPA	levo-dihydroxyphenylalanine

RDA	recommended daily allowance
DEXA	dual energy X-ray absorptiometry
RIA	radioimmunoassay
HOMA-IR	homeostasis model assessment of insulin resistance
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
DLW	doubly-labeled water
kcal	kilocalories
oz	ounce
NEAT	non-exercise activity thermogenesis

Figure 1.

Energy intake and total energy expenditure (TEE) adjusted for lean body mass (LBM). Mean $\pm$ SEM shown. P-values are shown for comparisons with baseline within each group. White bars = Observation group. Black bars = Nutrition group. (a) Liquid nutritional supplement was administered to the Nutrition group after the baseline visit and continued throughout the study. GH was added to both groups starting at 6 months. Energy intake adjusted for LBM increased within the Nutrition group in response to liquid nutrition supplementation alone and in combination with growth hormone therapy. P-values between groups NS. (b) TEE was assessed by the doubly-labeled water method and adjusted for lean body mass as assessed by DEXA. TEE adjusted for LBM trended higher in the Nutrition group in response to 6 months of liquid nutritional supplement, and was significantly higher after 6 months of GH combined with liquid nutritional supplement.

Figure 2.

Changes in growth parameters. Comparison between Observation and Nutrition groups for height-SDS (a) and weight-SDS (b). Mean $\pm$ SEM shown. White bars = Observation group. Black bars = Nutrition group. Symbols next to bars represent p-values for comparisons with baseline within each group (* = $p < 0.001$). Comparisons between groups at each time point are shown as p-values above the brackets over the bars.

Table 1
Baseline clinical characteristics of study subjects

	Observation (N=10)	Nutrition (N=10)
Age (y)	9.6 ± 1.0	9.0 ± 1.6
Bone age (y)	8.0 ± 1.6	7.0 ± 0.5
Height (cm)	123.5 ± 5.0	121.6 ± 9.7
Height-SDS	-2.1 ± 0.4	-2.0 ± 0.6
Height-SDS range	-3.0 to -1.5	-3.1 to -0.9
Height velocity (cm/yr)	3.8 ± 3.1	5.6 ± 2.6
Height velocity SDS range	-7.0 to 4.8	-6.1 to 4.1
Weight (kg)	23.1 ± 2.5	21.4 ± 4.4
BMI (kg/m²)	15.1 ± 0.9	14.3 ± 1.3
BMI-SDS	-0.9 ± 0.7	-1.6 ± 1.2
BMI-SDS range	-1.9 to 0.1	-3.9 to 0.1
Body fat (%)	19.7 ± 3.3	19.9 ± 3.2
Peak GH (ng/mL)	13.5 ± 6.5	17.8 ± 8.6

Data expressed as mean ± SD. P-values between groups NS.

Table 2
Hormonal and nutritional markers in the Observation and Nutrition groups

	Observation (N=10)				Nutrition (N=10)			
	0mo	6mo	12mo	18mo	0mo	6mo	12mo	18mo
IGF-1 (ng/mL)	187 ± 41	252 ± 46	666 ± 178 [#]	638 ± 154 [#]	180 ± 45	326 ± 93	788 ± 181 [†]	605 ± 124 [*]
IGFBP-3 (mg/L)	2.1 ± 0.3	2.8 ± 0.3	3.8 ± 0.6	4.3 ± 0.6	2.7 ± 0.5	2.7 ± 0.6	2.7 ± 0.7	2.5 ± 0.6
Precalalbumin (mg/dL)	18.5 ± 0.8	19.2 ± 0.7	21.2 ± 1.2	19.8 ± 0.95	18.3 ± 0.9	19.8 ± 0.9	20.0 ± 1.0	21.9 ± 1.2
Transferrin (mg/dL)	269 ± 9	270 ± 8	301 ± 9 [†]	283 ± 5	279 ± 14	294 ± 11	311 ± 9	298 ± 14
Ghrelin (pg/mL)	90 ± 15	84 ± 20	83 ± 8	139 ± 40	73 ± 16	175 ± 64	144 ± 36	128 ± 53
HOMA-IR (mU•mmol/L ²)	1.30 ± 0.26	1.82 ± 0.14	3.14 ± 0.57 [#]	2.81 ± 0.49	1.65 ± 0.35	1.37 ± 0.26	2.79 ± 0.71	2.34 ± 0.56

Mean ± SEM shown.

P-values between groups NS.

Symbols in table represent p-values for comparisons with baseline within each group after Bonferroni correction for multiple comparisons (

[#] p<0.05,

[†] p<0.01,

^{*} p<0.001).

SI unit conversion factors: IGF-1 (ng/mL) × 0.1307 to obtain nmol/L; IGFBP-3 (mg/L) × 0.0348 to obtain nmol/L; pre-albumin (mg/dL) × 10 to obtain mg/L; transferrin (mg/dL) × 0.01 to obtain g/L; ghrelin (pg/mL) × 3.371 to obtain pmol/L.