

# Growth Hormone Suppression after an Oral Glucose Load in Children

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**Background:** GH nonsuppression after oral glucose is diagnostic for GH excess, but normative data are lacking in children. Adult data cannot be extrapolated to children given the pubertal increase in GH concentration. In addition, because GH levels are higher in pubertal girls than boys, nadir GH may differ across gender.

**Objective:** Our objective was to determine whether nadir GH during an oral glucose tolerance test (OGTT) is gender and pubertal stage specific. We hypothesized that nadir GH would be higher in girls, and at the pubertal stage known to correspond with peak height velocity (Tanner 2–3 in girls and Tanner 3–4 in boys) and maximal GH concentrations.

**Subjects/ Methods:** A 2-h OGTT using 2.35 g/kg oral glucose (maximum 100 g) was performed in 64 girls and 43 boys, 9–17 yr (10th–90th

percentiles for body mass index). Girls were grouped as group 1 (Tanner 1), group 2 (Tanner 2–3), and group 3 (Tanner 4–5), and boys as group 1 (Tanner 1–2), group 2 (Tanner 3–4), and group 3 (Tanner 5).

**Results:** Nadir GH was higher in girls than boys, and in group 2 girls and boys than the other two groups. The upper limit for nadir GH was highest in group 2 girls (1.57 ng/ml), and lower for the other two groups of girls (0.64 ng/ml), and for boys (0.50 ng/ml). All but one girl, and all boys suppressed to less than 1.0 ng/ml. There were 16 girls and five boys who had a nadir GH of more than 0.3 ng/ml.

**Conclusion:** GH suppression after oral glucose is gender and pubertal stage specific. (*J Clin Endocrinol Metab* 92: 4623–4629, 2007)

GH SUPPRESSION AFTER a 100-g oral glucose tolerance test (OGTT) is a standard test for diagnosing GH excess in adults, but normative data are lacking in children. Although studies in adults using older RIAs determined that a normal glucose suppressed GH was less than 2 ng/ml, newer more sensitive assays have consistently reported lower cutoffs (1). The criterion now used for diagnosing GH excess in adults is a nadir GH of less than 1 ng/ml using immunoradiometric assays (IRMAs), with maximum suppression occurring at approximately 60 min. Recent studies using more sensitive assays have demonstrated GH suppression to even lower levels during an OGTT (2, 3), and investigators have suggested that the cutoff for GH suppression using very sensitive assays may be as low as 0.3 ng/ml in adults (4, 5). In addition to the sensitivity of the various GH assays, their calibration has been an ongoing issue (6, 7).

Studies examining GH suppression after oral glucose in children have reported a cutoff for normal GH suppression of 5 ng/ml using older RIA techniques, which had higher limits of detection than the more sensitive, currently used IRMAs (8). One study has since suggested that in tall children, GH suppression with 75-g oral glucose may be less than in adults, and reported nadir GH levels of  $2.1 \pm 0.3$  ng/ml

using an IRMA (9). In a small study, we observed that after 100-g oral glucose, GH (measured using an IRMA) suppressed to less than 1.5 ng/ml in healthy pubertal girls (10). However, this study was limited to girls and did not have sufficient numbers to group by pubertal stage.

Although GH secretion is age and gender dependent, normative data using sensitive assays for GH suppression with oral glucose do not exist for healthy children and adolescents. Importantly, despite the well-recognized pubertal increase in GH secretion, GH suppressibility at different pubertal stages has not been established. In normal children, GH and IGF-I levels begin to increase in early puberty, and peak 1 yr after peak height velocity, after which levels begin to decline and reach adult levels toward the end of puberty (11, 12). Peak height velocity occurs at different pubertal stages in girls (Tanner stages 2–3) vs. boys (Tanner stages 3–4) (13, 14), and GH also peaks at different Tanner stages. GH concentrations start to increase in girls at Tanner 2 and peak at Tanner 3 (15), whereas in boys, GH begins to increase at Tanner 3 and peak at Tanner 4 (16) [or a testicular volume of 10–15 ml (15)]. Adolescent girls with higher nocturnal GH secretion have a higher nadir GH after oral glucose than girls with lower nocturnal GH, although absolute decreases in GH concentrations do not differ (10). This suggests that individuals with higher GH concentrations during puberty may not suppress below a standard cutoff, and, therefore, gender and pubertal stage-specific standards for GH suppression with oral glucose need to be established. In addition, because GH levels are higher in pubertal children than adults, adult data cannot be extrapolated to children.

Therefore, it is critical to determine GH suppressibility in

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Abbreviations: AUC, Area under the curve; BMI, body mass index; IRMA, immunoradiometric assay; MGH, Massachusetts General Hospital; OGTT, oral glucose tolerance test; SDS, sd score; U/L, upper to lower segment ratio; WHR, waist to hip ratio.

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normal children based on pubertal stage and gender using sensitive GH assays. We hypothesized that GH suppressibility changes with pubertal timing in a gender-specific manner, such that nadir GH is: 1) higher in girls than boys, and 2) highest at the pubertal stage known to correspond to peak height velocity and maximal GH concentrations.

## Subjects and Methods

### Subject selection

Subjects were between 9 and 17 yr old with body mass index (BMI) between the 10th–90th percentiles for age. We recruited 43 boys and 64 girls across the five Tanner stages for a total of 107 eligible subjects: six boys and seven girls in Tanner stage 1, 11 boys and eight girls in Tanner 2, five boys and eight girls in Tanner 3, eight boys and 12 girls in Tanner 4, and 13 boys and 29 girls in Tanner 5. There was no overlap between these subjects and those from our initial pilot study (10). Subjects were excluded if: 1) they had diseases affecting glucose and GH metabolism, such as thyroid or pituitary disorders, Cushing's syndrome, diabetes mellitus, or renal failure; or 2) had taken medications known to affect glucose and GH metabolism within 3 months of the study, such as estrogen or thyroid supplements. Subjects were recruited from pediatric practices at Massachusetts General Hospital (MGH), MGH-affiliated health care centers, and community practices using mass mailing and fliers. The study was approved by our institutional review board, and informed consent and assent were obtained from parents and subjects based on institutional guidelines.

### Experimental protocol

A history and physical examination, including Tanner staging, were performed to determine eligibility. Breast staging for girls and genital staging for boys were used. Testicular volume was measured in boys using a Prader orchidometer; overall testicular volume no greater than 3 ml corresponded to Tanner 1, volume 4–6 ml to Tanner 2, volume greater than 6 ml to 12 ml to Tanner 3, volume greater than 12 ml to 15 ml to Tanner 4, and volume greater than 15 ml to Tanner 5. Staging by pubic hair was also performed. Tanner staging was performed by two pediatric endocrinologists, and agreement between their findings assessed and confirmed in 30 children before study initiation. Eligible subjects were studied at a single outpatient visit to the MGH General Clinical Research Center. Postmenarchal girls were examined during the early follicular phase of their menstrual cycles because GH levels fluctuate across the menstrual cycle (17). A subset of 66 subjects had measurements of upper to lower segment ratio (U/L) and waist to hip ratio (WHR), and 54 had percent body fat and the ratio of trunk to extremity fat assessed by dual-energy x-ray absorptiometry (Hologic 4500; Hologic, Inc., Waltham, MA).

A solution of glucose (2.35 g/kg up to a maximum of 100 g) was administered orally over 10 min. A maximum glucose load of 100 g was used based on standard dosing in adults to assess GH suppression. Blood samples were drawn fasting at baseline and 30, 60, 90, and 120 min after glucose administration for glucose, insulin, and GH. Bone age was estimated using left hand and wrist x-rays by a single pediatric endocrinologist blinded to the study group but not gender (18). Pregnancy was excluded in girls using a urine human chorionic gonadotropin test.

Grouping by pubertal stage was based on expected timing of peak height velocity. In girls, peak growth velocity typically occurs at Tanner stages 2–3 (mean age 11.5 yr), whereas in boys this occurs at Tanner 3–4 (mean age 13.5 yr) (13). GH peaks at Tanner 3 in girls (15), and highest GH levels have been reported at Tanner 4 or a testicular volume of 10–15 ml in boys (13, 16). Thus, girls were grouped as follows: prepubertal, group 1; early to midpubertal, group 2 (Tanner 2–3); and mid to late pubertal, group 3 (Tanner 4–5). Boys were grouped as follows: pre- and early pubertal, group 1 (Tanner 1–2); midpubertal, group 2 (Tanner 3–4); and late pubertal, group 3 (Tanner 5). Recruitment was aimed at enrolling equal numbers of subjects in the different pubertal stages. However, at the end of the study, we had recruited seven, 16, and 41 girls, and 19, 11, and 13 boys in groups 1, 2, and 3, respectively.

### Biochemical assays

Glucose was measured by the MGH laboratory (12); glucose levels may be converted to millimoles/liter by dividing by 18. We used a RIA to measure insulin (Linco Diagnostics, Inc., St. Charles, MO) [coefficient of variation 4.7–7.7%; detection limit of  $\mu\text{U/ml}$ ] and an IRMA to measure GH (Immulite 2000 Analyzer; Diagnostic Products Corp., Los Angeles, CA) (detection limit 0.01 ng/ml and intraassay coefficient of variation 5.7%). Samples were stored at  $-80^\circ\text{C}$  until analysis, and run in duplicate. We used Cluster to determine area under the curve (AUC) and mean values (13).

### Statistical methods

Data are described as mean  $\pm$  SD. Version 4 of JMP (SAS Institute, Inc., Cary, NC) was used for analysis. We performed natural log transformations for data not normally distributed. The Student *t* test was used for two-group comparisons of means. For three-group comparisons, we used ANOVA, followed by the Tukey-Kramer test to adjust for multiple comparisons. When logarithmic conversions were used, corresponding nontransformed values for the mean and range [(mean  $-$  2 SD) to (mean  $+$  2 SD)] are reported for ease of interpretation. Simple correlational analyses were used to determine predictors of GH concentrations during the OGTT. For data not normally distributed, we used Spearman's correlation. We examined GH suppression between genders and within genders for different pubertal stages.

## Results

### GH suppression in boys

Table 1 shows GH data for boys based on pubertal stage. Midpubertal boys (group 2) had higher log nadir GH than pre- to early pubertal (group 1) and late pubertal (group 3) boys. Log mean and AUC for GH were higher in group 2 than the other groups. Mean testicular volume was 3.5, 12.2, and 20.8 ml in groups 1, 2, and 3, respectively. The magnitude of GH decrease after oral glucose (baseline  $-$  nadir GH) did not differ among groups ( $1.7 \pm 2.6$ ,  $2.1 \pm 3.5$ , and  $0.8 \pm 1.3$  ng/ml in groups 1, 2, and 3, respectively). However, percent GH decrease was higher in group 1 than group 3 (78.4, 61.6, and 50.7% in groups 1, 2, and 3, respectively,  $P = 0.04$ ;  $P < 0.05$  for group 1 *vs.* 3). For boys, baseline GH predicted nadir GH ( $r = 0.66$ ;  $P < 0.0001$ ). Five boys (11.6%) had nadir GH more than 0.3 ng/ml (one in group 1, and two each in groups 2 and 3), only one boy (2.3%) had a nadir GH more than 0.5 ng/ml, and none had levels more than 1.0 ng/ml.

Figure 1 shows glucose and GH levels at different time points of the OGTT. Glucose peaked at 30 min in all groups, whereas GH reached its nadir at 90 min.

When pubic hair staging was used for grouping, similar trends were observed and are not reported. Grouping by chronological age and bone age quartiles or tertiles did not add to the analyses. For bone age quartiles, the mean and range [(mean  $-$  2 SD values) to (mean  $+$  2 SD values)] for nadir GH when transformed back from the natural log scale were as follows: 1) bone ages 9–11.5 yr, 0.11 ng/ml (0.03–0.43); 2) 11.5–13.0 yr, 0.11 ng/ml (0.03–0.40); 3) 13.0–16.0 yr, 0.21 ng/ml (0.07–0.63); and 4) 16.0–19.0 yr, 0.09 ng/ml (0.02–0.37) ( $P = 0.01$ ). Log nadir GH was higher in the third than fourth quartile, and trended higher in the third than the second quartile.

### GH suppression in girls

Table 2 shows GH data for girls grouped by pubertal stage. Early to midpubertal (group 2) girls had higher log nadir GH

**TABLE 1.** GH and other characteristics in boys 9–17 yr old

	Group 1 (n = 19)	Group 2 (n = 11)	Group 3 (n = 13)	P value
Age (yr)	11.3 ± 1.3 <sup>a,b</sup>	13.8 ± 0.9 <sup>b,c</sup>	15.8 ± 1.5 <sup>a,c</sup>	<0.0001
Bone age (yr)	11.2 ± 1.1 <sup>a,b</sup>	13.8 ± 1.0 <sup>b,c</sup>	17.0 ± 1.5 <sup>a,c</sup>	<0.0001
Height (cm)	145.4 ± 8.0 <sup>a,b</sup>	163.2 ± 10.2 <sup>b,c</sup>	173.2 ± 10.2 <sup>a,c</sup>	<0.0001
Weight (kg)	38.3 ± 6.0 <sup>a,b</sup>	50.5 ± 9.2 <sup>b,c</sup>	65.0 ± 8.0 <sup>a,c</sup>	<0.0001
BMI (kg/m <sup>2</sup> )	18.1 ± 1.7 <sup>b</sup>	18.8 ± 1.7 <sup>b</sup>	21.7 ± 2.1 <sup>a,c</sup>	<0.0001
Baseline GH [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml) <sup>d</sup>	0.76 (0.04–13.07)	0.98 (0.06–15.80)	0.31 (0.01–6.82)	Ns <sup>e</sup>
Nadir GH [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml) <sup>d</sup>	0.10 (0.03–0.39)	0.21 (0.09–0.48) <sup>b,c</sup>	0.10 (0.02–0.50)	0.01 <sup>e</sup>
GH AUC [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml 120 min) <sup>d</sup>	31.2 (4.3–225.9)	131.6 (21.3–812.4) <sup>b,c</sup>	36.2 (1.8–713.4)	0.005 <sup>e</sup>
Mean GH [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml) <sup>d</sup>	0.26 (0.04–1.88)	1.09 (0.18–6.75) <sup>b,c</sup>	0.25 (0.01–8.58)	0.008 <sup>e</sup>

Ns, Not significant.

<sup>a</sup> *P* < 0.05 compared with group 2.<sup>b</sup> *P* < 0.05 compared with group 3.<sup>c</sup> *P* < 0.05 compared with group 1.<sup>d</sup> Data derived from comparisons using natural log-transformed values. Where natural log transformations were necessary to approximate a normal distribution, to obtain a range of levels for pubertal stage that could be simply interpreted, the mean levels and range [(mean – 2 SD) to (mean + 2 SD)] obtained with log transformations using ANOVA were transformed back to a normal scale.<sup>e</sup> Natural log transformed variables were used to estimate statistical significance.

than the prepubertal (group 1) girls, and trended higher than the mid to late pubertal (group 3) girls. GH AUC and mean GH did not differ among groups. The absolute GH decrease after oral glucose did not differ ( $1.5 \pm 2.1$ ,  $1.2 \pm 2.2$ , and  $2.1 \pm 4.1$  ng/ml in groups 1, 2, and 3), and neither did the percent GH decrease (76.6, 57.0, and 60.6% in groups 1, 2, and 3, respectively). Baseline GH predicted nadir GH ( $r = 0.63$ ;  $P < 0.0001$ ). One girl (1.6%) had a nadir GH more than 1.0 ng/ml, five (7.8%) had levels more than 0.5 ng/ml, and 16 (25%) had levels more than 0.3 ng/ml. Of these 16 girls, seven were early to midpubertal, and nine were mid to late pubertal. Thus, 43.8% of early to midpubertal girls and 22.0% of mid to late pubertal girls had nadir GH of more than 0.3 ng/ml. The girl with nadir GH of more than 1.0 ng/ml was in Tanner

stage 3 of puberty, and of normal height [ $-1.03$  SD score (SDS)] and BMI ( $-1.24$  SDS).

In group 1, glucose peaked, and GH reached its nadir at 60 min, whereas in group 3, the glucose peak, and GH nadir occurred 30 min after oral glucose (Fig. 1). In group 2, nadir GH occurred at 60 min, 30 min after peak glucose.

When pubic hair staging was used for grouping, similar trends were observed and are not reported. As in boys, grouping by quartiles or tertiles of chronological and bone age did not add to the analyses, and we only report data for bone age quartiles. The mean and range [(mean – 2 SD values) to (mean + 2 SD values)] for nadir GH when transformed back from the natural log scale were as follows: 1) bone ages 8–11 yr, 0.13 ng/ml (0.02–0.76); 2) 11–14.5 yr, 0.22

**TABLE 2.** GH and other characteristics in girls 9–17 yr old

	Group 1 (n = 7)	Group 2 (n = 16)	Group 3 (n = 41)	P value
Age (yr)	10.4 ± 0.7 <sup>a,b</sup>	12.0 ± 1.3 <sup>b,c</sup>	15.0 ± 1.3 <sup>a,c</sup>	<0.0001
Bone age (yr)	9.8 ± 0.9 <sup>a,b</sup>	11.4 ± 1.7 <sup>b,c</sup>	15.5 ± 1.2 <sup>a,c</sup>	<0.0001
Height (cm)	139.7 ± 5.8 <sup>a,b</sup>	149.1 ± 9.0 <sup>b,c</sup>	163.0 ± 6.2 <sup>a,c</sup>	<0.0001
Weight (kg)	33.2 ± 3.2 <sup>b</sup>	39.7 ± 5.1 <sup>b</sup>	57.8 ± 9.2 <sup>a,c</sup>	<0.0001
BMI (kg/m <sup>2</sup> )	17.0 ± 1.8 <sup>b</sup>	17.8 ± 1.3 <sup>b</sup>	21.7 ± 3.0 <sup>a,c</sup>	<0.0001
Baseline GH [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml) <sup>e</sup>	0.73 (0.05–11.8)	0.69 (0.05–10.07)	0.68 (0.03–14.73)	Ns <sup>f</sup>
Nadir GH [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml) <sup>e</sup>	0.09 (0.03–0.23)	0.22 (0.03–1.57) <sup>c,d</sup>	0.16 (0.04–0.64)	0.03 <sup>f</sup>
GH AUC [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml 120 min) <sup>e</sup>	43.8 (2.6–735.1)	99.5 (5.5–1808.0)	71.5 (6.0–854.1)	Ns <sup>f</sup>
Mean GH [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml) <sup>e</sup>	0.36 (0.02–6.11)	0.84 (0.05–15.49)	0.59 (0.05–7.10)	Ns <sup>f</sup>

Ns, Not significant.

<sup>a</sup> *P* < 0.05 compared with group 2.<sup>b</sup> *P* < 0.05 compared with group 3.<sup>c</sup> *P* < 0.05 compared with group 1.<sup>d</sup> *P* < 0.1 compared with group 3.<sup>e</sup> Data derived from comparisons using natural log-transformed values. Where natural log transformations were necessary to approximate a normal distribution, to obtain a range of levels for pubertal stage that could be simply interpreted, the mean levels and range [(mean – 2 SD) to (mean + 2 SD)] obtained with log transformations using ANOVA were transformed back to a normal scale.<sup>f</sup> Natural log-transformed variables were used to estimate statistical significance.

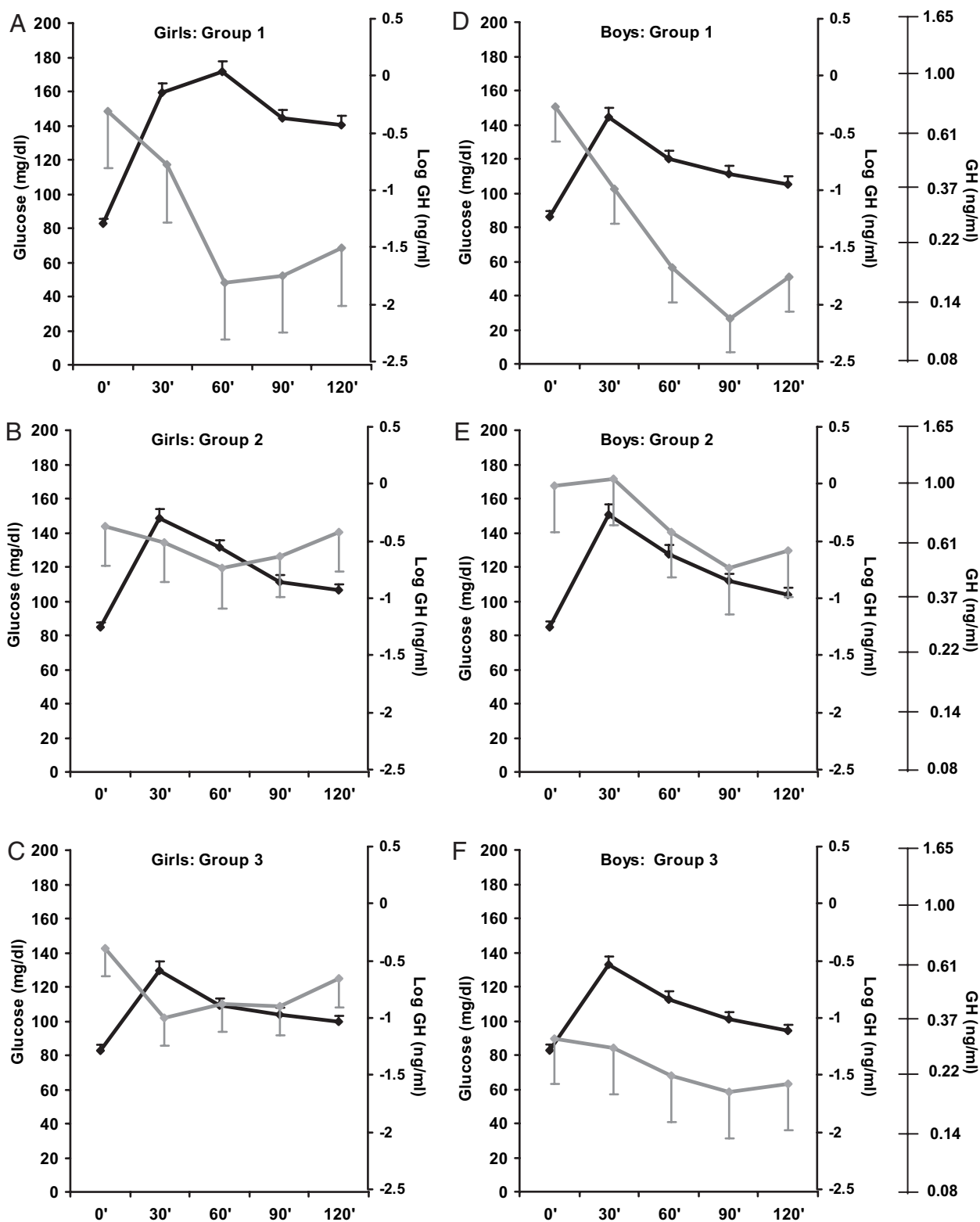


FIG. 1. Glucose and log GH levels after an oral glucose load in prepubertal girls (A) (group 1: Tanner 1), early to midpubertal girls (B) (group 2: Tanner 2 and 3), mid to late pubertal girls (C) (group 3: Tanner 4 and 5), prepubertal and early pubertal boys (D) (group 1: Tanner 1 and 2), midpubertal boys (E) (group 2: Tanner 3 and 4), and late pubertal boys (F) (group 3: Tanner 5). In girls, log GH levels were the lowest 30 or 60 min after oral glucose, whereas in boys, log GH levels were lowest 90 min after oral glucose in all groups. Corresponding nontransformed GH values are depicted to the *right* of the figure for ease of interpretation.



ng/ml (0.04–1.07); 3) 14.5–16.0 yr, 0.18 ng/ml (0.05–0.59); and 4) 16–18 yr, 0.14 ng/ml (0.03–0.63) ( $P = 0.20$ ).

#### GH suppression by gender

Boys and girls did not differ for age, bone age, or anthropometric measures (Table 3). Log nadir GH was higher in girls than boys after oral glucose, and log GH AUC and mean GH trended higher in girls. Higher log nadir GH and mean GH in girls compared with boys were primarily because of differences between the genders in group 3. These variables did not differ between girls and boys in groups 1 and 2. In group 3, log nadir GH was higher in girls than boys ( $-1.80 \pm 0.65$  vs.  $-2.32 \pm 0.81$  ng/ml;  $P = 0.02$ ), as was log mean GH ( $-0.52 \pm 1.24$  vs.  $-1.37 \pm 1.76$  ng/ml;  $P = 0.05$ ). Mean and range for log nadir GH when transformed back from the natural log scale were 0.16 ng/ml (0.04–0.61) in group 3 girls and 0.10 ng/ml (0.02–0.50) in group 3 boys. The absolute GH decrease after oral glucose did not differ ( $1.5 \pm 2.6$  ng/ml in girls vs.  $1.8 \pm 3.5$  ng/ml in boys), and neither did the percent decrease in GH (65.7% in girls vs. 61.1% in boys). Nadir GH correlated positively with baseline GH for all subjects ( $r = 0.64$ ;  $P < 0.0001$ ). AUC for glucose and insulin did not differ between genders.

#### Predictors of nadir GH levels

Overall, log nadir GH was predicted by log GH AUC and log mean GH in girls ( $r = 0.74$ ;  $P < 0.0001$ ) and boys ( $r = 0.78$ ;  $P < 0.0001$ ). We found no associations between nadir GH and peak glucose or insulin, or between log GH AUC and glucose and insulin AUC.

Among girls, an inverse association was noted between U/L and log nadir GH ( $r = -0.44$ ;  $P = 0.04$ ;  $n = 23$ ) and log GH AUC ( $r = -0.54$ ;  $P = 0.009$ ), consistent with known effects of GH on long bone growth. A weak inverse association was observed between percent body fat and log nadir GH ( $r = -0.27$ ;  $P = 0.08$ ) and of trunk to extremity fat to log GH AUC ( $r = -0.29$ ;  $P = 0.06$ ). Among boys, weak inverse associations were noted between log mean GH and WHR ( $r = -0.33$ ;  $P = 0.09$ ), BMI ( $r = -0.33$ ;  $P = 0.03$ ), and U/L ( $r = -0.26$ ;  $P = 0.09$ ).

#### GH and height

We observed positive associations between height and log nadir GH in group 2 boys ( $r = 0.57$ ;  $P = 0.07$ ) and girls ( $r = 0.52$ ;  $P = 0.04$ ), as well as between height and log GH AUC in group 2 ( $r = 0.57$ ;  $P = 0.02$ ), and group 3 girls ( $r = 0.38$ ;  $P = 0.02$ ). Associations with height SDS were weaker. No associations were observed between GH and height in group 1.

#### Discussion

Diagnosis of GH excess in children has been exceedingly difficult because of the lack of normative data regarding GH suppression after oral glucose using newer assays. Pediatricians have had to rely on IGF-I, which varies widely within a pubertal stage, and imaging studies to diagnose GH excess. Consequently, diagnosis and treatment are often delayed. Therefore, establishing normative data for GH suppression in healthy children at different pubertal stages using currently available assays is extremely important. In addition, although GH secretion during childhood is dependent upon pubertal stage, the impact of pubertal changes on GH suppressibility has not been established.

We demonstrate that early to midpubertal girls and midpubertal boys do not suppress their GH levels as much as children in other pubertal stages do after an oral glucose load, and girls have higher nadir GH levels than boys. Our findings are consistent with gender-specific data in adults that report higher nadir GH after oral glucose (19), and higher mean GH measured over 24 h in women than men (20). Higher GH levels in women are attributed to higher circulating estrogen, resulting in lower IGF-I secretion and a reciprocal increase in GH (21). Our data indicate that the extent of GH suppression (baseline – nadir GH) does not differ in boys vs. girls, and nadir GH is strongly associated with baseline GH. Therefore, higher nadir GH in girls is a consequence of higher baseline GH, and not gender-specific differences in suppressive effects of glucose on GH secretion.

GH increases at puberty (22–24), and higher nadir GH after oral glucose in early to midpubertal (group 2) girls is in agreement with the expected higher GH in Tanner stages 2–3

**TABLE 3.** GH and other characteristics in girls vs. boys 9–17 yr old

	Girls (n = 64)	Boys (n = 43)	P value
Age (yr)	13.7 $\pm$ 2.1	13.3 $\pm$ 2.3	Ns
Bone age (yr)	13.8 $\pm$ 2.6	13.6 $\pm$ 2.7	Ns
Weight (kg)	50.5 $\pm$ 12.6	49.5 $\pm$ 13.6	Ns
Height (cm)	157.0 $\pm$ 10.9	158.3 $\pm$ 15.0	Ns
BMI (kg/m <sup>2</sup> )	20.2 $\pm$ 3.2	19.3 $\pm$ 2.4	Ns
Baseline GH [mean and range (mean – 2 SD to mean + 2 SD D)] (ng/ml) <sup>a</sup>	0.62 (0.03–12.4)	0.68 (0.04–12.4)	
Nadir GH [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml) <sup>a</sup>	0.17 (0.04–0.79)	0.12 (0.03–0.52)	0.03
GH AUC [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml 120 min) <sup>a</sup>	73.7 (5.4–1012.3)	51.9 (3.4–804.3)	Ns
Mean GH [mean and range (mean – 2 SD to mean + 2 SD)] (ng/ml) <sup>a</sup>	0.62 (0.05–8.50)	0.41 (0.02–7.77)	Ns

Ns, Not significant.

<sup>a</sup> Data derived from comparisons using natural log-transformed values. Where natural log transformations were necessary to approximate a normal distribution, to obtain a range of levels for pubertal stage that could be simply interpreted, the mean levels and range [(mean – 2 SD) to (mean + 2 SD)] obtained with log transformations using ANOVA were transformed back to a normal scale.

of puberty (15), when peak height velocity occurs in girls (13). Similarly, higher nadir GH after oral glucose at midpuberty in boys is consistent with highest GH and peak growth velocity occurring at Tanner 4 puberty in boys. One study reported highest GH levels between testicular volumes of 10 and 15 ml, and consistent with these data, our group 2 boys had a mean testicular volume of 12.2 ml (95% confidence interval, 10.2–14.2 ml). Peak growth velocity was reported to occur at a mean age of 12.2 yr in girls and 13.9 yr in boys in one study (25), although there are also reports of peak height velocity occurring at 11.5 yr in girls and 13.5 yr in boys (13). In our study, group 2 girls and boys had the highest nadir GH after oral glucose, and the mean age was 12.0 yr for group 2 girls and 13.8 yr for group 2 boys, close to the reported ages for peak height velocity when GH levels may be expected to be highest. Of interest, we also observed a positive association between GH and absolute height in group 2 boys and girls. Our data indicate differences in GH suppression with oral glucose in girls *vs.* boys, and for different pubertal stages, and provide preliminary standards for GH suppression in children based on gender and pubertal stage. Larger studies, particularly in midpubertal children, are necessary to confirm these data.

Our data indicate that nadir GH occurs later in boys than in girls during the OGTT. Whereas in boys, nadir GH occurs 60 min after peak glucose, in girls, nadir GH occurs at the time or soon after glucose levels peak. The mechanism underlying this observation remains to be determined.

Of importance, although we demonstrate higher nadir GH concentrations in girls, and in early to midpubertal girls and midpubertal boys than at other pubertal stages, nadir levels are not as high as one may expect, given the higher GH concentrations in the pubertal years compared with adults (22–24), if we consider 1 ng/ml to be the cutoff for GH suppression in adults (1). All subjects except one suppressed to below this level in our study. This may be related to differences in assays used by our group compared with the assay used to determine adult reference data, and the higher sensitivity of currently used assays. Of importance, in addition to assay sensitivity for GH, assay calibration remains an issue because of the availability of different reference preparations (6, 7). Recent reports indicate that the upper limit of normal for nadir GH after oral glucose in adults may be as low as 0.3 ng/ml, when the assay sensitivity is similar to that of the assay used in this study (5), and that standards for GH suppression using newer assays may differ from those using older, less sensitive assays (3). Indeed, in our study, 25% of the girls and 12% of the boys had nadir GH values above 0.3 ng/ml, supporting our hypothesis that adolescent girls and boys do not suppress their GH values after oral glucose to the extent observed in adults. In addition, early to midpubertal girls were the least likely of all groups to suppress their GH values less than 0.3 ng/ml.

In a pilot study using the Nichols IRMA, we had previously determined that the mean + 2 sd value for nadir GH after 100-g oral glucose in pubertal girls is 1.5 ng/ml (10). For this study we used another IRMA (Immulite 2000 Analyzer), with an even lower detection limit (0.01 ng/ml) than the Nichols assay (0.05 ng/ml). In the current study, the upper limit for GH suppression in early to midpubertal girls, the

subset with the highest nadir GH levels, was 1.57 ng/ml, similar to the value reported earlier. However, only one girl in group 2 did not suppress to less than 1 ng/ml, and girls in other pubertal groups suppressed to less than 0.64 ng/ml. For boys, groups 2 and 3 had the highest value for the upper limit for nadir GH (0.48 and 0.50 ng/ml, respectively). Because the extent of GH suppression (baseline – nadir GH) after oral glucose did not differ across gender or pubertal stage (except for group 1 *vs.* group 3 boys), higher nadir GH in group 2 boys and girls is likely related to higher basal GH, rather than differences in GH suppressive effects of oral glucose. Although baseline (0 min) GH did not differ, GH assessed by frequent sampling is known to be higher in Tanner 3 girls and Tanner 4 boys than in other pubertal stages (15, 16).

The greatest separation of data was observed when children were grouped by pubertal stage rather than quartiles or tertiles of chronological age. This is expected because peak GH is associated with a specific pubertal stage rather than a specific chronological age. Because bone age correlates with pubertal stage, some separation was observed when boys were grouped by bone age quartiles.

We specifically chose to study normal weight children to avoid confounding effects of obesity. However, even among normal weight children, weak inverse associations were observed between GH and WHR, BMI, and percent body fat. These findings are consistent with associations reported by other investigators between GH levels and BMI (15), WHR, and percent body fat (22). Such associations may be attributable to known lipolytic effects of GH, particularly for trunk fat (26, 27), or may simply reflect the lower GH concentrations in children with greater fat mass (22). We observed weak inverse associations between GH and U/L, consistent with known effects of GH on long bone growth (13).

Thus, we demonstrate that GH nadir after a glucose load is highest in early to midpuberty in girls and midpuberty in boys, and for the first time provide gender and pubertal stage-specific normative data for GH suppression. We also demonstrate that criteria for GH suppression during an OGTT in childhood are dependent on gender and pubertal stage, rather than chronological age. It will be important to determine whether our observation that midpubertal girls fail to suppress their GH values after an OGTT to below established norms for adults is corroborated by studies with a larger number of midpubertal subjects.

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