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Sex Differences in Statural Growth Impairment in Crohn's Disease: Role of IGF-1

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Abstract

Background—Growth impairment in Crohn's disease (CD) is more common in males than females for unknown reasons. Since insulin-like growth factor 1 (IGF-1) is required for statural growth, we hypothesized that IGF-1 levels are lower in males with CD.

Methods—Sex differences in hormone Z scores based on chronological age (CA-Z) and bone age (BA-Z) were examined in a cross-sectional study of 82 CD patients < 21 years of age (43% female).

Results—IGF-1 CA-Z and BA-Z scores were 0.50 units ($p=.04$) and 1.24 units ($p=.003$) lower in males. Mean bone age (12.2 years) was lower than chronological age (13.1 years) ($p<.0001$). ESR, CRP, and albumin did not differ by sex ($p\geq.08$), but were associated with IGF-1 CA-Z and BA-Z scores ($p\leq.02$). Insulin-like growth factor binding protein 3 (IGFBP-3) CA-Z and BA-Z scores were 0.71 units ($p=.004$) and 1.26 units ($p<.001$) lower in males. Inflammatory markers were correlated with sex hormone CA-Z and BA-Z and pituitary hormone BA-Z scores in males ($p\leq.03$), but not females ($p\geq.25$). IGF-1 BA-Z scores were positively associated with height BA-Z scores ($p=.03$). Mean height BA-Z scores were lower in males ($p=.03$).

Conclusions—Lower IGF-1 levels in males may explain sex differences in growth impairment in CD. Inflammation appears to more adversely affect hormone levels and statural growth in males. Prospective longitudinal studies are needed to further clarify the role of IGF-1 in sex differences in statural growth impairment in pediatric CD.

Keywords

female; male; children; insulin-like growth factor 1; inflammatory bowel disease

INTRODUCTION

Growth impairment is common in Crohn's disease (CD). Some reports point to disease severity as the major determinant of growth^{1–3}. However, taken together, the available data suggest that the negative impact of disease severity on growth differs by sex. Our previously published results indicate that the overall course of CD is more severe in females^{4,5}, whereas males are at increased risk for growth failure⁴. Others reported that disease duration

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and average pediatric CD activity index (PCDAI) scores are similar in males and females with CD⁶, but in comparisons of CD patients and controls, found significant differences in growth parameter Z scores in males but not in females. Similarly, a poorer prognosis for linear growth has been repeatedly observed in males with pediatric CD^{1,7–8}.

Growth impairment may be an important early manifestation of a chronic inflammatory process, particularly in males. The underlying mechanisms for sex differences in growth impairment in CD are unclear. Insulin-like growth factor-1 (IGF-1) is both an endocrine and paracrine hormone required for statural growth. The primary aim of this study is to compare IGF-1 levels by sex in pediatric CD. We hypothesized that IGF-1 levels would be lower in males than females with CD. Our secondary aim is to identify determinants of IGF-1 levels.

PATIENTS AND METHODS

This cross-sectional study enrolled patients from January, 2007 through July, 2009. Pediatric patients with CD, age 0–21 years, followed in the University of California, San Francisco (UCSF) Pediatric Inflammatory Bowel Disease (IBD) and Gastroenterology clinics were consecutively approached and enrolled. Fliers were distributed to pediatric gastroenterologists around the San Francisco Bay Area. 82 patients completed the study. Seven patients were from outside institutions; they did not differ from UCSF patients in baseline growth measures. All patients were seen at the UCSF Children's Hospital for the study.

Inclusion and exclusion criteria

Because delayed puberty is common in patients with CD, we included patients up to 21 years of age. This was done in part to increase precision. More importantly, we included such patients to understand the impact of pubertal levels of sex hormones and pituitary hormones on IGF-1 and IGFBP-3 levels. Patients exposed to growth hormone (GH) were excluded. Patients with a history of corticosteroid use (intravenous, oral, intranasal, inhaled, rectal, topical) were required to be off steroids for at least two months prior to participation in the study, since more recent use would suppress the somatotrophic axis and interfere with accurate assessment of IGF-1 levels. History of corticosteroid use did not differ by sex.

We classified *disease location* as esophagus or stomach; small bowel, no colon; small bowel and colon; colon, no small bowel; and perianal. *Medication use* was self-reported and included 5-aminosalicylates, antibiotics, azathioprine/6-mercaptopurine, adalimumab, infliximab, and methotrexate. *Tanner stage* (TS) refers to breast development in females and testes/scrotum/penis development in males. We determined *chronological age* (CA) and *bone age* (BA) at the study visit. *Laboratory measures* included serum IGF-1, insulin-like growth factor binding protein three (IGFBP-3), testosterone, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, hematocrit, platelets, and alkaline phosphatase, and urine GH (uGH). Elevated WBC count was defined according to age-specific criteria. Decreased hematocrit was defined using the PCDAI criteria⁹. Platelet count >450,000/ml was categorized as elevated. Elevated alkaline phosphatase was defined according to sex and age-specific criteria.

Sex hormones influence the pubertal growth spurt through direct effects on bone and through indirect effects via GH and IGF-1. Although testosterone is the primary sex hormone in males and estradiol in females, estradiol is the primary hormone involved in skeletal maturation and the pubertal growth spurt in both sexes^{10,11}. We compared serum testosterone in males to estradiol in females because these hormones are markers of pubertal status in males and females, respectively. Thus, we assessed *sex hormone* levels using a

composite measure defined as the testosterone Z score in males and the estradiol Z score in females.

As LH is the primary regulator of testosterone synthesis in Leydig cells, and FSH is the primary regulator of estradiol synthesis in granulosa cells, via stimulation of aromatase, we assessed *pituitary hormone levels* using a composite measure defined as the LH Z score in males and the FSH Z score in females.

Urinary GH (uGH) levels are an indicator of integrated pituitary GH secretion^{12,13}. Because GH stimulates the production of IGF-1, the uGH/serum IGF-1 ratio may reflect GH resistance. Accordingly, we considered this measure in an exploratory analysis.

Weight and height were measured using a digital scale (Scale-Tronix, White Plains, NY) to the nearest 0.1 kg and stadiometer (Proscale, Accurate Technology, Inc., Cincinnati, OH) to the nearest 0.1 cm, respectively; BMI was calculated as the weight in kg divided by the square of the height in meters. Self-Tanner staging was performed¹⁴. Following detailed instructions, patients collected, froze, and submitted a first-morning void urine sample. A serum lab draw was performed. Tubes for serum hormone levels and the urine sample for GH levels were sent for processing to Esoterix Endocrinology (Calabasas Hills, CA). Routine clinical labs were sent to the UCSF clinical lab. Clinical information was collected. A left hand x-ray for BA was obtained and interpreted by one of the investigators (RL), using the standards of Greulich and Pyle¹⁵.

Statistical methods

Using reference values based in part on CA, we calculated Z-scores (CA-Z) for IGF-1, IGFBP-3, estradiol, testosterone, FSH, LH, and BMI; this was done for all patients (CA-Z). In addition, because pubertal growth acceleration correlates more closely with BA than with CA¹⁶, we also calculated Z-scores based on BA (BA-Z) for all 17 females $\leq$ CA 15 and 32 males $\leq$ CA 17 years, as epiphyses close at BA 15 in females and BA 17 years in males. Although females $>$ CA 15 and males $>$ CA 17 years could have open epiphyses, all patients in this age group were excluded from the BA analyses to avoid selective inclusion of only older patients with pubertal delay. We also performed a sensitivity analysis examining IGF-1 and IGFBP-3 CA-Z scores restricted to the 49 participants qualifying for the BA-Z sub-sample.

To calculate Z scores for weight, height, and BMI, we used the smoothed growth curves from NHANES¹⁷. IGF-1 and IGFBP-3 Z scores were determined using means and standard deviations (SDs) provided by Esoterix Endocrinology. SDs for pituitary hormones and sex hormones were computed from the mean and the upper and lower bounds of the normal ranges, accounting for asymmetry about the mean if present. For pituitary hormones and sex hormones, the means and ranges used to calculate Z scores were specific to sex, age, and TS.

Linear regression was used to assess adjusted and unadjusted associations of predictors with outcomes and to examine interactions. We log-transformed ESR, CRP, and albumin to down weight influential points and normalize the distribution. We also performed a sensitivity analysis in which we omitted Z-scores > 2 or < -2 . Fisher's exact and t-tests were used in assessing differences in categorical and continuous variables, and Pearson correlations were used to summarize relationships between continuous variables. To quantify predictor effects on a common scale, we calculated the increment in R-squared when each measure was added to a simpler model, then assessed the statistical significance of these additions using the likelihood ratio test.

The analysis was conducted using STATA Version 9 (College Station, TX).

ETHICAL CONSIDERATIONS

We obtained institutional review board approval for the study protocol, and informed consent and assent were obtained from parents and patients.

RESULTS

Baseline Characteristics

Eighty-two patients (35 female [43%]) participated in this study. Mean CA was 15.3 ± 3.5 [SD; range = 4.8, 20.7] years. Forty-nine children (60%) were eligible for analyses involving BA. Mean BA (12.2 ± 2.9 years) was significantly lower than mean CA (13.1 ± 2.6 years) ($p < .0001$). Baseline measures did not differ by sex (Tables 1 and 2). Mean height BA-Z scores were lower in males (Table 2).

Based on CA, a higher proportion of females had elevated alkaline phosphatase (46% in females versus 21% in males; $p = .03$). Based on BA, no patients had elevated alkaline phosphatase. CBC indices ($p \geq .23$) and the inflammatory markers, ESR ($p = .13$), CRP ($p = .08$), and albumin ($p = .89$), did not differ by sex. Median ESR was 10 (interquartile range: 6, 19); CRP 1.3 (0.5, 4.5); and albumin 4.1 (3.7, 4.4).

IGF-1 and IGFBP-3 Levels

IGF-1 and IGFBP-3 CA-Z and BA-Z scores were lower in males (Tables 3A and 3B). In a sensitivity analysis restricted to the 49 patients who qualified for BA analyses, the results were unchanged. IGF-1 Z scores were positively associated with height Z scores (CA-Z $p = .20$; BA-Z $p = .03$).

Table 4 shows that IGF-1 Z scores were inversely associated with ESR and CRP, and directly associated with albumin and alkaline phosphatase. IGFBP-3 Z scores were inversely associated with CRP. Table 5 shows that inflammatory markers predicted IGF-1 Z scores, BMI CA-Z scores predicted IGF-1 CA-Z scores, sex hormone Z scores predicted IGF-1 Z scores, and sex hormone CA-Z scores predicted IGFBP-3 CA-Z scores.

uGH/Serum IGF-1 and uGH/Serum IGFBP-3 Ratios

Eighty (98%) properly collected urine samples were submitted. The mean uGH/serum IGF-1 ratio was 0.03 ± 0.04 [range = 0.0008, 0.24]. uGH/serum IGF-1 ratio was higher in males. The sex difference in uGH/serum IGF-1 ratio depended on TS ($p = .01$), with higher ratios in males at TS 1 (0.09 ± 0.09 vs. 0.01 ± 0.01 ; $p = .02$) and 2 (0.07 ± 0.07 vs. 0.04 ± 0.06 ; $p = .04$), but similar ratios at later stages. ESR did not predict uGH/serum IGF-1 ratio ($p = .28$). CRP ($\Delta R^2 = 6.0$ percentage points, $p = .04$) and albumin ($\Delta R^2 = 17.1$ percentage points, $p < .0001$) predicted uGH/serum IGF-1 ratio. The mean uGH/serum IGFBP-3 ratio was 1.78 ± 2.11 [range = 0.08, 11.9], and did not differ by sex ($p = .86$).

Sex Hormone and Pituitary Hormone Levels

Average sex hormone CA-Z scores were -1.48 ± 2.00 [range = -4.9, 6.75] and BA-Z scores were -1.16 ± 2.69 [range = -4.9, 6.75]. Sex hormone CA-Z ($p = .98$) and BA-Z ($p = .19$) scores did not differ by sex. Average pituitary hormone CA-Z scores were -0.33 ± 1.09 [range = -2.51, 2.37] and BA-Z scores were -0.29 ± 1.48 [range = -2.29, 4.95]. While pituitary hormone CA-Z scores were similar by sex ($p = .39$), pituitary hormone BA-Z scores were lower in males at TS 1 (-2.2 ; $p = .01$) and 2 (-1.0 ; $p = .06$) (interaction $p = .02$). Pituitary hormone CA-Z scores were associated with sex hormone CA-Z scores ($\Delta R^2 = 13.7$).

percentage points, $p=.001$). The association appeared stronger in males ($p=.07$). Similarly, pituitary hormone BA-Z scores were associated with sex hormone BA-Z scores ($\Delta R^2 = 14.5$ percentage points, $p=.02$).

Table 6 shows that in males, inflammatory markers were associated with testosterone Z scores and LH BA-Z scores. In females, inflammatory markers were not associated with estradiol or FSH Z scores.

We assessed evidence for modification by sex of the relationship between inflammatory markers and hormone levels. We found that sex modified the effect of CRP on pituitary hormone BA-Z scores ($p=.05$); specifically, higher levels of CRP were associated with lower pituitary hormone BA-Z scores in males, not females. We found suggestive evidence that sex modified 1) the effect of albumin on IGF-1 BA-Z scores ($p=.07$); and 2) the effect of CRP ($p=.09$) and albumin ($p=.09$) on IGFBP-3 BA-Z scores. In each of these pathways, the effect of the inflammatory marker tended to be more pronounced in males. Similarly, sex modified the influence of sex hormone CA-Z scores on IGF-1 CA-Z scores ($p=.09$), with the effect marginally stronger in males.

Results were unchanged in sensitivity analyses in which we trimmed Z scores to remove outliers.

DISCUSSION

The sex differences in IGF-1 levels reported in this study provide a potential basis for understanding the etiology of growth impairment in CD. The mechanisms responsible for growth impairment in CD may also apply in other chronic inflammatory diseases.

BA was lower than CA in our series of pediatric patients with CD, consistent with prior studies^{3,18}. The importance of BA in interpreting growth in such patients was further demonstrated by observed sex differences in height BA-Z, but not CA-Z scores. We did not observe sex differences in BA delay. In contrast, others found BA was significantly delayed in males, not females⁶. This difference in results and its importance in explaining sex differences in growth impairment require clarification. We again identified sex differences in statural growth, as described in prior studies^{1,4,6-8}. Height BA-Z scores were significantly lower in males.

Our data show that IGF-1 levels are reduced in males compared with females, and the relationship between sex and IGF-1 levels was similar across TS's 1-5. Griffiths et al reported that in a cohort of 100 TS 1 and 2 children with CD, males had lower height Z scores at the time of diagnosis of CD, achieved less catch up growth, and had lower ultimate height Z scores¹. Their report corresponds with our findings that sex differences in growth impairment are apparent even in pre-pubertal children. Taken together, the data suggest that sex differences in growth impairment are not driven by timing of diagnosis of disease in relation to timing of pubertal growth spurt in pediatric patients.

Inflammation has been shown to exert negative effects on growth. Several investigators have implicated inflammatory mediators in impacting the GH-IGF-1 pathway at various points¹⁹⁻²⁷. Multiple correlations have been reported between IGF-1 and IGFBP-3 and inflammatory markers in CD²⁸⁻³¹, as in our study. IGF-1 is more sensitive than IGFBP-3 to nutritional deprivation³², whereas parallel reductions in IGF-1 and IGFBP-3 are more suggestive of defective GH action, i.e. deficiency or resistance. We measured urine GH levels as a screen for GH deficiency, and our results were not suggestive of GH deficiency in this cohort, consistent with other studies³³⁻³⁶. We found an association between IGFBP-3 and CRP, but not with BMI. Additionally, the inflammatory markers remained significant predictors of

IGF-1 levels after adjusting for BMI; BMI was not a significant predictor of IGF-1 in these models [data not shown]. BMI did not differ by sex in our study cohort and fails to explain the sex difference in IGF-1 levels. Hence, our results suggest that the observed reduction in IGF-1 levels in males compared with females is likely due to inflammation, rather than due to poor nutrition. Our data suggest that the effects of inflammation on hormone levels are more pronounced in males, and may explain the observed sex differences in IGF-1 and IGFBP-3 levels, even though inflammatory markers did not differ by sex. We are not aware of other reports of sex differences in IGF-1 and IGFBP-3 levels in CD for comparison.

Our data support that GH resistance associated with inflammation contributes to growth impairment in CD. The uGH/serum IGF-1 ratio was higher in TS 1 and 2 males, suggesting greater GH resistance in this group, and consistent with lower IGF-1 levels in males. It remains unclear why a sex difference in uGH/serum IGF-1 ratio was identified only at TS 1 and 2. Others have suggested that low estrogen concentrations could stimulate responsiveness to GH, whereas high concentrations, seen in adult females, could inhibit GH responsiveness³⁷. Therefore, sex differences in uGH/serum IGF-1 ratio at TS 3–5 with higher ratios in females might have been expected, but may have escaped detection because of possible sex differences in the effects of inflammation on growth. Perhaps the rise in testosterone with advancing pubertal stage in males offers a protective effect in TS 3–5 versus TS 1–2 males. However, IGF-1 levels were decreased in males compared with females across all TS's. Therefore, the relevance of increased uGH/serum IGF-1 ratios requires further study.

Inflammation may also exert an adverse effect on sex hormone levels, contributing to impaired growth. Inflammatory markers correlated with testosterone levels in males, but not with estradiol levels in females. Since sex hormone levels predict IGF-1 levels, inflammation should have a greater negative impact on IGF-1 levels in males. We found weak evidence in support of a greater impact of modifying factors in males, and that sex modified the influence of sex hormone CA-Z scores on IGF-1 CA-Z scores, with the effect slightly stronger in males. In a rat model of colitis, no significant differences in 17 β -estradiol concentrations in the colitic group versus controls were present in females³⁸, whereas testosterone was significantly reduced in colitic males. Correlations between disease state and androgens have been reported in other conditions. A reduction in testosterone has been observed in males with cystic fibrosis³⁹, and low androgen levels are present in juvenile rheumatoid arthritis⁴⁰ and systemic lupus erythematosus^{41,42}. Finally, inflammatory cytokines, such as TNF-alpha, may induce reductions in testosterone as described in *in vitro* models^{43,44}.

Inflammation may also suppress pituitary hormone levels. Our results showed that pituitary hormone BA-Z scores were lower in TS 1 and 2 males. This finding may contribute to the sex difference in uGH/serum IGF-1 ratio in TS 1 and 2 children. Inflammatory markers correlated with LH BA-Z scores in males, but not with FSH BA-Z scores in females. Furthermore, sex modified the effect of CRP on pituitary hormone BA-Z scores. Higher levels of CRP were associated with lower pituitary hormone BA-Z scores in males, not females, suggesting that the impact of inflammation on hormone levels may differ by sex. In a rat model of colitis, investigators reported that the profile of plasma LH and FSH concentrations was similar to levels observed in control female rats³⁸, suggesting that hypopituitarism may not be the cause of growth impairment in CD^{36,45}. In contrast, others have reported diminished plasma LH and FSH levels in CD^{46,47} and cystic fibrosis, to a lesser extent in females than males⁴⁸. Thus, the existing evidence is mixed and deserves further study to advance our understanding of the impact of CD on hypothalamic-pituitary function and statural growth.

LIMITATIONS

The cause of growth attenuation in CD is likely multifactorial^{49–51}. This study measures height instead of growth velocity. Growth velocity is a dynamic marker of general health and the ultimate outcome of interest for studying growth impairment. The cross-sectional study design did not permit growth velocity to be determined in our study population. Nevertheless, the relationships between sex, statural growth, IGF-1, and inflammation demonstrated in this study are consistent with a causal relationship between sex differences in IGF-1 levels and sex differences in growth impairment observed in pediatric patients with CD.

SUMMARY AND CONCLUSIONS

While the regulation of growth is a complicated process affected by many factors, we chose to focus on the inflammatory process and its impact on the endocrinologic mechanisms of growth. Our main finding is that IGF-1 Z-scores are lower in males than females. Lower IGF-1 levels in males may explain the sex differences in growth impairment in pediatric CD. Inflammatory markers did not differ by sex. Inflammation negatively affected IGF-1 and IGFBP-3 levels. Inflammatory markers were correlated with pituitary hormone and sex hormone levels in males, not females. Thus, the impact of inflammation on hormone levels and statural growth may differ in each sex.

The studies presented herein contribute a better understanding of underlying mechanisms involved in sex differences in growth impairment in pediatric CD, and may help identify patients at greatest risk for developing this important complication. Future prospective longitudinal investigations in a larger cohort of patients should focus on the ultimate outcome of interest, growth velocity. Studies of factors leading to sex differences in IGF-1 levels and growth impairment in pediatric CD, including the impact of the hypothalamic-pituitary-gonadal axis on IGF-1 levels, should incorporate serial measurements of BA, TS, hormone levels, inflammatory markers, including inflammatory cytokine levels, markers of bone formation, including bone-specific alkaline phosphatase, and nutritional measures. Our findings may eventually lead to improved understanding and management of growth in CD. In a broader context, the present observations may also provide a basis for mechanistic studies of growth impairment in many other chronic disorders of children and adolescents.

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Table 1

Demographics, Tanner Stage, Disease Location, and Medications by Sex

	Female (N=35)		Male (N=47)		P Value*
	N	%	N	%	
Age					
0-5	0	0%	1	2.1%	.87
6-12	7	20.0%	12	25.5%	
13-17	18	51.4%	20	42.6%	
18-20	10	28.6%	14	29.8%	
Race					
Caucasian	30	85.7%	35	74.5%	.27
Black/African American	0	0%	1	2.1%	
Asian	5	14.3%	7	14.9%	
Other	0	0%	4	8.5%	
Ethnicity					
Hispanic or Latino	2	5.7%	5	10.6%	.69
Not Hispanic or Latino	33	94.3%	42	89.4%	
Tanner Stage					
1	2	5.7%	6	12.8%	.46
2	8	22.9%	7	14.9%	
3	9	25.6%	7	14.9%	
4	8	22.9%	16	34.0%	
5	8	22.9%	11	23.4%	
Disease Location					
Esophagus or Stomach	3	8.6%	6	12.8%	.73
Small Bowel, No Colon	6	17.1%	6	12.8%	
Small Bowel and Colon	22	62.9%	31	66.0%	.90
Colon, No Small Bowel	7	20.0%	10	21.3%	
Perianal Disease	23	65.7%	25	55.6%	.49
Medications					

	Female (N=35)		Male (N=47)		P Value*
	N	%	N	%	
Adalimumab	2	5.7%	2	4.3%	.99
5-Aminosalicylate	22	62.9%	28	59.6%	.82
Antibiotics	4	11.4%	10	21.3%	.37
Azathioprine/6-mercaptopurine	17	48.6%	27	57.5%	.50
Infliximab	11	31.4%	9	19.2%	.30
Methotrexate	5	14.3%	2	4.3%	.13

* Fisher's exact test

Table 2

Chronological Age, Bone Age, and Anthropometric Measurements by Sex

	Female (N=35)	Male (N=47)	P Value ***
Age at Diagnosis of IBD (Years)	11.8 ± 3.8* (0.5,17.2)**	12.3 ± 3.8 (2.8,17.9)	.55
Time Since Diagnosis of IBD (Years)	3.6 ± 2.9 (0.05,11.9)	3.0±2.5 (0.008, 8.8)	.27
Age at Study Visit (Years)	15.4 ± 3.4 (7.6, 20.7)	15.2 ± 3.7 (4.8, 20.6)	.85
Weight CA-Z	-0.17 ± 0.97 (-2.27, 2.07)	-0.16 ± 1.20 (-3.49, 2.20)	.98
BMI CA-Z	-0.12 ± 0.97 (-2.24, 2.14)	-0.04 ± 1.10 (-2.78, 2.17)	.75
Height CA-Z	-0.24 ± 0.86 (-2.11, 1.35)	-0.35 ± 1.13 (-2.74, 2.34)	.63
	Female (N=17)	Male (N=32)	
Bone Age Delay (Years)	1.3 ±1.2 (-1.9, 2.7)	0.7 ±1.3 (-2.0, 3.1)	.10
Weight BA-Z	0.25 ± 0.63 (-1.02, 1.15)	0.03 ± 1.03 (-2.52, 1.97)	.43
BMI BA-Z	-0.02 ± 0.66 (-1.28, 0.92)	0.09 ± 0.96 (-2.58, 2.09)	.68
Height BA-Z	0.63 ± 0.91 (-1.37, 2.53)	-0.08 ± 1.15 (-3.29, 2.46)	.03

* Mean ± Standard Deviation

** Range

*** T-test

Table 3

3A: IGF-1 Z Scores by Sex						
Z Score	IGF-1 Z Scores [^]					P Val
	Female	Male	Sex Difference [*]	95% CI		
CA-Z ⁺ (N=82)	-0.97 ± 1.08 ^{**} (-2.87, 0.97) ^{***}	-1.46 ± 1.10 (-3.61, 0.94)	-0.50	-0.99, -0.02		.04
BA-Z (N=49)	-0.12 ± 1.49 (-2.73, 2.74)	-1.26 ± 1.16 (-3.23, 0.94)	-1.24	-2.03, -0.45		.003

3B: IGFBP-3 Z Scores by Sex						
Z Score	IGFBP-3 Z Scores [#]					P Val
	Female	Male	Sex Difference [*]	95% CI		
CA-Z ⁺ (N=82)	-0.25 ± 1.11 ^{**} (-1.79, 2.50) ^{***}	-0.95 ± 1.06 (-3.08, 1.73)	-0.71	-1.19, -0.23		.004
BA-Z (N=49)	0.27 ± 1.34 (-1.18, 3.44)	-0.98 ± 0.73 (-2.37, 1.03)	-1.26	-1.87, -0.65		<.001

* Females are the reference group. Adjusted for Tanner stage using linear regression.

** Mean ± Standard Deviation

*** Range

[^] Mean IGF-1 levels in females=260.0±92.4 (SD); in males=238.9±110.3

[#] Mean IGFBP-3 levels in females=3.5±0.8; in males=3.0±0.7

⁺ In a sensitivity analysis examining CA-Z scores in the subset of 49 patients who qualified for analyses based on BA, the results were unchanged.

Table 4

Correlation of Markers of Inflammation, Growth, and Nutrition with IGF-1 and IGFBP-3 Z scores

Variable	IGF-1 CA-Z (N=82)	IGF-1 BA-Z (N=49)	IGFBP-3 CA-Z (N=82)	IGFBP-3 BA-Z (N=49)
Albumin	0.27* (.02)**	.40 (.004)	−0.04 (.72)	.02 (.91)
ESR	−0.29 (.009)	−0.32 (.03)	−0.12 (.29)	−.04 (.81)
CRP	−0.44 ($<.0001$)	−0.45 (.001)	−0.24 (.03)	−0.31 (.03)
Alkaline Phosphatase	0.22 (.05)	.48 (.0005)	.02 (.86)	.24 (.10)
BMI CA-Z	0.09 (.40)	-- --	0.05 (.65)	-- --
BMI BA-Z	-- --	.16 (.26)	-- --	.02 (.91)

* Correlation Coefficient

** P Value

Table 5

Assessment of Inflammatory Markers, Nutrition Markers, and Sex Hormone Z Scores as Predictors of IGF Z Scores

Marker		Outcome			
		IGF-1 CA-Z	IGF-1 BA-Z	IGFBP-3 CA-Z	IGFBP-3 BA-Z
ESR	* ΔR^2	10.0	9.1	5.5	5.6
	P Val**	.002	.02	.07	.14
CRP	ΔR^2	17.1	13.7	3.5	3.6
	P Val	.0001	.003	.07	.11
Albumin	ΔR^2	6.7	19.5	0.2	0.0
	P Val	.01	.001	.65	.95
BMI	ΔR^2	10.7	3.2	0.2	0.2
	P Val	.007	.16	.67	.70
Sex Hormone Z	ΔR^2	13.1	11.3	11.3	0.4
	P Val	.002	.007	.004	.62

* ΔR^2 is the increase in R^2 when the marker is added to a baseline model for the outcome, including sex and Tanner stage as predictors in the baseline model.

** Likelihood ratio test

Table 6

Correlation of Inflammatory Markers with Pituitary and Sex Hormone Z scores

	Female				Male			
	Estradiol CA-Z (N=35)	Estradiol BA-Z (N=17)	FSH CA-Z (N=35)	FSH BA-Z (N=17)	Testosterone CA-Z (N=47)	Testosterone BA-Z (N=32)	LH CA-Z (N=47)	LH BA-Z (N=32)
ESR	-0.06* (.73)**	-.13 (.63)	-0.11 (.52)	-0.28 (.28)	-0.35 (.02)	-0.49 (.004)	-0.27 (.06)	-0.53 (.002)
CRP	-0.12 (.50)	0.07 (.80)	-0.08 (.64)	-0.06 (.82)	-0.31 (.03)	-0.39 (.03)	-0.12 (.43)	-0.52 (.003)
Albumin	0.18 (.29)	.23 (.38)	.20 (.25)	.20 (.44)	.40 (.005)	.48 (.005)	.26 (.07)	.51 (.003)

* Correlation Coefficient

** P Value