Title

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Journal

Inflammatory Bowel Diseases, 26(12)

ISSN

1078-0998

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Publication Date

2020-11-19

DOI

10.1093/ibd/izaa023

Peer reviewed

Research sponsored by the Crohn's & Colitis Foundation.

Introduction to and Screening Visit Results of the Multicenter Pediatric Crohn's Disease Growth Study

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Background: Statural growth impairment is more common in males with Crohn's disease (CD). We assessed sex differences in height Z score differences and bone age (BA) Z scores and characterized age of menarche in a novel contemporary cohort of pediatric CD patients undergoing screening for enrollment in the multicenter longitudinal Growth Study.

Methods: Crohn's disease patients (females with chronological age [CA] 5 years and older and younger than 14 years; males with CA 6 years and older and younger than 16 years) participated in a screening visit for the Growth Study. Height BA-Z scores are height Z scores calculated based on BA. Height CA-Z scores are height Z scores calculated based on CA. The height Z score difference equals height CA-Z score minus height BA-Z score.

Results: One hundred seventy-one patients (60% male) qualified for this analysis. Mean CA was 12.2 years. Mean height CA-Z score was −0.4, and mean height BA-Z score was 0.4 in females. Mean height CA-Z score was −0.1, and mean height BA-Z score was 0.2 in males. The absolute value of the mean height Z score difference was significantly greater in females (0.8) than males (0.3; $P = 0.005$). The mean BA-Z score in females (−1.0) was significantly lower than in males (−0.2; $P = 0.002$). The median CA at menarche was 13.6 (95% CI, 12.6–14.6) years.

Conclusions: Our screening visit data suggest that standardized height gain is lower in males with skeletal maturation and delayed puberty is common in females in CD. We are investigating these findings in the ongoing Growth Study.

Key Words: inflammatory bowel disease, sex differences, height velocity, height

INTRODUCTION

Statural growth is a dynamic marker of overall health in children and adolescents. Statural growth impairment is both a marker of and complication of poorly controlled pediatric Crohn's disease (CD) in up to 80% of patients,[1–16] more commonly in males.[1–3, 5, 10, 11, 15, 17, 18] Understanding the etiology of these sex differences in growth impairment may help us to develop new targeted medical treatment strategies to improve height velocity and to optimize current treatments in high-risk patients.[1, 19]

Bone age (BA) assessed by left hand x-ray is regarded as a valid measure of skeletal maturity[15, 20–23] and remaining growth potential. Determination of BA allows clinically meaningful interpretation of growth in the context of skeletal maturity in pediatric CD.[24, 25] In our earlier single-center, cross-sectional study of pediatric CD patients, mean BA Z scores (BA results

Received for publication December 31, 2019; Editorial Decision January 21, 2020.

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Summary: Our prospective multicenter longitudinal Growth Study screening visit data suggest that standardized height gain is lower in males with skeletal maturation, bone age Z scores are lower in females, and delayed puberty is common in females in pediatric Crohn's disease.

Author Contributions: NG obtained funding for this study and prepared the initial and final drafts of the manuscript. NG, RL, HA, and CSL contributed to the concept, design, data management and analyses. NG, RL, HA, FS, DK, AG, RG, AP, SG, and CSL contributed to data collection, data interpretation, and editing and revising the manuscript and provided final approval of the manuscript.

Supported by: NIH/NICHD R01HD075929 (NG), Crohn's and Colitis Foundation Senior Research Award 545496 (NG), Weill Cornell Medicine Department of Pediatrics (NG), and Weill Cornell Medicine Clinical and Translational Scientific Center NIH/NCATS UL1TR002384. The study sponsors had no role in the study design, collection, analysis, interpretation of data, or writing of the report.

Abbreviations: BA, bone age; BA-Z score, Z score calculated based on bone age; BMI, body mass index; CA, chronological age; CA-Z score, Z score calculated based on chronological age; CD, Crohn's disease; IBD, inflammatory bowel disease; NHANES, National Health and Nutrition Examination Survey; SD, standard deviation.

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doi: 10.1093/ibd/izaa023
Published online 19 March 2020

TABLE 1. Definitions of Variables

Variable	Definition
BA Z score	BA results standardized for sex and CA
Height CA-Z score	Height Z score calculated based on CA
Height BA-Z score	Height Z score calculated based on BA
Height Z score difference	Height CA-Z score minus height BA-Z score
Absolute value of the Height Z score difference	The actual magnitude of the Height Z score difference without regard to its sign

standardized for sex and chronological age [CA]) (Table 1) were lower in females,[24] raising the possibility of greater potential for catch-up growth once in remission in females and therefore less growth impairment in females. Chronological age at menarche was later in children with CD than healthy children,[26] supporting delayed puberty in females with CD[27].

Determining the height Z score difference (height Z scores calculated based on CA [height CA-Z scores] minus height Z scores calculated based on BA [height BA-Z scores]; Table 1) allows assessment of standardized height gain in the context of skeletal maturation up to the date these measurements are obtained. Assessment of sex differences in height Z score differences will provide further insight into the potential etiology of sex differences in statural growth impairment in CD. Enrolling a sufficient number of patients to examine sex differences in growth impairment requires multicenter investigation in a novel contemporary cohort.

The Sex Differences in Statural Growth Impairment in Pediatric Crohn's Disease study (also known as the Growth Study)[28] is an ongoing prospective multicenter longitudinal cohort study designed to investigate the underlying mechanisms of sex differences in statural growth impairment in pediatric CD and to develop sex-specific prediction models to identify children at highest risk for developing growth impairment refractory to standard therapeutic approaches. In this first report stemming from the Growth Study, our aims were to (1) assess sex differences in height Z score differences; (2) determine sex differences in BA Z scores; and (3) characterize the timing of menarche in a novel contemporary cohort of patients consenting/assenting to undergo screening for enrollment and participation in the Growth Study.

METHODS

Two hundred three CD patients (females with CA 5 years and older and younger than 14 years; males with CA 6 years and older and younger than 16 years) participated in a screening visit at 1 of 8 medical centers between April 2015 and July 2019 to determine eligibility for enrollment in the Growth Study (1 study visit every 6 months for a total of 5 study visits).[28] Chronological age criteria were established based on our prior cross-sectional study.[1, 24, 26] Puberty is of longer duration in males, explaining the broader age range for eligibility criteria in males. During the screening visit, a patient was deemed eligible to undergo a left hand x-ray for BA if she or he met the following specific criteria, based on our prior cross-sectional study[1, 24, 26]: (1) CD diagnosed (newly or existing because we could adjust for disease duration in our multivariate analyses) by standard clinical, endoscopic, histologic and radiologic criteria; (2) Tanner stage 1–4; (3) no standard of care BA result exceeding Growth Study eligibility criteria (standard of care BA older than 12 years for females or older than 14 years for males exceeds eligibility criteria in order to capture children with significant growth potential remaining, namely at least 3 bone age years of statural growth potential remaining, allowing us to adequately study height velocity during the 2-year follow-up period of the Growth Study[28]); (4) not having completed statural growth as clinically assessed by the standard of care pediatric gastroenterologist; (5) no liver disease; (6) no known cause of growth delay other than CD; (7) no other poorly controlled medical conditions; (8) no history of pregnancy; (9) no history of treatment with growth hormone (GH), testosterone, or estrogen; and (10) available for 24 months of follow-up. If a patient met these specific criteria and had not been exposed to corticosteroids (IV, oral, intranasal, inhaled, rectal, topical, eye drops, swish-and-spit/oral rinse, etc.) in the 56 days[29] preceding the screening visit, a left hand x-ray for BA was obtained. If a patient met these criteria and had been exposed to corticosteroids, the patient was rescreened after 56 days of being corticosteroid free because recent use suppresses the growth hormone axis.

If a patient was eligible for a left hand x-ray for BA based on these specific criteria, it was obtained as part of the screening visit. Bone age results determined whether a patient qualified for enrollment in the Growth Study. All x-rays were interpreted for BA by one of the investigators (RHL), using the standards of Greulich and Pyle,[20] for data analyses.

Race was self-classified as white, black or African American, Asian, American Indian or Alaskan native, native Hawaiian or other Pacific islander, other, unknown or declined. Asian was self-subclassified into South Asian or East Asian. Ethnicity was self-classified as Hispanic or Latino or not Hispanic or Latino. Tanner stage refers to breast development in females and testes/scrotum/penis development in males.

Chronological age and BA refer to the CA and BA of the patient at the screening visit. As BA reference values vary by sex and CA, BA results were transformed into BA Z scores using standard reference values.[30] High BA was defined as BA Z score >2; low BA was defined as BA Z score <−2. Clinical information was collected and self-Tanner staging was performed.[31]

Weight and height were measured using a digital scale to the nearest 0.1 kg and stadiometer to the nearest 0.1 cm, respectively; body mass index (BMI) was calculated as the weight in kg divided by the square of the height in meters. The Z scores

were calculated based on CA and BA for weight, height, and BMI (ie, weight, height, or BMI CA-Z score and weight, height, or BMI BA-Z score) using reference tables from the Centers for Disease Control and Prevention, National Center for Health Statistics.[32] The height Z score difference was calculated as height CA-Z score minus height BA-Z score.

Statistical Analyses

Descriptive statistics were generated for participants' demographic characteristics and key variables of interest. These variables were compared between males and females using the *t* test for continuous variables and χ^2 test for categorical variables. We employed linear regression to assess the sex difference for all outcomes. We also evaluated whether the sex difference was confounded by race, Tanner stage, or steroid exposure via multiple linear regression analyses. Race (white compared with non-white) and Tanner stage (Tanner stage 1 and 2 compared with Tanner stage 3 and 4) were dichotomized due to small numbers in each category when left as multilevel categories. We reported the mean, standard deviation, and range for each outcome by sex and then the *P* values corresponding to the comparison between males and females; *P* values <0.05 were considered statistically significant. Kaplan-Meier curves were generated to show the cumulative incidence of menarche by CA and BA. The SIR/XS version 19 relational database management system software was used to capture and store the data; CITRIX application-server was used to securely transmit the data to SIR/XS over the internet. Data were analyzed using SPSS Version 26.

Ethical Considerations

Each participating site obtained institutional review board approval for the study protocol, and written informed consent and assent were obtained from parents and patients before participation in the screening visit.

RESULTS

As of July 2019, 203 patients completed a screening visit. One hundred seventy-one patients (84%) qualified to obtain a BA and are included in this analysis. Table 2 shows demographic and Tanner stage information for these 171 patients (102 [60%] males). Race and ethnicity did not differ by sex ($P = 0.867$ and $P = 0.686$, respectively). One hundred sixty-five (96.4%) participants were born in the United States, 1 was born (0.6%) in Canada, 2 were born (1.2%) in India, 1 was born (0.6%) in Mexico, 1 was born (0.6%) in Germany, and 1 was born (0.6%) in South Africa. Tanner stage did not differ by sex ($P = 0.845$). The mean CA at screening visit for these patients was 12.2 ± 1.8 (SD; range, 7.3–15.9) years. The mean CA at screening visit for females was 11.6 ± 1.7 (range, 14.0–13.9] years and for males was 12.6 year ± 1.8 (range, 8.5–15.9) years ($P < 0.001$).

The mean height Z score difference was −0.3 ± 1.1 (SD; range, −3.9 to 2.0) in males and −0.8 ± 1.3 (−3.9 to 2.1) in females. The absolute value of the mean height Z score difference (Table 1) was significantly greater in females than males ($P = 0.005$; Fig. 1). The mean weight Z score difference was −0.2 ± 0.8 (range: −3.3 to 1.6) in males and −0.6 ± 0.9 (−3.2 to 1.2) in females. The absolute value of the mean weight Z score difference was significantly greater in females than males ($P = 0.003$). The mean BMI Z score difference was −0.1 ± 0.3 (−1.3 to 0.7) in males and −0.2 ± 0.4 (−1.1 to 0.5) in females. The absolute value of the mean BMI Z score difference was significantly greater in females than males ($P = 0.008$). Results did not change when adjusted for race, Tanner stage, or history of steroid exposure.

The mean BA at screening visit for all patients was 11.6 ± 2.4 (SD; range, 6.0–17.0) years. The mean BA-Z score at screening visit for females (−1.0 ± 1.7; range, −5.4 to 2.5) was significantly lower than in males (−0.2 ± 1.6; range, −5.1 to 4.0; $P = 0.002$). Seventeen (24.6%) females and 7 (6.9%) males ($P = 0.001$) had BA Z score <−2.0. 3 (4.3%) females and 8 (7.8%) males ($P = 0.528$) had BA Z score >2.0. Results did not change when adjusted for race, Tanner stage, or history of steroid exposure.

Menarche had occurred in 16 (23.2%) of 69 females. Figure 2 shows the cumulative incidence of menarche by CA. The median CA at menarche was 13.6 years (95% CI, 12.6 to 14.6 years). Figure 3 shows the corresponding estimate of the cumulative incidence of menarche on the BA time scale for CD patients.

DISCUSSION

Analyses of our data collected from a novel contemporary cohort of pediatric CD patients (females with CA 5 years and older and younger than 14 years; males with CA 6 years and older and younger than 16 years) participating in a screening visit for the Growth Study revealed that the absolute value of the mean height Z score difference was greater in females than males, indicating that standardized height gain is lower in males with BA progression (ie, skeletal maturation) up to the date of the screening visit, reflecting poorer statural growth in males. Higher frequency of growth impairment in males with CD has now been reported by several investigators.[1–3, 5, 10, 11, 15, 17, 18] Though our data suggest that BA progression was intact in both males and females at the time of the screening visit (ie, mean BA Z scores for each sex >−2), mean BA Z scores were lower in females, suggesting the possibility of greater potential for catch-up growth and therefore less growth impairment in females. Fourteen percent of all patients had BA Z scores <−2, which is 6 times what is expected (2.3%) for the general population. The frequency of BA Z scores <−2 was significantly greater in females. The median CA at menarche was older than reports in healthy females,[26, 33] supporting delayed puberty in females with CD, as in our

TABLE 2. Demographics and Tanner Stage

	N	Percent
Sex		
Female	69	40.4%
Male	102	59.6%
Race		
Asian	8	4.7%
East Asian	3	
South Asian	5	
Black/African American	19	11.1%
Other	4	2.3%
White	139	81.3%
Declined	1	0.6%
Ethnicity		
Hispanic or Latino	6	3.5%
Not Hispanic or Latino	165	96.5%

			Males		Females	
Tanner Stage			**N**	**%**	**N**	**%**
1	53	31.2%	30	29.4%	23	33.8%
2	45	26.5%	26	25.5%	19	27.9%
3	34	20.0%	22	21.6%	12	17.6%
4	38	22.3%	24	23.5%	14	20.6%

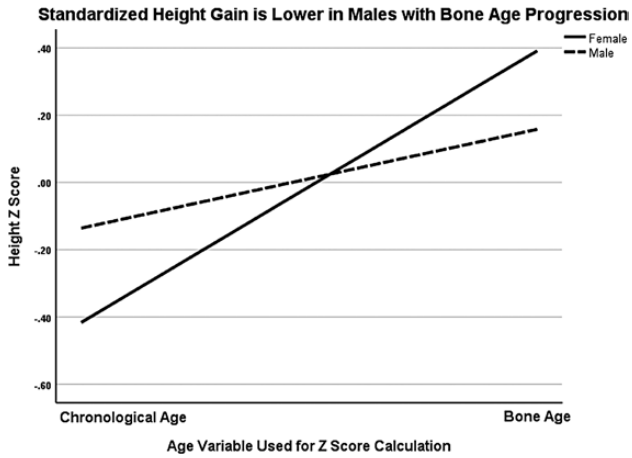

FIGURE 1. Mean height CA-Z score was −0.4 ± 1.0 (standard deviation), and mean height BA-Z score was 0.4 ± 1.2 in females. Mean height CA-Z score was −0.1 ± 1.0, and mean height BA-Z score was 0.2 ± 0.9 in males. The slope of each regression line represents the mean height z score difference. The significantly steeper slope for females (solid regression line) than that for males (dashed regression line) indicates a significantly greater mean height Z score difference in females than in males ($P = 0.005$).

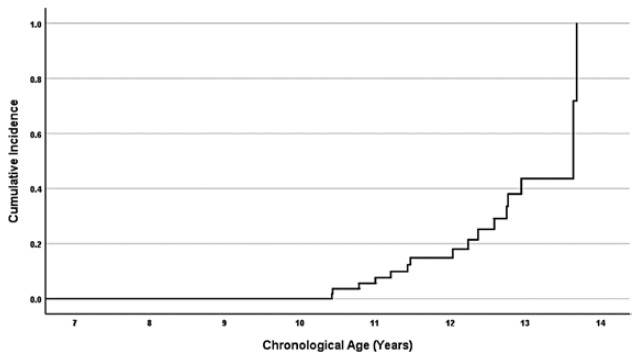

FIGURE 2. Cumulative incidence of menarche in females by chronological age (years). The Kaplan-Meier survival curve shows the cumulative incidence of menarche at CA 11, 12, 13, and 14 years was 7.6% (95% CI, 0.3–14.5%), 18.0% (6.4–29.6%), 43.6% (24.4–62.8%), and 100% in female pediatric Crohn's disease patients participating in a screening visit (N = 69).

prior cross-sectional study.[26] Bone age at the time of menarche in CD is similar to that in previous reports of healthy children,[34–36] as in our prior cross-sectional study.[26]

In our current report of pediatric CD patients, the median CA at menarche was 13.6 years, similar to our prior report of 13.9 years.[26] We previously reported the median CA of menarche in the 2007–2008 National Health and Nutrition Examination Survey (NHANES) cohort was 12.0 years,[26] similar to the 12.4 years reported in the third NHANES cohort.[33] Delayed menarche is often seen in children with chronic

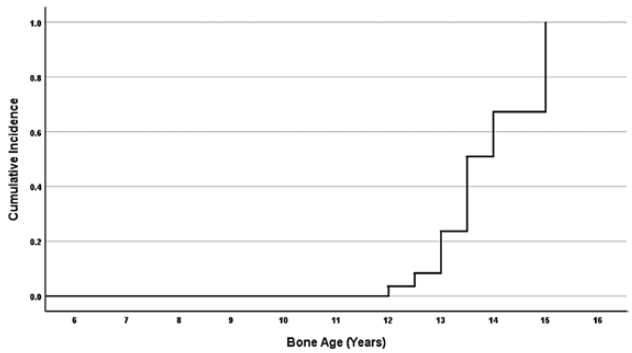

FIGURE 3. Cumulative incidence of menarche in females by bone age (years). The Kaplan-Meier survival curve shows the cumulative incidence of menarche based on BA in female pediatric Crohn's disease patients participating in a screening visit (N = 69). The probability of menarche was 68% at BA 14.0 years and increased to 100% at BA greater than 15.0 years.

inflammatory conditions, such as juvenile idiopathic arthritis, systemic lupus erythematosus, and cystic fibrosis.[37] Bone age at menarche has been reported as 13.0 years,[35] 13.1 years,[36] and 13.5 years[34] in healthy children, similar to BA at the time of menarche in CD in this cohort and in the cohort in our prior cross-sectional study.[26]

Considering the varying definitions of growth impairment used in different studies, taken together, the existing literature suggests that the frequency of statural growth impairment in pediatric CD has not changed in over 25 years,[1–16] despite the introduction of several new biologic therapeutic agents to the IBD armamentarium. Because treatment strategies for improving growth impairment and final adult height in CD remain suboptimal,[3, 8] a better understanding of the underlying mechanisms of growth impairment is required.

We are using the male-female dichotomy in risk for growth impairment in CD as a window for understanding the effects of inflammation on growth in both sexes.[28] Sex is an important biological variable. Studying sex differences in growth impairment in CD will contribute to a deeper useful understanding of mechanisms of growth impairment and thus lead to the development of new targeted medical treatment strategies to improve height velocity and final adult height and to optimize current treatments in high-risk patients in both sexes.

The impact of CD on growth is mediated by many factors including inflammation, genetics, nutrition, and medications. The defining hallmark of CD is inflammation. Growth impairment may be associated with ongoing intestinal inflammation, even in the absence of intestinal symptoms. Insulin-like growth factor-1 (IGF-1) is the primary mediator of GH's effects on statural growth, and sex steroids have a direct effect on the pubertal growth spurt. In our prior single-center, cross-sectional study,[1] we found that IGF-1 Z scores were lower in males. Nonspecific inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin levels predicted IGF-1 Z scores but did not differ by sex, and were associated with testosterone and luteinizing hormone Z scores in males but not with estradiol and follicle stimulating hormone Z scores in females. These results suggest that the inflammation characteristic of CD has worse effects on hormone levels in males and that these negative inflammatory effects may explain the increased susceptibility to growth impairment in males. However, the specific underlying mechanisms of this sex difference in risk for growth impairment in CD remains poorly understood. We are investigating these intriguing single-center, cross-sectional findings and the findings from the screening visit of the Growth Study reported in this article in the ongoing prospective multicenter longitudinal Growth Study.

For patients qualifying for enrollment in the prospective multicenter longitudinal Growth Study[28] based on screening visit BA results (ie, BA results that show potential for significant growth in stature remaining), we are obtaining serial measurements of growth and BA, allowing us to examine standardized height velocity and standardized BA progression. We will clarify determinants of BA and patterns of BA advancement by sex in this prospective longitudinal study. We are collecting serial measurements of inflammatory markers and hormone levels, nutrient intake assessments, and clinically important variables. We will determine sex differences in the impact of inflammation on the hypothalamic-pituitary-gonadal axis, the growth hormone/IGF-1 axis, and height velocity. We will identify factors that classify a patient as high risk for developing growth impairment refractory to standard approaches to therapy. These patients may benefit from early introduction of aggressive medical therapies.

SUMMARY AND CONCLUSIONS

Our screening visit data suggest that standardized height gain is lower in males than females with skeletal maturation, supporting more frequent growth impairment in males. The higher frequency of growth impairment in males seems to be due to this lower standardized height gain with BA progression rather than advanced BA progression. In addition, our data support that delayed puberty is common in females with CD. The persistence of a sex difference in growth impairment in a novel contemporary cohort, despite the introduction of new treatment agents since the publication of earlier studies, suggests that in the future our approach to treatment will likely be sex-specific.

We are investigating these initial findings in the ongoing prospective multicenter longitudinal Growth Study.[28] Addressing these critical gaps in our understanding of the underlying mechanisms of sex differences in growth impairment in CD will have significant implications for the clinical management of these patients. Determining the specific pathways affected by inflammation in CD will allow us to identify targeted medical treatment strategies requiring further study. Developing sex-specific prediction models to identify patients

at highest risk for growth impairment refractory to standard therapeutic approaches will identify candidates for appropriate early aggressive therapy. Multicenter prospective longitudinal collaborations are required to advance our science and therefore the care of our patients.

ACKNOWLEDGEMENTS

The authors thank Dr. Joel Rosh and his team for screening/enrolling patients and submitting data for the study. They thank the patients at all sites for participating in this study and their families for their support. They thank their colleagues for informing patients and families about the Growth Study. They thank the entire multicenter Growth Study team.

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