

World Journal of *Gastroenterology*

World J Gastroenterol 2018 May 14; 24(18): 1925-2046



**REVIEW**

- 1925** Gastrointestinal stromal tumors: A multidisciplinary challenge
Sanchez-Hidalgo JM, Duran-Martinez M, Molero-Payan R, Rufian-Peña S, Arjona-Sanchez A, Casado-Adam A, Cosano-Alvarez A, Briceño-Delgado J
- 1942** New therapeutic options opened by the molecular classification of gastric cancer
Chivu-Economescu M, Matei L, Necula LG, Dragu DL, Bleotu C, Diaconu CC
- 1962** Ambiguous roles of innate lymphoid cells in chronic development of liver diseases
Shen Y, Li J, Wang SQ, Jiang W

MINIREVIEWS

- 1978** Laparoscopic gastrojejunostomy for gastric outlet obstruction in patients with unresectable hepatopancreatobiliary cancers: A personal series and systematic review of the literature
Manuel-Vázquez A, Latorre-Fragua R, Ramiro-Pérez C, López-Marciano A, De la Plaza-Llamas R, Ramia JM
- 1989** Mouse models for investigating the underlying mechanisms of nonalcoholic steatohepatitis-derived hepatocellular carcinoma
Takakura K, Oikawa T, Tomita Y, Mizuno Y, Nakano M, Saeki C, Torisu Y, Saruta M

ORIGINAL ARTICLE**Basic Study**

- 1995** Microbiota modification by probiotic supplementation reduces colitis associated colon cancer in mice
Mendes MC, Paulino DS, Brambilla SR, Camargo JA, Persinoti GF, Carnevalheira JB
- 2009** Ischemia/reperfusion injury in porcine intestine - Viability assessment
Strand-Amundsen RJ, Reims HM, Reinholt FP, Ruud TE, Yang R, Høgetveit JO, Tønnessen TI

Clinical Trials Study

- 2024** Quantitative assessment of hepatic fibrosis in chronic hepatitis B and C: T1 mapping on Gd-EOB-DTPA-enhanced liver magnetic resonance imaging
Pan S, Wang XQ, Guo QY

Observational Study

- 2036** Thiopurines are negatively associated with anthropometric parameters in pediatric Crohn's disease
Gupta N, Lustig RH, Chao C, Vittinghoff E, Andrews H, Leu CS

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Andrew Stewart Day, MD, Professor, Paediatrics Department, University of Otago, Christchurch 8041, New Zealand

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports[®] cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Yan Huang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Jiao Wang*
Proofing Editorial Office Director: *Ze-Mao Gong*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

Stephen C Strom, PhD, Professor, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE
Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE
May 14, 2018

COPYRIGHT
© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.f6publishing.com>

Observational Study

Thiopurines are negatively associated with anthropometric parameters in pediatric Crohn's disease

Neera Gupta, Robert H Lustig, Cewin Chao, Eric Vittinghoff, Howard Andrews, Cheng-Shiun Leu

Neera Gupta, Division of Gastroenterology and Nutrition, Department of Pediatrics, Weill Cornell Medicine, New York, NY 10021, United States

Robert H Lustig, Division of Endocrinology, Department of Pediatrics, University of California, San Francisco, San Francisco, CA 94158, United States

Cewin Chao, Department of Nutrition and Food Services, University of California, San Francisco, San Francisco, CA 94143, United States

Eric Vittinghoff, Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA 94158, United States

Howard Andrews, Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY 10032, United States

Cheng-Shiun Leu, Department of Biostatistics, Columbia University Medical Center, New York, NY 10032, United States

ORCID number: Neera Gupta (0000-0002-9571-3913); Robert H Lustig (0000-0001-6983-2639); Cewin Chao (0000-0002-5711-926X); Eric Vittinghoff (0000-0001-8535-0920); Howard Andrews (0000-0002-7726-0551); Cheng-Shiun Leu (0000-0002-0301-8316).

Author contributions: Gupta N initial concept, secured funding; Gupta N, Lustig RH, Vittinghoff E and Leu CS study design; Gupta N data collection; Lustig RH bone age interpretation; Chao C anthropometric measurements; Gupta N and Leu CS data management; Gupta N, Vittinghoff E and Leu CS statistical analyses; Gupta N, Lustig RH, Chao C, Vittinghoff E, Andrews H and Leu CS data interpretation; Gupta N initial manuscript preparation; Gupta N, Lustig RH, Chao C, Vittinghoff E, Andrews H and Leu CS manuscript editing and revising; Gupta N finalized submission.

Supported by National Institutes of Health, No. DK077734 (NG); Children's Digestive Health and Nutrition Foundation (now known as North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Foundation)/Crohn's and Colitis

Foundation of America (now known as Crohn's and Colitis Foundation) Award for New Investigators, No. CDHNF-06-002 (NG); Crohn's and Colitis Foundation of America (now known as Crohn's and Colitis Foundation) Career Development Award, No. Award ID 1743 (NG); University of California San Francisco Department of Pediatrics Pediatric Clinical Research Center Clinical Research Pilot Funding Award (NG), and National Institutes of Health/National Center for Research Resources University of California San Francisco-Clinical and Translational Science Institute, No. UL1 RR024131.

Institutional review board statement: We obtained Institutional Review Board Approval for the study protocol.

Conflict-of-interest statement: Robert H Lustig wrote two trade books on metabolic health, but not related to the issues of this paper. The other authors have no conflicts of interest relevant to this article to disclose.

STROBE statement: The guidelines of the STROBE Statement have been adopted.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Neera Gupta, MD, MAS, Associate Professor, Division of Gastroenterology and Nutrition, Department of Pediatrics, Weill Cornell Medicine, 505 East 70th Street, Helmsley Tower, 3rd Floor, New York, NY 10021, United States. neg9020@med.cornell.edu
Telephone: +1-646-9623869
Fax: +1-646-9620246

Received: February 3, 2018

Peer-review started: February 3, 2018

First decision: February 20, 2018
 Revised: April 12, 2018
 Accepted: April 26, 2018
 Article in press: April 26, 2018
 Published online: May 14, 2018

Group Inc. All rights reserved.

Abstract

AIM

To determine the distribution of anthropometric parameter (AP)-z-scores and characterize associations between medications/serum biomarkers and AP-z-scores in pediatric Crohn's disease (CD).

METHODS

CD patients [$<$ chronological age (CA) 21 years] were enrolled in a cross-sectional study. Descriptive statistics were generated for participants' demographic characteristics and key variables of interest. Paired *t*-tests were used to compare AP-z-scores calculated based on CA (CA z-scores) and bone age (BA) (BA z-scores) for interpretation of AP's. Linear regression was utilized to examine associations between medications and serum biomarkers with AP-z-scores calculated based on CA ($n = 82$) and BA ($n = 49$). We reported regression coefficients as well as their corresponding p-values and 95% confidence intervals.

RESULTS

Mean CA at the time of the study visit was 15.3 ± 3.5 (SD; range = 4.8-20.7) years. Mean triceps skinfold ($P = 0.039$), subscapular skinfold ($P = 0.002$) and mid-arm circumference (MAC) ($P = 0.001$) BA z-scores were higher than corresponding CA z-scores. Medications were positively associated with subscapular skinfold [adalimumab ($P = 0.018$) and methotrexate ($P = 0.027$)] and BMI CA z-scores [adalimumab ($P = 0.029$)]. Azathioprine/6-mercaptopurine were negatively associated with MAC ($P = 0.045$), subscapular skinfold ($P = 0.014$), weight ($P = 0.002$) and BMI ($P = 0.013$) CA z-scores. ESR, CRP, and WBC count were negatively associated, while albumin and IGF-1 BA z-scores were positively associated, with specific AP z-scores ($P < 0.05$). Mean height CA z-scores were higher in females, not males, treated with infliximab ($P = 0.038$). Hemoglobin ($P = 0.018$) was positively associated, while platelets ($P = 0.005$), ESR ($P = 0.003$) and CRP ($P = 0.039$) were negatively associated with height CA z-scores in males, not females.

CONCLUSION

Our results suggest poor efficacy of thiopurines and a possible sex difference in statural growth response to infliximab in pediatric CD. Prospective longitudinal studies are required.

Key words: Inflammatory bowel disease; Azathioprine/6-mercaptopurine; Biologics; Nutrition

© The Author(s) 2018. Published by Baishideng Publishing

Core tip: Azathioprine/6-mercaptopurine were negatively associated with specific anthropometric parameters, suggesting a possible negative effect vs poor efficacy of thiopurines in pediatric Crohn's disease (CD). Infliximab was positively associated with standardized height in females only, suggesting a possible sex difference in response to infliximab from the standpoint of statural growth in pediatric CD. Specific serum biomarkers were associated with standardized height in males only, supporting that inflammation has a more detrimental effect on statural growth in males with pediatric CD.

Gupta N, Lustig RH, Chao C, Vittinghoff E, Andrews H, Leu CS. Thiopurines are negatively associated with anthropometric parameters in pediatric Crohn's disease. *World J Gastroenterol* 2018; 24(18): 2036-2046 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i18/2036.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i18.2036>

INTRODUCTION

Several studies document alterations in anthropometric parameters in pediatric Crohn's disease (CD) such as lean mass deficits^[1-5], reductions in fat free mass^[6,7], fat mass deficits^[3,5,7], low body mass index (BMI)^[1-3,5-8], high BMI^[7,8], and low height^[1-3,5,9,10]. Similar to impaired statural growth (height velocity), a dynamic marker of disease status, body composition deficits may reflect poorly controlled disease despite the absence of overt clinical intestinal symptoms.

Delayed bone age (BA) is common in pediatric CD^[10-16]. BA assessed by left hand X-ray is regarded as a valid measure of skeletal maturity^[13-14,17-19]. Determination of BA allows clinically meaningful interpretation of growth in the context of skeletal maturity in pediatric CD^[11]. Mean height, weight and BMI z-scores calculated based on BA (BA z-scores) are higher than corresponding z-scores calculated based on chronological age (CA) (CA z-scores) in pediatric CD^[11].

The impact of accounting for BA in the interpretation of body composition is unclear. Accurate interpretation of body composition is important since it reflects nutritional^[4] and disease status. Not only is nutritional status an important determinant of pubertal development and growth velocity^[20], it is a prognostic factor for disease course^[21-28]. Several factors affect nutritional status, including inflammation, medications, nutrient intake, and hormones^[4,29,30]. The association between medications and serum inflammatory and hormonal biomarkers with anthropometric measurements is not well delineated in pediatric CD, particularly after adjusting for maturational status (BA).

Nutritional status is an important factor to consider when making therapeutic decisions given its association with poor outcomes^[21-28]. Yet, the impact of treatments

on anthropometric measurements is poorly defined and has not received sufficient attention^[31]. While there are well-documented sex differences in risk for statural growth impairment^[9-10,14,21,32-35], sex differences in nutritional status require further study. Data regarding the relationship between medications and serum biomarkers with anthropometric parameters by sex, an important biological variable, are lacking.

Here we assessed body composition by skinfold measurements in pediatric CD. Our aims were to (1) determine the distribution of anthropometric parameters based on CA (CA z-scores) and BA (BA z-scores); and (2) characterize the associations between medications and serum biomarkers with anthropometric parameter z-scores in pediatric CD.

MATERIALS AND METHODS

Pediatric CD patients < CA 21 years enrolled in this cross-sectional study at University of California, San Francisco (UCSF) between January 2007 and July 2009 as previously described^[10-11,36]. We excluded patients who received growth hormone ever or corticosteroids within 2 mo prior to study participation since more recent use would suppress the somatotrophic axis and interfere with accurate assessment of insulin-like growth factor-1 (IGF-1) levels. Eighty-two patients completed the study.

Mid-arm circumference measurements and skinfold thickness measurements were collected to the nearest 0.1 mm from the non-dominant side of the body in triplicate and averaged. A measuring tape was used for mid-arm circumference measurements and Lange skinfold calipers were used for skinfold thickness measurements. The mid-arm circumference measurement was obtained at the mid-point between the olecranon process and acromion. The triceps skinfold measurement was obtained at the mid-point of the upper arm, halfway between the acromion and the olecranon. The subscapular skinfold was measured at a 45° angle just below the inferior angle of the scapula. One of two registered dietitians obtained the measurements. Both were trained using standardized NHANES methodologies with established inter-rater reliability^[37]. Weight and height were measured using a digital scale (Scale-Tronix, White Plains, NY, United States) to the nearest 0.1 kg and stadiometer (Proscale, Accurate Technology, Inc., Cincinnati, OH, United States) 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. Self-Tanner staging was performed^[38]. Left hand x-rays obtained for BA were blindly interpreted by RL using the standards of Greulich and Pyle^[17].

Medications of interest included adalimumab, 5-aminosalicylates, antibiotics, azathioprine/6-mercaptopurine (thiopurines), infliximab, and methotrexate.

We classified disease location as esophagus or stomach; small bowel, no colon; small bowel and colon; colon, no small bowel; perianal.

A lab draw was performed to measure serum IGF-1, insulin-like growth factor binding protein 3 (IGFBP-3), testosterone, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), albumin, alkaline phosphatase, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin, platelets, and white blood cell (WBC) count. Tubes for serum hormone levels and routine clinical labs were processed by Esoterix Endocrinology (Calabasas Hills, CA, United States) and UCSF clinical lab, respectively. Clinical information was collected.

Statistical analysis

We calculated CA z-scores for IGF-1, IGFBP-3, estradiol, testosterone, FSH, LH, mid-arm circumference, triceps skinfold, subscapular skinfold, weight, height, and BMI using reference values based in part on CA. Because pubertal growth acceleration correlates more closely with BA than CA^[39], we also calculated BA z-scores for all 17 females ≤ CA 15 and 32 males ≤ CA 17 years, as epiphyses close at BA 15 in females and 17 years in males. We excluded all females > CA 15 and males > CA 17 years from BA analyses because sufficient reference data on variability of BA beyond these CA thresholds are not available. We transformed mid-arm circumference, triceps skinfold, subscapular skinfold, weight, height, and BMI measurements to z-scores^[40-45]. Means and standard deviations (SDs) provided by Esoterix Endocrinology were used to calculate IGF-1 and IGFBP-3 z-scores. The mean and the upper and lower bounds of the normal ranges (specific to sex, age, and Tanner stage), accounting for asymmetry about the mean if present, were used to compute SDs for gonadotropins and sex hormones. Low and high z-scores are defined as z-scores < -2.0 and > 2.0, respectively.

Descriptive statistics were generated for participants' demographic characteristics and key variables of interest. Paired t-tests were used to compare CA z-scores and BA z-scores for interpretation of anthropometric parameters. We employed linear regression to assess the associations between predictors (medications and serum biomarkers) and outcomes (anthropometric parameter CA z-scores and BA z-scores). For outcomes based on CA z-scores ($n = 82$), we also conducted analyses including CA at study visit, sex, CRP, albumin, ESR, and hemoglobin in the model to adjust for potential confounding. We conducted additional analyses adjusting for disease activity indices, disease duration, stricturing disease and penetrating disease in these models. We analyzed height CA z-scores separately by sex because of well-established sex differences in risk for statural growth impairment^[9-10,14,21,32-35]. We reported regression coefficients as well as their corresponding p-values and 95% confidence intervals (CI); P -values < 0.05 were considered as statistically significant. Data were analyzed using IBM SPSS Statistics 23.

Ethical considerations

We obtained Institutional Review Board Approval for the study protocol. Informed consent/assent were obtained

Table 1 Demographics, Tanner stage, disease location, and medications

Item	n (%)
Race	
Asian	12 (14.6)
East Asian	6
South Asian	6
Black/African American	1 (1.2)
Other	4 (4.9)
White	65 (79.3)
Ethnicity	
Hispanic or Latino	7 (8.5)
Not Hispanic or Latino	75 (91.5)
Tanner stage	
1	8 (9.8)
2	15 (18.3)
3	16 (19.5)
4	24 (29.3)
5	19 (23.2)
Disease location	
Esophagus or stomach	9 (11)
Small bowel, no colon	12 (14.6)
Colon, no small bowel	17 (20.7)
Small bowel and colon	53 (64.6)
Perianal disease	49 (59.8)
Medication	
Adalimumab	4 (4.9)
5-Aminosalicylates	50 (61.0)
Antibiotics	14 (17.1)
Azathioprine/6-Mercaptopurine	44 (53.7)
Infliximab	20 (24.4)
Methotrexate	7 (8.5)
Steroids ever	55 (67.1)

from parents/patients.

RESULTS

Participant characteristics

82 patients completed the study; 35 (43%) were female^[10]. Mean CA at the time of the study visit was 15.3 ± 3.5 (SD; range = 4.8-20.7) years^[10]. Mean CA at the time of inflammatory bowel disease (IBD) diagnosis was 12.1 ± 3.8 (0.5-17.9) years. Mean time since IBD diagnosis was 3.4 ± 2.8 (0.01-12.0) years. Race/ethnicity, Tanner stage, disease location, and medications are summarized in Table 1. History of corticosteroid use did not differ by sex^[10].

Monotherapy vs combination therapy

Of the 44 patients on azathioprine/6-mercaptopurine, 33 (75%) were on thiopurine monotherapy, 10 (23%) were on combination therapy with infliximab and 1 (2%) was on combination therapy with adalimumab.

Of the 7 patients on methotrexate, 3 (43%) were on monotherapy, 2 (28.5%) were on combination therapy with infliximab and 2 (28.5%) were on combination therapy with adalimumab.

Of the 20 patients on infliximab, 8 (40%) were on monotherapy, 10 (50%) were on combination therapy with thiopurines and 2 (10%) were on combination therapy with methotrexate.

Of the 4 patients on adalimumab, 1 (25%) was on monotherapy, 1 (25%) was on combination therapy with thiopurines, 2 (50%) were on combination therapy with methotrexate.

Anthropometric parameters

Anthropometric parameters are summarized in Table 2.

Bone age vs chronological age for the interpretation of anthropometric parameters

For the 49 patients qualifying for BA analyses, mean BA (12.2 ± 2.9 years) was significantly lower than mean CA (13.1 ± 2.6 years) ($P < 0.0001$)^[10]. Mid-arm circumference (0.35 units, 95%CI: 0.14-0.55; $P = 0.001$), subscapular skinfold (0.10 units, 95%CI: 0.04-0.16; $P = 0.002$), and triceps skinfold (0.05 units, 95%CI: 0.003-0.11; $P = 0.039$) BA z-scores were systematically higher than corresponding CA z-scores.

Medications, serum biomarkers, and anthropometric parameters

Tables 3 and 4 show the unadjusted and adjusted associations, respectively, between medication treatment, serum biomarkers and anthropometric parameter CA z-scores (height CA z-scores presented separately) that achieved statistical significance. Infliximab was not statistically significantly associated with mid-arm circumference, triceps skinfold, subscapular skinfold, weight or BMI CA z-scores (data not shown). Results did not change when disease activity indices, disease duration, stricturing disease or penetrating disease were included in the adjusted models.

Table 5 shows the unadjusted associations between serum biomarkers and anthropometric parameter BA z-scores (height BA z-scores presented separately). Medication treatments were not statistically significantly associated with anthropometric parameter BA z-scores.

Table 6 shows the unadjusted associations between medications, serum biomarkers and height CA z-scores by sex.

Table 7 shows the unadjusted association between serum biomarkers and height BA z-scores. Medications were not statistically significantly associated with height BA z-scores.

DISCUSSION

In our prospective, cross-sectional study, azathioprine/6-mercaptopurine were negatively associated with lean tissue mass (mid-arm circumference CA z-scores) and fat store (subscapular CA z-scores) measurements, and weight CA z-scores and BMI CA z-scores in pediatric CD. We previously reported thiopurine treatment was associated with lower standardized BA results^[11]. From a mechanistic perspective, it is unlikely these associations represents a direct negative impact of thiopurines on skeletal maturation or anthropometric parameters. When examining the association between

Table 2 Summary of anthropometric parameters

Variable (<i>n</i>)	Mean \pm SD	Range	Percent with z-scores > 2 (%)	Percent with z-scores < -2 (%)
Mid-arm circumference-CA-z-score <i>n</i> = 82	-0.64 \pm 1.39	-5.03 to 2.88	2	17
Mid-arm circumference-BA-z-score <i>n</i> = 49	-0.54 \pm 1.30	-2.86 to 2.50	2	16
Subscapular skinfold-CA-z-score <i>n</i> = 81	0.59 \pm 0.83	-1.56 to 2.31	3	0
Subscapular skinfold-BA-z-score <i>n</i> = 48	0.64 \pm 0.87	-1.17 to 2.27	4	0
Triceps-CA-z-score <i>n</i> = 81	1.02 \pm 0.74	-0.88 to 2.79	11	0
Triceps-BA-z-score <i>n</i> = 49	1.10 \pm 0.72	-1.17 to 2.47	8	0
Height-CA-z-score <i>n</i> = 82	-0.30 \pm 1.02	-2.74 to 2.34	1	6
Height-BA-z-score <i>n</i> = 49	0.17 \pm 1.12	-3.29 to 2.53	4	2
Weight CA-z-score <i>n</i> = 82	-0.17 \pm 1.10	-3.49 to 2.20	4	5
Weight BA-z-score <i>n</i> = 49	0.11 \pm 0.91	-2.52 to 1.97	0	2
BMI-CA-z-score <i>n</i> = 82	-0.07 \pm 1.04	-2.78 to 2.17	4	4
BMI BA-z-score <i>n</i> = 49	0.05 \pm 0.86	-2.58 to 2.09	2	2

BA z-score: z score based on bone age; BMI: Body mass index; CA z-score: z score based on chronological age.

Table 3 Significant associations between medications/serum biomarkers and anthropometric parameters [z-scores based on chronological age (*n* = 82)] - unadjusted analyses

Variable	Mid-arm circumference CA-z-scores	Subscapular skinfold CA-z-scores	Weight CA-z-scores	BMI CA-z-scores
Adalimumab		0.90 ¹ (0.08, 1.72) ² 0.033 ³		1.09 (0.05, 2.13) 0.04
Azathioprine	-0.65 (-1.25, -0.05) 0.033	-0.5 (-0.85, -0.14) 0.006	-0.7 (-1.16, -0.23) 0.004	-0.56 (-1.004, -0.12) 0.014
Methotrexate		0.75 (0.06, 1.43) 0.032		
ESR	-0.024 (-0.05, -0.002) 0.036		-0.03 (-0.05, -0.02) 0.0003	-0.02 (-0.04, -0.006) 0.009
Hemoglobin			0.19 (0.04, 0.34) 0.015	

¹Regression coefficient for unadjusted analyses [*i.e.*, one medication or serum biomarker (independent variable) per model and no adjustment for potential confounding]; ²(95% confidence interval); ³P-value. BMI: Body mass index; CA z-score: z score based on chronological age; ESR: Erythrocyte sedimentation rate.

azathioprine/6-mercaptopurine and BA z-scores for these specific anthropometric parameters, the direction of the association remained negative between thiopurines and subscapular skinfold BA z-scores (though did not achieve statistical significance due to smaller sample size (*n* = 49 for BA analyses vs *n* = 82 for CA analyses). This continued negative association between thiopurines and subscapular skinfold BA z-scores in combination with our previously reported finding of a negative association between thiopurines and standardized BA results^[11] calls into question the efficacy of thiopurines for treating pediatric CD. Our findings highlight the importance of considering BA in the interpretation of anthropometric parameters because its inclusion clarifies the relationship between medications and these outcomes.

Previously published data on the impact of thiopurines on anthropometry for comparison to our findings are limited, but also raise concerns about the efficacy of these medications. Csontos *et al.*^[31] reported no statistically significant difference in the change in fat free mass index, skeletal muscle index, or body fat mass index in adult IBD patients on vs not on

azathioprine during initiation of biologic therapy. In newly diagnosed CD children randomized to treatment with 6-mercaptopurine plus steroids vs placebo plus steroids, Markowitz *et al.*^[46] did not detect a difference in statural growth.

Regarding a possible negative impact of utilizing thiopurines, in a pediatric IBD cohort, Hyams *et al.*^[47] reported thiopurine exposure is an important preceding event for the development of malignancy or hemophagocytic lymphohistiocytosis. Our data identify another negative signal associated with thiopurines, given the constellation of findings of statistically significant negative associations between azathioprine/6-mercaptopurine and mid-arm circumference, subscapular skinfold, weight and BMI CA z-scores and persistent negative association with subscapular skinfold BA z-scores (though did not achieve statistical significance due to smaller sample size available for BA analyses), in combination with our previously reported finding of a statistically significant association with lower standardized BA results^[11]. Prospective longitudinal study is required to examine the longitudinal pattern of these associations and to investigate whether

Table 4 Significant associations between medications/serum biomarkers and anthropometric parameters [z-scores based on chronological age (*n* = 82)] - adjusted analyses

Variable	Mid-arm circumference CA-z-scores	Subscapular skinfold CA-z-scores	Weight CA-z-scores	BMI CA-z-scores
Adalimumab		1.02 ¹ (0.18, 1.86) ²		1.17 (0.13, 2.21)
Azathioprine	-0.64 (-1.26, -0.02)	0.018 ³ -0.47 (-0.83, -0.10)	-0.73 (-1.17, -0.29)	0.029 -0.58 (-1.03, -0.12)
Methotrexate	0.045	0.014 0.81 (0.10, 1.53)	0.002	0.013
ESR		0.027	-0.03 (-0.05, -0.01)	-0.03 (-0.05, -0.004)
			0.01	0.024

¹Regression coefficient for adjusted analyses [*i.e.*, one medication or serum biomarker (independent variable) per model and CA at study visit, sex, CRP, albumin, ESR and hemoglobin are included in the model to adjust for potential confounding]; ²(95% confidence interval); ³P-value. BMI: Body mass index; CA z-score: z score based on chronological age; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 5 Significant associations between serum biomarkers and anthropometric parameters [z-scores based on bone age (*n* = 49)] - unadjusted analyses

Variable	Mid-arm circumference BA-z-scores	Subscapular skinfold BA-z-scores	Triceps skinfold BA-z-scores	Weight BA-z-scores	BMI BA-z-scores
WBC	-0.19 ¹ (-0.36, -0.02) ²	-0.12 (-0.24, -0.01)		-0.16 (-0.28, -0.04)	
ESR	0.029 ³	0.04		0.008 -0.03 (-0.04, -0.01)	-0.02 (-0.03, -0.001)
CRP			-0.03 (-0.07, -0.0001)	0.003 -0.06 (-0.10, -0.02)	0.037
Albumin			0.049	0.008 0.73 (0.28, 1.18)	
IGF-1 BA-z-scores				0.002 0.2 (0.01, 0.38)	
				0.039	

¹Regression Coefficient for Unadjusted Analyses [*i.e.*, one serum biomarker (independent variable) per model and no adjustment for potential confounding]; ²(95% confidence interval); ³P-value. BA z-score: z score based on bone age; BMI: Body mass index; WBC: White blood cell; ESR: Erythrocyte sedimentation rate; IGF-1: Insulin-like growth factor-1; CRP: C-reactive protein.

these findings represents a lack of efficacy of thiopurines (given that anthropometric parameters and skeletal maturation reflect nutritional status/disease status) vs a direct negative impact of thiopurines in pediatric CD. Patients with lower body composition z-scores and lower standardized BA results were not selectively placed on thiopurines vs another medication such as methotrexate, infliximab, or adalimumab as these measurements were obtained at the time of the study.

Adalimumab and methotrexate were positively associated (statistically significant) with measurements of fat mass [subscapular CA z-scores (adalimumab/methotrexate)] and BMI CA z-scores (adalimumab). While these medications were not statistically significantly associated with these outcome BA z-scores due to a smaller sample size available for BA analyses, the direction of these associations (positive) remained

unchanged and the effect sizes were similar to only mildly decreased compared with the statistically significant positive associations between these medications and these outcome CA z-scores, supporting a positive association between adalimumab and methotrexate with these anthropometric parameter BA z-scores.

Similar to our finding of a positive association between the anti-tumor necrosis factor alpha (TNF- α) agent, adalimumab, and BMI, Diamanti *et al.*^[48] reported that weight and BMI improved in children treated with infliximab, but not with mesalazine and azathioprine. Wiese *et al.*^[49] reported a significant increase in BMI with infliximab treatment in adult CD.

In a pediatric CD study, investigators reported specific medications were associated with greater increases in race- and sex-specific z-scores for both lean mass (infliximab) and fat mass (infliximab, glucocorticoid,

Table 6 Significant associations between medications/serum biomarkers and height z-scores by sex (based on chronological age (female *n* = 35; male *n* = 47)) - unadjusted analyses

Variable	Height CA z-scores	Point estimate ¹	95%CI	P value
Infliximab	Females	0.65	0.04, 1.25	0.038
CRP	Males	-0.04	-0.079, -0.002	0.039
ESR	Males	-0.03	-0.051, -0.011	0.003
Hemoglobin	Males	0.23	0.04, 0.42	0.018
Platelets	Males	-0.004	-0.006, -0.001	0.005

¹Regression coefficient for unadjusted analyses [*i.e.*, one medication or serum biomarker (independent variable) per model and no adjustment for potential confounding]. CA z-score: z score based on chronological age; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 7 Significant associations between serum biomarkers and height z-scores [based on bone age (*n* = 49)] - unadjusted analyses

Variable	Height BA z-scores	Point estimate ¹	95%CI	P value
Albumin	Males and females	0.8	0.22, 1.36	0.008
CRP	Males and females	-0.06	-0.11, -0.006	0.03
ESR	Males and females	-0.02	-0.05, -0.003	0.029
IGF-1 BA z-scores	Males and females	0.26	0.03, 0.48	0.025

¹Regression coefficient for unadjusted analyses [*i.e.*, one serum biomarker (independent variable) per model and no adjustment for potential confounding]. BA z-score: z score based on bone age; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; IGF-1: Insulin-like growth factor-1; CRP: C-reactive protein.

and methotrexate) relative to height^[50]. Similarly, we identified a positive association between methotrexate and subscapular skinfold CA z-scores. In a CD patient cohort, age 5-25 years, Sentongo *et al.*^[14] reported triceps skinfold z-scores, also a measure of adiposity, were significantly correlated with corticosteroid exposure. Our findings do not reveal a statistically significant association between history of corticosteroid therapy and current anthropometric parameters.

Csontos *et al.*^[31] reported baseline BMI increased significantly during initiation of adalimumab/infliximab therapy in adult IBD, in agreement with our identified positive association between adalimumab and BMI. They found fat free mass index also increased. They found no significant differences between the effects of adalimumab and infliximab on body composition, whereas we identified significant associations between body composition and adalimumab only, not infliximab. Notably, fat free mass index and skeletal muscle mass index significantly improved only in males. Subramaniam *et al.*^[51] reported infliximab was associated with significant gains in muscle volume that correlated with male sex in adult CD^[51]. Supporting these sex differences in response to infliximab, in a mouse model of pulmonary inflammation in which TNF- α was over expressed in mouse lungs, lower body and muscle mass were evident only in males^[52].

Our study does not reveal a sex difference in the association between medications and body composition, but does identify a statistically significant positive association between infliximab and height CA z-scores in females only. A positive relationship between infliximab and height BA z-scores was also identified in females only, but did not reach statistical significance, likely due to the smaller sample size available for BA analyses (*n*

= 17 females for BA analyses vs *n* = 35 females for CA analyses). The combination of findings described here between infliximab and height z-scores (based on CA and BA) supports a possible sex difference in response to infliximab from the standpoint of statural growth. Taken together, these findings of sex differences in response to infliximab add to the growing body of literature indicating that there may be sex differences in the molecular pathways affecting statural growth and body composition in CD. Our findings in combination with the existing literature raise an intriguing question: does TNF- α play an important role in compromising body composition in CD males but statural growth in females, and if so, why? Tang *et al.*^[52] speculated that estrogen has protective effects against the actions of TNF- α . Ordas *et al.*^[53] reported that clearance of monoclonal antibodies is higher in men. Ternant *et al.*^[54] theorized that the central volume of distribution may be higher in men because for a given body weight, plasma volume is lower in women.

We found hemoglobin was positively associated, while platelets, ESR, and CRP were negatively associated, with height CA z-scores in males only, supporting our previously reported findings of a greater detrimental effect of inflammation on statural growth in males^[10]. Several investigators have documented that growth impairment is more frequent in males^[9,10,14,21,32-35]. Perhaps the molecular pathways that lead to growth impairment in males are different than in females, and less responsive to currently used medications, such as infliximab. As expected, albumin and IGF-1 BA z-scores were positively associated, while ESR and CRP were negatively associated with height BA z-scores. In contrast, no treatment (5-aminosalicylate, corticosteroids, immunomodulators, infliximab, nutritional therapy,

surgical resection) was associated with height, weight or BMI at maximal follow up in a pediatric CD cohort in Northern France^[21].

The relationships between medications and anthropometric parameters may reflect efficacy of medications, side effects of medications, or confounding by indication. Since body composition measurements were obtained as part of a study protocol and not standard of care, it is unlikely these relationships reflect confounding by indication since these body composition measurements were not available to the care provider. Our results suggest methotrexate, infliximab and adalimumab are more effective than thiopurines for treating pediatric CD.

As expected, body composition BA z-scores were systematically higher than corresponding body composition CA z-scores. Patients did not exhibit severe deficiencies in fat stores, as reflected by standardized subscapular and triceps skinfold measurements. Depending on the measurement obtained, 3% to 11% had subscapular or triceps skinfold measurement CA z-scores or BA z-scores > 2.0, reflecting excess fat stores. In contrast, 16%-17% had deficiencies in lean mass tissue as reflected by mid-arm circumference z-score measurements < -2.0 and only 2% with mid-arm circumference z-score measurements > 2.0. We identified a negative association between thiopurines and mid-arm circumference CA z-scores. The published literature surrounding the relationship between medications and lean mass tissue is conflicting^[31,50-51]. More studies are needed to identify the most effective treatments for improving lean mass tissue in pediatric CD.

Correlations between inflammatory markers/disease activity indices and anthropometric parameters have been reported by other investigators^[5,14,50,55,56], similar to our findings. Enhancing our understanding of the specific inflammatory cytokines involved in molecular pathways affecting body composition and growth is critical for optimizing treatment.

Limitations

The etiology of compromised nutritional status/disease status is multifactorial. The cross-sectional study design does not permit longitudinal assessment of changes in anthropometric parameters with respect to medication treatment and serum biomarkers to be determined. Within-subjects characterization of the influence of disease activity and hormone levels on changes in anthropometric parameters may clarify the effects of long-term inflammation on nutritional status/disease status. Nevertheless, our results suggest a mechanistic relationship between medications, inflammation and anthropometric status/disease status, as well as a difference by sex. Prospective longitudinal study, collecting additional markers of disease activity/disease status such as fecal calprotectin, cross-sectional imaging and endoscopic assessment, is required as a next step

to further investigate these intriguing findings and would allow further risk stratification which will improve patient counseling, guide expectations, and facilitate an individualized treatment approach. Future studies should examine the impact of monotherapy vs combination therapy (including duration of treatment and drug levels) on anthropometric status/disease status.

Summary and Conclusions

Complex processes regulate body composition and growth in pediatric CD. We examined the relationship between medication treatments and serum inflammatory and hormonal biomarkers with anthropometric parameters in a well-characterized pediatric CD cohort. Our findings reinforce the importance of accounting for BA when interpreting anthropometric parameters in pediatric CD. The main findings of our study raise intriguing questions.

Thiopurines were negatively associated with specific anthropometric parameters. Do thiopurines have a negative effect on nutritional status/disease status? Alternatively, is the efficacy of thiopurines suboptimal? This interesting finding may have significant implications for pediatric CD treatment and requires further investigation in a prospective longitudinal study to determine if thiopurines should continue to be utilized as a treatment for pediatric CD.

Infliximab was positively associated with standardized height in females only. Is there a sex difference in response to infliximab from the standpoint of statural growth? Specific serum biomarkers were associated with standardized height in males only, supporting the hypothesis that inflammation has a more detrimental effect on statural growth in males. The combination of these findings lends further support to the theory that sex differences in the molecular pathways driving statural growth impairment in pediatric CD exist and should be delineated in a prospective longitudinal study utilizing height velocity BA z-scores as the primary outcome. An improved understanding of this sex difference in response to treatment would be a huge step towards enhancing risk prediction and individualized treatment.

The studies presented herein contribute to a better understanding of the relationship between medications and serum inflammatory and hormonal biomarkers with anthropometric parameters in pediatric CD. These findings serve as a foundation on which to build future studies with the goal of identifying patients at highest risk for poor outcomes, enhancing treatment algorithms, and ultimately developing individual treatment approaches based on risk stratification. The present study may provide a basis for mechanistic studies in many pediatric chronic inflammatory conditions.

ARTICLE HIGHLIGHTS

Research background

Similar to impaired statural growth (height velocity), a dynamic marker of

disease status, body composition deficits may reflect poorly controlled disease despite the absence of overt clinical intestinal symptoms. Delayed bone age (BA) is common in pediatric Crohn's disease (CD). Determination of BA allows clinically meaningful interpretation of growth in the context of skeletal maturity in pediatric CD. The impact of accounting for BA in the interpretation of body composition is unclear. Accurate interpretation of body composition is important since it reflects nutritional and disease status. Not only is nutritional status an important determinant of pubertal development and growth velocity, it is a prognostic factor for disease course. The association between medications and serum inflammatory and hormonal biomarkers with anthropometric measurements is not well delineated in pediatric CD, particularly after adjusting for maturational status (BA).

Research motivation

Nutritional status is an important factor to consider when making therapeutic decisions given its association with poor outcomes. Yet, the impact of treatments on anthropometric measurements is poorly defined and has not received sufficient attention.

Research objectives

Our aims were to determine the distribution of anthropometric parameters based on CA (CA z-scores) and BA (BA z-scores) and characterize the associations between medications and serum biomarkers with anthropometric parameter z-scores in pediatric CD.

Research methods

CD patients [$<$ chronological age (CA) 21 years] were prospectively enrolled in a cross-sectional study. Descriptive statistics were generated for participants' demographic characteristics and key variables of interest. Paired *t*-tests were used to compare anthropometric parameter z-scores calculated based on CA (CA z-scores) and BA (BA z-scores) for interpretation of anthropometric parameters. Linear regression was utilized to examine associations between medications and serum biomarkers with anthropometric parameter z-scores calculated based on CA ($n = 82$) and BA ($n = 49$). We reported regression coefficients as well as their corresponding p-values and 95% confidence intervals.

Research results

Mean CA at the time of the study visit was 15.3 ± 3.5 (standard deviation; range = 4.8-20.7) years. Mean triceps skinfold, subscapular skinfold and mid-arm circumference (MAC) BA z-scores were higher than corresponding CA z-scores. Medications were positively associated with subscapular skinfold (adalimumab and methotrexate) and BMI (adalimumab) CA z-scores. Azathioprine/6-mercaptopurine were negatively associated with MAC, subscapular skinfold, weight and BMI CA z-scores. ESR, CRP, and WBC count were negatively associated, while albumin and IGF-1 BA z-scores were positively associated with specific AP z-scores. Mean height CA z-scores were higher in females, not males, treated with infliximab. Hemoglobin was positively associated, while platelets, ESR and CRP were negatively associated with height CA z-scores in males, not females.

Research conclusions

Our findings reinforce the importance of accounting for BA when interpreting anthropometric parameters in pediatric CD. The main findings of our study raise intriguing questions. Thiopurines were negatively associated with specific anthropometric parameters. Do thiopurines have a negative effect on nutritional status/disease status? Alternatively, is the efficacy of thiopurines suboptimal? Infliximab was positively associated with standardized height in females only. Is there a sex difference in response to infliximab from the standpoint of statural growth? Specific serum biomarkers were associated with standardized height in males only, supporting the hypothesis that inflammation has a more detrimental effect on statural growth in males. Our results suggest a mechanistic relationship between medications, inflammation and anthropometric status/disease status, as well as a difference by sex. The studies presented herein contribute to a better understanding of the relationship between medications and serum inflammatory and hormonal biomarkers with anthropometric parameters in pediatric CD. Prospective longitudinal study is required as a next step to further investigate these intriguing findings and would allow further risk

stratification which will improve patient counseling, guide expectations, and facilitate an individualized treatment approach.

Research perspectives

These findings serve as a foundation on which to build future studies with the goal of identifying patients at highest risk for poor outcomes, enhancing treatment algorithms, and ultimately developing individual treatment approaches based on risk stratification. The present study may provide a basis for mechanistic studies in many pediatric chronic inflammatory conditions.

ACKNOWLEDGMENTS

We thank the patients for participating in this study. We thank Dr. Keith C Mages, Clinical Medical Librarian at the Samuel J Wood Library, Weill Cornell Medicine, for library services.

REFERENCES

- 1 **Burnham JM**, Shults J, Semeao E, Foster B, Zemel BS, Stallings VA, Leonard MB. Whole body BMC in pediatric Crohn disease: independent effects of altered growth, maturation, and body composition. *J Bone Miner Res* 2004; **19**: 1961-1968 [PMID: 15537438 DOI: 10.1359/JBMR.040908]
- 2 **Burnham JM**, Shults J, Semeao E, Foster BJ, Zemel BS, Stallings VA, Leonard MB. Body-composition alterations consistent with cachexia in children and young adults with Crohn disease. *Am J Clin Nutr* 2005; **82**: 413-420 [PMID: 16087987 DOI: 10.1093/ajcn/82.2.413]
- 3 **Boot AM**, Bouquet J, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. *Gut* 1998; **42**: 188-194 [PMID: 9536942 DOI: 10.1136/gut.42.2.188]
- 4 **Jahnsen J**, Falch JA, Mowinkel P, Aadland E. Body composition in patients with inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2003; **98**: 1556-1562 [PMID: 12873577 DOI: 10.1111/j.1572-0241.2003.07520.x]
- 5 **Thayu M**, Shults J, Burnham JM, Zemel BS, Baldassano RN, Leonard MB. Gender differences in body composition deficits at diagnosis in children and adolescents with Crohn's disease. *Inflamm Bowel Dis* 2007; **13**: 1121-1128 [PMID: 17427245 DOI: 10.1002/ibd.20149]
- 6 **Sylvester FA**, Leopold S, Lincoln M, Hyams JS, Griffiths AM, Lerer T. A two-year longitudinal study of persistent lean tissue deficits in children with Crohn's disease. *Clin Gastroenterol Hepatol* 2009; **7**: 452-455 [PMID: 19249399 DOI: 10.1016/j.cgh.2008.12.017]
- 7 **Sousa Guerreiro C**, Cravo M, Costa AR, Miranda A, Tavares L, Moura-Santos P, Marques Vidal P, Nobre Leitão C. A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. *Am J Gastroenterol* 2007; **102**: 2551-2556 [PMID: 17680845 DOI: 10.1111/j.1572-0241.2007.01439.x]
- 8 **Kugathasan S**, Nebel J, Skelton JA, Markowitz J, Keljo D, Rosh J, LeLeiko N, Mack D, Griffiths A, Bousvaros A, Evans J, Mezooff A, Moyer S, Oliva-Hemker M, Otley A, Pfefferkorn M, Crandall W, Wyllie R, Hyams J; Wisconsin Pediatric Inflammatory Bowel Disease Alliance; Pediatric Inflammatory Bowel Disease Collaborative Research Group. Body mass index in children with newly diagnosed inflammatory bowel disease: observations from two multicenter North American inception cohorts. *J Pediatr* 2007; **151**: 523-527 [PMID: 17961699 DOI: 10.1016/j.jpeds.2007.04.004]
- 9 **Gupta N**, Bostrom AG, Kirschner BS, Ferry GD, Winter HS, Baldassano RN, Gold BD, Abramson O, Smith T, Cohen SA, Heyman MB. Gender differences in presentation and course of disease in pediatric patients with Crohn disease. *Pediatrics* 2007; **120**: e1418-e1425 [PMID: 18055660 DOI: 10.1542/

- peds.2007-0905]
- 10 **Gupta N**, Lustig RH, Kohn MA, McCracken M, Vittinghoff E. Sex differences in statural growth impairment in Crohn's disease: role of IGF-1. *Inflamm Bowel Dis* 2011; **17**: 2318-2325 [PMID: 21287667 DOI: 10.1002/ibd.21617]
 - 11 **Gupta N**, Lustig RH, Kohn MA, Vittinghoff E. Determination of bone age in pediatric patients with Crohn's disease should become part of routine care. *Inflamm Bowel Dis* 2013; **19**: 61-65 [PMID: 22552908 DOI: 10.1002/ibd.22979]
 - 12 **Motil KJ**, Grand RJ, Davis-Kraft L, Ferlic LL, Smith EO. Growth failure in children with inflammatory bowel disease: a prospective study. *Gastroenterology* 1993; **105**: 681-691 [PMID: 8359640 DOI: 10.1016/0016-5085(93)90883-E]
 - 13 **Hill RJ**, Brookes DS, Lewindon PJ, Withers GD, Ee LC, Connor FL, Cleghorn GJ, Davies PS. Bone health in children with inflammatory bowel disease: adjusting for bone age. *J Pediatr Gastroenterol Nutr* 2009; **48**: 538-543 [PMID: 19367176 DOI: 10.1097/MPG.0b013e31818cb4b6]
 - 14 **Sentongo TA**, Semeao EJ, Piccoli DA, Stallings VA, Zemel BS. Growth, body composition, and nutritional status in children and adolescents with Crohn's disease. *J Pediatr Gastroenterol Nutr* 2000; **31**: 33-40 [PMID: 10896068 DOI: 10.1097/00005176-200007000-00009]
 - 15 **McCaffery TD**, Nasr K, Lawrence AM, Kirsner JB. Severe growth retardation in children with inflammatory bowel disease. *Pediatrics* 1970; **45**: 386-393 [PMID: 4315271]
 - 16 **Savage MO**, Beattie RM, Camacho-Hübner C, Walker-Smith JA, Sanderson IR. Growth in Crohn's disease. *Acta Paediatr Suppl* 1999; **88**: 89-92 [PMID: 10102061 DOI: 10.1111/j.1651-2227.1999.tb14360.x]
 - 17 **Greulich WW**, Pyle SI. Radiographic Atlas of Skeletal Development of the Hand and Wrist, 2nd ed. Stanford, CA: Stanford University Press 1959 [DOI: 10.1017/S1120962300018680]
 - 18 **Jones G**, Ma D. Skeletal age deviation assessed by the Tanner-Whitehouse 2 method is associated with bone mass and fracture risk in children. *Bone* 2005; **36**: 352-357 [PMID: 15780962 DOI: 10.1016/j.bone.2004.11.001]
 - 19 **Johnson W**, Stovitz SD, Choh AC, Czerwinski SA, Towne B, Demerath EW. Patterns of linear growth and skeletal maturation from birth to 18 years of age in overweight young adults. *Int J Obes (Lond)* 2012; **36**: 535-541 [PMID: 22124455 DOI: 10.1038/ijo.2011.238]
 - 20 **Forbes A**, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, Shamir R, Stadelova K, Wierdsma N, Wiskin AE, Bischoff SC. ESPEN guideline: Clinical nutrition in inflammatory bowel disease. *Clin Nutr* 2017; **36**: 321-347 [PMID: 28131521 DOI: 10.1016/j.clnu.2016.12.027]
 - 21 **Vasseur F**, Gower-Rousseau C, Vernier-Massouille G, Dupas JL, Merle V, Merlin B, Lerebours E, Savoye G, Salomez JL, Cortot A, Colombel JF, Turck D. Nutritional status and growth in pediatric Crohn's disease: a population-based study. *Am J Gastroenterol* 2010; **105**: 1893-1900 [PMID: 20145606 DOI: 10.1038/ajg.2010.20]
 - 22 **Ananthakrishnan AN**, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. *J Crohns Colitis* 2013; **7**: 107-112 [PMID: 22440891 DOI: 10.1016/j.crohns.2012.02.015]
 - 23 **Nguyen GC**, Munsell M, Harris ML. Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. *Inflamm Bowel Dis* 2008; **14**: 1105-1111 [PMID: 18302272 DOI: 10.1002/ibd.20429]
 - 24 **Ananthakrishnan AN**, McGinley EL, Binion DG, Saeian K. A novel risk score to stratify severity of Crohn's disease hospitalizations. *Am J Gastroenterol* 2010; **105**: 1799-1807 [PMID: 20216534 DOI: 10.1038/ajg.2010.105]
 - 25 **Gajendran M**, Umapathy C, Loganathan P, Hashash JG, Koutroubakis IE, Binion DG. Analysis of Hospital-Based Emergency Department Visits for Inflammatory Bowel Disease in the USA. *Dig Dis Sci* 2016; **61**: 389-399 [PMID: 26423080 DOI: 10.1007/s10620-015-3895-2]
 - 26 **Wallaert JB**, De Martino RR, Marsicovetere PS, Goodney PP, Finlayson SR, Murray JJ, Holubar SD. Venous thromboembolism after surgery for inflammatory bowel disease: are there modifiable risk factors? Data from ACS NSQIP. *Dis Colon Rectum* 2012; **55**: 1138-1144 [PMID: 23044674 DOI: 10.1097/DCR.0b013e3182698f60]
 - 27 **Nguyen DL**, Parekh N, Bechtold ML, Jamal MM. National Trends and In-Hospital Outcomes of Adult Patients With Inflammatory Bowel Disease Receiving Parenteral Nutrition Support. *J Parenter Enteral Nutr* 2016; **40**: 412-416 [PMID: 24687967 DOI: 10.1177/0148607114528715]
 - 28 **Addolorato G**, Capristo E, Stefanini GF, Gasbarrini G. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. *Scand J Gastroenterol* 1997; **32**: 1013-1021 [PMID: 9361174 DOI: 10.3109/00365529709011218]
 - 29 **Forbes GB**. Perspectives on body composition. *Curr Opin Clin Nutr Metab Care* 2002; **5**: 25-30 [PMID: 11790945 DOI: 10.1097/00075197-200201000-00005]
 - 30 **Thangarajah D**, Hyde MJ, Konteti VK, Santhakumaran S, Frost G, Fell JM. Systematic review: Body composition in children with inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **42**: 142-157 [PMID: 26043941 DOI: 10.1111/apt.13218]
 - 31 **Csontos ÁA**, Molnár A, Piri Z, Katona B, Dakó S, Pálfi E, Miheller P. The Effect of anti-TNF α Induction Therapy on the Nutritional Status and Dietary Intake in Inflammatory Bowel Disease. *J Gastrointest Liver Dis* 2016; **25**: 49-56 [PMID: 27014753 DOI: 10.15403/jgld.2014.1121.251.tnf]
 - 32 **Gupta N**. Summary of "Growth and nutritional status in pediatric Crohn's disease" with a focus on sex differences in statural growth impairment. *J Pediatr Gastroenterol Nutr* 2011; **53**: 227-228 [PMID: 21788770 DOI: 10.1097/MPG.0b013e31821d37dc]
 - 33 **Griffiths AM**, Nguyen P, Smith C, MacMillan JH, Sherman PM. Growth and clinical course of children with Crohn's disease. *Gut* 1993; **34**: 939-943 [PMID: 8344582 DOI: 10.1136/gut.34.7.939]
 - 34 **Pigneur B**, Seksik P, Viola S, Viala J, Beaugerie L, Girardet JP, Rummelle FM, Cosnes J. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis* 2010; **16**: 953-961 [PMID: 19834970 DOI: 10.1002/ibd.21152]
 - 35 **Mason A**, Malik S, McMillan M, McNeilly JD, Bishop J, McGrogan P, Russell RK, Ahmed SF. A prospective longitudinal study of growth and pubertal progress in adolescents with inflammatory bowel disease. *Horm Res Paediatr* 2015; **83**: 45-54 [PMID: 25531796 DOI: 10.1159/000369457]
 - 36 **Gupta N**, Lustig RH, Kohn MA, Vittinghoff E. Menarche in pediatric patients with Crohn's disease. *Dig Dis Sci* 2012; **57**: 2975-2981 [PMID: 22744430 DOI: 10.1007/s10620-012-2235-z]
 - 37 **Centers for Disease Control and Prevention**. National Health and Nutrition Examination Survey (NHANES) Anthropometry Manual. Available from: URL: https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/Anthropometry_Procedures_Manual.pdf
 - 38 **Morris NM**, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. *J Youth Adolesc* 1980; **9**: 271-280 [PMID: 24318082 DOI: 10.1007/BF02088471]
 - 39 **Smith DW**. Growth and its disorders: basics and standards, approach and classifications, growth deficiency disorders, growth excess disorders, obesity. *Major Probl Clin Pediatr* 1977; **15**: 1-155 [PMID: 190484]
 - 40 **McDowell MA**, Fryar CD, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2003-2006. *Natl Health Stat Report* 2008; **10**: 1-48 [PMID: 25585443 DOI: 10.1037/e623932009-001]
 - 41 **McDowell MA**, Fryar CD, Hirsch R, Ogden CL. Anthropometric reference data for children and adults: U.S. population, 1999-2002. *Adv Data* 2005; **361**: 1-5 [PMID: 16018338]
 - 42 **Frisancho AR**. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr* 1981; **34**: 2540-2545 [PMID: 6975564 DOI: 10.1093/ajcn/34.11.2540]

- 43 **Tanner JM**, Whitehouse RH. Revised standards for triceps and subscapular skinfolds in British children. *Arch Dis Child* 1975; **50**: 142-145 [PMID: 1130819 DOI: 10.1136/adc.50.2.142]
- 44 **Davies PS**, Day JM, Cole TJ. Converting Tanner-Whitehouse reference tricep and subscapular skinfold measurements to standard deviation scores. *Eur J Clin Nutr* 1993; **47**: 559-566 [PMID: 8404792]
- 45 **Centers for Disease Control and Prevention**. CDC Growth Charts: Percentile Data Files with LMS Values. Available from: URL: https://www.cdc.gov/growthcharts/percentile_data_files.htm
- 46 **Markowitz J**, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119**: 895-902 [PMID: 11040176 DOI: 10.1053/gast.2000.18144]
- 47 **Hyams JS**, Dubinsky MC, Baldassano RN, Colletti RB, Cucchiara S, Escher J, Faubion W, Fell J, Gold BD, Griffiths A, Koletzko S, Kugathasan S, Markowitz J, Ruemmele FM, Veereman G, Winter H, Masel N, Shin CR, Tang KL, Thayu M. Infliximab Is Not Associated With Increased Risk of Malignancy or Hemophagocytic Lymphohistiocytosis in Pediatric Patients With Inflammatory Bowel Disease. *Gastroenterology* 2017; **152**: 1901-1914.e3 [PMID: 28193515 DOI: 10.1053/j.gastro.2017.02.004]
- 48 **Diamanti A**, Basso MS, Gambarara M, Papadatou B, Bracci F, Noto C, Castro M. Positive impact of blocking tumor necrosis factor alpha on the nutritional status in pediatric Crohn's disease patients. *Int J Colorectal Dis* 2009; **24**: 19-25 [PMID: 18797887 DOI: 10.1007/s00384-008-0578-x]
- 49 **Wiese D**, Lashner B, Seidner D. Measurement of nutrition status in Crohn's disease patients receiving infliximab therapy. *Nutr Clin Pract* 2008; **23**: 551-556 [PMID: 18849561 DOI: 10.1177/0884533608323421]
- 50 **Thayu M**, Denson LA, Shults J, Zemel BS, Burnham JM, Baldassano RN, Howard KM, Ryan A, Leonard MB. Determinants of changes in linear growth and body composition in incident pediatric Crohn's disease. *Gastroenterology* 2010; **139**: 430-438 [PMID: 20417635 DOI: 10.1053/j.gastro.2010.04.044]
- 51 **Subramaniam K**, Fallon K, Ruut T, Lane D, McKay R, Shadbolt B, Ang S, Cook M, Platten J, Pavli P, Taupin D. Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. *Aliment Pharmacol Ther* 2015; **41**: 419-428 [PMID: 25580985 DOI: 10.1111/apt.13058]
- 52 **Tang K**, Murano G, Wagner H, Nogueira L, Wagner PD, Tang A, Dalton ND, Gu Y, Peterson KL, Breen EC. Impaired exercise capacity and skeletal muscle function in a mouse model of pulmonary inflammation. *J Appl Physiol (1985)* 2013; **114**: 1340-1350 [PMID: 23449936 DOI: 10.1152/jappphysiol.00607.2012]
- 53 **Ordás I**, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther* 2012; **91**: 635-646 [PMID: 22357456 DOI: 10.1038/clpt.2011.328]
- 54 **Ternant D**, Aubourg A, Magdelaine-Beuzelin C, Degenne D, Watier H, Picon L, Paintaud G. Infliximab pharmacokinetics in inflammatory bowel disease patients. *Ther Drug Monit* 2008; **30**: 523-529 [PMID: 18641542 DOI: 10.1097/FTD.0b013e318180e300]
- 55 **Schneider SM**, Al-Jaouni R, Filippi J, Wiroth JB, Zeanandin G, Arab K, Hébuterne X. Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. *Inflamm Bowel Dis* 2008; **14**: 1562-1568 [PMID: 18478564 DOI: 10.1002/ibd.20504]
- 56 **Reimund JM**, Arondel Y, Escalin G, Finck G, Baumann R, Duclos B. Immune activation and nutritional status in adult Crohn's disease patients. *Dig Liver Dis* 2005; **37**: 424-431 [PMID: 15893281 DOI: 10.1016/j.dld.2005.01.010]

P- Reviewer: Gazouli M, Nielsen OH, Vasudevan A **S- Editor:** Ma YJ

L- Editor: A **E- Editor:** Huang Y





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



ISSN 1007-9327

