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Author/s:

Jois, A;Perera, S;Simm, P;Alex, G

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## Original Article



# Use of Dual-Energy X-ray Absorptiometry in Children with Inflammatory Bowel Disease: A Large Single Centre Study

Asha Jois ,<sup>1</sup> Sajini Perera ,<sup>2</sup> Peter Simm ,<sup>3</sup> and George Alex <sup>1</sup>

<sup>1</sup>Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Victoria, Australia

<sup>2</sup>General Medicine, Royal Children's Hospital, Victoria, Australia

<sup>3</sup>Department of Endocrinology, Royal Children's Hospital, Victoria, Australia

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### Correspondence to

Asha Jois

Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria 3052, Australia.

Email: Asha.Jois@rch.org.au

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### ORCID iDs

Asha Jois

<https://orcid.org/0000-0003-3966-1183>

Sajini Perera

<https://orcid.org/0000-0003-0160-7595>

Peter Simm

<https://orcid.org/0000-0003-4056-5201>

George Alex

<https://orcid.org/0000-0002-5157-8983>

### Conflict of Interest

The authors have no financial conflicts of interest.

## ABSTRACT

**Purpose:** Low bone mineral density (BMD) is a complication in children with inflammatory bowel disease (IBD). There are limited data evaluating dual-energy x-ray absorptiometry (DXA) as a screening tool for low BMD in children with IBD. We performed a single site retrospective analysis of DXA use.

**Methods:** Children aged 5–18 years with IBD diagnosed between 2013 to 2017 at the Royal Children's Hospital, Australia, were included. Patient demographics, measures of disease activity, DXA scores, and factors related to BMD were collected.

**Results:** Over a median follow up of 5.1 (4–6.4) years, 72/239 (30.1%) children underwent DXA, and 28/239 (11.7%) children had a second DXA. Our DXA practice differed to consensus guidelines regarding initial screening based on height and/or body mass index (BMI) z-score (8/17 [47.1%]), and repeat surveillance (13/42 [31.0%]). Children had a median lumbar spine (LS) z-score  $-0.80$  ( $-1.65$ – $0.075$ ). Children with LS z-score  $\leq -2.0$  ( $n=14$ ) had lower weight (6.57 [1.78–23.7] vs. 51.1 [26.5–68.7],  $p=0.0002$ ) and height centiles (3.62 [1.17–17.1] vs. 42 [16.9–67.1],  $p=0.0001$ ), and higher faecal calprotectin (FCP) (3041 [1182–4192] vs. 585 [139–2419],  $p=0.009$ ) compared to children with LS z-score  $> -2.0$ . No fractures were reported. Of 28 children who underwent a second DXA 1.6 (1.1–2.2) years following initial DXA, no significant change in z-scores occurred.

**Conclusion:** Children with IBD had low BMD. In addition to height centile and weight centile, FCP was associated with lower BMD, and should be considered in DXA screening guidelines. Greater clinician awareness of DXA consensus guidelines is required. Future prospective studies are required.

**Keywords:** Inflammatory bowel disease; Child; Absorptiometry, photon

## INTRODUCTION

Low bone mineral density (BMD) is a known complication in children with inflammatory bowel disease (IBD) [1]. Factors such as systemic inflammation, pubertal delay, malnutrition, and corticosteroid exposure are all thought to contribute to impaired bone mineralisation [2]. Low BMD is associated with an increased risk of fractures in childhood, however

data are conflicting and limited in IBD [3-5]. Interventions such as increased calcium intake and/or supplementation, optimising vitamin D levels, weight bearing exercise, and ensuring appropriate pubertal development may all improve BMD. Bone mass accrual is at its highest in the first two decades of life, signifying an important period for detection and intervention [6]. Dual-energy x-ray absorptiometry (DXA) is a safe, widely available screening tool for low BMD [7]. Consensus guidelines recommend screening children with IBD for low BMD with DXA in those with height velocity, height z-score, weight or body mass index (BMI) z-score < -2.0 standard deviations (SD), or if downward crossing height, weight or BMI percentile curves, primary or secondary amenorrhoea, delayed puberty, severe inflammatory disease course, or 6 months or longer of continuous use of corticosteroids [8]. These guidelines recommend obtaining serial DXA scans every 1-2 years in those with a z-score of total body or spine  $\leq -1.0$  SD at any point. However, there is a paucity of data to guide the use of DXA in children with IBD [9-20], and frequent DXA surveillance is costly. It remains unclear when to commence screening, in which patients, and the optimal time interval between scans in childhood. Furthermore, no study has demonstrated if there is any improvement in low BMD over time. Our study aimed to determine the current DXA surveillance practices at a tertiary paediatric hospital, identify factors which are associated with lower BMD, and to assess changes in BMD over time in children with IBD.

## MATERIALS AND METHODS

### Participant selection

Patients aged between 5 and 18 years managed at the Royal Children's Hospital (RCH) Gastroenterology outpatient clinic and diagnosed with IBD between 01/01/2013 and 01/01/2017 inclusive were identified using electronic medical record software (EMR) and existing RCH IBD outpatient databases. Exclusion criteria included any comorbidities resulting in risk factors for low BMD such as immobility or prolonged steroid exposure for a different medical condition, or if insufficient data were available in the EMR.

### Data collection

Data were extracted from the EMR from routine clinical care and all data were de-identified on collection. Patient demographics were obtained including age, sex, BMI, IBD subtype, age at diagnosis, and disease duration. Weight, height and BMI centiles and z-scores were calculated based on the sex specific weight, height and BMI charts from the US Centers for Disease Control. Most recent anthropometric variables were recorded. Date of diagnosis was defined as the date of initial endoscopy with biopsy confirming IBD. Disease activity was measured using serum levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin and faecal calprotectin (FCP) averaged from values obtained within 6 months prior to and 6 months following the date of each DXA. Calprotectin was measured by fluorescence-immunoassay on the Phadia 250 instrument (Thermo Fisher AUS Pty Ltd., Sydney, Australia) performed on an automated analyser (Immunocap 250). Prescribed medications were obtained including use of exclusive enteral nutrition, corticosteroids, 5-Aminosalicylic Acid (5-ASA), immunomodulators and biologics in the 12 month period surrounding the date of each DXA. We collected information on bone health and intervention strategies including Vitamin D and calcium levels, use of Vitamin D and calcium supplementation, referral to RCH Endocrinology outpatient clinic and use of bisphosphonate therapy, as well as occurrence of fractures.

At date of DXA we collected data on age, disease duration, frequency of DXA surveillance and DEXA variables including lumbar spine z-score, height adjusted (HAZ) lumbar spine z-score, hip z-score, total body less head z-score and percentage body fat.

DXA values were obtained using bone densitometers (QDR 4500 Elite and Horizon; Hologic, Inc., Bedford, MA, USA). All scans were analysed using Hologic software and reviewed by a single investigator for quality assurance. Height-adjusted measurements were obtained using inbuilt software from the Hologic system using data obtained from the BMD in Childhood Study, and validated using an independent cross-sectional sample of healthy children from the Reference Data Project [21].

### Outcome measures and statistical analysis

We compared patient demographics of those who had at least one DXA performed compared to those who did not. In order to compare patients with low BMD to those without low BMD, we categorically grouped patients into lumbar z-score  $\leq -2.0$  SD and lumbar z-score  $> -2.0$  SD. We selected lumbar z-score for analysis as it is a preferred skeletal site for BMD measurement in children based on the International Society for Clinical Densitometry paediatric position statements [22]. All statistical analyses were performed using GraphPad Prism version 9.0.0 for Windows, GraphPad Software, CA, USA. All grouped comparisons were assessed for normality using the Shapiro-Wilk test. For continuous group comparisons, the unpaired *t*-test and the Mann-Whitney U-test were used for normally distributed and non normally distributed data respectively. The Fisher exact test was used for categorical group comparison. Data are presented as median (interquartile range) unless otherwise specified. Confidence intervals for odds ratios were determined via the Baptista-Pike method.

This study was retrospective and used de-identified patient information that was collected in routine clinical care, there was no written informed consent obtained, and this was approved by the Royal Children's Hospital Human Research Ethics Committee (reference number QA/63012/RCHM-2020).

## RESULTS

Two hundred and fifty-one children met inclusion criteria. Twelve children were excluded due to insufficient data or comorbidities impacting on DXA score (e.g., immobility). Children were followed over a median of 5.1 years (4–6.4) post diagnosis. No fractures were reported throughout the study period based on chart review.

Seventy-two of two hundred and thirty-nine (30.1%) children had at least one DXA over the study period. DXA was performed at a median 11 months following diagnosis (1.25–28.8). Patient demographics of those who had DXA compared to those without DXA screening are described in **Table 1**. Children who had DXA performed had a lower weight centile ( $p=0.03$ ), and were more likely to have Crohn's disease (OR 2.18,  $p=0.01$ ). There were otherwise no differences in other anthropometric variables or sex between the two groups.

DXA scores are described in **Table 2**. As opposed to the expected 50% for normal distribution of z-scores, 18/72 (25.0%) patients had LS z-score  $> 0$  SD. Children with LS z-score  $\leq -2.0$  SD (low BMD) were compared to children with LS z-score  $> -2.0$  SD in **Table 3**. Children with low BMD had lower weight ( $p=0.0002$ ) and height ( $p=0.0001$ ) centiles. There was no difference

**Table 1.** Patient demographics

Demographics	DXA (n=72)	Non-DXA (n=167)	p-value
Male (%)	47.2 (34/72)	73.6 (95/167)	0.203
Age at diagnosis (yr)	12 (10–13.9)	12 (7.8–14.3)	0.537
Disease duration (yr)	5.4 (4.1–6.6)	4.9 (3.9–6.3)	0.100
Weight (kg)	56.1 (45.8–66.2)	58.5 (39.4–68.3)	0.868
Weight (centile)	48.7 (17.1–78.2)	59.7 (31.4–84.7)	0.032
Height (m)	1.64 (1.58–1.71)	1.63 (1.49–1.71)	0.167
Height (centile)	40.8 (16.9–60.4)	47.3 (21.9–73.2)	0.173
Height (z-score)*	-0.205 (-0.930–1.52)	-0.030 (-0.740–0.660)	0.254
BMI (kg/m <sup>2</sup> )	20.6 (18.4–23.2)	20.9 (17.8–24.0)	0.870
BMI (z-score)	0.275 (-0.778–0.753)	0.295 (-0.375–1.04)	0.180
Crohn's (%)	66.7 (48/72)	47.9 (80/167)	0.010
	19/72 UC, 5/72 IBDU	71/167 UC, 16/167 IBDU	
TI involvement (%)	52.1 (25/48)	41.3 (33/80)	0.273

Values are presented as number (%) or median (interquartile range).

DXA: dual-energy x-ray absorptiometry, BMI: body mass index, UC: ulcerative colitis, IBDU: inflammatory bowel disease un-specified, TI: terminal ileum.

\*Normally distributed data, unpaired t-test performed.

All numerical data are not normally distributed and analysed with Mann-Whitney U-test unless otherwise specified.

**Table 2.** Initial DXA Z-scores

DXA variable	DXA 1 (n=72)
Lumbar spine z-score	-0.80 (-1.65–0.075)
Height adjusted lumbar spine z-score	-0.650 (-1.18–0.100)
Hip z-score	-1.30 (-1.80–-0.350)
Total body less head z-score	-1.40 (-2.55–-0.700)
Body fat (%)	28.1 (22.6–35.5)

Values are presented as median (interquartile range) unless otherwise specified.

DXA: dual-energy x-ray absorptiometry.

**Table 3.** Low DXA Z-score and associated variables

Demographics	DXA Z-score>-2.0 (n=58)	DXA Z-score≤-2.0 (n=14)	p-value
Males (%)	51.7 (30/58)	71.4 (4/14)	0.237
Age at DXA (yr)	13.6 (11.1–15.6)	14.4 (12.9–15.4)	0.391
Disease Duration at DXA (mo)	13.5 (1.75–30.5)	2.5 (0.75–25.5)	0.262
Weight (kg)	43.5 (31.3–43.5)	37 (27–44)	0.083
Weight (%)	51.1 (26.5–68.7)	6.57 (1.78–23.7)	0.0002
Height (m)	1.57 (1.41–1.66)	1.49 (1.35–1.56)	0.148
Height (%)	42 (16.9–67.1)	3.62 (1.17–17.1)	0.0001
BMI (kg/m <sup>2</sup> )	18.3 (16.4–21.1)	15.1 (10.2–16.6)	0.063
Steroids (wk/yr)	0 (0–12)	4 (0–9)	0.706
CRP (mg/L)	8 (5–18.7)	13.5 (6.95–40.4)	0.208
ESR (mm/hr)	15 (6.95–35.6)	16 (7.38–23)	0.904
Body fat (%)*	27 (22.4–35)	28.2 (24.4–35.8)	0.481
Calprotectin (µg/g)	585 (139–2,419)	3,041 (1,182–4,192)	0.009
Albumin (g/L)	41.2 (37.5–43)	39.5 (34.3–41.6)	0.168
Vitamin D (nmol/L)*	45.5 (33.5–73.9)	62 (38.7–84)	0.332
Vitamin D supplement (%)	42.9 (24/56)	75.0 (9/12)	0.059
Calcium (nmol/L)*	2.33 (2.23–2.41)	2.31 (2.22–2.43)	0.886
Calcium supplement (%)	1.75 (1/57)	33.3 (3/12)	0.003
		OR 16 (95% CI 2.93–89.1)	
Endocrinology referral (%)	17.9 (10/56)	64.3 (9/14)	0.001
		OR 9.61 (95% CI 2.65–31.0)	
5-ASA (%)	49.1 (28/57)	21.4 (3/14)	0.076
Immunomodulator use (%)	76.4 (42/55)	85.7 (12/14)	0.718
Biologic use (%)	36.4 (20/55)	42.9 (6/14)	0.760

Values are presented as number (%) or median (interquartile range).

DXA: dual-energy x-ray absorptiometry, OR: odds ratio, CI: confidence interval, BMI: body mass index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, 5-ASA: 5-aminosalicylic acid.

\*Normally distributed data–unpaired t-test performed.

All numerical data are not normally distributed and analysed with Mann-Whitney U-test unless otherwise specified.

**Table 4.** Serial DXA scores

DXA variable	DXA 1 (n=28)	DXA 2 (n=28)	p-value
Lumbar spine z-score*	-1.15 (-2.25--0.60)	-1.70 (-2.20--0.90)	0.606
Height adjusted lumbar spine z-core	-1.10 (-1.70--0.70)	-1.15 (1.83--0.400)	0.737
Hip z-core	-1.65 (-2.30--0.80)	-1.70 (-2.40--1.00)	0.900
Total body less head z-core*	-1.80 (-3.35--1.20)	-1.95 (-3.00--1.15)	0.673
Body fat (%)*	28.1 (20.2--35.2)	29.6 (22.0--36.9)	0.323

Values are presented as median (interquartile range) unless otherwise specified.

DXA: dual-energy x-ray absorptiometry.

\*Normally distributed data-unpaired t-test performed.

All numerical data are not normally distributed and analysed with Mann-Whitney U-test unless otherwise specified.

in cumulative exposure to steroids, serum inflammatory markers (ESR, CRP, albumin), or current use of 5-ASA, immunomodulator or biologic therapy. Children with low BMD had a higher FCP ( $p=0.009$ ). They also had higher odds of calcium supplementation ( $p=0.003$ ) and endocrinology referral ( $p=0.001$ ).

Of those children who had one DXA, 28/72 (38.9%) had at least one additional DXA over the study period at a median of 2.2 years (1.4–2.9) since diagnosis, and 1.6 years (1.1–2.2) following initial DXA. Serial DXA scores are detailed in **Table 4**. There was no significant difference in z-scores between DXA 1 and DXA 2.

Based on consensus guidelines [8], 17/239 (7.1%) children met criteria for DXA screening based on height and/or BMI z-score  $< -2.0$  SD. Of these, 8/17 (47.1%) children in our cohort had DXA performed over the period of observation. Forty-seven of seventy-two (65.3%) patients met guidelines for serial DXA in 1–2 years due to a lumbar spine or total body less head z-score  $< -1.0$  SD. Of these patients, 13/42 (31.0%) had a repeat DXA during the follow-up period.

## DISCUSSION

In our tertiary IBD cohort, we characterised the frequency and timing of DXA surveillance, DXA scores and their associated risk factors, BMD change over time, and rate of detected fractures. Several studies have previously analysed DXA scores in children, with varying results [1,9,11,13,19]. Our cohort of children had higher median lumbar z-score compared to previous reports in children with IBD [23], and lower scores of total body less head z-scores [11,14]. The improvement in lumbar z-scores is likely in part attributable to a decreased use of steroids over time with improved understanding of the benefits of escalating maintenance therapy to achieve clinical remission and prevent flares of disease activity. Our study found that children with low BMD defined as LS z-score  $\leq -2.0$  SD had lower weight centile and height centile compared to children with LS z-score  $> -2.0$  SD, consistent with previous studies [4,9,16].

The number of patients where DXA was performed was lower than that recommended by consensus guidelines. Fewer patients underwent an initial DXA scan than those indicated by their anthropometric data, with likely additional patients meeting criteria for pubertal delay and prolonged steroid use which were not documented in our study. Once initial DXA was performed, repeat DXA scans were also not performed according to consensus recommendations, with some patients with identified low BMD not receiving surveillance DXA within the study period, while others with normal BMD underwent serial scans. This finding suggests that there may be limited awareness of the current recommendations, and highlights the need for increased education among practitioners.

Interestingly, while serum markers of inflammation (CRP, ESR, albumin) did not differ between groups, children with LS z-score  $\leq -2.0$  had significantly higher FCP. To our knowledge, this is the first study to date to have looked for a correlation between FCP and BMD. Other signs of inflammatory disease activity, such as the Pediatric Ulcerative Colitis Activity Index and IL-6, have been associated with reduced BMD in children [15] and adults [24]. However, IL-6 is not routinely used in clinical practice, and therefore not currently useful in identifying children at higher risk of low BMD. FCP is a highly sensitive and specific marker of IBD mucosal active inflammation [25], which may explain its association with low BMD as a consequence of disease activity, as compared to more general markers of systemic inflammation. FCP may be a valuable tool to identify children with a high inflammatory burden requiring DXA surveillance.

Despite higher rates of endocrinology referral and calcium supplementation, there was no significant difference in rate of Vitamin D supplementation, Vitamin D level or calcium level in children with low BMD compared to those with higher BMD. This implies that despite detecting low BMD, we may not be increasing our intervention rates accordingly to improve long-term outcomes.

When comparing DXA scores over time, we found no significant change in DXA scores on repeat scanning performed at a median of 1.6 years following initial DXA, however the number of children with repeat scans was lower than consensus recommendations, limiting the validity of this finding. This finding is consistent with the few studies that have compared DXA z-scores over time in childhood during follow up times varying from 1 to 5 years [4,13,15-17,19,20]. Conversely, Sigurdsson et al. [18] prospectively followed children with IBD into young adulthood, at which point they demonstrated improved mean LS z-score in young adulthood, suggesting that catch-up bone mass accrual may be achieved over a longer period of time. The frequency of DXA surveillance in childhood could be reduced, improving cost effectiveness while still detecting changes over time. Conversely, we may need to increase interventions when low BMD is detected, which may in turn lead to improved DXA scores in a shorter time frame.

There was no evidence of fracture during the follow up period in our cohort of children. Laakso et al. [4] prospectively screened for vertebral fractures in children with IBD with low BMD, and detected a 6% rate of vertebral fractures during a 14.5 year follow-up period. Given the retrospective nature of our study, and reliance on documentation in the clinical record, while we did not find any fractures in our cohort, they may be under-detected or undocumented in the medical record in children with IBD with low BMD. Children may have presented to other health care providers with fracture, resulting in under-detection.

There are inherent limitations to a retrospective study design, including an incomplete data set. For example, we were unable to calculate Pediatric Crohn's Disease Activity Index or Pediatric Ulcerative Colitis Activity Index scores to assess severity of disease in the low BMD group compared to those without low BMD. We did not have information on bone age or pubertal status, however previous studies have shown that low BMD has persisted after adjusting for these factors, suggesting they are not the only contributors to low BMD in this cohort [1,9,15].

Our study population is from a tertiary paediatric hospital, and unlikely to be representative of the total paediatric IBD cohort managed in the community. Furthermore, we were unable

to analyse BMD with HAZ-scores due to low numbers of patients with HAZ-scores calculated and entered into the EMR.

In conclusion, our findings suggest that children with IBD have low BMD. Children with higher FCP should be considered in guidelines for screening for low BMD. Larger studies are required to support this finding, and to detect an optimal cut-off value that may suggest lower BMD. The interval between scans in current guidelines may be too short to detect significant improvement following intervention. Identifying children with low BMD provides an opportunity for intervening at an important developmental stage for optimisation of bone mass accrual. Increased awareness of current consensus recommendations through the development of a hospital protocol may aid in appropriate use of DXA. Larger, prospective studies are required to confirm our findings.

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