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Long Title: Bone mineral density and vertebral fractures in teenage and young adult patients with acute lymphoblastic leukaemia and lymphoblastic lymphoma. A report from the British OsteoNecrosis Study (BONES)

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- Aidan Kirk- writing and data analysis
- Beki James- conceptualisation, design, supervising, methodology, writing, funding acquisition
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- Nadia Amin (corresponding author) - project administration, conceptualisation, investigation, methodology, analysis, writing

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Abstract

Introduction

The British Osteonecrosis Study (BONES) is the first multicentre prospective study assessing bone health and vertebral fractures in patients aged 10-24 in the UK undergoing treatment for acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma (LBL).

Methods

61 patients were recruited from 3 tertiary centres in the UK. Dual-energy x-ray absorptiometry (DXA) scans with vertebral fracture analysis were performed within 4 weeks of diagnosis and annually for 3 years. Subjective pain assessments were performed at the same timepoints.

Results

Bone mineral density (assessing total body less head (TBLH) significantly reduced after 2-years, compared to baseline (estimate = -0.964, 95% CI [-1.357, -0.572]), with greatest decrease occurring within the first year. Vertebral fracture prevalence was 4.9%, with 2 further patients experiencing incident vertebral fractures. All vertebral fractures occurred in male patients, 75% of whom were British Asian. Back pain was not a predictor of low BMD or vertebral fractures.

Discussion

We report a lower vertebral fracture prevalence in patients aged 10-24 with ALL than has been previously reported in a cohort of younger patients. Male British Asian patients appeared to be at higher risk of vertebral fractures in our study. BMD and pain were not predictors of vertebral fractures.

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy[1]. Improved cure rates for both ALL and lymphoblastic lymphoma (LBL) in recent decades has increased focus on identifying and addressing causes of morbidity related to both the malignancy and treatment sequelae. Bone health is an important area of concern, with reduced bone mineral density (BMD) in children with ALL being reported around the time of diagnosis[2-5] and through the treatment period[4,5].

Multiple factors impact bone health. Leukaemia itself exerts an adverse local effect on bone by occupying the bone marrow niche and releasing cytokines, promoting osteoclast-mediated resorption of bone[6]. Glucocorticoids are used extensively in the treatment of ALL and LBL and increase the risk of fractures through a variety of mechanisms, including a reduction in BMD[7], calcium depletion, and suppression of growth hormone and sex hormones[8]. Glucocorticoids also reduce bone turnover and promote bone fragility through direct action on all bone cell types, having been shown to induce osteoblast apoptosis[9-11], increase osteocyte autophagy[12,13], and suppress osteoclast precursor proliferation and impair osteoclast function with prolonged use[14]. Glucocorticoids preferentially target trabecular-rich bone[7], putting the vertebrae, with a trabecular bone: cortical bone ratio of 75:25[15] at particular risk of glucocorticoid-induced damage. The reduction in BMD seen in children and young people treated for leukaemia has consistently been found to improve after completion of

treatment[16-20]. Despite this reversibility, the bone loss caused by both the leukaemia and chemotherapy increases the risk of osteoporosis, pain and fractures in patients with ALL and LBL.

The 2019 official position of the International Society for Clinical Densitometry (ISCD) defines a diagnosis of paediatric osteoporosis as either presence of vertebral compression fractures, in the absence of high-energy trauma or local disease, or a BMD Z-score of ≤-2 alongside a clinically significant fracture history[21]. Dual-energy X-ray absorptiometry (DXA) is the preferred method for assessing bone mineral content (BMC) and areal BMD, with the posterior-anterior spine and total body less head (TBLH) the preferred sites for measurement[21]. DXA also allows for detection of vertebral fractures at comparable image quality and accuracy to the previously favoured lateral spine radiographs[22-24], thereby reducing radiation exposure and scan burden for patients.

Historically, vertebral fractures in childhood ALL were considered infrequent[25], however a much higher prevalence and incidence have recently been suggested. The Canadian STOPP programme, a prospective study of 186 newly diagnosed children aged between 1 month and 17 years with ALL, found a vertebral compression fracture prevalence of 16% within 30 days of diagnosis[5]. At 6 years, the study found a cumulative vertebral fracture incidence of 32.5%, 71.3% of which occurred in the first 2 years[26]. Glucocorticoid exposure ($p=0.01$), prevalent vertebral fractures ($p=0.01$) and decreased age ($p<0.01$) were all found to be risk factors for developing incident vertebral fractures[26].

The British Osteonecrosis Study (BONES) is the first multicentre prospective study assessing bone health and vertebral fractures in patients aged 10-24 in the UK undergoing treatment for ALL or LBL.

Study Aim: To investigate the longitudinal effect of ALL and LBL disease and treatment on bone health of patients aged 10-24 years.

Objectives:

1. To understand bone mineral density (BMD) changes over 3 years from initial diagnosis of ALL/LBL.
2. To assess the rate of vertebral fractures in this cohort.
3. To correlate physical symptoms with low BMD or presence of vertebral fractures.

Methods

The British OsteoNEcrosis Study (BONES) was a multicentre prospective longitudinal cohort study, based at three tertiary centres in the UK: Leeds Teaching Hospitals Trust, Birmingham Children's Hospital and Southampton Children's Hospital[27]. Eligible study participants were aged 10-24 years at diagnosis of ALL or LBL under standard criteria.

Patients were treated according to the standard protocols of the national UKALL 2011 trial (ISRCTN64515327)[28]. Male patients received treatment for 3 years and female patients for 2 years. Exact steroid doses were not requested, with assumptions made that treatment would be as per standard UKALL 2011 protocols. Baseline demographic data, including age at diagnosis, sex, ethnic background (White British, British Asian, Black, Other), socioeconomic status (deprivation decile, based on index of multiple deprivation), height and weight were collected at diagnosis. Baseline clinical data, including clinical phenotype, pubertal status, symptom duration and the presence or absence of lymphadenopathy, hepatomegaly, splenomegaly and bone pain at diagnosis, and **treatment regimen (A, B or C)** were also collected using a dedicated clinical report form.

BMD and vertebral fracture data were collected using DXA scans within 4 weeks of diagnosis and annually for 3 years. DXA and vertebral fracture assessment results were reviewed, with size adjustment for lumbar spine bone density (BMAD)[29] and total body less head (TBLH) for patients aged under 18 years. For patients aged over 18 years, T scores were used for the lumbar spine and hip. The thoracic and lumbar vertebrae were assessed for vertebral fractures (T4-L4 where possible), using the Genant semi-quantitative method[30]. **DXA scans were read routinely by radiologists at each centre and were interpreted locally without central review. DXA machines were different at each centre and were not cross calibrated.**

Ethical approval for the study (IRAS project ID 185365) was granted by the Yorkshire and the Humber Sheffield research ethics committee on 12/07/2016. REC reference: 16/YH/0206. A substantial amendment was submitted prior to initiation of the study at any sites on 12/03/2017, with a REC favourable opinion received on 12/04/2017. A further substantial amendment was submitted on 17/01/2018, with REC approval granted on 14/02/2018. Trial registration number: NCT02598401. Date of registration: 05/11/2015. Written parental and patient consent was obtained at each recruiting centre.

Data analysis

Linear mixed models were performed for TBLH and BMAD to evaluate changes in BMD over time. Both models were adjusted for relevant confounders (treatment regimen, sex, age, centre) using directed acyclic graphs (DAGs) (Supplementary Figure 1). Baseline characteristics were described using frequencies and percentages for categorical data, and means and standard deviations or medians and interquartile ranges for normally and non-normally distributed continuous data, respectively.

Descriptive analysis was used for patients with vertebral fractures. Independent t-tests compared bone density between groups reporting different levels of back pain. Data analysis was carried out using SPSS 29. The directed acyclic graph (DAG) was developed and analysed using DAGitty version 3.1.

Results

Demographics

61 patients were enrolled to the BONES study in total. Five patients withdrew or were withdrawn before any data were collected. Baseline demographic and clinical data of the remaining 56 patients can be seen in Table 1. 44 patients had a DXA scan within 4 weeks of diagnosis (*Induction* timepoint). Demographic and clinical data for these patients largely reflects the overall cohort and can be seen in Table 1.

Of the patients from whom data were collected, 25 were recruited from the Leeds centre (18/25 had a DXA scan), 16 from the Birmingham centre (15/16 had a DXA scan) and 15 from the Southampton centre (11/15 had a DXA scan). Due to the older age of some patients, not all those who had DXA scans were eligible for TBLH or BMAD calculation. Pubertal status data were collected for 23 patients who had a DXA scan (52.3%). Of these, 8.7% were Tanner stage 1 and 69.6% were Tanner stage 5. Median age was 14 years for both those who had pubertal status recorded and those who did not.

Table 1: Baseline demographic and clinical data for whole cohort and for patients who had at least one DXA scan							
Whole cohort				**Patients who had DXA**			
Demographic variable		**% (number of patients)**	**Median (IQR)**	**Demographic variable**		**% (number of patients)**	**Median (IQR)**
Age at diagnosis (years) [n=56]	10-15	70 (39)		**Age at diagnosis (years) [n=44]**	10-15	68 (30)	
	16-19	21 (12)			16-19	25 (11)	
	20+	9 (5)			20+	7 (3)	
	Overall		14 (4)		Overall		14 (4)
Ethnicity [n=56]	White British	59 (33)		**Ethnicity [n=44]**	White British	55 (24)	
	British Asian	16 (9)			British Asian	18 (8)	
	Black	0			Black	0	
	Other	7 (4)			Other	7 (3)	
	Not specified	18 (10)			Not specified	20 (9)	
Sex [n=56]	Male	61 (34)		**Sex [n=44]**	Male	59 (26)	
	Female	39 (22)			Female	41 (18)	
BMI SDS [n=39]			0.67	**BMI SDS [n=32]**			0.67
Deprivation decile [n=50]			6(3)	**Deprivation decile [n=37]**			6(3)
Pubertal Status [n=56]	Pre-pubertal	8.9 (5)		**Pubertal Status [n=44]**	Pre-pubertal	5 (2)	
	In puberty	10.7 (6)			In puberty	11 (5)	
	Completed Puberty	35.7 (20)			Completed Puberty	36 (16)	
	Not specified	44.6 (25)			Not specified	48 (21)	
Clinical phenotype [n=56]	B-ALL	80 (45)		**Clinical phenotype [n=44]**	B-ALL	80 (35)	
	T-ALL	11 (6)			T-ALL	11 (5)	
	B-LBL	2 (1)			B-LBL	2 (1)	
	T-LBL	7 (4)			T-LBL	7 (3)	
Symptom duration (days) [n=42]			21 (21)	**Symptom duration (days) [n=42]**			21 (26)
Clinical features at diagnosis [n=49]	Lymphadenopathy	40 (17)		**Clinical features at diagnosis [n=38]**	Lymphadenopathy	40 (15)	
	Hepatomegaly	21 (9)			Hepatomegaly	21 (8)	
	Splenomegaly	29 (12)			Splenomegaly	26 (10)	
	Bone pain	26 (11)			Bone pain	24 (9)	
Highest white cell count before treatment ($x10^9$) [n=51]	<5	31 (16)		**Highest white cell count before treatment ($x10^9$) [n=40]**	<5	32.5 (13)	
	5-20	31 (16)			5-20	27.5 (11)	
	20-50	16 (8)			20-50	15 (6)	
	>50	22 (11)			>50	25 (10)	
	Overall		11.6 $x10^9$ (27 $x10^9$)		Overall		13.65 $x10^9$ (40 $x10^9$)

Attrition rate

Of the 44 patients who had a DXA scan at induction, 29 (66%) had one at the 1-year timepoint, 27 (61%) at the 2-year timepoint and 16 (36%) at the 3-year timepoint. Attrition rate was greater in female patients, with 22% having a DXA at 3 years, compared to 46% of male patients. 37 patients were assessed for back pain at induction, 16 (43%) at 1 year and 3 (8.1%) at 3 years.

12 patients officially withdrew or were withdrawn from the study, following at least one DXA scan, due to not wanting additional scans after treatment ended (6), moving away from centre (3) and relapse or failure to achieve remission (3). Missed appointments, without officially withdrawing, accounted for the remaining DXA attrition.

Bone Mineral Density

Full BMD data for the patients who had DXA scans and were eligible for TBLH or BMAD calculation can be seen in Table 2.

Table 2: Bone mineral density data

Total body less head (TBLH) z-score					**Lumbar spine bone mineral apparent density (BMAD) z-score**				
	Induction	1 year	2 years	3 years		Induction	1 year	2 years	3 years
Patients (n)	41	28	25	15	Patients (n)	38	23	20	11
Mean (SD)	-0.36 (1.02)	-0.97 (1.21)	-1.31 (1.88)	-1.03 (1.27)	Mean (SD)	-0.74 (1.69)	-0.7 (1.55)	-1.14 (1.46)	-1.06 (1.73)
Median (IQR)	-0.2 (1.4)	-1.1 (1.55)	-1.4 (1.1)	-1 (1.4)	Median (IQR)	-0.6 (2.01)	-0.8 (1.9)	-1.4 (1.49)	-1.6 (3.13)

Statistical analysis

<u>Total Body Less Head (TBLH)</u>

Linear mixed modelling found timepoint to be a significant predictor of TBLH (P<0.001). Compared to induction, TBLH was significantly lower after 1 year (estimate=-0.768, 95% CI [-0.996, -0.541], p<0.001), 2 years (estimate=-0.964, 95% CI [-1.357, -0.572], p<0.001) and 3 years (estimate=-0.694, 95% CI [-1.265, -0.124], p=0.018). Full estimates of fixed effects, compared to induction, can be seen in Table 3.

Pairwise comparisons of estimated marginal means indicated a significant decrease in TBLH between Induction and 1 year (mean difference=0.768, p<0.001) and between Induction and 2 years (mean difference=0.964, p<0.001). There was no significant difference in TBLH between induction and 3 years (mean difference=0.694, p=0.107) (see Figure 1). A Bonferroni correction was applied to control for multiple comparisons.

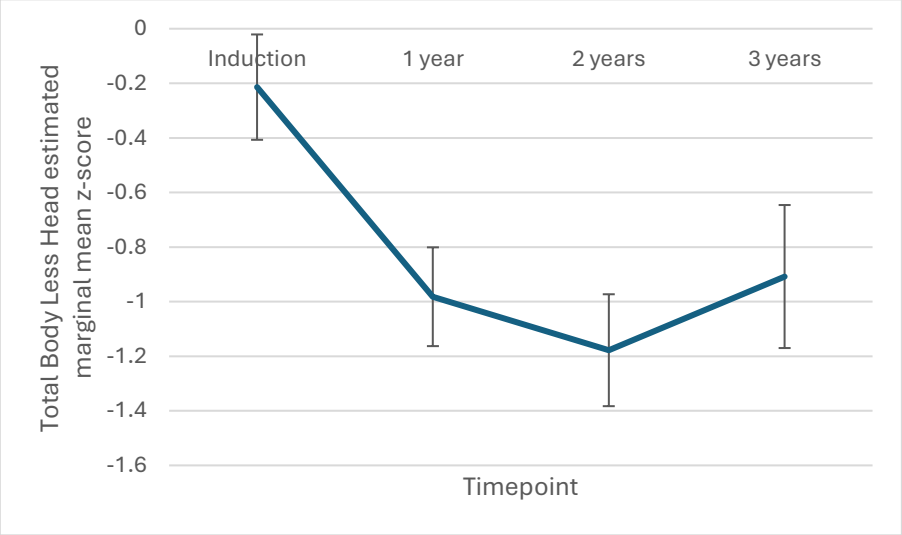

Figure 1: Estimated marginal means of bone mineral density over time, using total body less head (TBLH) z-scores

Lumbar Spine Bone Density (BMAD)

Timepoint was not found to be a significant predictor of BMAD (p=0.885). Compared to induction, BMAD was not found to be significantly different at any of the measured timepoints (see Table 3). Estimated marginal means showed no significant difference across timepoints, as indicated by non-significant pairwise comparisons.

Table 3: Estimates of fixed effects for TBLH and BMAD

	TBLH				BMAD			
Timepoint	**Estimate**	**95% CI upper bound**	**95% CI lower bound**	**p-value**	**Estimate**	**95% CI upper bound**	**95% CI lower bound**	**p-value**
Induction	-0.007	-0.907	0.893	-	0.218	-1.133	1.568	-
1 year	-0.768	-0.996	-0.541	<0.001	-0.037	-0.505	0.430	0.874
2 years	-0.964	-1.357	-0.572	<0.001	-0.164	-0.906	0.577	0.661
3 years	-0.694	-1.265	-0.124	0.018	-0.002	-1.055	1.051	0.988

Vertebral fractures

Two patients, hereafter referred to as patients A and B, were found to have vertebral fractures at Induction timepoint, giving a vertebral fracture prevalence of 4.9% around time of diagnosis. Patient A, a British Asian male, was in puberty and aged 10-15 years at diagnosis of B-ALL, which was treated with regimen C. BMI SDS was +2.01. DXA scan within 4 weeks of diagnosis demonstrated multiple vertebral compression fractures. Bisphosphonate treatment, using annual zoledronate infusions, was initiated at this point. Vertebral fractures fully resolved by end of treatment. Patient B, a British Asian male, was aged 10-15 years and pre-pubertal at diagnosis of B-ALL, which was treated with regimen B. BMI SDS was -0.67. Bone pain, but not back pain, was reported at diagnosis. Zolendronic acid infusions, given 6-monthly, were initiated shortly after initial DXA scan found extensive vertebral compression fractures, and were continued for 4 years. Vertebral fractures did not fully resolve by treatment end however the severity of many fractures improved over time.

Incident fractures were noted in 2 patients, one at 1 year post-diagnosis (patient C), and one at 2 years post-diagnosis (patient D). Patient C, a White British male, was aged 16-19 years when diagnosed with T-ALL. BMI SDS was +2.68, and regimen C was required. Patient C was too old for BMAD scoring, so only TBLH scores were available. Back pain at time of fracture diagnosis was 9/10. Patient D, a British Asian male, was over 20 years of age at diagnosis of T-ALL. As such, Patient D was too old for TBLH or BMAD scoring. Back pain at time of fracture diagnosis was 6/10 . Once diagnosed, vertebral fractures remained unchanged throughout treatment for patients C and D. Details of DXA results, vertebral fractures and pain for patients A-D are detailed in Table 4.

Table 4: DXA results and back pain scoring for Patients A, B, C and D over time				
Patient A				
Timepoint	**Diagnosis**	**1 year**	**2 years**	**3 years**
Back pain	0/10	7/10	0/10	0/10
TBLH z-score	+1.2	+0.2	+0.2	+0.4
BMAD z-score	+1.9	+1.4	+1.7	+1.3
Vertebral fractures	Grade 1: T5, T6, T7, L2	Grade 1: T5, T7, L2	Grade 1: T5, T7	Nil
Patient B				
Timepoint	**Diagnosis**	**1 year**	**2 years**	**4 years**
Back pain	0/10	7/10	5/10	Not reported
TBLH z-score	-1.9	-1.9	-1.7	-0.4
BMAD z-score	-5.2	-1.7	-0.8	0.4
Vertebral fractures	Grade 1: L3 Grade 2: T5, T12, L4 Grade 3: T6, T7, T8, T9, T10, T11, L1, L2, L5	Grade 1: T4, L3, L4, L5 Grade 2: T6, T12, L2 Grade 3: T7, T8, T9, T10, T11, L1	Grade 1: T6, L3, L5 Grade 2: T8, T12, L2, L4 Grade 3: T7, T9, T10, T11, L1	Grade 1: T6, T8, T10, L3, L4 Grade 2: T7, T9, T12, L2 Grade 3: T11, L1
Patient C				
Timepoint	**Diagnosis**	**1 year**	**2 years**	**3 years**
Back pain	0/10	9/10	Not reported	Not reported
TBLH z-score	0	-0.7	-0.8	-0.7
Vertebral fractures	Nil	T11 (Grade 1)	T11 (Grade 1)	T11 (Grade 1)
Patient D				
Timepoint	**Diagnosis**	**1 year**	**2 years**	**3 years**
Back pain	0/10	0/10	6/10	Not reported
Vertebral fractures	Nil	Did not attend	T11 (Grade 1)	T11 (Grade 1)

Back pain

Self-reported back pain has only been analysed at baseline, within 4 weeks of diagnosis, due to the high attrition rate. Back pain varied considerably between patients. 59.5% of patients reported back pain of 0/10, while 18.9% had scores of ≥5/10. No significant difference in mean BMD z-scores was found between patients reporting 0/10 pain and those reporting ≥5/10 pain for TBLH (p=0.365) or BMAD (p=0.097), or between patients reporting 0/10 pain and those reporting ≥1/10 pain for TBLH (p=0.249) or BMAD (p=0.058).

BMD varied considerably within identical pain scores. In patients reporting 0/10 pain, TBLH z-scores ranged from 1.2 to -1.5, while BMAD z-scores ranged from 1.9 to -5.2. For patients reporting back pain of ≥5/10 , TBLH z-scores ranged from 1.3 to -2.5, both occurring in patients reporting pain of 5/10. BMAD z-scores in this group ranged from 1.3 to -3.3, with pain scores of 5 and 8 respectively. Full back pain data can be seen in Supplementary Table 1.

Discussion

This work provides novel data on the bone health of patients aged between 10 and 24 years with ALL and LBL. Previous research has studied incidence of vertebral fractures in all patients under 18 years[2,4,5]. In the STOPP study, median age was 5.3 years, 75% of participants were aged 9.7 years and under, and 78% of patients were pre-pubertal. In comparison, our cohort's median age was 14 years and, where reported, the majority were in or had completed puberty. This difference in population demography may explain the lower prevalence of vertebral fractures, due to the protective role of oestrogen and testosterone in reducing bone fragility. **Spontaneous resolution of vertebral fractures is unlikely in older patients and this is reflected by the disease course seen in patients C and D, who both showed persistent fractures by the end of treatment. In contrast, the younger patients A and B showed considerable improvements to their more extensive**

vertebral fracture patterns, with Patient A experiencing full resolution. The extent and severity of Patient B's fractures likely accounted for their failure to fully resolve, however other, patient specific factors may also have influenced this.

In our study, timepoint was found to be a significant predictor of BMD (TBLH). BMD at both the 1-year and 2-year timepoints was significantly reduced, compared to at induction, with an increased mean difference between induction and 2-years, compared to 1-year, suggesting that BMD reduces continuously for up to 2 years post-diagnosis. BMAD was preserved throughout the study. Our finding that BMD (TBLH) loss plateaus, and possibly begins to recover between years 2 and 3, supports previous research findings that BMD normalises over time as treatment ends[16-20]. Larger and longer-lasting studies are needed to assess the speed of this recovery.

Overall, four patients received bisphosphonates during the study. Three patients were commenced on bisphosphonates after diagnosis of vertebral fractures and remained on them throughout treatment. One patient received 12 months of zoledronic acid for low BMD and significant back pain. It is unlikely that bisphosphonate therapy influenced the overall BMD outcomes, due to the small number of patients receiving them, one of whom was too old for BMD assessment.

All four vertebral fractures identified in our cohort occurred in male patients and 75% affected British Asian patients, despite them comprising just 18% of the cohort who had spinal imaging. It is recognised that there are ethnic variations in bone fragility and bone density. In this cohort, Asian typically refers to patients of South Asian ethnicity, although this was not specifically recorded. There is limited research comparing bone fragility in this group with other ethnicities. Our results found an overrepresentation of British Asian males with vertebral fractures, but it is not possible to elucidate the reasons for this. Incident vertebral fractures may reflect greater leukaemic infiltrate. It is of note that vertebral fractures did not always correlate with low BMD or increased back pain, suggesting imaging limited to patients with those features may result in missed diagnoses.

Back pain in leukaemia is multifactorial and may be related to lumbar punctures, physical limitations and chemotherapeutic agents. Our study suggests that self-reported pain in isolation is not a useful identifier of low BMD or vertebral fractures. In patients A and B, who both had multiple vertebral fractures around the time of induction, self-reported back pain was 0/10. These scores increased after 1 year of maintenance therapy, possibly suggesting patients at presentation are distracted by other symptoms and thus may not recognise fractures at this early stage. This is supported by patients C and D, who developed fractures during their maintenance treatment and who both reported back pain at the time these were identified. This supports the use of spinal imaging at baseline, to identify vertebral fractures that would otherwise go unrecognised.

Limitations

There are several limitations to this study. An increased number of patients at all, but especially later, timepoints would provide more robust data and would enable random effect modelling and nesting of patients within centres. The attrition rate was due to the impact of the COVID-19 pandemic, missed appointments, failure to achieve remission on standard treatment regimens, patient death and early withdrawal from the study due to active treatment ending. There are numerous challenges for engagement in longitudinal adolescent health studies, and it is recognised that studies in adolescents often suffer from engagement and retention difficulties [31,32].

DXA scans were interpreted at each separate tertiary centre, rather than images being centralised and reviewed by one clinician. Differences in operator, scanner, reporter and local quality assurance programmes can all risk differences in the reporting of BMD and of vertebral fractures[33], although all reports were collated centrally to assess quality and accuracy.

Conclusions

Our study supports the routine use of spinal imaging (vertebral fracture assessment or spine x-rays) for all paediatric and young adult patients with leukaemia, with national standardisation of imaging for children and young people with ALL and LBL. Our results suggest that the risk of vertebral fractures is lower than in younger age groups but remains higher than in the healthy paediatric population. Presence or absence of back pain and low BMD cannot be used to identify patients with vertebral fractures. Ethnicity may have an impact on vertebral fracture development, and larger studies would be valuable to assess this further.

Our data suggests that while most patients will see a reduction in BMD during their treatment, this loss is typically transient, and improvement is usually seen after cessation of treatment. This should be discussed with patients and support should be provided to enable participation in behaviours that support improved BMD during treatment, such as adequate calcium and vitamin D intake, and weight-bearing exercises.

Areas for further research

Larger studies looking at vertebral fractures in young people treated for ALL or LBL would provide more data to help future work on treatment options and outcomes for these patients. AllTogether, a European treatment protocol for young people with ALL presents an opportunity for large international studies that would help development of robust evidence and guidelines.

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