

Aggravated bone density decline following symptomatic osteonecrosis in children with acute lymphoblastic leukemia

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ABSTRACT

Osteonecrosis and decline of bone density are serious side effects during and after treatment of childhood acute lymphoblastic leukemia. It is unknown whether osteonecrosis and low bone density occur together in the same patients, or whether these two osteogenic side-effects can mutually influence each other's development. Bone density and the incidence of symptomatic osteonecrosis were prospectively assessed in a national cohort of 466 patients with acute lymphoblastic leukemia (4-18 years of age) who were treated according to the dexamethasone-based Dutch Child Oncology Group-ALL9 protocol. Bone mineral density of the lumbar spine (BMD_{LS}) (n=466) and of the total body (BMD_{TB}) (n=106) was measured by dual X-ray absorptiometry. Bone density was expressed as age- and gender-matched standard deviation scores. Thirty patients (6.4%) suffered from symptomatic osteonecrosis. At baseline, BMD_{LS} and BMD_{TB} did not differ between patients who did or did not develop osteonecrosis. At cessation of treatment, patients with osteonecrosis had lower mean BMD_{LS} and BMD_{TB} than patients without osteonecrosis (respectively, with osteonecrosis: -2.16 versus without osteonecrosis: -1.21, $P<0.01$ and with osteonecrosis: -1.73 versus without osteonecrosis: -0.57, $P<0.01$). Multivariate linear models showed that patients with osteonecrosis had steeper BMD_{LS} and BMD_{TB} declines during follow-up than patients without osteonecrosis (interaction group time, $P<0.01$ and $P<0.01$). We conclude that bone density status at the diagnosis of acute lymphoblastic leukemia does not seem to influence the occurrence of symptomatic osteonecrosis. Bone density declines from the time that osteonecrosis is diagnosed; this suggests that the already existing decrease in bone density during acute lymphoblastic leukemia therapy is further aggravated by factors such as restriction of weight-bearing activities and destruction of bone architecture due to osteonecrosis. Osteonecrosis can, therefore, be considered a risk factor for low bone density in children with acute lymphoblastic leukemia.

Introduction

As survival rates of children with acute lymphoblastic leukemia (ALL) have substantially improved, the understanding of both short- and long-term side effects of ALL treatment has become increasingly important.¹ Severe osteogenic side-effects of ALL treatment include osteonecrosis²⁻¹¹ and bone mineral density (BMD) loss,¹²⁻¹⁷ which often occur during and shortly after antileukemic treatment. Both side effects may lead to adverse events, such as pain, fractures and consequent movement disability.^{17,18}

Osteonecrosis is a condition caused by compromised bone vascularization which leads to several local processes, including bone infarction, trabecular thinning, bone weakness, edema within the bone, local infarction, and risk of subsequent adjacent joint destruction.¹⁹ Although some components of antileukemic treatment, especially glucocorticoids, are considered to play a critical role in the etiology of osteonecrosis, the pathogenesis is not fully understood.²⁰

We and others have shown that BMD is already low when

ALL is diagnosed, and that the final BMD loss at cessation of ALL treatment is mainly determined by BMD values at the start of treatment.^{17,21,22} This suggests that the disease itself and genetic variation in genes that influence bone density may be important risk factors for BMD loss. The final BMD loss is also determined by treatment with certain drugs, e.g. corticosteroids²³ and folate antagonists,²⁴ irradiation, physical inactivity, and nutritional deficiencies.²⁵

Although osteonecrosis and BMD loss have been extensively investigated during and after treatment of pediatric ALL,^{6,15-17} it is unknown whether these two osteogenic side effects occur together in individual ALL patients, or whether they may aggravate each other's development.

In this study, we prospectively evaluated the occurrence of symptomatic osteonecrosis and change in BMD in pediatric ALL patients who were older than 4 years of age at diagnosis, and treated according to the dexamethasone-based Dutch Child Oncology Group (DCOG)-ALL9 protocol.^{6,7,26} Our aim was to examine whether osteonecrosis and BMD decline occur together and whether these two osteogenic side-effects

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may influence each other's development during treatment for pediatric ALL.

Methods

Study population

This study is based on a subset of a previously described cohort. The children (4-18 years old) had newly diagnosed ALL and were treated in The Netherlands according to the Dutch Childhood Oncology Group (DCOG) – ALL9 protocol between January 1997 and November 2004.^{17,26} As previously described, patients were stratified into a non-high-risk treatment group and a high-risk group.²⁶ Briefly, high-risk criteria were: white blood cell count higher than $50 \times 10^9/L$, T-cell immunophenotype, mediastinal mass, central nervous system involvement, testicular involvement, and genetic aberrations [translocation t(9;22), *BCR-ABL1*, or any 11q23/*MLL* gene rearrangements]. All other patients were classified as non-high risk. The 2-year treatment schedules included dexamethasone during an induction period of 6 weeks, and repeated pulses of dexamethasone for 2 weeks every 7 weeks during maintenance therapy (total cumulative dose: high-risk, 1,244 mg/m²; non-high-risk, 1,370 mg/m²). None of the patients received irradiation to the central nervous system.²⁶

For the current study, patients were prospectively evaluated from diagnosis until 1 year after cessation of treatment, and data were obtained from case report forms, which were collected centrally by the DCOG. For patients who did not complete the ALL9-protocol (because of toxicity, relapse, hematopoietic stem-cell transplantation, or death), data before going off study were included in the database. Patients with syndromes or pre-existent diseases affecting BMD were excluded (*Online Supplementary Figure S1*). The ethical review boards approved the study (trial number NTR460/SNWLK-ALL-9) and written informed consent according to the Helsinki agreement was obtained from all parents and from patients ≥ 12 years old.

Outcome measures

Bone mineral density

BMD was measured at diagnosis (T0), after 32 weeks of treatment (T1), at the end of the treatment protocol (T2, 109 weeks) and 1 year after cessation of therapy (T3) (Figure 1).⁷ As previously described,^{17,22} only pediatric ALL patients who were 4 years of age and older at T3 were included for dual energy X-ray absorptiometry measurements (DXA; by Lunar DPX-L scanner, Madison, WI, USA or Hologic scanner, Waltham, MA, USA), as control BMD values are only available for this age group. BMD of the lumbar spine (BMD_{LS}) was measured with a Hologic or Lunar DXA scanner. In addition, in a subset of the cohort, BMD of the total body (BMD_{TB}) was measured with a Lunar DXA scanner in one treatment center.^{17,22} DXA results of the Hologic scanner were compared with the manufacturer's own reference data and DXA results of the Lunar scanner were compared with data from healthy Dutch children, measured on the same scanner.²⁷ Analyses were performed with age- and sex-matched standard deviation scores (SDS) of BMD, and BMD was categorized into BMD < -1 SDS and BMD < -2 SDS, as previously described.^{28,29}

Osteonecrosis

Symptomatic osteonecrosis was defined as persistent pain in the arms or legs, not resulting from vincristine administration, with typical findings on magnetic resonance imaging.^{30,31} From here on, we refer to *symptomatic* osteonecrosis as ON. ON was graded according to the National Cancer Institute (NCI) Common Terminology criteria for Adverse Events, version 3.0.³² As previ-

ously described,⁷ patients were considered as ON subjects when they developed ON (NCI grade 2 to 4) during, or within the first year after cessation of treatment. Magnetic resonance imaging was performed of any anatomic location in which symptoms of ON occurred.

Fractures

All reported fractures were symptomatic, and confirmed by X-ray. Fractures were included in the analyses when they were reported between the day of ALL diagnosis and 1 year after discontinuation of therapy. Clinically significant fractures were defined as vertebral compression fractures, fractures of long bones in the lower limbs, and/or two or more fractures or fractures without preceding trauma.^{17,33}

Statistical analysis

To compare baseline characteristics between patients with and without ON, or with and without a DXA scan, we used the chi-squared (χ^2) test for categorical variables, the two-sample t-test for continuous variables with a normal distribution, and the Mann-Whitney U test for continuous variables with a skewed distribution.

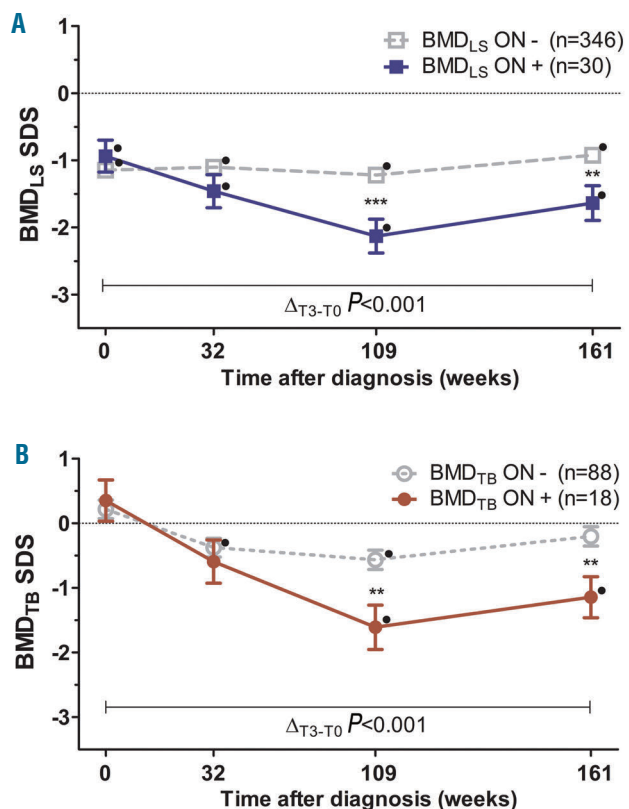


Figure 1. Comparison of sequential BMD measurements in pediatric ALL patients (4-18 years of age) with and without ON. BMD of the (A) lumbar spine (n=466) and (B) total body (n=106) in pediatric ALL patients (4-18 years of age) with and without ON during and after the treatment of pediatric ALL. The dots represent the mean and the whiskers represent the standard error of the mean BMD. The “*” represents the comparison of BMD between patients with and without ON and the “•” represents the comparison of BMD between patients and the healthy population. Abbreviations: T0 = at diagnosis; T1 = start of maintenance therapy (32 weeks); T2 = at cessation of therapy (109 weeks); T3 = 1 year after cessation of therapy (161 weeks); BMD_{LS} = bone mineral density of the lumbar spine; BMD_{TB} = bone mineral density of total body; Δ_{T3-T0} = interaction group time * ON; ** = P-value < 0.01; *** = P-value < 0.001; • = P < 0.05.

The one-sample t-test was used at each time point (T0 to T3) to compare BMD SDS measurements of ALL patients with reference values of healthy children. The two-sample t-test was used to compare BMD SDS measured at all the different time points between patients with or without ON. The χ^2 test was used to examine whether patients with ON had BMD <-1 SDS, BMD <-2 SDS or fractures at cessation of treatment more often than patients without ON. If numbers in the χ^2 -test analyses were smaller than 5, the Fisher exact test was used.

To analyze differences of BMD SDS change during total follow-up (Δ T0-T3) between patients with and without ON, a linear mixed model was used with an unstructured repeated covariance type. The model was defined as "follow-up time", "ON" and the interaction variable "follow-up time*ON". Differences in BMD change between ON-positive and ON-negative patients at each moment were estimated using a model without intercept defined by the interaction variable "follow-up time*ON".

For the multivariate analyses we verified that there was no over adjustment by the additional variables age and risk group, because they could be correlated with each other or ON incidence.^{6,17} This was done by testing collinearity, which is not present when the variance inflation factor is <10 in regression models with ON incidence, age or risk group. The variance inflation factor provides an index that measures the amount of bias associated with over adjustment.³⁴ The multivariate linear mixed model with BMD change as an outcome measure included the variables: "follow-up time", "ON", "age at diagnosis", "risk group", "follow-up time*risk group", "ON*risk group", and "follow-up time*ON*risk group". A *P*-value ≤ 0.10 of the interaction variable was considered statistically significant. For these analyses, age at diagnosis was used as a continuous variable.

To examine effect modification by age and risk group, we also performed stratified analyses by age and/or risk group. The interaction terms "age", "age*ON", and "follow-up time*age*ON", and "risk group", "risk group *ON", and "follow-up time* risk group *ON" were added to the univariate model. For these analyses, age was dichotomized into age <10 years and age ≥ 10 years.

To support the previous analyses, we also used an alternative analysis to examine whether patients with ON had greater bone loss than patients without ON. For each patient with ON, we randomly selected four control patients without ON.^{35,36} Subsequently, BMD measurements of each ON patient and their controls were divided into measurements before the detection of ON ($M=-2$, $M=-1$) and measurements after the detection of ON ($M=+1$, $M=+2$). A paired sample t-test was used to examine the BMD change before and after the moment that ON occurred in the patients with ON, and their controls. To study whether this BMD change ($M=-1$ to $M=+1$) was dependent on ON occurrence and thus independent of the amount of treatment received, the two-sample t-test was used to compare BMD change ($M=-1$ to $M=+1$) between patients with ON and the selected controls without ON.

Statistical analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and, unless stated otherwise, *P*-values ≤ 0.05 (two-sided) were considered statistically significant.

Results

Seven hundred and fifty-one patients were treated according to the DCOG-ALL9 protocol, of whom 58 were excluded because of pre-existing conditions ($n=35$), lack of follow-up data ($n=20$), or other miscellaneous reasons ($n=3$). Of the remaining 693 patients, 575 were older than 4 years (Online Supplementary Figure S4), and DXA scans

were available for 466 of them. Patients with a DXA scan ($n=466$) did not differ from patients without a DXA scan ($n=109$) with regard to age >10 years ($P=0.955$), gender ($P=0.369$), ON occurrence ($P=0.312$), ALL immunophenotype ($P=0.472$), risk protocol ($P=0.822$), or frequency of clinically significant fractures ($P=0.306$).

A subset of 332 of the 466 patients (72%) had a DXA scan at the end of treatment (T2). DXA scans were unavailable at T2 for a variety of factors: second malignancy, death, relapse, progressive disease, stem cell transplantation, treatment toxicity, loss of follow-up or issues related to patients' logistics. Patients with a DXA scan at T2 ($n=332$) were comparable to those without a DXA scan ($n=132$) with regard to gender ($P=0.640$), prevalence of ON ($P=0.812$), and clinically significant fractures ($P=0.364$). However, patients without a DXA scan at T2 were older (percentage >10 years: 36% versus 24% in those with DXA, $P=0.009$), were more often treated with the high-risk protocol (41% versus 25%, $P<0.001$) and more often had T-ALL (25% versus 12%, $P=0.002$). Patients with a DXA scan at T3 ($n=231$) were comparable to those without a DXA scan ($n=235$) with regard to gender ($P=0.534$), age >10 years ($P=0.148$), prevalence of ON ($P=0.118$), immunophenotype ($P=0.122$), risk protocol ($P=0.055$) and clinically significant fractures ($P=0.364$).

One patient had surgery due to a fracture of the right femoral head with three pins, and since surgery may lead to ON, we excluded this patient from the analyses from that point onward.

Osteonecrosis

Thirty patients (6.4%) among the 466 included (>4 years) were diagnosed with ON in the period between diagnosis and 1 year after cessation of ALL treatment. The median time between diagnosis of ALL and occurrence of ON was 14 months (range, 1-33 months). ON was diagnosed in weight-bearing joints of the lower limbs of all affected patients;⁶ the joints involved were hips ($n=19$), knees ($n=22$), and ankles ($n=6$). In five of the 30 patients, ON was also diagnosed in the upper extremities [shoulders ($n=4$), elbows ($n=1$) or wrists ($n=1$)]. Patients with ON were significantly older than patients without ON ($P<0.001$, Table 1). In 64% ($n=18$) of the patients chemotherapy was adjusted because of ON; in eight patients the use of corticosteroids was discontinued, in seven patients the dose of corticosteroids was reduced, and three patients were switched from dexamethasone to prednisone. Every patient with ON had received instructions to reduce weight-bearing activities.

Bone mineral density

At cessation of treatment (T2), mean BMD_{LS} was -1.28 SDS (SD: 1.27, $n=332$) and was significantly lower than that in the patients' healthy peers ($P<0.01$). In the single center subset, BMD_{TB} was -0.74 SDS (SD: 1.29, $n=65$) and also significantly lower than that in the patients' healthy peers ($P<0.01$).

Co-occurrence of osteonecrosis and low bone mineral density

BMD_{LS} and BMD_{TB} were not different at baseline between patients who did or did not develop ON (T0: mean BMD_{LS} with ON -0.90 versus -1.14 without ON, $P=0.359$ and mean BMD_{TB} with ON 0.07 versus 0.25 without ON, $P=0.650$). At cessation of treatment (T2), patients

with ON had significantly lower mean BMD than patients without ON (T2: BMD_{LS} -2.16 versus -1.21, $P<0.001$ and BMD_{TB} -1.73 versus -0.57, $P=0.008$, Figure 1). One year after cessation of treatment, BMD in patients with ON was again lower than in patients without ON (T3: BMD_{LS} with ON -1.68 versus -0.94 without ON, $P=0.008$; BMD_{TB} with ON -1.18 versus -0.42 without ON, $P=0.019$) (Figure 1). Patients with ON were also more likely to have BMD <-1 SDS (T2: BMD_{LS} with ON 90% versus 60% without ON, $P=0.004$; BMD_{TB} with ON 90% versus without ON 33%, $P<0.001$) and BMD <-2 SDS (BMD_{LS} with ON 62% versus 25% without ON, $P<0.001$; BMD_{TB} with ON 30% versus 15% without ON, $P=NA$) than patients without ON (Figure 2, Online Supplementary Figure S2).

Although patients with ON more often had a clinical fracture during follow-up than patients without ON, this difference was not statistically significantly different (with ON: 12% versus without ON: 6%; $P=0.165$) (Table 1, Figure 2). Of the four patients who had ON and a fracture, two had a fracture related to trauma (talus; distal tibia avulsion), one had vertebral collapse without preceding

trauma, and one had a fracture of the left tibial plateau without preceding trauma 2 months after the diagnosis of ON at the same location.

Bone mineral density change and osteonecrosis

The trend of BMD_{SDS} change during follow-up was different between patients with and without ON, as the interaction term between group (with ON versus without ON) and BMD at a measurement time was significant (interaction group time, BMD_{LS}: $P<0.001$ and BMD_{TB}: $P<0.001$) (Figure 1).

Correction for risk protocol and age at diagnosis

There was no overcorrection in the multivariate analyses for BMD_{SDS} change, because ON and age, ON or risk group, and age and risk group were not collinear as the variance inflation factor was <10 . After correction for age at diagnosis and risk group, BMD change during follow-up was still significantly different for BMD_{LS} and BMD_{TB} in patients with ON (interaction group time, BMD_{LS}: $P<0.001$ and BMD_{TB}: $P=0.007$) (Online Supplementary Figure S2).

Table 1. Characteristics of pediatric ALL patients (4-18 years of age) with and without ON.

	Without ON (n=436) N (%), median (range)		With ON (n=30) N (%), median (range)		P-value
Age at diagnosis years	5.5	(1.0-16.6)	13.5	(5.0-17.1)	$<0.001^a$
Age group					
<10 years	337	(77%)	2	(7%)	$<0.001^c$
≥ 10 years	99	(23%)	28	(93%)	
Gender					
male	277	(64%)	14	(47%)	0.065 ^b
female	159	(36%)	16	(53%)	
Immunophenotype					
BCP-ALL	354	(85%)	25	(84%)	0.818
T-ALL	63	(15%)	5	(6%)	
Risk group					
non-high risk	310	(71%)	20	(67%)	0.605 ^b
high risk	126	(29%)	10	(33%)	
Clinically significant fractures during treatment					
no	392	(94%)	25	(86%)	0.165 ^c
yes	25	(6%)	4	(14%)	

^aMann-Whitney U test; ^bChi-squared test; ^cFisher exact test; ALL: acute lymphoblastic leukemia; BCP: B-cell precursor; ON: symptomatic osteonecrosis; n: number.

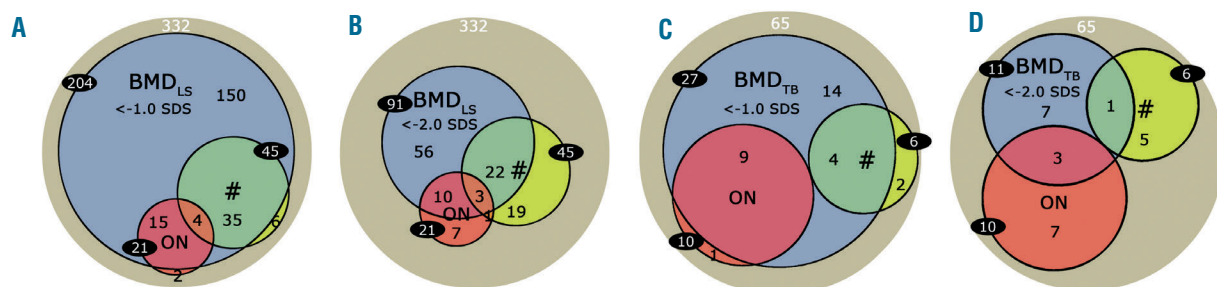


Figure 2. These area-proportional Venn diagrams represent the co-occurrence of osteonecrosis, low BMD and fractures in pediatric ALL patients with a BMD measurement at cessation of ALL treatment (T2). The numbers represent the absolute number of patients in each circle or zone. Each zone is proportional to the absolute number of patients assigned to the zone. Abbreviations: BMD_{LS}: bone mineral density of the lumbar spine; BMD_{TB}: bone mineral density of total body; SDS: standard deviation score; ON: symptomatic osteonecrosis; #: fractures.

Effect modification by age and risk group

The interaction terms, "ON*risk group*follow-up time" (interaction group time, BMD_{LS} $P=0.78$ and BMD_{TB} $P=NA$) and "ON*age ≥ 10 *follow-up time" (interaction group time, BMD_{LS} $P=0.36$ and BMD_{TB} $P=0.40$) were not statistically significant. Stratified analyses for age were only possible in the group of patients ≥ 10 years, because there were too few patients (only two) with ON in the group < 10 years. In the subgroup of patients ≥ 10 years, the BMD values were lower in patients with ON than in patients without ON, however the results were not statistically significant and weakened by low numbers of patients (interaction group time, BMD_{LS} $P=0.45$ and BMD_{TB} $P=0.15$, *Online Supplementary Figure S3*).

Stratified analyses for risk group showed that the difference seems to be more pronounced in the non-high-risk group; however, patients treated with a high-risk protocol also seem to have a lower BMD when they were diagnosed with ON during treatment (*Online Supplementary Figure S4*). Stratified analyses for risk group in the subgroup of patient ≥ 10 years of age were not possible because the numbers in the high-risk group were too small (patients with ON: $n=10$).

Time of osteonecrosis diagnosis as benchmark

To study the influence of ON occurrence on BMD loss, we performed analyses using the randomly selected controls. These analyses showed that BMD was not significantly different between patients with or without ON at the last DXA scan before the detection of ON ($M=-1$, BMD_{LS} $P=0.402$, BMD_{TB} $P=0.742$) (Figure 3). Interestingly, patients with ON had a significantly greater decline in BMD after the detection of ON (between $M=-1$ to $M=+1$) [mean BMD_{LS} -0.43 (SD: 0.95), $P=0.032$; BMD_{TB} -1.13 (SD: 0.28), $P=0.004$] (Figure 3). This mean BMD decline ($M=-1$ to $M=+1$) was more prominent in patients with ON than in the randomly selected controls [BMD_{LS} -0.43 (SD: 0.95) versus 0.05 (SD: 1.06), $P=0.046$; BMD_{TB} -1.13 (SD: 0.95) ver-

sus -0.17 (SD: 0.98), $P=0.004$] (Figure 3). This subsequently resulted in a lower BMD in patients with ON than in controls without ON at $M=+1$ (BMD_{LS} , $P=0.020$; BMD_{TB} , $P=0.015$).

Discussion

This prospective study emphasizes once again that severe osteogenic side effects - such as ON and low BMD - frequently occur during and after treatment for childhood ALL.^{6,15-17} The development of ON was not related to BMD at the start of the antileukemic treatment. Comparable data were found in one previous smaller study of 38 patients that used quantitative ultrasound.³⁷

In our cohort of children between 4-18 years old with ALL, BMD_{LS} and BMD_{TB} were lower than in their healthy peers, with values similar to those in most earlier reports.^{15,16} Patients with ON had an even lower BMD at the end of treatment compared to patients without ON. In addition, we observed a steeper decline of BMD during antileukemic treatment in patients with ON, even after correction for age at diagnosis. This BMD decline occurred especially after the diagnosis of ON. This suggests that patients who develop ON during antileukemic therapy may be in need of extra medical care for low BMD or osteoporosis. Thus, low bone density and bone density loss seem to be influenced by the occurrence of ON, as well as previously identified factors such as age and weight at diagnosis, B-cell-immunophenotype, use of corticosteroids, folate antagonists or irradiation, physical inactivity, and nutritional deficiencies.^{17,21-25}

Bone density loss in patients with ON is most likely affected by a combination of avoidance of weight-bearing activities and sports activities³⁷ and by ON itself.³⁸ Previous studies in healthy volunteers and astronauts have shown that "skeletal unloading" induces osteopenia,³⁹⁻⁴¹ with a 3% loss of BMD after 12 weeks.⁴² This might be due to a

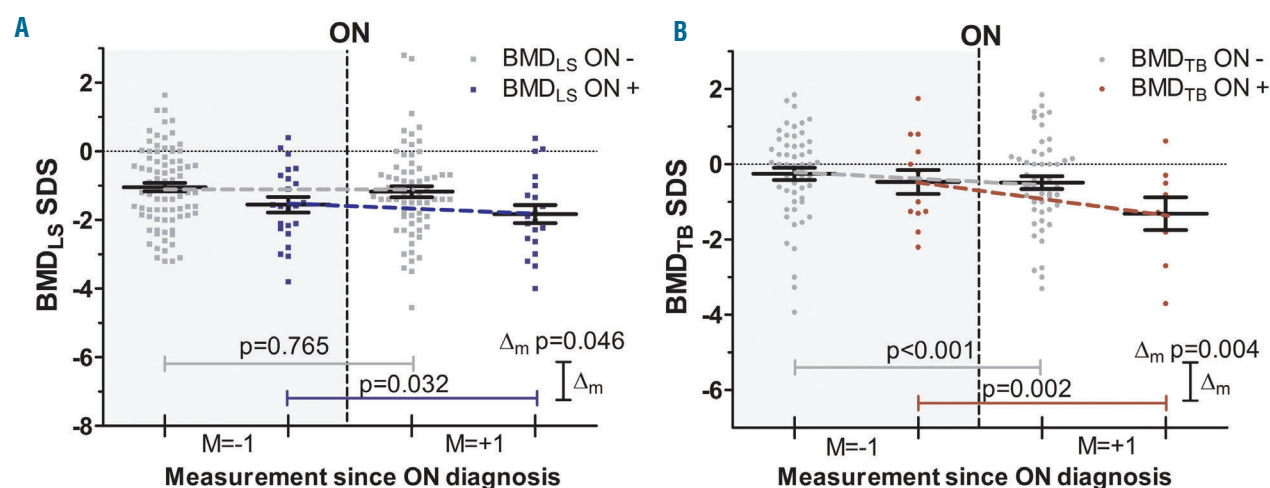


Figure 3. BMD measurements relative to the diagnosis of ON in pediatric ALL patients (4-18 years of age) with ON as compared to randomly selected controls without ON. BMD measurements relative to the diagnosis of ON for (A) lumbar spine BMD and (B) total body BMD. The line and whiskers represent the mean and standard error of BMD. The dotted line per patient group represents the slope between measurements before and after the diagnosis of ON. The BMD measurements from $M=-2$ to $M=+2$ can include BMD measurements at different time points during treatment (T_0 to T_3). Δ_m = BMD change before and after the diagnosis of ON in the groups of patients with or without ON; ON-: patients without ON; ON+: patients with ON.

decrease in osteoblast recruitment and bone formation,^{43,44} as there is no stress of weight on these bones. BMD loss may also occur due to ON itself; the fact that the BMD_{TB} decline seems to be more pronounced than the BMD_{LS} decline supports this idea. ON causes local destruction of the bone,³⁸ and ON is not usually located in the lumbar spine, but it is located in bones measured by DXA of the total body.

It is unknown whether interventions may overcome the negative influence of skeletal unloading and ON on the decline of BMD. Weight-bearing activities may stimulate BMD gain, but these activities need to be restricted in patients with ON to avoid joint damage.¹¹ Muscle training without weight bearing to the vulnerable joints affected by ON - such as swimming - improves physical performance; however swimming does not improve BMD.^{45,46} Further studies need to establish whether excessive BMD loss could be prevented in patients with ON by other interventions such as dietary supplementation with calcium, vitamin D and the use of bisphosphonates.^{11,47,48} Only symptomatic patients were assessed in our study; however asymptomatic patients may also have bone destruction and possible BMD loss. A recent report by Kaste *et al.* described that early detection of ON with magnetic resonance imaging in patients above the age of 10 is feasible; these patients could then benefit from early therapy to reduce BMD loss as well.¹⁰

Low BMD values were still present 1 year after cessation of treatment in patients who had ON, even though some patients have radiological and clinical improvement of ON.²⁰ This is not surprising, as the effect of avoidance of weight-bearing activities for several months is likely to continue after cessation of treatment. Previous studies have shown that bone loss or its destruction can recover, although the recovery process is slow⁴⁹ and during this period there may be a high risk of fractures.¹⁷ We did not

find a higher risk of fractures in patients who had ON, but this may be due to the low number of patients with fractures in our study.

One limitation of our study may be the fact that patients who were older or who were treated with a high-risk treatment protocol were more likely to be lost to follow-up at the end of treatment. Furthermore, older age at diagnosis is a risk factor for a more rapid decline of BMD_{LS} during treatment and is also associated with an increased risk of having ON.^{6,17}

Although there was insufficient power to examine the association between ON and BMD between age groups and risk groups accurately, our findings indicate that ON and BMD decline occur independently in any of these groups. Since ON mainly occurs in the older group, it would be worthwhile validating our findings in a large, prospective study focusing particularly on children who are older than 10 years of age.

We conclude with our preliminary findings that symptomatic ON is accompanied by a decline in BMD during antileukemic therapy in pediatric ALL patients. The fact that this occurs from the moment of ON diagnosis, suggest that the already existing BMD decline during ALL therapy is further aggravated by restriction of weight-bearing activities and destruction of bone architecture due to ON.

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Authorship and Disclosures

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