Highlights

- Bone mass deficits in children with leukemia following HSCT are multifactorial.
- Attention is needed to children with less potential to recover from low BMD.
- Risk factors for ON include older age at HSCT, steroids, cGvHD and prior ON.
- Management of ON in children with ALL following HSCT remains challenging.
Review article

Guidance to bone morbidity in children and adolescents undergoing allogeneic hematopoietic stem cell transplantation

Short title: Bone morbidity in children after HSCT

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) is widely performed in children and adolescents with hematologic diseases including very high-risk leukemia. With increasing success and survival rates, the long-term sequelae of HSCT have become important. Here, we provide guidance to the prevention and treatment of the most common bone morbidities – osteoporosis and osteonecrosis – emerging in the context of HSCT in children and adolescents. We give an overview on definitions, symptoms and diagnostics and propose an algorithm for clinical practice based on discussions within the International BFM SCT Committee and the Pediatric Disease Working Party of the European Society for Blood and Marrow Transplantation, our expert knowledge and a literature review.
Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the standard of care in children with very high-risk acute leukemia. (1-3) Through advances in donor selection and supportive care strategies, cure rates in patients with high-risk acute lymphoblastic leukemia (ALL) are approaching 70% in large multi-institutional trials. (4) However, this success comes at the cost of complications and sequelae from chemotherapy and HSCT with negative impact on quality of life (QoL). These complications are increasingly being recognized and become the focus of research in childhood leukemia survivors. (5, 6) Whilst little is known on complications specifically attributable to allogeneic HSCT in children with high-risk leukemia compared to chemotherapy alone, their overall greater number and severity are uncontroversial. (7-9) Notably, side effects vary between conditioning regimens, e.g., depending on the use of total body irradation and the drugs administered.

One of the most prevalent and debilitating complications from ALL therapy and HSCT is bone morbidity including osteoporosis (OP) and osteonecrosis (ON). (7) Reported incidences range between 20-60% for reduced bone mass accrual, including OP, and 4-40% for ON, respectively. However, these estimates are mostly based on retrospective studies using dual energy X-ray absorptiometry (DXA) for bone mineral density (BMD) assessment, and include several HSCT approaches and heterogeneous underlying diseases. (10-15)

In the setting of leukemia, clinically relevant fractures are associated with low BMD. A prospective surveillance study in children (STOPP) confirmed a vertebral fracture prevalence of 16% already at diagnosis of ALL. (16) The proportion of children with fractures at any skeletal site over the 6- year observation period was 36%, with 71% of all incident fractures occurring in the first 2 years of chemotherapy. (17) Other studies reported a two- to six-fold increase in the fracture rates during chemotherapy compared with healthy controls. (18-20) Due to lack of vertebral fractures assessment (VFA) and only DXA based studies, it is difficult to determine the real extent of bone morbidity in older studies. (16, 21, 22) Noteworthy, studies exploring bone health in children and adolescents prior to and following allogeneic HSCT for high-risk ALL are very sparse. In the STOPP study, only 4.8% of 186 ALL patients underwent HSCT. Across all ALL patients, predictors for incident fractures were cumulative corticosteroid dose and vertebral fractures at diagnosis. (17) Hence, it remains unclear
whether allogeneic HSCT adds additional risk to bone health compared to standard ALL treatment. Notwithstanding, a number of studies reporting on quantitative computed tomography (QCT) measures in long-term survivors of allogeneic HSCT in childhood demonstrated significant deficits including growth, spine and tibia trabecular volumetric BMD, cortical dimensions, and muscle cross-sectional area at a median of 5 years after HSCT. (12, 23)

Timely recognition of bone disease is crucial for initiation of treatment and for prevention of fractures, pain, loss of mobility and deformity and, thus, reducing long-term morbidity and adverse consequences on QoL. Therefore, assessment of bone health is indicated at diagnosis of leukemia and regularly after allogeneic HSCT.

Here, we present guidance to the most important bone morbidities ‘reduced bone mass accrual / OP’ and ‘ON’ in children and adolescents undergoing allogeneic HSCT and recommendations for clinical practice. For patients affected by sickle cell disease, specific guidelines should be considered, as – compared to other HSCT patients - further mechanisms add to their bone disease. (24-26)

Methods

In order to improve outcome of allogeneic HSCT in children and adolescents, the International BFM Stem Cell Transplantation (I-BFM SCT) Committee and the Pediatric Disease Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) address and discuss various topics associated with allogeneic HSCT in working groups aiming at providing guidance for care. As ‘bone morbidity’ is a complex topic requiring particular consideration, a pediatric bone specialist and member of the European Society for Pediatric Endocrinology (ESPE) working group on bone and growth plate was involved in this process to approach this topic as an interdisciplinary team.

To search for evidence in the field of acute leukemia/HSCT and low BMD/OP/ON, a PubMed-based literature search was conducted using the MeSH terms children/adolescents, acute leukemia (ALL, AML, leukemia), HSCT, and low BMD, reduced bone mass accrual, osteoporosis, vertebral fractures, and osteonecrosis, respectively. The titles and abstracts of identified articles were checked against the cohort and conditions reported (only those studies were kept which primarily reported on children and adolescents, leukemia and allogeneic HSCT). Preference was given to articles written in English.
One author (MK) prepared an evidence-based summary of the literature relating to the topics bone mass deficits and osteonecrosis and circulated it among all authors. The best available evidence was used to develop recommendations. Recommendations and evidence are described as follows: Level of evidence (LoE) I: Evidence from at least one randomized trial, Level II: Evidence from cohort studies, case control studies, time series, Level III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees), and provide our practice whenever no evidence is available. Authors presented the revised summaries to the group for discussion at three consecutive rounds. All authors approved the recommendations of this guidance. This guidance includes the cumulative evidence up to the end of 2018.

As OP and ON are two completely different conditions with regard to the underlying pathophysiology, risk factors, diagnostic steps, and treatment, we subsequently summarize our guidance in two paragraphs. The paragraphs are consistently structured in a brief overview on definitions, symptoms, diagnostics, and a summary of published evidence including incidence and risk factors (supplemented by an overview of studies) followed by our suggestion for clinical practice (including a diagnostic workflow). In addition, references on treatment recommendations are given, whenever available.

Recommendations

Low bone mass accrual and osteoporosis

Definition: According to the International Society for Clinical Densitometry (ISCD), low BMD is defined as a low bone mineral content or areal BMD Z-score that is less than or equal to -2.0, adjusted for age, gender, and body size, as appropriate. The diagnosis of OP requires at least one vertebral compression fracture or a combination of low BMD and a clinically significant fracture history. The latter is defined as at least two long bone fractures before the age of 10 years, or three or more long-bone fractures before the age of 19 years, in the absence of high-energy trauma. (27)

Symptoms: Vertebral fractures often remain asymptomatic and, thus, will be missed and OP not diagnosed unless imaging is performed. However, back pain is a well-known sign of vertebral fractures.
**Diagnostics:** Bone mass is measured using a dual-energy X-ray absorptiometry (DXA) scan of the lumbar spine (L1-L4) and/or whole body and expressed relative to age- and body size-matched (Z-score) norms. (28) Low bone mass is defined as a BMD Z-score at or below -2.0. For children under the age of 5 years, DXA reference values are lacking as children have to lay still during measurement. Since BMD is underestimated in children with short stature and since chronically ill children are frequently short, adjustments for height and bone volume are necessary. Typical adjustments used are the calculation of lumbar spine bone mineral apparent density (BMAD, in g/cm³) or BMD adjustments for height Z-score at the lumbar spine and removing the head from the total body scan (total body less head BMD). (27, 29)

Suspected (extremity) fractures should be confirmed using conventional x-ray. Particular attention is needed to vertebral compression fractures. These are usually not recognized clinically at the time of their occurrence. However, their detection confirms the presence of OP and poses a substantial risk for subsequent fractures independent of BMD. (30) Noteworthy, a BMD Z-score >-2.0 does not preclude the possibility of skeletal fragility and increased fracture risk. Thus, screening for vertebral fractures using vertebral fracture assessment (VFA) by DXA, lateral spine x-rays, or MRI at regular intervals is necessary. (30, 31)

**Summary of published evidence:** It was long believed that adolescents who fail to appropriately accrue bone mass and/or lose part of it as after HSCT are at risk for life-long osteopenia, early onset OP, and fractures. (5, 7, 12, 14, 18, 32, 33) However, this ‘peak bone mass’ concept has been heavily disputed. (34) Moreover, a number of studies demonstrated, that children with ALL have the potential to recover from the leukemia- and treatment-related skeletal morbidities, once the skeleton regains its adaptive biomechanical competence. (23, 35, 36)

The development of bone mass deficits in children and adolescents with leukemia undergoing allogeneic HSCT is multifactorial in origin, including the underlying (malignant) disease, osteotoxic chemo- and particularly glucocorticoid therapy, prolonged reduced physical activity and poor muscle mass, poor nutrition, total body irradiation, immunosuppressive therapies, and cytokine activation
such as graft versus host disease (GvHD). In addition, cranial and spinal radiation, untreated hypogonadism, growth hormone deficiency, vitamin D deficiency, and hypophosphatemia are risk factors for incomplete bone mass accrual and accelerated bone resorption.

To go beyond, various studies demonstrated that myeloablative treatment regimens directly damage osteoprogenitor (OPG) cells, thereby negatively affecting the RANKL-OPG system and bone formation. GvHD and dysregulation of the immune system activate osteoclasts and reduce the number and function of osteoblasts.

The STOPP prospective trial has demonstrated that vertebral fractures are most frequent and severe in the first 2 years of ALL therapy. In survivors of childhood HSCT, who are at potentially greater risk for inadequate bone accrual and metabolism, having had more osteotoxic therapy, the incidence of clinically asymptomatic and symptomatic fractures still needs to be studied.

An overview on studies reporting on BMD deficits and fractures in children, adolescents and young adults following HSCT is given in table 1.

Suggestions for clinical practice (prevention):

To date, there is no evidence that shows a benefit for the prevention of fractures or bone mass deficits in ALL, or in the context of HSCT. The first biochemical signs of osteomalacia is an increasing parathyroid hormone (PTH) and indicates low dietary calcium, low vitamin D status or malabsorption. Osteoporosis, in contrast to osteomalacia and rickets, cannot be prevented by giving vitamin D.

We therefore only provide general recommendations:

→ Measurement of calcium, phosphorus, alkaline phosphatase (ALP), PTH, and 25-hydroxy vitamin D (25(OH)D) on a regular basis (e.g. every six months during the first year, afterwards yearly; adapted in patients with chronic GvHD (cGvHD)). (LoE 2) (17, 35, 48)

→ Adequate calcium and vitamin D intake are important for preventing osteomalacia and rickets but will not prevent or treat osteoporosis. The minimum intakes known to prevent rickets are ≥ 500 mg/day of calcium and 10 µg (400 IU)/day of vitamin D; higher vitamin D intakes (12.5-25 µg or 500-1,000 IU) have been recommended for children and adolescents at-risk of vitamin D deficiency due to factors and conditions that reduce synthesis or intake (e.g. restricted exposure to
sun, high latitude during winter/spring season, and low dietary calcium intake). Target 25(OH)D levels should be above 50 nmol/L. There is no benefit in higher 25(OH)D levels from vitamin D supplementation. (LoE 1) (50, 51) The regular use of dairy products and vitamin D supplements should be taken into account especially in countries in which this is common practice (for instance in Scandinavia). (52, 53)

→ Linear growth should be evaluated prior to and on a regular basis after HSCT. (LoE 2) (12, 17, 18, 54-56)

→ Pubertal delay due to hypogonadism and other endocrinopathies need to be assessed on a regular basis and if necessary pediatric endocrinologists consulted. (LoE 2) (35, 42, 48, 57-63)

→ Muscle force enhances bone accrual. Thus, promoting physical activity and exercise during and after HSCT is of particular importance, within the limits of illness. (LoE 2) (62) Regular age-adapted work programs should be established.

→ Yearly screening by DXA scan of the lumbar spine (L1-L4) and whole body should be performed prior to and 12 months after HSCT. (LoE 2) (17, 64) In case of the presence of vertebral fractures, age and taking into consideration growth potential and future health, the endocrine team should be consulted for consideration of bisphosphonate (BP) therapy.

→ Yearly screening for vertebral fractures using either DXA VFA or lateral spine X-rays should be performed and assessed by a pediatric radiologist using the Genant score. (LoE 2) (17, 65) For stable patients without new risk factors and no vertebral fractures, spine X-ray screening for vertebral fractures can be stopped 2 years after HSCT.

→ In patients with back pain at any time, lateral spine radiographs or MRI should be conducted to check for vertebral fractures. (LoE 2) (17)

A diagnostic workflow for low BMD and fractures is depicted in figure 1.

Suggestions for clinical practice (treatment):

Principally, assessment of treatment indication and OP treatment should be performed in consultation with the pediatric endocrinologist or metabolic bone specialist.
→ Basically, diagnosis and treatment of OP in children and adolescents should follow the ISCD guidance of pediatric OP. *(LoE 2)* (27) Therein, BP treatment is reserved for older patients with overt bone fragility and low potential for BMD restitution and vertebral body reshaping.

→ In case of significant functional impairment limiting QoL, age becomes less important and treatment may be initiated. *(LoE 2)* (27)

→ However, the ISCD guidance only provides recommendations for children with standard ALL. As in children and adolescents with ALL undergoing HSCT more complications and poor outcome are probably more likely, BP therapy may be used in younger patients with serious complications, bone pain and therefore less potential for recovery, as long as ISCD criteria of OP are fulfilled. *(LoE 3)* (17, 23, 60)

**References on prevention and treatment recommendations:** By mineral ion supplementation according to the general consensus, osteomalacia and rickets can be prevented. (49) In marked contrast to that, low BMD and OP cannot be prevented by dietary or supplemental calcium and vitamin D therapy. Only few studies have assessed the efficacy of BPs in increasing BMD and reducing pain due to vertebral fractures in children with ALL. (66, 67) To date, there is no evidence supporting the routine use of bone-targeted therapy such as BPs in the absence of fractures in children with ALL undergoing HSCT and low BMD. Hence, attention is needed to secondary prevention in children with less potential to recover spontaneously from low BMD and/or fractures and therefore increased risk of disease progression and disability. (48)

In children and adolescents, the potential to recover from bone fragility depends on the severity of bone morbidity, the remaining growth potential, and the persistence of risk factors. Consequently, children with limited or no potential of recovery including children of older age with restricted linear growth potential qualify for bone-targeted therapy. Furthermore, younger children with potential for spontaneous recovery may warrant BP treatment if OP due to pain and functional limitation significantly impacts their QoL. (27, 48)

The treatment of leukemia- and HSCT-related osteoporotic fractures should follow these general principles of bone-targeted treatment of OP in children.
For the future, alternative agents may become further treatment options. For example, the receptor activator of nuclear factor κB ligand (RANKL) inhibitor denosumab operates by inhibiting bone resorption and, to a lesser degree, bone formation, and is commonly used in postmenopausal women. (68) Efficacy and particularly safety in children need prospective studies. Under development but far from routine use are other promising therapies which target bone formation pathways (anti-transforming growth factor beta antibody and anti-sclerostin antibody). (69-71)

**Osteonecrosis (ON)**

*Definition:* ON - also known as avascular necrosis – is defined as the death of a bone segment due to an imbalance between the actual and required blood flow due to various reasons. (72)

*Symptoms:* The clinical picture of ON is multifaceted and usually depends on ON stage and location. Most commonly, ON occurs in the midshaft of long bones and remains asymptomatic and completely harmless. However, in ON affecting the major joints, this is frequently associated with pain. At first, the pain is mostly stress-induced, caused by the pressure on the affected bone, typically on the lower limbs. Subsequently, it becomes more constant and appears also at rest. In case of further disease progression, including joint collapse, the joint surface loses its smooth shape and severe pain interferes with daily life. Other symptoms include restrictions in activities of daily living such as climbing stairs and putting on shoes as well as gait abnormalities, while particularly joint swelling, mobility restrictions and stiffening and taking a relieving posture are generally symptoms of a far progressed joint disease. The time between first symptoms and collapse of the bone may vary from several months to more than a year.

*Diagnoses:* Magnetic resonance imaging (MRI) is the only appropriate imaging to show osteonecrotic lesions and allowing their grading. Standard X-ray images may look normal in early stages and become significant in advanced stages only.
Summary of published evidence: Risk factors for the development of ON include older age at HSCT, steroid treatment, cGvHD and ON prior to HSCT. Other factors such as gender, obesity, total body irradiation and other immunosuppressants have only inconsistently been reported to increase the incidence of ON. (11, 13, 73-75) In addition, children already presenting with grade 1 ON at MRI screening within 6-8 months of ALL therapy are at increased risk of developing symptomatic ON grade 2 to 4. (76)

In an MRI-based single center study, the prevalence of ON in children following HSCT is reported to be approximately 30%. (15) In contrast, the cumulative incidence of symptomatic ON following HSCT in children and adolescents is reported to be 4-9%. (10, 11, 75) Most ON are diagnosed within two years following HSCT with hips and knees being most frequently affected (75) with lesion size being the best predictor of clinical outcome in hip ON. (77) In the majority of symptomatic patients, the clinical course is multi-articular and bilateral. Empirically, most commonly, ON in the hips and shoulders are diagnosed already in an advanced stage and it is hard to impede further disease progression, whereas ON in the knees may improve over time. Typically, diaphyseal lesions evolve favorably, are not associated with fractures and do not need MRI follow-up. (78)

An overview of studies reporting on ON in children, adolescents and young adults following HSCT is given in table 3.

Suggestions for clinical practice:

→ Prior to and at each follow-up evaluation following HSCT, patients should be asked for pain. In addition, age-appropriate pain self-assessment scores, assessment of self-care ADLs and monitoring of the gait pattern should be included in routine clinical evaluation. (LoE 3)

→ MRI screening of asymptomatic patients to identify (asymptomatic) ON prior to and/or following allogeneic HSCT should only be performed within studies, as no evidence-based interventions are available yet. (LoE 3) (79)

→ In case of a pre-existing ON diagnosis before HSCT, the use of steroids might be limited and alternative immunosuppressants might be chosen for subsequent lines of treatment in multiple
resistant GvHD. However, there are no studies supporting this recommendation and, hence, focus should be laid on best possible GvHD treatment. (LoE 3)

→ Physicians in charge should be aware of ON as a frequent and debilitating complication, in order to accelerate the diagnostic process at the onset of the first symptoms. This becomes even more important, when patients are referred back to the referring centers and are not managed within the tertiary transplant centers. (LoE 3)

→ In symptomatic patients, ON should be investigated by MRI. (LoE 3) (79) As ON in weight-bearing joints most commonly occur in multiple locations, we would recommend to do lower limb MRI including hips, knees, and ankles. (LoE 2) (80)

→ As evidence is lacking, the use of crutches is controversially discussed. In other ON conditions such as Perthes disease, reduced weight bearing is a regular part of care aiming at reducing pain and mechanic destruction. In case crutches are used, upper limb MRI including shoulders should be considered to exclude extended still asymptomatic ON. (LoE 3)

→ In patients presenting with persisting symptoms suggestive of ON but without corresponding findings in a first MRI, other reasons for pain should be sought and MRI should be repeated after 3 months. (LoE 3)

→ For reasons of comparability, ON should be classified according to the radiological classification system developed by Niinimäki et al., (LoE 2) (81) which allows to score all joints and districts. In addition, there are joint specific classification systems (Steinberg, Ficat and ARCO) for grading ON of the hips. In addition, the Delphi consensus on ON by the Ponte Di Legno toxicity working group can be used for clinical classification. (LoE 3) (79)

A diagnostic workflow for ON is depicted in Figure 2.

References on treatment recommendations: Management of ON in children and adolescents with ALL following HSCT is challenging and evidence-based guidelines or consensus on management of these children is still lacking. Effective pain management is crucial. Beyond that, treatment should be decided on an individual basis, in close collaboration with orthopedic surgeons and the pain team. If
possible, affected patients should be enrolled in prospective clinical trials evaluating treatment options.

Previous studies in children and adolescents with ALL exploring pharmacological interventions for ON including BPs and prostacyclin analogs lack sufficient quality evidence, as previously reviewed; (82)) studies in children with ON after allogeneic HSCT are completely missing. New therapies targeting pathways in bone metabolism such as anti-sclerostin antibody may deserve prospective clinical trials in children after allogeneic HSCT.

In general, surgical management is based on patient factors and lesion characteristics. In late stage ON with joint infarction, surgical interventions comprise arthroplasty and surface replacement. In precollapse lesions, joint-preserving procedures including core decompression (CD) may be attempted. In non-cancer related ON, data indicate that CD combined with cellular therapies (autologous or allogeneic bone marrow cells, mesenchymal stem cells, human bone morphogenetic protein), vascularized bone grafts, avascular grafts, combinations of the aforementioned or rotational osteotomies is beneficial. (83-89)

Therapeutic approaches in children and adolescents with ALL have been previously reviewed. (82, 90, 91)

**Summarizing remarks and outlook**

Children and adolescents undergoing allogeneic HSCT are at increased risk of OP and ON. Bone health monitoring is therefore an important component of the care plan for these patients. The combination of international efforts and prospective intervention studies incorporating standardized diagnostic strategies and novel therapeutic treatment options will be necessary to determine the true scale of bone morbidity in those patients. Both the I-BFM SCT and the PDWP of EBMT provide a strong basis to establish prospective studies on bone morbidity in children and adolescents undergoing allogeneic HSCT.

**Conflict of Interest**
M. Kuhlen, M. Kunstreich, DD, RN, EB, AL, AW, PW, WH, PB, CP, and AB declare that they have no conflict of interest.

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M. Kuhlen screened the literature, collected data and wrote the manuscript. M. Kunstreich screened the literature, collected the data, compiled the tables and drafted the figures. RN, DD, AL, EB, AW, PB, and CP critically revised the manuscript for important intellectual content. WH screened the literature and critically revised the manuscript for important intellectual content. AB screened the literature and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Figure legends

**Figure 1**

Figure 1: Workflow for prevention of osteomalacia and rickets and assessment of bone mass deficits and osteoporosis in children and adolescents undergoing hematopoietic stem cell transplantation.

**Legend:** Alkaline phosphatase, ALP; calcium, Ca; Dual-Energy X-Ray Absorptiometry, DXA; Hematopoietic stem cell transplantation, HSCT; Insulin-like growth factor 1, IGF-1; Parathyroid hormone, PTH; vertebral fracture assessment, VFA. *Minimum intakes of vitamin D and dietary calcium are given.*
Figure 2: Diagnostic workflow for children and adolescents undergoing hematopoietic stem cell transplantation (HSCT) and/or being suspicious of osteonecrosis following HSCT.

Legend: Activities of daily living, ADLs; Magnetic Resonance Imaging, MRI; osteonecrosis, ON; Turbo inversion recovery magnitude, TIRM; T1-weighted MRI scans, T1. *Some preliminary data suggest that interventions including core decompression plus mesenchymal stem cells may provide improved outcome if patients are treated at an early / precollapse stage. These data still need to be confirmed in children and adolescents with acute lymphoblastic leukemia. (reviewed in (90))
### Table 1: Overview of studies on bone mass deficits and fractures in children and adolescents after hematopoietic stem cell transplantation

| Reference          | Year  | Study design        | Study population                                                                 | HSCT          | Disease                  | Age at HSCT (in years) | Incidence: | Follow up (in years) | Methods                                                                 | Z Score | Risk factors and other important findings |
|--------------------|-------|---------------------|----------------------------------------------------------------------------------|---------------|--------------------------|------------------------|------------|----------------------|-------------------------------------------------------------------------|---------|-------------------------------------------|
| Ward et al. [8]    | 2018  | prospective, multicenter cohort study | 186 pts recipients of allogeneic HSCT                                            | ALL           | n.a.                     | 6 years                | spine radiographs,  spine bone mineral density (BMD) | across all pts cumulative corticosteroid dose vertebral fractures at diagnosis | 0,94    |                             |
| Bechard et al. [1] | 2015  | prospective, multicenter cohort study | 26 pts allogeneic (12 pts sibling related)                                        | ALL           | 7 pts ALL, 3 pts AML, 3 pts MDS, 3 pts CML, 2 pts lymphoma | 7 yrs (±2)            | whole body DXA       | 0,44 (0,24)                                                                   |         |                             |
| Mostoufi-Moab et al. [4] | 2012 | cross sectional     | 55 pts HSCT recipients / 985 healthy controls                                   | allogeneic    | Leukemia, Bone marrow failure syndrome | 5-26                    | 0,84 (±1,2)            | Vitamin D deficiency                                                                 |         |                             |
| Petryk et al. [6]  | 2006  | longitudinal       | 49 pts allogeneic, 2 pts autologous                                            | Fanconi anemia, 10 pts ALL, 8 pts AML, 6 pts, adrenoleukodystrophy, 5 pts AA, 3 pts CML, 3 pts metachromatic leukodystrophy, 4 pts others | 5-18            | 0,84 (-1,29 to -0,39) | osteocalcin possible biomarker for vulnerable pts                  |         |                             |
| Petryk et al. [7]  | 2014  | cross sectional    | 75 pts HSCT recipients / 92 healthy siblings                                    | 116 pts allogeneic 35 pts autologous 26 pts lymphoid malignancy 78 pts myeloid | 24,388,6      | DXA of lumbar spine BMD Areal LBMDA L2-L4 | 0,84 (-1,29 to -0,39) | osteocalcin possible biomarker for vulnerable pts                  |         |                             |
malignancy 17 pts, 13 pts allogeneic 3 pts autologous 3 pts AML 3 pts ALL 14 pts 6,99 (0,38-2,97) 1 pt osteoporosis 3 pts osteopenia 11,55 (3,25-22,53) TBMD 0,167 (0,167) 0,176 (0,176) 0,664 (0,176)

Refrains et al. [5] 2007 cross sectional 17 pts 13 pts allogeneic 4 pts autologous 3 pts AML 3 pts ALL 14 pts 6,99 (0,38-2,97) 1 pt osteoporosis 3 pts osteopenia 11,55 (3,25-22,53) TBMD 0,167 (0,167) 0,176 (0,176) 0,664 (0,176)

Campos et al. [2] 2014 retrospective case-control study 30 pts/25 controls 25 pts related allogeneic 25 pts unrelated allogeneic 5 pts AML 5 pts ALL 5 pts MDS 17 pts Fanconi anemia 5 pts adrenoleukodystrophy 10 pts severe aplastic anemia 5 pts CML 5 pts Wiskott-Aldrich syndrome 5 pts other 10,4 +/-4,6 whole body and lumbar spine DXA -1,14 (-1,53 to -0,74) (TB BMD +/-0,62) 0,750 +/-0,167 1,8 BMD 0,664 +/-0,176

Kasie et al. [1] 2004 retrospective 48 pts allogeneic 40 pts 10 pts AML 10 pts MDS 10 pts CML 5 pts other leukemias 5 pts other bone marrow failure 10,3 (6,6-10,4) 21% pts osteoporosis 26% pts osteopenia 5,1 (1,0-10,2) QC T MRI QC T Z Score 0,88 (3,3 to +2,33) decreased BMD risk factor for ON

Legend: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMD, bone mineral density; CML, chronic myeloid leukemia; DXA, dual energy X-ray absorptiometry; GVHD, graft-versus-host disease; RICT, hematopoietic stem cell transplantation; LBMD(A), lumbar BMD; MDS, myelo-dysplastic syndrome; ON, osteonecrosis; pts, patients; pQCT, peripheral quantitative computed tomography; SD, standard deviation; TB1, total body irradiation; TBMD, tibia BMD, yrs, years)
| Reference | Year | Study design | HSCT | Disease | Study population | Age | Incidence | Risk factors |
|-----------|------|--------------|------|---------|------------------|-----|-----------|--------------|
| Leung et al. [4] | 2007 | prospective | allogeneic | ALL, 84 pts myeloid malignancy, 40 pts lymphoblastic leukemia, 31 pts non malignancy | 155 pts | median 9.5 yrs (0.5-21.4) | 20 of 155 pts (13%) | • female sex  
• age >8 yrs at HSCT |
| Faraci et al. [1] | 2006 | retrospective case control study | allogeneic | ALL, 8 pts AML, 2 pts CML, 3 pts NHL, 6 pts non-malignant | 43 pts (ON, allogeneic HSCT) matched to 129 controls | mean age 13.1 yrs | Multivariate logistic regression analysis  
• cGVHD (OR 1.7:0.7)  
• TBI (OR 2.9:2.0)  
• Older Age (OR 1.46) |
| Sharma et al. [5] | 2012 | retrospective MRI control study | allogeneic | ALL, NHL, 118 pts malignant, 33 pts non-malignant | 149 pts | median 19 yrs (0-25 yrs) | 44 pts (ON) of 149 pts (29.9%) | • Age ≥10 yrs at HSCT (p=0.05)  
• pre alloHSCT MRI positive (p<0.01) |
| Kohlin et al. [3] | 2018 | retrospective | allogeneic | ALL | 53 pts | median 10.3 yrs (0.3-26 yrs) | Cumulative incidence of ON at 5 years 9% (SD 1%) | • age at HSCT >10 yrs  
• diagnosis of ON prior to HSCT 
• cGVHD |
| Giraud et al. [2] | 2013 | retrospective | 191 pts allogeneic, 65 pts autologous | ALL, 177 pts ALL, 79 pts AML | 255 HSCT | 6.65 (±0.31) | 13 pts (ON) of 255 HSCT (5.1%: 1%-7.09) | Older age at HSCT (>10 yrs)  
Higher total steroid dose post-transplant (>2,055mg/m²) (cGVHD) |
| Kaste et al. [4] | 2004 | prospective | allogeneic | ALL, 10 pts AML, 10 pts NHL, 3 pts CML, 1 pts non leukemia | 48 pts | mean 10.3 yrs (1.6-20.4) | 13 of 48 pts (44%) | Female sex |

**Legend:** ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CI, cumulative incidence; CML, chronic myeloid leukemia; (a) (c) (HV), acute (chronic) graft versus host disease; HL, Hodgkin lymphoma; HSCT; hematopoietic stem cell transplantation; HR, hazard ratio; MDS, myelodysplastic syndrome; MRI, magnetic resonance imaging; NHL, Non-Hodgkin lymphoma; ON, (symptomatic) osteonecrosis; OR, odds ratio; pts, patients; IR, interval rate; SD, standard deviation; TBI, total body irradiation; yr(s), year(s)