Review Article

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Bone Complications in Allogenic Hematopoietic Stem Cell Transplantation

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Abstract

Allogenic hematopoietic stem cell transplantation (allogenic HSCT) is employed to treat benign and malignant hematologic disorders. Increased use of allogenic HSCT has improved outcomes and patient survival, but has led to increased complications. Bone complications following HSCT include osteopenia, osteoporosis, avascular necrosis (AVN) and fracture. These complications decrease patient quality of life and increase morbidity. Allogenic HSCT-associated bone loss is linked to multiple factors including pre-transplant physiologic risk, myeloablative regimens, total-body irradiation, graft-versus-host disease (GVHD), immunosuppressive regimens, secondary hypogonadism, intestinal malabsorption and renal dysfunction. However, the precise molecular causes of HSCT-associated bone loss remain to be determined. Herein, we summarize the epidemiology, risk factors, and pathophysiology of allogenic HSCT-related bone loss and fracture. Also, review is made of the current modalities for prevention and treatment of these complications.

Keywords: Allogenic hematopoietic stem cell transplantation, Bone density, Osteopenia, Fracture

Introduction

Allogenic hematopoietic stem cell transplantation (allogenic HSCT) has become a standard treatment for numerous benign and malignant hematologic disorders. Wider application of HSCT has resulted in improvement in outcomes and increased patient survival, which has led to increased complications [1]. Bone-related complications are especially common following HSCT including osteopenia, osteoporosis, avascular necrosis (AVN) and bone fracture. These complications decrease patient quality of life and increase morbidity [2].

Allogenic HSCT-associated bone loss is linked to several factors including pre-transplant physiologic risk, myeloablative regimens, total-body irradiation,

graft-versus-host disease (GVHD), immunosuppressive regimens, secondary hypogonadism, intestinal malabsorption and renal dysfunction. However, the exact molecular causes of HSCT-associated bone loss remain to be fully determined. Loss of bone mineral density (BMD) may occur within three years of HSCT with decreased lumbar spine and femoral neck bone density. The incidence of AVN is higher in patients undergoing allogenic, as opposed to autologous, HSCT, due, in part, to the increased risk of chronic GVHD and the accompanying high-dose corticosteroid use [3]. The most typically affected area is the femoral head [4]. Fracture risk is significantly increased over that for the general population after HSCT [5]. Extending this, subgroup analysis in Asian populations confirmed a higher rate of osteoporosis and fracture in autologous HSCT patients

compared to non-HSCT patients [6]. Taken together, studies point to increased bone-related complications following allogenic HSCT.

Herein, we summarize the epidemiology, risk factors, and pathophysiology of allogenic HSCT-related bone loss and fracture and review the current modalities for prevention and treatment of these complications.

Search criteria

We performed a literature search of review articles, clinical trials, case series and case reports. The search was conducted through April 30, 2019. We used the PubMed database for identifying articles. The initial keywords used were “HSCT” and “bone loss” and this returned 1,073 potential articles. To remove possibly irrelevant articles, the key word phrases “HSCT and osteopenia”, “HSCT and osteoporosis”, “HSCT and avascular necrosis” and “HSCT and fracture” were employed and returned 248, 112, 85 and 95 articles respectively. Only articles written in English were included in this review. The title and abstract of references were then screened and a total of 85 articles that dealt with HSCT-related osseous complications were deemed relevant for review. Data were extracted from full-text articles by one author (S.S.). Information extracted included author name, country where the study was conducted, publication year, study methodology (study design, method of randomization, inclusion and exclusion criteria, primary and secondary endpoints, and dropout rate), patients’ baseline characteristics, and study interventions.

Risk factors for fractures

Patients undergoing allogenic-HSCT were likely to have normal bone mineral density because of their youth and the lower likelihood of pre-existing illness [4]. Indeed, pre-allogenic HSCT patients have the same risk for osteoporosis as the general population [7]. There were no data found that suggested any significant difference in BMD before transplant among allogenic-HSCT and autologous-HSCT patients. The classic risk factors for osteoporosis in the general population are: advanced age, female sex, history of a fragility fracture, family history of osteoporosis, current smoking, corticosteroid use, rheumatoid arthritis, secondary osteoporosis (resulting from type 1 diabetes, osteogenesis imperfecta, hypothyroidism and hypogonadism, premature menopause, chronic malnutrition or malabsorption, and chronic liver disease) and alcohol use >3 units/day [8].

In assessing the risk of fracture, The Fracture Risk Assessment Tool (FRAX) has proved useful. The results of this assessment predict the 10 year risk of a major fracture in normal populations. Risk factor-associated conditions should be screened for and treated as indicated in the normal population [9].

HSCT-associated fracture risk factors

Radiation therapy: In allogenic HSCT patients, pre-transplant radiation is a risk factor for fracture [10]. At the cellular level, radiation increases osteoclast activity and decreases osteoblast activity by promoting apoptotic cell death. Direct cytotoxic effects of radiation on endothelial cells of the intrinsic and extrinsic bone vasculature also contribute to tissue ischemia and dysregulate bone homeostasis [10]. Cranial and total-body irradiation cause central hypogonadism, hypopituitarism and growth hormone deficiency promoting decreased BMD, especially in children [11]. Importantly, osteopenia and fractures have been localized to the area of prior radiation [12]. BMD was significantly decreased in children with lymphoblastic leukemia or Non-Hodgkin lymphoma undergoing chemotherapy with cranial irradiation compared to those receiving chemotherapy, HSCT and total-body irradiation [13]. It is not known in HSCT patients if radiation sensitivity is site-specific.

Myeloablative chemotherapy: Myeloablative regimens are frequently employed to decrease hematopoietic cells prior to allogenic HSCT [14]. Reduced intensity therapeutic regimens and non-myeloablative regimens are increasingly incorporated into allogenic HSCT protocols. Well-known myeloablative regimens include cyclophosphamide with total-body irradiation, busulfan/cyclophosphamide, fludarabine/cyclophosphamide, BEAM (BCNU, etoposide, cytosine arabinoside, melphalan), CVP (carmustine, etoposide, and cyclophosphamide) and melphalan [15]. Chemotherapy-associated bone loss was reported after treatment with cyclophosphamide, methotrexate and fluorouracil (MMF). One year after receiving this regimen, patients had lumbar spine and femoral neck BMD loss of 7.7% and 4.6% respectively [16]. Methotrexate directly reduces bone marrow progenitor cells and induces cell differentiation towards adipocytes [17]. These changes contribute to osteopenia and have been observed in patients with rheumatoid arthritis [18]. Cyclophosphamide is known to cause nephrotoxicity that impairs reabsorption of phosphate and magnesium thus decreasing osteoblastic activity and vitamin D synthesis [19,20]. Further myeloablative chemotherapy

causes bone loss by inhibition of osteoblasts activity and promotion of miscommunication between host-derived osteoblasts and donor-derived bone marrow cells [21].

Consequences of myeloablative chemotherapy

Hypogonadism: Chemotherapeutic agents are well-known to cause toxic effect to Leydig cells in men and ovarian cells in women. Rates of ovarian insufficiency vary from 75% to as high as 92-100% [22]. Destruction of sex-hormone producing cells contributes to hypogonadism [23]. Loss of estrogen leads to bone loss in women, while loss of androgens leads to the same in men [24]. Cancellous bone loss, especially in the spine and femoral neck, is a hallmark of estrogen deficiency. Estrogen receptors (ERs) can be found on both osteoblasts and osteoclasts. Activation of ERs increases bone formation via upregulating transcription of IGF-1 and TGF- β and by suppressing osteoclastic activity via decreased transcription of osteoclast-activating factors [25]. Estrogen-ER signaling also plays an important role in longitudinal bone growth [26].

In men, testosterone exerts a direct benefit on bone health, in part, via direct effects on ERs [26]. Studies indicate that androgens play a role in the proliferation of pro-osteoblasts and the differentiation of osteoblasts [27]. Testosterone, via aromatization to estradiol, exerts its impact on cancellous bone, whereas cortical bone is under direct androgen effect [28]. To mitigate fracture, sex hormone replacement in allogenic HSCT recipients should be started as soon as the primary disease is in complete remission [29].

Risk factors before and after allogenic HSCT: Graft-versus-host-disease (GVHD) is a common complication following HSCT. Individuals receiving allogenic HSCT have an increased incidence GVHD compared to autologous HSCT recipients secondary to immune activation of donor cells (the graft) towards the self-antigens of the transplant recipient [30]. Data indicate a prevalence of osteopenia (41.8%) and osteoporosis (31.6%) in allogenic HSCT patients with chronic (>3 years) GVHD. Unexpectedly, loss of bone health in these individuals was not associated with an increased risk of fracture [31]. Allogenic HSCT-associated changes in bone homeostasis are associated with changes in cytokine levels including IL-1 β , IL-6, IFN γ , and TNF- α and TGF- β [32]. All of these cytokines affect bone remodeling and, in excess, cause bone loss by increasing apoptosis of osteocytes and osteoblasts and decreasing proliferation and differentiation of bone precursor cells [33].

Impact of treatment for GVHD on bone homeostasis: Prolonged treatment with high-dose glucocorticoids (GCs) and other immunosuppressive agents in individuals with GVHD promotes decreased BMD [34]. Immunosuppressive therapy with calcineurin inhibitors also affects bone remodeling. Additionally, pre-transplant GVHD prophylaxis with cyclosporine and methotrexate [2] has a negative impact on bone remodeling [35,36]. GCs negatively impact bone remodeling by increasing osteoclast activity, inhibiting proliferation of osteoblasts, and increasing apoptosis of osteoblasts and mature osteocytes [37]. Furthermore, GCs affect the endocrine system, decreasing androgen and estrogen secretion, and increasing parathyroid hormone secretion through reduction of calcium reabsorption from the kidney and intestine [21]. The accepted GC dosage for acute GVHD starts at 2 mg/kg bodyweight while in cases of chronic GVHD begins with prednisolone (1-2 mg/kg/d) in combination with cyclosporine A and/or mycophenolate mofetil. GCs are initially administered at high doses and then tapered over time [38]. Individuals on high-dose GCs are rapidly weaned after transplantation and this becomes more urgent when the individual is also on other immunosuppressive agents. The first 3-12 months after transplantation is the most vulnerable time for GC-associated bone loss, especially in the trabecular bone. Ultimately, the cumulative dose of GCs (and other immunosuppressive agents) determines the degree of bone loss [22].

The calcineurin inhibitors cyclosporine and tacrolimus are associated with post-transplantation bone loss [38]. However, the exact mechanism by which cyclosporine promotes abnormal bone remodeling is still unclear. Some studies show that cyclosporine increases bone turnover rate by inhibiting the proliferation of osteoblasts and decreasing the storage of magnesium, that is itself important for vitamin D synthesis [39]. Tacrolimus has been reported to cause rapid bone loss, not only in HSCT transplantation, but also in individuals who undergo renal and cardiac transplantation [40-42]. However, tacrolimus usage could, in theory, lead to less bone loss by limiting the need for GCs in post-transplant patients.

Vitamin D deficiency: Vitamin D increases intestinal absorption of calcium and phosphorous and has a crucial role in bone mineralization. Consistent with this, vitamin D deficiency causes hypocalcemia and secondary hyperparathyroidism leading to phosphaturia and decreased bone mineralization [43]. If severe, vitamin D deficiency may cause osteomalacia. A retrospective

study found vitamin D deficiency in 20% of individuals after transplantation [44]. This is relevant since other studies showed that some patients undergoing allogeneic HSCT have vitamin D deficiency [44]. Patients with low vitamin D levels are at an increased risk for loss of BMD. Further, there is a high incidence of vitamin D deficiency, not only in post-allogeneic HSCT patients (58%), but also in pre-allogeneic HSCT individuals (70%) [45]. Bone resorption and metabolic demand for vitamin D dramatically increased after transplantation and vitamin D promotes differentiation of hematopoietic stem cells [46]. Prolonged vitamin D deficiency (> 6 months) was noted to develop in some patients after allogeneic HSCT. Conversely, the nature of the initial disease leading to HSCT, the patient gender and the donor status impact post-transplantation vitamin D levels. Also, factors such as prolonged hospitalization, lack of sun exposure, immobilization and multiple infusions may impinge upon vitamin D levels [47]. Vitamin D deficiency was noted to occur as soon as one month after transplantation with 25(OH)-vitamin D levels decreased to 8 ± 3 ng/ml despite pre-transplantation vitamin D supplementation. In these cases, parathyroid hormone levels were found rising and peaked 14 days after transplantation indicating secondary hyperparathyroidism from vitamin D deficiency [7]. Vitamin D and calcium supplementation should generally be prescribed prior to HSCT [48].

Nutritional: Total parenteral nutrition (TPN) is used to improve the nutritional status of patients who experience severe illness or have intestinal failure. However, long-term TPN can cause metabolic bone disease resulting in osteomalacia and osteoporosis [49,50]. TPN contains amino acids, dextrose, calcium and sodium. Nonetheless, while phosphorous in TPN can diminish urinary calcium loss it can also promote secondary hyperparathyroidism eventually leading to bone loss [51]. In addition, metabolic acidosis from excessive amino acids or D-lactate, from bacterial overgrowth in TPN, can contribute to bone loss by alterations of nonvolatile acids [51]. For evaluation of TPN-associated bone disease, close monitoring of standard chemistry panels, iPTH, 25-hydroxyvitamin D, TSG, N-telopeptide collagen, urine N-telopeptide antigen, 24-hour calcium, magnesium and results from DEXA scans is useful. The correct preparation of TPN is needed to prevent TPN-associated bone loss. However, optimization of mineral components in TPN should be done with caution to prevent negative calcium balance [52].

Growth factor supplementation: Granulocyte colony-stimulating factor (G-CSF) is an important cytokine secreted by osteoblasts. G-CSF and other colony-stimulating factors promote granulocyte and osteoclast proliferation resulting in increased bone resorption [53]. G-CSF is used following high-dose chemotherapy for stabilization of hematopoietic stem cells and is standard care for HSCT patients. In children with severe chronic neutropenia, extended G-CSF use correlates significantly with lower BMD but this correlation is not seen in adults [54]. Contrasting this, a recent study in animals showed significantly improved bone formation with G-CSF treatment [55]. Together these data suggest a need for further study into the role of G-CSF in allogeneic HSCT-related loss of BMD.

Osteoporosis and osteopenia

Epidemiology: The incidence of osteopenia and osteoporosis prior to allogeneic HSCT ranges from 3-43% and 0-29% respectively [47,56,57]. The prevalence of osteopenia in adults 4-6 years after HSCT is 50%, while the rate of osteoporosis 2 years after HSCT is 20% [58]. The number of long-term survivors of allogeneic and autologous HSCT that experience significant bone complications, including osteoporosis and AVN, is 50% [58]. A study among Taiwanese individuals revealed a 2.53 times higher risk of osteoporosis in the HSCT group compared to the non-HSCT group after adjusting for sex, age, comorbidities, and cancer type [6]. Bone loss and HSCT are temporally related occurring within 6-12 months after transplantation [2]. In long-term survivors of allogeneic HSCT, the rate of osteopenia of the femoral neck was 52% and this was higher than levels of osteopenia in the lumbar spine and whole body even up to 13 years after transplantation [59]. Analysis one year after transplantation revealed decreased BMD at the proximal femoral neck and lumbar spine in 12.3% and 4.8% of subjects respectively [60]. Recovery of BMD starts in the lumbar spine followed by the femoral neck, although the process is slow and decreased BMD may persist for many years. Most patients with allogeneic HSCT-associated loss of BMD never experience a return to pre-transplant BMD levels [15]. The reasons for this are many and include prolonged glucocorticoid, calcineurin inhibitor and other immunosuppressive therapy, GVHD and vitamin D deficiency. On the other hand, autologous HSCT patients recovered BMD in the spine, but not in the femoral neck, within 2 years of transplant. These differences between autologous versus allogeneic HSCT could be attributable to the increased rates of GVHD and the subsequent need for immune suppression in allogeneic HSCT recipients [61].

Avascular necrosis (AVN): AVN is a painful complication of HSCT. Post-HSCT patients that experience AVN often require surgery that adversely impacts their quality of life. The cumulative incidence of AVN 10 year after allogeneic HSCT was 5.4%. Male sex, older age, diagnosis of acute leukemia, TBI-based conditioning regimens, chronic GVHD, exposure to CSA, GC, tacrolimus, MMF and exposure to greater than 3 immunosuppressive agents were associated with a significant risk for developing AVN after allogeneic HSCT [62-64]. In terms of anatomic location, AVN was found in the hip (64%), knee (61%), ankle (29%), shoulder (21%), and elbow (7%). Initial treatment for AVN is conservative. However, more than 50% of individuals with severe pain eventually undergo surgery including decompression or replacement of the knee or hip [65]. AVN of the jaw (AVN-J) is a common complication of cancer patients who are treated with bisphosphonate and denosumab and can present with exposed and necrotic bone in up to 94% of subjects [66]. The prevalence and incidence of AVN-J in allogeneic HSCT is not known [66]. Still, the incidence of AVN-J was 0.01% in individuals with prostate or lung cancer, or multiple myeloma compared with 0.001% in the general population [66].

Fracture: In a cohort of men aged 45-64 years who received HSCT, the incidence of fracture was 7-9 times greater compared to the normal population [5]. Multiple myeloma, solid tumor and autologous HSCT increased the risk of fracture. Post-HSCT, the rate of fracture by anatomic site, was vertebral (53%), clavicle and/or rib (18%), upper limb (10%), femoral (7%), lower limb other than femoral (7%), hip (3%), sacrum (1%) and other locations (1%) [5,67]. Similarly, two US studies and an Asian population study revealed a 1.40 times higher risk of fracture in HSCT patients compared to non-HSCT patients (95% CI 0.83-2.40). The incidence fracture rate was 4.89 per 1000-person years in the HSCT group. Here too, the most common site of fracture was vertebral (68.4%) [6]. Of note, BMD loss does not always correlate with the risk of fracture development.

Molecular pathways involved in allogeneic HSCT bone loss

Cytokine imbalance can dysregulate bone cell cross-talk to increase BMD loss. Osteoblast-derived receptor activator of nuclear factor- κ B ligand (RANKL) binds to the transmembrane RANK receptor on osteoclasts and osteoclast precursors to enhance bone resorption [68]. In contrast, the cytokine receptor osteoprotegerin (OPG) inhibits osteoclast function by impeding RANKL-

stimulated osteoblasts [69]. G-CSF, cytokine storm, immunosuppressives, immobilization, vitamin D deficiency, and impaired kidney and liver function are known to increase the RANKL/OPG ratio [70] and are associated with BMD loss.

Members of the tumor necrosis factor superfamily, which are increased with estrogen deficiency, inflammation and cancer, enhance production of RANKL by stromal cells [71]. TNF- α inhibits osteo-blastogenesis and increases osteoclast formation and activity resulting in bone resorption [72]. Other inflammatory cytokines such as IL-1, IL-7, and INF γ mimic RANKL in its effect on bone cells, whereas IL-23 may inhibit osteoclast formation [73,74]. Of relevance, cytokine storm that occurs within the first 3 weeks following allogeneic HSCT predicted the extent of bone loss during first 12 months post-transplantation [60]. While all allogeneic HSCT patients who are followed long enough experience some degree of bone loss, a definite relationship between cytokine levels and bone loss has yet to be demonstrated [60,75].

Prevention modalities

Prior to allogeneic HSCT, adult patients should be evaluated for bone status including assessment of markers of bone formation like bone alkaline phosphatase or osteocalcin, and bone resorption like C-telopeptide or N-telopeptide, PTH as well as 25-hydroxy vitamin D, Ca²⁺, albumin, phosphate and magnesium, morning urine calcium/creatinine, and BMD by dual energy X-ray absorptiometry (DXA) or quantitative DXA [76]. Early screening for osteopenia and osteoporosis before HSCT is of benefit when combined with interventions to prevent long-term complications [77]. According to EBMT, CIBMTR and ASBMT guidelines, femoral neck, hip and spine BMD should be measured by DXA before HSCT [78]. Osteopenia is defined as a T-score between -1 and -2.5 and osteoporosis is defined as a Z-score of less than -2.5. In children and patients <50 years in age, the Z-score is preferred for evaluating BMD [79]. If osteoporosis is found, treatment should not be delayed. Most guidelines suggested that DXA should be determined 12 months after transplantation in patients who were treated with bisphosphonate. However, if the patient did not receive any treatment prior to transplantation, DXA should be repeated 3 months after HSCT due to unpredictable bone loss after HSCT. Patients treated with bisphosphonate due to postmenopausal osteoporosis or immunosuppressive drugs (prednisolone equivalent of > 5 mg daily for > 3 months) may qualify for earlier follow-up [2,76].

Another tool for screening fracture risk is the calculated FRAX score, which, when integrated with BMD, can predict the 10-year probability of a major osteoporotic fracture [80]. FRAX is used extensively in the setting of non-transplant patients for evaluating the need for treatment of osteoporosis. A recent study revealed that FRAX might be useful for aiding in making preventive treatment decisions before transplantation in patients over the age of 50 [80]. However, some questions still surround the accuracy of the scoring system and widespread application as a screening tool has not occurred [80]. Magnetic resonance imaging (MRI) remains the most sensitive modality for detecting AVN but use of this modality for screening is not recommended [34]. Clinicians should be highly suspicious of AVN based on history and physical examination especially in patient with joint symptoms, a history of prior radiation and prolonged corticosteroid use [81]. Likewise, coexisting secondary causes of bone loss should be comprehensively evaluated in HSCT patients including measurement of calcium, phosphate, TSH, ALP, creatinine, 5-hydroxy vitamin D, PTH, FSH, and LH and testosterone levels as many of these may be amenable to modification.

Non-pharmacological bone loss preventive measures including physical exercise, fall prevention, and smoking and alcohol cessation can be of use when tailored to patients. Similarly, pharmacological preventive measures are generally applicable to HSCT patients and should begin with prophylactic calcium and vitamin D supplementation. Due to the high risk of fracture, hormone replacement therapy (HRT) can be used in women with hypogonadal pre-menopause and in men with hypogonadism. However, chronic GVHD and its associated cutaneous, intestinal and liver dysfunction can result in impaired absorption of HRT [35]. Inadequate HRT dosing for prevention of fractures in woman with premature ovarian failure was reported [82] suggesting a need for dosage increase. Also, HRT can increase the possibility of cardiovascular complications such as thromboembolism and stroke, an important consideration in woman. Breast cancer risk needs to be discussed in detail when estrogen replacement therapy is considered [55]. Finally, bisphosphonate therapy should be started prophylactically in patients who are at high risk of bone loss and fracture or who already have developed osteoporosis [81].

Treatment of bone loss in allogenic HSCT patients

General suggestions to prevent and treat bone loss

and osteoporosis in post-HSCT patients are the same as for the general population. They apply to all patients regardless of pre-transplant BMD.

Non-pharmacological therapy: Counseling that emphasizes abstaining from alcohol and tobacco, mobilization soon after transplantation and fall prevention are useful. Regular weight bearing and muscle strengthening exercises are also helpful. One study suggested that 30 minutes of resistance exercise, three times per week for six months, can restore BMD toward pre-transplantation levels [83]. These results were obtained in a cohort of heart transplantation patients and have yet to be verified in HSCT patients.

Calcium and vitamin D: The prevalence of vitamin D deficiency among HSCT patients is very high and negatively impacts bone metabolism [44]. Calcium and vitamin D should be prescribed to all patients before and after allogenic HSCT. Of note, calcium and vitamin D alone, or in combination, may be inadequate for preventing bone loss after HSCT [57]. Still, an adequate supplement of calcium (800-1200 mg/day) and vitamin D (at least 800 IU/day or 20 micrograms/day) is strongly recommended. Higher vitamin D doses should be employed to treat patients with overt vitamin D deficiency. It is known that calcium and vitamin D reduce the risk of fracture in patients with osteoporosis [84]. Both supplementation of calcium and vitamin D along with anti-resorptive therapy can have an important role in the treatment HSCT-associated BMD [85].

Bisphosphonate: Bisphosphonates are considered an effective medication to prevent HSCT-induced bone loss [86]. Zoledronic acid are the most often used agents. Both oral and intravenous bisphosphonates can be administered but many studies favor intravenous administration [87,88]. Individuals on bisphosphonate regimens showed increased BMD in the femoral neck, lumbar spine and less decrease in BMD from baseline until 12 months after HSCT compared with control patients [56]. A number of randomized controlled trials have studied the efficacy of bisphosphonate treatment in patient after HSCT. Bisphosphonates are usually compared to therapy with calcium and vitamin D alone or together. In one study, patients with allogenic HSCT were randomly assigned to receive calcium and vitamin D versus calcium and vitamin D plus 60 mg of pamidronate intravenously. Patients who received pamidronate were found to have decreased BMD in the femoral neck and hip but no significant loss of BMD in the lumbar spine

(0% in the pamidronate group versus 2.9% in the control group) [89]. In another study, an even higher dose of pamidronate was used and confirmed prevention of BMD loss in the lumbar spine although decreased BMD at the femoral neck and hip persisted. Some data indicate that the primary benefit of pamidronate is for individuals who receive high-dose corticosteroids or prolonged cyclosporine therapy [86]. Zoledronic acid 4 mg intravenously pre- and post-HSCT showed greater improvement in BMD at both the femoral neck (mean change in BMD 0.018 versus -0.054 in the control group) and the lumbar spine (mean change in BMD 0.48 versus -0.057 in the control group) at 12 months [90]. Prophylactic treatment with bisphosphonates should be given to all HSCT patients with high risk of bone loss and fracture, including those still pre-transplant regardless of T score, with a history of prior osteoporosis or vertebral or other bone fracture, as well as patients receiving corticosteroids and cyclosporine to prevent GVHD. However, evidence of a relationship between bisphosphonate therapy and fracture rates after HSCT is still unavailable. AVN-J can occur with bisphosphonate use and result in bone exposure in the buccal cavity [91]. Bisphosphonate-related AVN-J was reported in 1.3% patients with advanced cancer with bony metastasis [92]. However, data suggest no significant increased risk of AVN-J in patients who undergo HSCT and receive bisphosphonates [93]. Of benefit, the risk of bisphosphonate-related AVN-J can be lowered by intensive maintenance dental care [94].

Hormone replacement therapy (HRT): Patients who undergo HSCT usually receive myeloablative and glucocorticoid therapy and are likely to develop hypogonadism. Estrogen/progesterone replacement therapy is widely suggested for hypogonadal premenopausal women for prevention of bone loss associated with estrogen deficiency [82]. This recommendation is based on findings in women with ovarian failure [95]. HRT was superior, when combined with oral contraceptives, at increasing BMD in the lumbar spine in patients with premature ovarian failure [96]. Higher doses of estrogen/progesterone may be needed as data indicate that standard HRT doses are not adequate at preventing fractures in woman with premature ovarian failure [12]. In men, it was found that serum testosterone was decreased at 3 and 6 months post-HSCT and recovered within 12 months [70]. In view of this, male patients with symptomatic hypogonadism should be considered candidates for testosterone therapy.

Denosumab: Denosumab is a monoclonal antibody

and bone anti-resorptive medication that targets RANKL and is approved for treatment of postmenopausal osteoporosis [97]. In postmenopausal osteoporosis, treatment with denosumab resulted in a significant reduction in vertebral, non-vertebral and hip fractures [98]. In liver transplant patients, denosumab treatment decreased the prevalence of osteoporosis in the lumbar spine and proximal femur during the first year after transplantation [99]. Denosumab use has been reported in HSCT patients after transplantation. In one report, denosumab was used to treat hypercalcemia post-HSCT in an individual with osteoporosis [100]. Unfortunately, no data was provided about BMD and fractures. In a second study, denosumab treatment was associated with improved BMD in patients undergoing dialysis following allogenic HSCT [100,101]. Nonetheless, there are still no prospective clinical trials testing the efficacy of denosumab following allogenic HSCT.

Parathyroid hormone-derived peptides:

Treatment with teriparatide, a recombinant human parathyroid hormone (PTH), resulted in improvement in BMD in patients with glucocorticoid-induced osteoporosis [102]. Meta-analysis suggests that combination therapy with parathyroid hormone analogs and anti-resorptive agents improves lumbar spine and total hip BMD over monotherapy and this does not appear to increase serious adverse events in patient with osteoporosis [103]. Combination therapy has the further benefit of reducing fracture risk [103]. However, there is no data on the use of PTH analogs in individuals undergoing HSCT.

Conclusions

Individuals undergoing allogenic HSCT are at a high risk for osteopenia, osteoporosis, AVN and fracture. As survival increases in these patients, bone health problems become a significant factor increasing morbidity and decreasing the quality of life. Appropriate screening with pre-transplant bone mineral density (BMD) analysis and assessment for secondary osteoporosis is important. General recommendations included routine supplementation of calcium and vitamin D. Non-pharmacological interventions to prevent osteoporosis are also appropriate. For those patients with osteoporosis fracture and high-risk of bone loss, treatment with bisphosphonates before allogenic HSCT is warranted. Still, overly aggressive treatment and monitoring should be avoided due to the other morbidities inherent in allogenic HSCT (Table 1).

Table 1: HSCT-related osseous complications.

Complications	Management
Osteopenia and Osteoporosis	<p><i>Non-pharmacological therapy</i>; abstaining from alcohol and tobacco, mobilization soon after transplantation and fall prevention is useful. 30 minutes of resistance exercise, three times per week for six months, can restore BMD toward pre-transplantation levels [83].</p> <p>Calcium and vitamin D; Adequate supplement of calcium (800-1200 mg/day) and vitamin D (at least 800 IU/day or 20 micrograms/day) [84]</p> <p>Bisphosphonate; Zoledronic acid are the most often used agents. Both oral and intravenous bisphosphonates can be administered but many studies favor intravenous administration [87,88]. Prophylactic treatment with bisphosphonates should be given to all HSCT patients with high risk of bone loss and fracture, including those still pre-transplant regardless of T score, with a history of prior osteoporosis or vertebral or other bone fracture, as well as patients receiving corticosteroids and cyclosporine to prevent GVHD. However, evidence of a relationship between bisphosphonate therapy and fracture rates after HSCT is still unavailable [88].</p> <p>Hormone replacement therapy; HRT is suggested for hypogonadal premenopausal women for prevention of bone loss. Higher doses than standard HRT are suggested in woman with premature ovarian failure. There is no direct evidence of a benefit in use of HRT in patients that underwent HSCT [82]. In men, testosterone therapy is suggested in cases of symptomatic hypogonadism [104].</p> <p>Parathyroid hormone-derived peptides; Use of these may improve BMD in patients with glucocorticoid-induced osteoporosis, but there is no strong evidence in individuals undergoing HSCT [102].</p> <p>Denosumab; Denosumab treatment was associated with improved BMD in patients undergoing dialysis following allogenic HSCT. Nonetheless, there are still no prospective clinical trials testing the efficacy of denosumab following allogenic HSCT [101].</p>
Avascular necrosis (AVN)	Initial treatment for AVN is conservative. However, more than 50% of individuals with severe pain eventually undergo surgery including decompression or replacement of the knee or hip [65].
Bone fracture	It is dependent on the site and severity of fracture, so prevention of falling, and treatment and mitigation of osteopenia and osteoporosis to reduce risk of fracture is very important.

Declarations**Ethics approval and consent to participate**

N/A

Consent for publication

The authors have reviewed the final manuscript and consent to its publication.

Availability of data and material

N/A

Competing interests

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Author contributions

S.S. and B.S. conceived of the study. S.S. conducted the literature search and abstracted information. J.S.I. provided critical feedback. S.S., J.S.I. and B.S. wrote, edited and approved the final manuscript.

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References

1. Savani BN. How can we improve life expectancy and quality of life in long-term survivors after allogeneic stem cell transplantation? *Semin Hematol*.

- 2012;49(1):1-3. Doi: <https://dx.doi.org/10.1053/j.seminhematol.2011.10.014>
2. Schulte CMS, Beelen DW. Bone loss following hematopoietic stem cell transplantation: a long-term follow-up. *Blood*. 2004;103(10):3635-3643. Doi: <https://dx.doi.org/10.1182/blood-2003-09-3081>
3. Serio B, Pezzullo L, Fontana R, et al. Accelerated bone mass senescence after hematopoietic stem cell transplantation. *Transl Med UniSa*. 2013;5:7-13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3728811/>
4. McClune B, Majhail NS, Flowers MED. Bone loss and avascular necrosis of bone after hematopoietic cell transplantation. *Semin Hematol*. 2012;49(1):59-65. Doi: <https://dx.doi.org/10.1053/j.seminhematol.2011.10.007>
5. Pundole XN, Barbo AG, Lin H, et al. Increased incidence of fractures in recipients of hematopoietic stem-cell transplantation. *J Clin Oncol*. 2015;33(12):1364-1370. Doi: <https://dx.doi.org/10.1200/JCO.2014.57.8195>
6. Lin JN, Chen HJ, Yang CH, et al. Risk of osteoporosis and pathologic fractures in cancer patients who underwent hematopoietic stem cell transplantation: a nationwide retrospective cohort study. *Oncotarget*. 2017;8(21):34811-34819. Doi: <https://dx.doi.org/10.18632/oncotarget.16746>
7. Schulte C, Beelen DW, Schaefer UW, et al. Bone loss in long-term survivors after transplantation of hematopoietic stem cells: a prospective study. *Osteoporos Int*. 2000;11(4):344-353. Doi: <https://dx.doi.org/10.1007/s001980070124>
8. Sözen T, Özişik L, Başaran NÇ. An overview and management of osteoporosis. *Eur J Rheumatol*. 2017;4(1):46-56. Doi: <https://dx.doi.org/10.5152/eurjrheum.2016.048>
9. Unnanuntana A, Gladnick BP, Donnelly E, et al. The assessment of fracture risk. *J Bone Joint Surg Am*. 2010;92(3):743-753. Doi: <https://dx.doi.org/10.2106/JBJS.I.00919>
10. Higham CE, Faithfull S. Bone health and pelvic radiotherapy. *Clin Oncol (R Coll Radiol)*. 2015;27(11):668-678. Doi: <https://dx.doi.org/10.1016/j.clon.2015.07.006>
11. Kang MJ, Lim JS. Bone mineral density deficits in childhood cancer survivors: Pathophysiology, prevalence, screening, and management. *Korean J Pediatr*. 2013;56(2):60-67. Doi: <https://dx.doi.org/10.3345/kjp.2013.56.2.60>
12. Wilson CL, Ness KK. Bone mineral density deficits and fractures in survivors of childhood cancer. *Curr Osteoporos Rep*. 2013;11(4):329-337. Doi: <https://dx.doi.org/10.1007/s11914-013-0165-0>
13. Benmiloud S, Steffens M, Beauloye V, et al. Long-term effects on bone mineral density of different therapeutic schemes for acute lymphoblastic leukemia or non-hodgkin lymphoma during childhood. *HRP*. 2010;74(4):241-250. Doi: <https://dx.doi.org/10.1159/000313397>
14. Pandit A, Garg MK, Kotwal N, et al. Changes in bone mineral density and bone turnover markers in patients undergoing hematopoietic stem cell transplant. *Indian J Endocr Metab*. 2015;19(3):393. Doi: <https://dx.doi.org/10.4103/2230-8210.152785>
15. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. *Blood*. 2014;124(3):344-353. Doi: <https://dx.doi.org/10.1182/blood-2014-02-514778>
16. Hadji P, Ziller M, Maskow C, et al. The influence of chemotherapy on bone mineral density, quantitative ultrasonometry and bone turnover in pre-menopausal women with breast cancer. *Eur J Cancer*. 2009;45(18):3205-3212. Doi: <https://dx.doi.org/10.1016/j.ejca.2009.09.026>
17. Georgiou KR, Scherer MA, Fan C-M, et al. Methotrexate chemotherapy reduces osteogenesis but increases adipogenic potential in the bone marrow. *J Cell Physiol*. 2012;227(3):909-918. Doi: <https://dx.doi.org/10.1002/jcp.22807>
18. Świerkot J, Gruszecka K, Matuszewska A, et al. Assessment of the effect of methotrexate therapy on bone metabolism in patients with rheumatoid arthritis. *Arch Immunol Ther Exp (Warsz)*. 2015;63(5):397-404. Doi: <https://dx.doi.org/10.1007/s00005-015-0338-x>
19. Rehman MU, Tahir M, Ali F, et al. Cyclophosphamide-induced nephrotoxicity, genotoxicity, and damage in kidney genomic DNA of Swiss albino mice: the protective effect of Ellagic acid. *Mol Cell Biochem*. 2012;365(1-2):119-127. Doi: <https://dx.doi.org/10.1007/s11010-012-1250-x>
20. Wissing MD. Chemotherapy- and irradiation-induced bone loss in adults with solid tumors. *Curr Osteoporos Rep*. 2015;13(3):140-145. Doi: <https://dx.doi.org/10.1007/s11914-015-0266-z>
21. Osterberg A, Engelmann R, Müller-Hilke B. Allogeneic yet major histocompatibility complex-matched bone marrow transplantation in mice results in an impairment of osteoblasts and a significantly reduced trabecular bone. *J Bone Miner Metab*. 2018;36(4):420-430. Doi: <https://dx.doi.org/10.1007/s00774-017-0859-y>
22. Ebeling PR, Thomas DM, Erbas B, et al. Mechanisms of bone loss following allogeneic and autologous

- hemopoietic stem cell transplantation. *J Bone Miner Res.* 1999;14(3):342-350. Doi: <https://dx.doi.org/10.1359/jbmr.1999.14.3.342>
23. Kiserud CE, Fosså A, Bjørø T, et al. Gonadal function in male patients after treatment for malignant lymphomas, with emphasis on chemotherapy. *Br J Cancer.* 2009;100(3):455-463. Doi: <https://dx.doi.org/10.1038/sj.bjc.6604892>
24. Weilbaecher KN. Mechanisms of osteoporosis after hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2000;6(2A):165-174. <https://www.ncbi.nlm.nih.gov/pubmed/10816024>
25. Hawse JR, Subramaniam M, Ingle JN, et al. Estrogen-TGFbeta cross-talk in bone and other cell types: role of TIEG, Runx2, and other transcription factors. *J Cell Biochem.* 2008;103(2):383-392. Doi: <https://dx.doi.org/10.1002/jcb.21425>
26. Clarke BL, Khosla S. Androgens and bone. *Steroids.* 2009;74(3):296-305. Doi: <https://dx.doi.org/10.1016/j.steroids.2008.10.003>
27. Mohamad N-V, Soelaiman I-N, Chin K-Y. A concise review of testosterone and bone health. *Clin Interv Aging.* 2016;11:1317-1324. Doi: <https://dx.doi.org/10.2147/CIA.S115472>
28. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. *Nat Rev Endocrinol.* 2013;9(12):699-712. Doi: <https://dx.doi.org/10.1038/nrendo.2013.179>
29. Kodama M, Komura H, Shimizu S, et al. Efficacy of hormone therapy for osteoporosis in adolescent girls after hematopoietic stem cell transplantation: a longitudinal study. *Fertility and Sterility.* 2011;95(2):731-735. Doi: <https://dx.doi.org/10.1016/j.fertnstert.2010.09.037>
30. Hammami MB, Talkin R, Al-Taei AM, et al. Autologous graft-versus-host disease of the gastrointestinal tract in patients with multiple myeloma and hematopoietic stem cell transplantation. *Gastroenterology Res.* 2018;11(1):52-57. Doi: <https://dx.doi.org/10.14740/gr925w>
31. Savani BN, Donohue T, Kozanas E, et al. Increased risk of bone loss without fracture risk in long-term survivors after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant.* 2007;13(5):517-520. Doi: <https://dx.doi.org/10.1016/j.bbmt.2007.01.085>
32. Imamura M, Hashino S, Kobayashi H, et al. Serum cytokine levels in bone marrow transplantation: synergistic interaction of interleukin-6, interferon-gamma, and tumor necrosis factor-alpha in graft-versus-host disease. *Bone Marrow Transplant.* 1994;13(6):745-751. <https://www.ncbi.nlm.nih.gov/pubmed/7920309>
33. Kwan Tat S, Padrines M, Théoleyre S, et al. IL-6, RANKL, TNF-alpha/IL-1: interrelations in bone resorption pathophysiology. *Cytokine Growth Factor Rev.* 2004;15(1):49-60. <https://www.ncbi.nlm.nih.gov/pubmed/14746813>
34. Hautmann AH, Elad S, Lawitschka A, et al. Metabolic bone diseases in patients after allogeneic hematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease. *Transpl Int.* 2011;24(9):867-879. Doi: <https://dx.doi.org/10.1111/j.1432-2277.2011.01264.x>
35. Lee SJ, Vogelsang G, Flowers MED. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2003;9(4):215-233. Doi: <https://dx.doi.org/10.1053/bbmt.2003.50026>
36. Lee SJ. Classification systems for chronic graft-versus-host disease. *Blood.* 2017;129(1):30-37. Doi: <https://dx.doi.org/10.1182/blood-2016-07-686642>
37. Komori T. Cell death in chondrocytes, osteoblasts, and osteocytes. *Int J Mol Sci.* 2016;17(12). Doi: <https://dx.doi.org/10.3390/ijms17122045>
38. Jacobsohn DA, Vogelsang GB. Acute graft versus host disease. *Orphanet J Rare Dis.* 2007;2(1):35. Doi: <https://dx.doi.org/10.1186/1750-1172-2-35>
39. Panday K, Gona A, Humphrey MB. Medication-induced osteoporosis: screening and treatment strategies. *Ther Adv Musculoskelet Dis.* 2014;6(5):185-202. Doi: <https://dx.doi.org/10.1177/1759720X14546350>
40. Stempfle HU, Werner C, Echtler S, et al. Rapid trabecular bone loss after cardiac transplantation using FK506 (Tacrolimus)-based immunosuppression. *Transplant Proc.* 1998;30(4):1132-1133. Doi: [https://dx.doi.org/10.1016/s0041-1345\(98\)00181-x](https://dx.doi.org/10.1016/s0041-1345(98)00181-x)
41. Park KM, Hay JE, Lee SG, et al. Bone loss after orthotopic liver transplantation: FK 506 versus cyclosporine. *Transplant Proc.* 1996;28(3):1738-1740.
42. Stern JM, Sullivan KM, Ott SM, et al. Bone density loss after allogeneic hematopoietic stem cell transplantation: a prospective study. *Biol Blood Marrow Transplant.* 2001;7(5):257-264. Doi: <https://dx.doi.org/10.1053/bbmt.2001.v7.pm11400947>
43. Christakos S, Ajibade DV, Dhawan P, et al. Vitamin D: metabolism. *Endocrinol Metab Clin North Am.* 2010;39(2):243-253, table of contents. Doi: <https://dx.doi.org/10.1016/j.ecl.2010.02.002>
44. Sproat L, Bolwell B, Rybicki L, et al. Vitamin D level after allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant.* 2011;17(7):1079-1083. Doi: <https://dx.doi.org/10.1016/j.bbmt.2010.12.704>

45. Joseph RW, Alousi A, Konda B, et al. High incidence of vitamin D deficiency in patients undergoing allogeneic stem cell transplantation. *Am. J. Hematol.* 2011;86(11):954-956. Doi: <https://dx.doi.org/10.1002/ajh.22143>
46. Perkins SL, Kling SJ, Ross FP, et al. 1,25 dihydroxyvitamin D3 stimulates differentiation of committed murine bone marrow-derived macrophage precursor cells. *Endocrinology.* 1995;136(12):5643-5650. Doi: <https://dx.doi.org/10.1210/endo.136.12.7588319>
47. Massenkeil G, Fiene C, Rosen O, et al. Loss of bone mass and vitamin D deficiency after hematopoietic stem cell transplantation: standard prophylactic measures fail to prevent osteoporosis. *Leukemia.* 2001;15(11):1701-1705. Doi: <https://dx.doi.org/10.1038/sj.leu.2402264>
48. Kananen K, Volin L, Laitinen K, et al. Prevention of bone loss after allogeneic stem cell transplantation by calcium, vitamin D, and sex hormone replacement with or without pamidronate. *J Clin Endocrinol Metab.* 2005;90(7):3877-3885. Doi: <https://dx.doi.org/10.1210/jc.2004-2161>
49. Diamanti A, Bizzarri C, Basso MS, et al. How does long-term parenteral nutrition impact the bone mineral status of children with intestinal failure? *J Bone Miner Metab.* 2010;28(3):351-358. Doi: <https://dx.doi.org/10.1007/s00774-009-0140-0>
50. Seidner DL. Parenteral nutrition-associated metabolic bone disease. *JPEN J Parenter Enteral Nutr.* 2002;26(5 Suppl):S37-42. Doi: <https://dx.doi.org/10.1177/014860710202600511>
51. Klein GL, Coburn JW. Total parenteral nutrition and its effects on bone metabolism. *Crit Rev Clin Lab Sci.* 1994;31(2):135-167. Doi: <https://dx.doi.org/10.3109/10408369409084675>
52. Lipkin EW, Ott SM, Chesnut CH, et al. Mineral loss in the parenteral nutrition patient. *Am J Clin Nutr.* 1988;47(3):515-523. Doi: <https://dx.doi.org/10.1093/ajcn/47.3.515>
53. Takamatsu Y, Simmons PJ, Moore RJ, et al. Osteoclast-mediated bone resorption is stimulated during short-term administration of granulocyte colony-stimulating factor but is not responsible for hematopoietic progenitor cell mobilization. *Blood.* 1998;92(9):3465-3473. <https://www.ncbi.nlm.nih.gov/pubmed/9787189>
54. DiMeglio LA, Bolyard AA, Marrero TM, et al. The risk of low bone mineral density with long-term G-CSF therapy for severe chronic neutropenia. *Blood.* 2010;116(21):1484-1484.
55. Herrmann M, Zeiter S, Eberli U, et al. Five days granulocyte colony-stimulating factor treatment increases bone formation and reduces gap size of a rat segmental bone defect: a pilot study. *Front Bioeng Biotechnol.* 2018;6. Doi: <https://dx.doi.org/10.3389/fbioe.2018.00005>
56. Tauchmanová L, De Simone G, Musella T, et al. Effects of various antireabsorptive treatments on bone mineral density in hypogonadal young women after allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2006;37(1):81-88. Doi: <https://dx.doi.org/10.1038/sj.bmt.1705196>
57. Välimäki MJ, Kinnunen K, Volin L, et al. A prospective study of bone loss and turnover after allogeneic bone marrow transplantation: effect of calcium supplementation with or without calcitonin. *Bone Marrow Transplant.* 1999;23(4):355-361. Doi: <https://dx.doi.org/10.1038/sj.bmt.1701586>
58. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. *Expert Rev Hematol.* 2011;4(4):437-452; quiz 453-454. Doi: <https://dx.doi.org/10.1586/ehm.11.39>
59. Buchs N, Helg C, Collao C, et al. Allogeneic bone marrow transplantation is associated with a preferential femoral neck bone loss. *Osteoporos Int.* 2001;12(10):880-886. Doi: <https://dx.doi.org/10.1007/s001980170041>
60. Lee WY, Baek KH, Rhee EJ, et al. Impact of circulating bone-resorbing cytokines on the subsequent bone loss following bone marrow transplantation. *Bone Marrow Transplant.* 2004;34(1):89-94. Doi: <https://dx.doi.org/10.1038/sj.bmt.1704535>
61. Gandhi MK, Lekamwasam S, Inman I, et al. Significant and persistent loss of bone mineral density in the femoral neck after haematopoietic stem cell transplantation: long-term follow-up of a prospective study. *Br J Haematol.* 2003;121(3):462-468. Doi: <https://dx.doi.org/10.1046/j.1365-2141.2003.04303.x>
62. Campbell S, Sun C-L, Kurian S, et al. Predictors of avascular necrosis of bone in long-term survivors of hematopoietic cell transplantation. *Cancer.* 2009;115(18):4127-4135. Doi: <https://dx.doi.org/10.1002/cncr.24474>
63. Tauchmanová L, De Rosa G, Serio B, et al. Avascular necrosis in long-term survivors after allogeneic or autologous stem cell transplantation: a single center experience and a review. *Cancer.* 2003;97(10):2453-2461. Doi: <https://dx.doi.org/10.1002/cncr.11373>
64. Fink JC, Leisenring WM, Sullivan KM, et al. Avascular necrosis following bone marrow transplantation: a case-control study. *Bone.* 1998;22(1):67-71. Doi: [https://dx.doi.org/10.1016/S8756-7582\(98\)00041-9](https://dx.doi.org/10.1016/S8756-7582(98)00041-9)

- [https://dx.doi.org/10.1016/s8756-3282\(97\)00219-6](https://dx.doi.org/10.1016/s8756-3282(97)00219-6)
65. Enright H, Haake R, Weisdorf D. Avascular necrosis of bone: a common serious complication of allogeneic bone marrow transplantation. *Am J Med.* 1990;89(6):733-738. Doi: [https://dx.doi.org/10.1016/0002-9343\(90\)90214-x](https://dx.doi.org/10.1016/0002-9343(90)90214-x)
 66. Mücke T, Krestan CR, Mitchell DA, et al. Bisphosphonate and medication-related osteonecrosis of the jaw: a review. *Semin Musculoskelet Radiol.* 2016;20(3):305-314. Doi: <https://dx.doi.org/10.1055/s-0036-1592367>
 67. Bagcchi S. Stem-cell transplantation increases fracture risk. *Lancet Oncol.* 2015;16(5):e201. Doi: [https://dx.doi.org/10.1016/S1470-2045\(15\)70146-4](https://dx.doi.org/10.1016/S1470-2045(15)70146-4)
 68. Feng X, Teitelbaum SL. Osteoclasts: new insights. *Bone Res.* 2013;1(1):11-26. Doi: <https://dx.doi.org/10.4248/BR201301003>
 69. Ricci P, Tauchmanova L, Risitano AM, et al. Imbalance of the osteoprotegerin/RANKL ratio in bone marrow microenvironment after allogeneic hemopoietic stem cell transplantation. *Transplantation.* 2006;82(11):1449-1456. Doi: <https://dx.doi.org/10.1097/01.tp.0000244588.42519.72>
 70. Tauchmanová L, Colao A, Lombardi G, et al. Bone loss and its management in long-term survivors from allogeneic stem cell transplantation. *J Clin Endocrinol Metab.* 2007;92(12):4536-4545. Doi: <https://dx.doi.org/10.1210/jc.2006-2870>
 71. Zupan J, Jeras M, Marc J. Osteoimmunology and the influence of pro-inflammatory cytokines on osteoclasts. *Biochem Med (Zagreb).* 2013;23(1):43-63. <https://www.ncbi.nlm.nih.gov/pubmed/23457765>
 72. Lam J, Takeshita S, Barker JE, et al. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest.* 2000;106(12):1481-1488. Doi: <https://dx.doi.org/10.1172/JCI11176>
 73. Gao Y, Grassi F, Ryan MR, et al. IFN-gamma stimulates osteoclast formation and bone loss in vivo via antigen-driven T cell activation. *J Clin Invest.* 2007;117(1):122-132. Doi: <https://dx.doi.org/10.1172/JCI30074>
 74. Quinn JMW, Sims NA, Saleh H, et al. IL-23 inhibits osteoclastogenesis indirectly through lymphocytes and is required for the maintenance of bone mass in mice. *J Immunol.* 2008;181(8):5720-5729. Doi: <https://dx.doi.org/10.4049/jimmunol.181.8.5720>
 75. Baek KH, Oh KW, Lee WY, et al. Changes in the serum sex steroids, IL-7 and RANKL-OPG system after bone marrow transplantation: influences on bone and mineral metabolism. *Bone.* 2006;39(6):1352-1360. Doi: <https://dx.doi.org/10.1016/j.bone.2006.06.011>
 76. McClune BL, Polgreen LE, Burmeister LA, et al. Screening, prevention and management of osteoporosis and bone loss in adult and pediatric hematopoietic cell transplant recipients. *Bone Marrow Transplant.* 2011;46(1):1-9. Doi: <https://dx.doi.org/10.1038/bmt.2010.198>
 77. Kashyap A, Kandeel F, Yamauchi D, et al. Effects of allogeneic bone marrow transplantation on recipient bone mineral density: A prospective study. *Biol Blood Marrow Transplant.* 2000;6(3A):344-351. <https://www.ncbi.nlm.nih.gov/pubmed/10905772>
 78. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplant.* 2012;47(3):337-341. Doi: <https://dx.doi.org/10.1038/bmt.2012.5>
 79. Katz S. Prevention, detection, and treatment of osteopenia and osteoporosis. *Gastroenterol Hepatol (N Y).* 2013;9(3):176-178. <https://www.ncbi.nlm.nih.gov/pubmed/23961268>
 80. Pundole X, Murphy WA, Ebede CC, et al. Fracture risk prediction using FRAX in patients following hematopoietic stem cell transplantation. *Arch Osteoporos.* 2018;13(1):38. Doi: <https://dx.doi.org/10.1007/s11657-018-0453-5>
 81. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplant.* 2012;47(3):337-341. Doi: <https://dx.doi.org/10.1038/bmt.2012.5>
 82. Webber L, Anderson RA, Davies M, et al. HRT for women with premature ovarian insufficiency: a comprehensive review. *Hum Reprod Open.* 2017;2017(2):hox007. Doi: <https://dx.doi.org/10.1093/hropen/hox007>
 83. Braith RW, Mills RM, Welsch MA, et al. Resistance exercise training restores bone mineral density in heart transplant recipients. *J Am Coll Cardiol.* 1996;28(6):1471-1477. Doi: [https://dx.doi.org/10.1016/s0735-1097\(96\)00347-6](https://dx.doi.org/10.1016/s0735-1097(96)00347-6)
 84. Sunycz JA. The use of calcium and vitamin D in the management of osteoporosis. *Ther Clin Risk Manag.* 2008;4(4):827-836. Doi: <https://dx.doi.org/10.2147/tcrm.s3552>
 85. Tauchmanová L, Salleri C, Esposito M, et al. Beneficial treatment with risedronate in long-term survivors after allogeneic stem cell transplantation for hematological malignancies. *Osteoporos Int.* 2003;14(12):1013-1019. Doi: <https://dx.doi.org/10.1007/s00198-003-1520-2>
 86. Grigg AP, Shuttleworth P, Reynolds J, et al. Pamidronate reduces bone loss after allogeneic stem cell transplantation. *None.* 2006;91(10):3835-3843.

Doi: <https://dx.doi.org/10.1210/jc.2006-0684>

87. D'Souza AB, Grigg AP, Szer J, et al. Zoledronic acid prevents bone loss after allogeneic haemopoietic stem cell transplantation. *Intern Med J*. 2006;36(9):600-603. Doi: <https://dx.doi.org/10.1111/j.1445-5994.2006.01154.x>
88. Hausmann A, Hill W, Stemmler HJ, et al. Bone loss after allogeneic haematopoietic stem cell transplantation: a pilot study on the use of zoledronic Acid. *Chemother Res Pract*. 2012;2012:858590. Doi: <https://dx.doi.org/10.1155/2012/858590>
89. Pundole X, Cheema HI, Petitto GS, et al. Prevention and treatment of bone loss and fractures in patients undergoing a hematopoietic stem cell transplant: a systematic review and meta-analysis. *Bone Marrow Transplant*. 2017;52(5):663-670. Doi: <https://dx.doi.org/10.1038/bmt.2016.312>
90. Hari P, DeFor TE, Vesole DH, et al. Intermittent zoledronic acid prevents bone loss in adults after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2013;19(9):1361-1367. Doi: <https://dx.doi.org/10.1016/j.bbmt.2013.06.015>
91. Gupta S, Gupta H, Mandhyan D, et al. Bisphosphonates related osteonecrosis of the jaw. *National Journal of Maxillofacial Surgery*. 2013;4(2):151. Doi: <https://dx.doi.org/10.4103/0975-5950.127643>
92. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Ann Oncol*. 2012;23(5):1341-1347. Doi: <https://dx.doi.org/10.1093/annonc/mdr435>
93. Mawardi H, Glotzbecker B, Richardson P, et al. Hematopoietic cell transplantation in patients with medication-related osteonecrosis of the jaws. *Biol Blood Marrow Transplant*. 2016;22(2):344-348. Doi: <https://dx.doi.org/10.1016/j.bbmt.2015.08.021>
94. Kajizono M, Sada H, Sugiura Y, et al. Incidence and risk factors of osteonecrosis of the jaw in advanced cancer patients after treatment with zoledronic acid or denosumab: a retrospective cohort study. *Biol Pharm Bull*. 2015;38(12):1850-1855. Doi: <https://dx.doi.org/10.1248/bpb.b15-00385>
95. Cartwright B, Robinson J, Seed PT, et al. Hormone replacement therapy versus the combined oral contraceptive pill in premature ovarian failure: a randomized controlled trial of the effects on bone mineral density. *J Clin Endocrinol Metab*. 2016;101(9):3497-3505. Doi: <https://dx.doi.org/10.1210/jc.2015-4063>
96. Eastell R. Management of osteoporosis due to ovarian failure. *Med Pediatr Oncol*. 2003;41(3):222-227. Doi: <https://dx.doi.org/10.1002/mpo.10341>
97. Słopień R, Rynio P, Kubala E, et al. Denosumab-a new medication in the treatment of postmenopausal osteoporosis. *Prz Menopauzalny*. 2017;16(3):75-78. Doi: <https://dx.doi.org/10.5114/pm.2017.70581>
98. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361(8):756-765. Doi: <https://dx.doi.org/10.1056/NEJMoa0809493>
99. Brunova J, Kratochvilova S, Stepankova J. Osteoporosis therapy with denosumab in organ transplant recipients. *Front Endocrinol*. 2018;9. Doi: <https://dx.doi.org/10.3389/fendo.2018.00162>
100. Shroff R, Beringer O, Rao K, Hofbauer LC, Schulz A. Denosumab for post-transplantation hypercalcemia in osteopetrosis. *New England Journal of Medicine*. 2012;367(18):1766-1767. Doi: <https://dx.doi.org/10.1056/NEJMc1206193>
101. Pundole X, Partow K, Lu H. Denosumab increases bone mineral density in a young osteoporotic woman on dialysis after allogeneic stem cell transplantation for hematologic malignancy. *IBMS BoneKEy*. 2014;11. Doi: <https://dx.doi.org/10.1038/bonekey.2014.58>
102. Seno T, Yamamoto A, Kukida Y, et al. Once-weekly teriparatide improves glucocorticoid-induced osteoporosis in patients with inadequate response to bisphosphonates. *Springerplus*. 2016;5(1). Doi: <https://dx.doi.org/10.1186/s40064-016-2704-5>
103. Lou S, Lv H, Yin P, et al. Combination therapy with parathyroid hormone analogs and antiresorptive agents for osteoporosis: a systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int*. 2019;30(1):59-70. Doi: <https://dx.doi.org/10.1007/s00198-018-4790-4>
104. Kananen K, Volin L, Laitinen K, et al. Prevention of bone loss after allogeneic stem cell transplantation by calcium, vitamin D, and sex hormone replacement with or without pamidronate. *J Clin Endocrinol Metab*. 2005;90(7):3877-85. Doi: <https://academic.oup.com/jcem/article/90/7/3877/2837210>

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