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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 indicted 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-1β, IL-6, IFNγ, 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 calcicneurin 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 calcicneurin 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 allogenic 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 allogenic 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 allogenic HSCT-related loss of BMD.

**Osteoporosis and osteopenia**

**Epidemiology:** The incidence of osteopenia and osteoporosis prior to allogenic 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 allogenic 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 allogenic 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 allogenic 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 allogenic 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 allogenic 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 allogenic HSCT bone loss

Cytokine imbalance can dysregulate bone cell cross-talk to increase BMD loss. Osteoblast-derived receptor activator of nuclear factor-κB 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 INFγ 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 allogenic HSCT predicted the extent of bone loss during first 12 months post-transplantation [60]. While all allogenic 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 allogenic 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].

patients

Treatment of bone loss in allogenic HSCT

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.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Management</th>
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<tr>
<td>Osteopenia and Osteoporosis</td>
<td><em>Non-pharmacological therapy:</em> 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]. 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] 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]. 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]. 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]. 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].</td>
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<tr>
<td>Avascular necrosis (AVN)</td>
<td>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].</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>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.</td>
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### 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**

The authors have no conflicts of interest to report.

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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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