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Biomaterial scaffolds for treating osteoporotic bone

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Abstract

Healing fractures resulting from osteoporosis or cancer remains a significant clinical challenge. In these populations, healing is often impaired not only due to age and disease, but also by other therapeutic interventions such as radiation, steroids, and chemotherapy. Despite substantial improvements in the treatment of osteoporosis over the few decades, osteoporotic fractures are still a major clinical challenge in the elderly population due to impaired healing. Similar fractures with impaired healing are also prevalent in cancer patients, especially those with tumor growing in bone. Treatment options for cancer patients are further complicated by the fact that bone anabolic therapies are contraindicated in patients with tumors. Therefore, many patients undergo surgery to repair the fracture, and bone grafts are often used to stabilize orthopaedic implants and provide a scaffold for ingrowth of new bone. Both synthetic and naturally occurring biomaterials have been investigated as bone grafts for repair of osteoporotic fractures, including calcium phosphate bone cements, resorbable polymers, and allograft or autograft bone. In order to re-establish normal bone repair, bone grafts have been augmented with anabolic agents, such as mesenchymal stem cells (MSC) or recombinant human bone morphogenetic protein-2 (rhBMP2). These developing approaches to bone grafting are anticipated to improve the clinical management of osteoporotic and cancer-induced fractures.

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Keywords

Scaffold; bone graft; osteoporosis; fracture; cancer-induced bone disease

Introduction

Osteoporotic patients are typically treated with anabolic agents that stimulate bone formation (e.g., parathyroid hormone (PTH)) or anti-resorptive agents that inhibit bone resorption (e.g., bisphosphonates, calcitonin, raloxifene, and estrogen) to slow the progression of disease [1]. However, in many patients this loss of bone mass results in osteoporotic fractures, which account for approximately 1.5 million fractures in the US each year and are a significant cause of morbidity, mortality, and hospitalization. Treatment of osteoporotic fractures is challenging due to diminished capacity for fracture healing [2–4], and the reduced healing capacity of osteoporotic patients correlates with a much higher (~50%) failure rate of implant fixation compared to younger patients [5–7]. Since the bone is unlikely to heal on its own in osteoporotic fractures due to impaired healing, patients will frequently undergo surgical procedures to fix damaged bone using screws or fixation plates. Due to the high porosity and low strength of the osteoporotic cancellous bone, implants are often augmented with bone void fillers to improve outcomes. Restoration of normal bone repair through local delivery of biologics that enhance osteogenic differentiation has also been investigated to reduce the high complication rate associated with implant failure [2].

Cancer patients often develop bone metastatic diseases. Similar to osteoporotic patients, they are often treated with bisphosphonates, though typically given at higher doses. However, even with treatment, patients will eventually experience fractures, which are often slow to heal, significantly impeding their mobility and quality of life. While surgeries can improve quality of life, they are not a cure and are instead performed for palliative purposes. Bone surgeries performed on patients with traumatic bone injury are rarely effective in cancer patients, due to impaired healing from drug treatments as well as the tumor itself [8]. Patients with metastases to the proximal femur (one of the most common) typically undergo cemented endoprosthetic replacement/arthroplasty, which is similar to a hip replacement, while other long bone metastases are often repaired using locked intramedullary nails [8]. Lesions in the spine are typically treated using vertebroplasty, and other sites are often repaired using bone cements. Despite the improvements of treatment approaches over time, these surgeries are not without risk and patient's survival after surgery is often short (whether from complications from surgery or from wide-spread disease) [9, 10].

Oral cancer comprises another disease often associated with rapid bone loss, resulting from both radiation treatments as well as tumor growth. To reduce morbidity associated with the disease, patients frequently require treatments consisting of tumor removal, reconstruction of the mandibular defect with vascularized bone from the fibula, and subsequent placement of dental implants [11]. Transplantation of the fibula flap introduces a significant source of patient morbidity, and is thus another limitation of the vascular bone graft approach. Importantly, current available therapies only address the need for bone regeneration without targeting the tumor, and thus therapeutic improvements are needed.

Regeneration of bone lost from osteoporosis or cancer presents the challenge of healing in patients with reduced repair mechanisms. These fractures frequently do not heal, may require multiple surgeries, and frequently re-fracture the same site. Recent reports from the German bone evaluation study (BEST) reported a 360-day re-fracture rate of 69% in osteoporosis patients treated with parathyroid hormone (PTH) and 85% in patients that do not receive medication [12]. Thus, there is a compelling need for improved bone grafts for healing osteoporotic fractures. In this review, we will highlight two recent strategies for significantly reducing the high complication rate resulting from implant failure and long-term immobilization: (1) osteoconductive bone grafts that provide mechanical stability and enhance osseointegration of the implant, and (2) osteoinductive bone grafts that enhance healing by re-establishing normal bone repair (i.e., coupling of the bone remodeling units) in osteoporotic patients (Figure 1).

Biological Challenges of Healing Osteoporotic Bone

Patients with osteoporosis suffer a reduction in bone mineral density that can result from multiple pathological conditions and can lead to an increased risk of fracture. While bone mass is a major predictor of osteoporosis, other factors such as the material properties of bone can also affect the fracture risk [13]. A common observation associated with osteoporosis is that the bone deposition by osteoblasts cannot keep up with osteoclast-mediated bone resorption, ultimately resulting in a net loss of bone over time [14]. Furthermore, the healing potential of osteoporotic patients is impaired, in part due to reduced ability of mesenchymal stem cells (MSCs) to differentiate into osteoblasts and form new bone [2, 15]. MSCs from post-menopausal women exhibit a lower growth rate and deficient osteogenic potential compared to pre-menopausal women [16], and MSCs from osteoporotic patients synthesize less type I collagen [17]. The reduction in the number of MSCs with osteogenic potential during aging has been suggested to contribute to the age-related reduction in number of osteoblasts [18]. The use of intermittent PTH (or Forteo) stimulates osteoblast differentiation and is the only treatment that promotes healing and new bone formation in osteoporotic patients.

While patients with tumor-induced bone disease also experience an increase in osteoclast-mediated bone destruction that osteoblasts cannot repair, they often suffer more pronounced bone loss compared to osteoporotic patients due to the anti-cancer therapies [19]. Cancer patients are frequently treated with chemotherapeutic agents, radiation therapy, and/or steroids that can induce bone loss or necrosis, further complicating their ability to heal fractures or to heal from surgery [20]. Since PTH is contraindicated in cancer patients, there are no drugs used in cancer patients that stimulate new bone formation. While the anti-resorptive drugs (Denosumab and bisphosphonates) can successfully reduce bone destruction, they do not stimulate new bone and are associated with side-effects when given at high doses to cancer patients [21]. Better treatments are clearly needed for patients with osteoporosis or tumor-induced bone loss that enhance bone regeneration while reducing tumor growth.

Bone Grafts and Scaffolds for Healing Osteoporotic Fractures

The use of autogenous bone grafts has helped improve the impaired healing of patients with osteoporotic fractures. Autograft (bone harvested from the patient) or allograft (donor bone) bone is frequently used to enhance healing and fill space left by the fracture [22]. One study has reported that osteoporotic patients with acetabular fractures treated with total hip replacement supported by a fixation device and autografting of the acetabulum showed incorporation of the graft and good functional outcomes after 11 – 84 months [23]. In another study, treatment of osteoporotic humeral shaft non-unions with a vascularized fibular graft was found to achieve successful union in a small clinical study [24]. However, the bone harvesting surgical procedure is associated with additional morbidity, and the amount of autograft available is limited [25]. These limitations of autograft have generated considerable interest in synthetic scaffolds, which aim to reduce the high complication rate due to implant failure by addressing the need for stabilization of fixation devices and/or acceleration of fracture healing [2].

Typically, the primary failure mode for internal fixation devices is failure of the weak osteoporotic cancellous bone rather than the implant [26], which is consistent with observations that fractures in osteoporotic patients often present metaphyseal voids that are more extensive compared to younger patients [27]. Bone graft and bone substitutes are reported to be beneficial in maintaining metaphyseal reduction. Ideally, augmentation of osteoporotic fractures with osteoconductive bone grafts both maintains reduction of the fracture and also provides a scaffold for ingrowth of new bone near the interface between host bone and the fixation device. Settable calcium phosphate cements (CPCs) offer the advantages of good adhesion to bone, remodeling and consequent replacement with new bone, injectability [28], and reduced reliance on internal fixation devices [26], and are often used to fill voids caused by severe osteoporosis or comminution of the host bone [26]. Augmentation with CPCs has been reported to enhance the fixation stability of femoral neck and trochanteric fractures [29] as well fractures of the intertrochanteric crest [30]. While treatment of fragility fractures frequently focuses on the proximal femur, upper extremity fractures to the humerus and radius account for 33% of fractures in elderly patients [31]. Osteoporotic proximal humeral fractures are challenging to treat due to poor bone quality and unstable fixation [31]. Augmentation of proximal humeral fractures with Norian, an injectable hydroxyapatite (HA) cement, maintained reduction and promoted unions in all patients at 1 year follow-up [32]. Augmentation with CPCs has also been reported to maintain fixation of unstable distal radius fractures [27, 33, 34].

In order to improve the bioactivity or mechanical properties of the graft, calcium phosphate cements have been modified with other ions or polymers. Strontium (Sr)-substituted HA cements showed improved Sr and Ca release compared to stoichiometric HA granules [35], which is anticipated to enhance bone healing *in vivo* due to the anabolic and anti-catabolic properties of Sr [36]. Another study has reported that silicate-substituted calcium phosphate promoted osteogenic differentiation of MSCs [37]. Calcium phosphate/silk hybrid scaffolds have been fabricated as a composite bone graft for stimulating bone formation and reversing bone loss [38]. The hybrid scaffolds showed increased new bone formation and decreased

bone resorption compared to the silk scaffold when implanted in the distal femoral epiphysis in ovariectomized rats.

While osteoconductive cements and scaffolds improve implant stability and provide a pathway for ingrowth of new bone, they do not address the impaired healing potential of osteoporotic bone. Thus, a number of approaches using osteoinductive scaffolds and grafts have been investigated to improve healing by stimulating osteoblast differentiation. Platelet-rich plasma (PRP) enhances healing of segmental femoral defects through expression of TGF-β1 and the osteoinductive factor bone morphogenetic protein-2 (BMP-2) [39]. In an osteoporotic model of ovariectomized mice, PRP enhanced healing by promoting new bone formation and suppressing adipogenesis within the bone marrow [40]. By providing a surface on which new bone can grow, local delivery of biologics (such as PRP or recombinant human BMP-2 (rhBMP-2)) from a scaffold is known to enhance bone formation [41, 42]. Local delivery of rhBMP-7 from poly(lactic glycolic) acid (PLGA) microspheres increased the mechanical strength of vertebral bodies in ovariectomized sheep [43]. In another study, sustained release of rhBMP-2 from gelatin microsphere/CPC composite scaffolds enhanced new bone formation compared to the CPC alone in osteoporotic goats [44]. Local delivery of MSCs from scaffolds has also been investigated as a strategy for healing osteoporotic fractures. Delivery of MSCs from PLGA/collagen Type I microspheres enhanced healing of trabecular bone defects in ovariectomized rats compared to MSCs alone [45]. However, healing of large cortical bone defects requires that the scaffold also deliver osteoinductive cues to induce differentiation of MSCs to osteoblasts. Delivery of an MSC sheet from osteoinductive calcined bovine bone increased new bone formation compared to individual MSCs in 8-mm calvarial defects in ovariectomized rats [46]. Other studies have shown that local delivery of MSCs transfected with *BMP-2* from calcium phosphate scaffolds enhanced bone healing compared to untreated MSCs in cortical bone defects in the mandible [47] or femur [48] of osteoporotic rats. Mesoporous-glass/silk scaffolds seeded with MSCs transfected with both PDGF and BMP-2 have also been shown to increase new bone formation in segmental femoral defects in ovariectomized rats compared to BMP-2 alone [49].

Strategies for Healing Bone Damaged by Cancer-Induced Disease

Healing of fractures caused by cancer-induced bone disease (CIBD) presents additional challenges. Since expression of BMP receptors is up-regulated on cell membranes of certain cancers [50–52], local delivery of growth factors such as rhBMP-2 presents potential risks of stimulating tumor growth. In many cancer patients, management of pain is the primary concern (versus bone regeneration) due to the often limited life expectancy of the patient [53]. For example, malignant tumoral pathologies in the L5 vertebrae are typically stabilized using a titanium cage filled with poly(methyl methacrylate) (PMMA) bone cement, which effectively manages pain [54]. However, other studies have investigated the potential of vascularized autogenous bone grafts as a more regenerative approach compared to PMMA bone cement. Orthopaedic CIBD fractures have been successfully reconstructed using autogenous bone grafts. In one study, thirteen patients who underwent resection for a malignant pelvic lesion and were reconstructed with a total hip replacement augmented with an ipsilateral femoral autograft experienced a low (8%) probability of revision for

mechanical failure after 2 years [55]. A recent case report has noted that the use of a free vascularized fibula graft resulted in a functional and pain-free hip for a patient with a large cavitary defect of the femoral head after resection of a chondroblastoma [56]. Additional studies report found that reconstruction of the distal radius with a free vascularized fibula graft after resection of a giant cell tumor resulted in good functional outcomes at 4 years [57].

Oral cancer patients present another challenge for healing CIBD fractures and bone damage. Bone destruction in the craniomaxillofacial (CMF) complex can result in dramatic changes in appearance, altered dentition, and reduced ability to speak. Thus, surgical intervention is required not only for palliative care but also to restore normal function. Oral cancer patients often require fixation or mandibulectomy (marginal or segmental) to remove tumor that has invaded the mandible or to repair treatment-induced bone destruction [11, 58]. The current one-stage procedure comprising tumor excision followed by immediate reconstruction of the excised mandible with vascularized bone has proven to be the most reliable and cost-effective approach for treatment of segmental mandible defects [11]. Since partial resections in patients with mandibular invasion may lead to recurrence [59], surgeons often are inclined to take large negative margins, which introduces cosmetic and functional defects [58, 59]. In order to preserve function, the clinical standard of care for reconstruction of large segmental mandibulectomies utilizes a vascularized free flap, in which a portion of the fibula is removed and grafted into the mandibular defect [11]. After grafting, patients frequently are treated with radiation monthly prior to placement of dental implants [60]. While success rates exceeding 90% have been reported for many types of mandibular surgeries, radiotherapy has been reported to lower success rates [60–63]. Thus, the radiation treatment intended to prevent recurrence in cancer patients can lead to complications such as osteoradionecrosis [64], resulting in failure of the graft and revision surgeries [63]. Despite these aggressive therapies of large surgical margins and radiation, recent studies have reported recurrence rates varying between 13 – 34% after mandibulectomy, which underscores the need for new approaches for reducing tumor recurrence while improving healing [58, 60, 61, 65, 66].

Recent studies have reported that nonvascular bone grafts (NVBGs), which are available in greater quantity and do not require an invasive harvesting procedure, can achieve successful outcomes for patients treated for marginal mandibulectomy or small segmental defects [67–69]. However, patients with large defects still have few options beyond the fibula free flap. While BMP-2 and other growth factors are used for healing CMF bone defects, the concern of stimulating tumor growth has prevented the use of these bone anabolic agents for oral cancer [70, 71]. Alternatively, the use of PRP has been effective for the treatment of refractory bisphosphonate-induced osteonecrosis of the jaw (BRONJ); however, it is unclear whether the increased concentration of growth factors will have negative effects on cancerous or pre-cancerous lesions [72].

Conclusions

Despite the introduction of new therapies for slowing the progression of disease in osteoporotic and CIBD patients, the loss of bone mass associated with these diseases results

in pathologic fractures, which are difficult to treat due to impaired bone healing. New bone grafting strategies addressing the need for implant stabilization, bone ingrowth, and re-establishment of normal bone repair continue to be developed. Promising strategies include non-vascularized bone grafts and synthetic osteoconductive bone cements and scaffolds augmented with osteoinductive agents such as platelet rich plasma, rhBMP-2, and/or MSCs have shown promise in preclinical studies and clinical trials. Many groups continue to investigate improved strategies to enhance the mechanical properties of the graft and to stimulate improved healing. While similar approaches can be taken in cancer patients that suffer fractures, more research is needed to find drugs that can both stimulate healing while inhibiting tumor growth.

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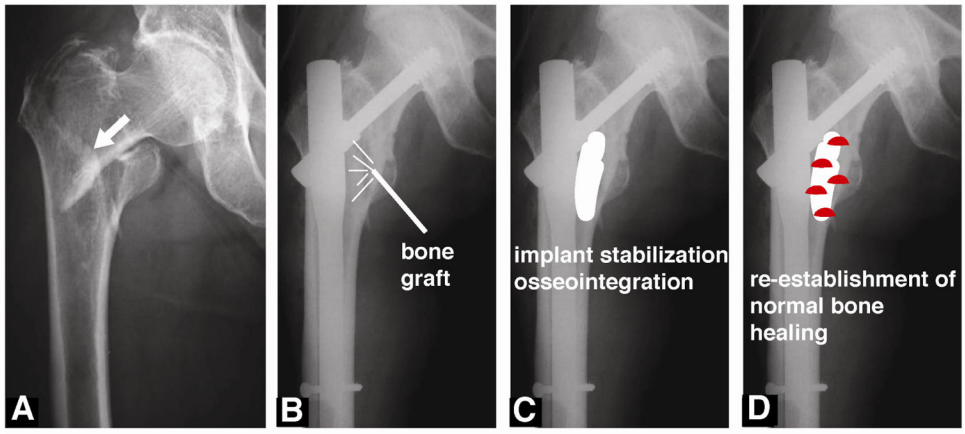

Figure 1. Strategies for healing osteoporotic and cancer-induced bone disease (CIBD) fractures

(A) Pre-operative radiograph of a hip fracture (arrow) in an 84 year-old female patient. (B) Postoperative radiograph showing fixation of the fracture with an intra-medullary hip lag screw coated with hydroxyapatite (HA). (C) Stabilization and osseointegration of implants using osteoconductive bone grafts. (D) Re-establishment of normal bone healing by local delivery of biologics (e.g., mesenchymal stem cells, rhBMP-2, or platelet-rich plasma (shown in red)) from bone grafts and scaffolds. Adapted from A Moroni et al. Can we improve fixation and outcomes? Use of bone substitutes. J Orthop Trauma 23:422–425, 2009 [29].