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Biomechanics of implant fixation in osteoporotic bone

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Abstract

Purpose of review: The purpose of this review is to critically evaluate the current literature regarding implant fixation in osteoporotic bone.

Recent findings: Clinical studies have not only demonstrated the growing prevalence of osteoporosis in patients undergoing total joint replacement (TJR) but may also indicate a significant gap in screening and treatment of this co-morbidity. Osteoporosis negatively impacts bone in multiple ways beyond the mere loss of bone mass including, compromising skeletal regenerative capacity, architectural deterioration, and bone matrix quality, all of which could diminish implant fixation. Recent findings in both pre-clinical animal models and in clinical studies indicate encouraging results for the use osteoporosis drugs to promote implant fixation.

Summary: Implant fixation in osteoporotic bone presents an increasing clinical challenge that may be benefitted by increased screening and usage of osteoporosis drugs.

Keywords

Implant; Fixation; Osteoporosis; Total Joint Replacement

Introduction

Total joint replacement (TJR) surgery is an increasingly common procedure in the United States. In 2010 it was estimated that a total of 2.5 million Americans were living with total hip replacements (THR) with another 4.7 million Americans living with total knee replacements (TKR) [1]. The number of patients with TJRs is expected to increase considerably, as recent estimates project the number of annual THR and TKR surgeries performed in the US to grow to 635,000 and 1.26 million, respectively, by the year 2030 [2].

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Osteoporosis is a metabolic bone disease associated with low bone mass and poor bone quality that increases the risk for fragility fractures (reviewed in detail here [3]). Clinically, osteoporosis is defined using dual energy X-ray absorptiometry (DXA) measures of bone mineral density (BMD). A BMD 2.5 standard deviations or more below the mean for a healthy 30-year old adult is defined as osteoporosis and between 1 and 2.5 standard deviations below is defined as osteopenia, or a state of low bone mass that is less severe than osteoporosis. The total number of people with osteoporosis in the US was estimated at 10.2 million in the year 2010, with an additional 43.4 million being classified as osteopenic [4]. Current models project the combined prevalence of osteoporosis and osteopenia to increase to over 70 million by 2030 [4].

Although a growing number of patients less than 65 years of age are receiving TJR surgery [5, 6], the majority of people living with TJRs are between 60-89 years of age [1]. The prevalence of TJRs is higher in women [1], a demographic that is at a four-fold greater risk for osteoporosis than men [4]. Due to the overlapping risk factors, it is not surprising that osteoporosis and osteopenia are common in patients undergoing TJR (Figure 1) [7-14]. Similar results are noted in a population of patients with end-stage osteoarthritis, the most common indication for TJR, wherein 23% and 43% of patients were noted to have osteoporosis and osteopenia, respectively [8]. Despite the high frequency of osteoporosis or osteopenia in patients undergoing TJR surgery, BMD screening is rarely performed prior to surgery [15, 16], with one chart review finding that only 15% of patients undergoing primary TJR received BMD assessment prior to surgery [17]. Even when patients are properly screened, many TJR patients are not being treated for osteoporosis [18], which is perhaps not surprising given the treatment gap that exists in the general population [19]. This critical lack of screening for osteoporosis is particularly worrisome in the elderly population, where osteoporosis has been reported as one of the strongest risk factors for implant survival [20] and is associated with an increased revision rate [21].

As osteoporosis and osteopenia are common and likely to become even more prevalent in TJR patients, it is important to understand the unique challenges that this co-morbidity presents. The current review describes the factors that influence implant fixation, how osteoporosis affects these factors, and treatment strategies being tested to promote implant fixation in osteoporotic bone. We will specifically concentrate on orthopedic implant fixation rather than fracture fixation devices, such as screws, plates, or nails. For a recent detailed review of the biomechanics of fracture fixation devices, we refer the reviewer here [22]. Additionally, while the majority of our review will focus on the establishment of implant fixation in osteoporosis, which is necessary for the success of cementless TJR, it has been postulated that cemented strategies could help alleviate some of the concerns associated with cementless TJR success in the aging population [23], including in patients with osteoporosis [24].

Implant fixation

Concomitant with the increasing demand for TJR surgery, there is a projected doubling in the number of revision surgeries needed to correct failed implants [25]. Mechanical loosening, or loss of implant fixation, is one of the most common causes for revision THR

[26] and TKR [27] surgery. Radiostereometric analysis (RSA) demonstrated that early migration is a strong predictor of clinical failure [28-31] and is linked to an increased risk of revision due to mechanical instability, or loss of implant fixation [32]. Importantly, low BMD is one factor that has been associated with greater femoral stem migration [33, 34]. Therefore, it is critical to establish early implant fixation to prevent the likelihood of revision TJR surgeries.

Implant fixation is divided into two types (cementless and cemented) with quite different underlying mechanisms [35]. Most of this review considers cementless fixation, although we do make comments relevant to the use of bone cement. Cementless implant fixation is achieved primarily through osseointegration, which is defined histologically as the direct contact between host bone and the implant surface, without intervening fibrous tissue [12] or clinically via radiographic features [36]. The establishment of cementless implant fixation is dependent on intramembranous bone regeneration which is initiated as a result of the surgically induced disruption of the bone marrow cavity or trabecular bone bed [37]. Critical factors in this process are impaired in osteoporotic bone, including reduced angiogenesis in the healing tissue, a reduced pool of progenitor cells, and impaired differentiation of bone forming osteoblasts necessary to establish implant fixation through osseointegration (fracture healing in osteoporosis is reviewed here [38]). Proper osseointegration prevents the formation of a fibrous membrane and directs the transfer of forces from the implant to host bone. Depending upon where the forces are transmitted, there may be stress-shielding, leading to periprosthetic bone loss due to changes in mechanical signals (reviewed in more detail here [39]).

Factors contributing to implant fixation strength

A variety of factors, both extrinsic and intrinsic, contribute to successful osseointegration and subsequent implant fixation, including several factors directly impacted by osteoporosis. These factors, described in detail below, contribute to the increased risk of implant component migration [33, 34] and elevated bone loss following THR surgery [40] noted in patients with low preoperative BMD, as well as, the loss of implant fixation strength noted in preclinical animal models [41].

The defining clinical characteristic of osteoporosis patients is low bone mass, which increases the susceptibility to fragility fractures. Therefore, it is perhaps not surprising that low preoperative BMD is a risk factor for periprosthetic fracture [42, 43]. Periprosthetic fracture represents a severe clinical challenge due to the relatively complicated and expensive surgical care [44]. The complications following surgical intervention to treat periprosthetic fracture include bone loss and loss of implant fixation [45], therefore increasing the risk of subsequent implant failure.

The early establishment of osseointegration and the long-term maintenance of implant fixation are regulated by the sustained process of bone remodeling [46, 47]. Bone remodeling describes the coordinated activity of the bone resorbing cells, osteoclasts, and the bone forming cells, osteoblasts. Imbalanced bone remodeling, wherein osteoclastic bone resorption outpaces bone formation, is the proximate cause for low BMD in osteoporosis

[3]. In the context of TJR surgery, various preclinical animal studies have found that induced osteoporosis, in the form of orchiectomy (ORX) or ovariectomy (OVX), leads to significantly less periprosthetic bone mass and reduced osseointegration [41, 48], which may be caused by this aberrant bone remodeling process. Liang et al. reported reduced histological indices of bone formation in the periprosthetic trabecular bone of OVX rats compared to sham controls, including significantly decreased mineral apposition rate, mineralizing surface and bone formation rates [49]. In contrast, Li et al. reported slightly elevated periprosthetic trabecular bone remodeling rates in OVX rats when compared to sham controls in a longitudinal investigation of the dynamics of bone remodeling following transcortical implant placement [50]. Interestingly, the authors noted compartment-specific differences, as OVX showed transiently reduced bone formation rates in the endocortical and periosteal compartments when compared to sham controls [50]. One limitation of these two studies is the use of transcortical implantation strategies, which don't model the intra-medullary approach used in TJR surgeries. Our laboratory has reported on histological bone remodeling rates in OVX rats using an intramedullary implantation strategy [51, 52]. Although neither study was designed to directly compare remodeling in OVX and sham rats, we are presenting a re-evaluation of the data in the current review (Table 1). The results show that histomorphometric indices of bone formation within the periprosthetic trabecular bone and endocortical surfaces were significantly elevated in the OVX group compared to the sham group, with a trend toward increased eroded surface, a measure of bone resorption. The current data are consistent with the idea that an altered remodeling kinetics in osteoporosis also exists in the periprosthetic environment.

The average age of TJR patients is decreasing and the desired lifespan of orthopedic implants is increasing, therefore more patients will be aging with implants. Although menopause is the most commonly studied cause of osteoporosis, age-related bone loss and bone quality deterioration can also lead to osteoporosis [53]. Therefore, it is possible that the development of osteoporosis in patients with TJRs may emerge as a clinical concern and cause of implant fixation loss. To study the effects of osteoporosis development on established implant fixation, Li et al. performed OVX surgery in rats with osseointegrated intramedullary implants and found that the induction of osteoporosis caused a loss of osseointegration and implant fixation strength [54]. Future work is needed to understand the role of aging or the menopausal transition and the subsequent changes in bone remodeling on implant fixation in well-functioning TJRs.

In addition to bone mass loss, osteoporotic bone is characterized by architectural deterioration, including decreased trabecular number and trabecular and cortical thinning. These architectural changes may be important because the importance of peri-implant bone structure has also been implicated as a contributing factor to loss of implant fixation strength. For example, a loss of trabecular number [55] and cortical thinning [56] have been identified as critical factors contributing to bone-implant fixation strength using preclinical rodent models and finite element modeling, respectively. While these studies have clearly demonstrated that bone quality can negatively affect implant fixation in uncemented implantation approaches, the same does not appear to be true when bone cement is used. In a clinical observational study, Huang et al. found that lower trabecular bone quality, particularly a higher structure model index (SMI) and greater trabecular spacing, was

associated with better post-operative outcomes in post-menopausal women undergoing cemented TKR surgery [57]. The authors attributed this finding to better penetration of bone cement, which likely resulted in improved component fixation [57]. Therefore, it appears likely that the link between implant fixation and bone architecture is context dependent.

In addition to cemented vs uncemented surgical approaches, the implant surface preparation may also determine the role of bone architecture on implant fixation strength. In a recent study, our laboratory assessed the relative contribution of bone-implant contact, trabecular bone, and cortical bone properties to implant fixation strength in implants with either smooth or rough surfaces, and found that bone-implant contact contributes the most to implant fixation strength in smooth-surfaced implants whereas cortical bone thickness contributes the most in rough-surfaced implants [58]. When the implant is press fitted into the marrow canal, cortical bone attachment in the rough-surfaced implant may be stronger than smooth-surfaced implants, leading to a larger contribution of cortical bone thickness to implant fixation strength than bone-implant contact. Whether this relationship remains true in osteoporosis models requires further investigation.

Another open question is the role of bone matrix quality on implant fixation in osteoporotic bone. Several studies have reported changes in both the mineral and protein components of bone matrix in osteoporotic bone (reviewed here [59, 60]). Although, new techniques have considerably improved our capability to measure bone matrix quality at the bone-implant interface [61], to our knowledge there has been no direct comparison of the interfacial bone matrix quality between normal and osteoporotic bone.

Measures to assess implant fixation

Although direct measurements of implant fixation strength clinically are impossible, experiments in preclinical animal models commonly incorporate mechanical testing measurements to probe the contribution of disease, implant coatings or pharmaceutical treatments on the strength of the bone-implant interface. Gao et al. provided a detailed review on mechanical testing strategies used to assess implant fixation strength at both the macro and microscale [62]. For additional reading describing the methodology for performing the commonly employed pull-out or push-out testing of implant fixation strength, the reader is referred to a review on the technical aspects of these techniques [63].

One limitation of most ex vivo mechanical testing strategies is an inability to directly correlate implant fixation strength and osseointegration within the same sample due to inability to image bone-implant contact in a non-destructive manner. New high resolution imaging strategies have overcome the technical challenges of non-destructive imaging of bone-implant contact by microcomputed tomography, which was validated by backscatter scanning electron microscopy [64]. This approach has enabled the direct comparison of how the different bone compartments contribute to implant fixation strength within the same sample [58]. Additional high resolution imaging techniques, such as synchrotron-based X-ray tomography [65] and neutron tomography [66] have similarly been used to non-destructively assess the bone-implant interface and perform in situ loading to monitor damage accumulation in the interfacial region. Although three-dimensional and non-

destructive to the tissue of interest, due to size constraints and the radiation exposure concerns, these imaging techniques are limited to ex vivo evaluation.

Clinical strategies have primarily relied on X-ray imaging or dual energy X-ray absorptiometry (DXA) to infer implant stability based on the presence of peri-implant radiographic lesions or loss of peri-implant bone mineral density (BMD), respectively. The development [67] and subsequent standardization [68] of RSA for orthopedic applications has considerably increased the number of clinical studies aimed at improving implant fixation (described in detail below). RSA can be used to assess implant migration, a surrogate measure of implant fixation, and importantly, early implant migration appears to be a strong predictor of late loosening, or loss of implant fixation [32, 69]. RSA has confirmed that low BMD contributes to implant migration [33, 34, 70]. As RSA analysis requires X-ray imaging and expert interpretation, there have been efforts to identify more rapid clinical assessments of implant fixation that can be performed with less-specialized instrumentation.

Circulating biomarkers have shown some promise to predict end-stage orthopedic implant failure (reviewed here [71]), as well as, early implant migration as assessed by RSA [72]. Our lab has recently identified a panel of biomarkers that can predict radiographic loosening up to 6-years prior to clinical presentation [73] and in preclinical models, we have determined that circulating biomarkers can in-fact reflect implant fixation strength [74]. Nazari-Farsani et al. reported that cortical thickness measured in the radius using pulse-echo ultraasonometry is able to predict femoral stem subsidence following THR surgery, which may be a reflection of the systemic bone loss due to osteoporosis [75].

Methods to Improve Implant Fixation Strength.

We previously reviewed the literature on pharmacological treatments to improve fixation strength in preclinical animal models and noted that the majority of the research has been aimed at repurposing drugs for osteoporosis [41]. Recently evaluated pharmacological agents that have been reported to improve implant fixation in preclinical models of osteoporosis have included lycopene [76], osteoprotegerin [77], and lithium chloride [78]. Our lab and others have been investigated sclerostin antibody, a new anabolic, or bone building, treatment strategy for osteoporosis, as a means to promote implant fixation in preclinical models. Sclerostin antibody treatment dramatically increases implant fixation strength in both metabolically normal [79, 52] and osteoporotic rats [80]. Importantly, sclerostin antibody is now clinically approved for osteoporosis [81], therefore, it is likely that data will soon emerge investigate the use of this anabolic agent on clinical orthopedic implant fixation.

Recent experiments have also included a considerable amount of effort on the use of pro-osteogenic surfaces, including controlled drug release, to promote osseointegration and implant fixation (reviewed here [82]). The advantage of tailored implant surfaces is the ability to promote sustained release of the drug of interest. For example, Jiu et al. demonstrated that the slow release of zoledronic acid significantly enhanced osseointegration and increased implant fixation strength in a rat OVX model [83]. Although

not designed to directly compare systemic vs. local administration, He et al. performed a detailed meta-analysis of the preclinical data to determine the effects of zoledronic acid and found that both strategies are effective at increasing implant osseointegration in osteoporotic models [84]. Lotz et al. demonstrated that surface enhancement on its own can improve osseointegration in OVX models [85], suggesting that systemic pharmaceutical treatments may not be necessary.

Clinical efforts to promote osseointegration and implant fixation have focused on the use of systemic osteoporosis drugs, which tend to target bone resorption (anti-catabolic) or bone formation (anabolic). The most commonly prescribed treatments for osteoporosis are bisphosphonates, a class of anti-catabolic drugs which have been evaluated in several TJR clinical trials. Overall, the data have demonstrated a 50% reduction in the revision surgery risk for patients receiving TJR [86]. The mechanism driving the reduced revision risk is likely the action of bisphosphonates on osteoclasts, preventing the loss of periprosthetic bone mass, which is commonly noted in osteoporotic patients [87-89]. Although this maintenance of bone mass would be predicted to increase implant fixation, direct assessment of implant stability in patients taking either zoledronate [90] or risedronate [91] did not note any differences in femoral stem migration. Zoledronate did limit migration of the femoral cup, however [92]. Interestingly, despite the increased bone mass in bisphosphonate-treated TJR patients, there are also reports of increased periprosthetic fracture risk [93]. It is currently unclear whether this increased fracture risk is associated with changes in the bone-implant interface or due to bisphosphonate-induced changes in the bone matrix that have been implicated in the development of fragility fractures in bisphosphonate-treatment patients [94].

Denosumab is a recently approved anti-catabolic treatment for osteoporosis that has also been evaluated in TJR patients. Denosumab is a soluble antagonist to receptor activator of nuclear factor kappa- β ligand (RANKL), which inhibits the differentiation of osteoclasts and is proven effective in reducing the fracture risk in post-menopausal osteoporotic women [95]. Similar to what is seen with bisphosphonate administration, patients receiving Denosumab following TJR have less bone loss following surgery [96, 97], but no effect on femoral stem migration in THR [97]. Denosumab did prevent stem migration in patients receiving cemented TKR, which the authors suggest could be due in part to the larger involvement of trabecular bone in the knee vs hip [98].

Anabolic treatments aimed at building bone mass have also been evaluated as a means to improve implant fixation. Teriparatide is a clinically approved treatment strategy to build bone and subsequently reduce fracture risk in osteoporosis patients [99]. Although, teriparatide treatment has been reported to preserve or even increase periprosthetic BMD following TJR surgery [100, 101], the post-operative periprosthetic BMD was found to be comparable to alendronate [102]. The effects of teriparatide on implant fixation, measured by implant component migration, appear to be dependent on surgical site and surgical strategy. Ledin et al. found no effect of teriparatide on cemented TKR components [103], while Huang et al. reported decreased migration in cementless THR components [104].

Altogether, these studies suggest that both anti-catabolic and anabolic strategies may be effective at preventing early loss of implant fixation or preserving peri-implant bone mass, but there has not been much attention paid to restoring lost fixation strength. Interestingly, an ongoing clinical trial aimed at using Denosumab to restore bone loss in patients with radiographically-confirmed peri-implant lesions is underway, but to date, no results have been posted [105]. A previous trial with alendronate aimed at slowing the progression of established loosening was unsuccessful [106]. In addition to preventing early migration, the bone building capabilities of teriparatide make it a good candidate to restore lost periprosthetic BMD and implant fixation. Indeed, several clinical case studies have reported that teriparatide treatment improves clinical signs of implant fixation loss [107, 108], but further clinical trials are necessary to confirm whether teriparatide represents a viable strategy to restore implant fixation and prevent revision surgery.

Conclusion

Implant fixation in osteoporotic bone presents an increasing clinical challenge that may be greatly benefitted by increased screening and use of osteoporosis drugs. The pathophysiology of osteoporosis results in low bone mass which significantly increases the risk for implant loosening. To make matters worse, osteoporosis also alters the establishment of early and maintenance of late stage implant fixation as well as bone architecture leading to loss of fixation. Fortunately, assessing implant fixation in both the pre-clinical and clinical settings and careful study of pharmacological agents have identified several osteoporosis drugs, of various mechanisms, that may be useful in avoiding implant loosening. In tandem, early diagnosis of osteoporosis in combination with effective preventive treatments could result in a significant benefit for patients with osteoporosis undergoing implant surgery.

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Figure 1:

Representation of the prevalence of osteoporosis [4] and TJR surgery [109, 110] in the US based on 2010 estimates. In total, an estimated 23% of patients awaiting TJR surgery have clinically defined osteoporosis [8], which equates to a total of just over 214,000 patients.

Table 1:

Histological indices of bone formation and resorption measured comparing SHAM and OVX rats by group and time post-implantation. Data adapted from [51, 52].

	4 weeks post-implant		8 week post-implant		12 weeks post-implant		Two-Way ANOVA		
	SHAM	OVX	SHAM	OVX	SHAM	OVX	Group	Time	Group X Time
Trabecular Compartment									
MS/BS (%)	16.0 (4.7)	22.8 (4.3)	19.9 (7.3)	17.8 (2.2)	14.9 (4.1)	21.7 (5.7)	0.025	0.854	0.046
MAR ($\mu\text{m}/\text{d}$)	0.77 (0.13)	1.12 (0.38)	0.96 (0.16)	0.82 (0.10)	0.70 (0.09)	0.99 (0.40) *	0.037	0.601	0.033
BFR/BS ($\mu\text{m}^3/\mu\text{m}^2/\text{day}$)	46.5 (19.2)	95.0 (37.0)	72.1 (35.0)	53.8 (11.5)	38.3 (11.4)	77.2 (29.9)	0.010	0.455	0.006
ES/BS (%)	4.7 (1.5)	6.8 (2.6)	3.6 (1.5)	6.6 (4.1)	5.9 (3.0)	5.4 (1.0)	0.082	0.794	0.230
Endocortical Compartment									
MS/BS (%)	19.0 (8.1)	35.9 (15.6) *	21.4 (11.8)	20.6 (4.2)	14.1 (6.9)	24.4 (9.2)	0.011	0.115	0.099
MAR ($\mu\text{m}/\text{d}$)	0.75 (0.14)	1.54 (0.50)	1.07 (0.15)	0.94 (0.21)	0.79 (0.14)	0.94 (0.19)	0.003	0.031	<0.001
BFR/BS ($\mu\text{m}^3/\mu\text{m}^2/\text{day}$)	52.9 (23.6)	209.2 (113.6) *	84.9 (52.4)	70.6 (22.1)	40.9 (20.6)	86.7 (45.6)	0.002	0.013	0.002
ES/BS (%)	5.0 (1.5)	5.3 (3.7)	2.0 (1.3)	6.9 (6.1)	5.0 (2.9)	6.3 (1.6)	0.060	0.683	0.211
Periosteal Compartment									
MS/BS (%)	57.7 (28.4)	73.2 (21.7)	43.6 (21.1)	25.4 (16.7)	18.9 (6.4)	29.9 (14.9)	0.659	<0.001	0.076
MAR ($\mu\text{m}/\text{d}$)	1.11 (0.19)	1.28 (0.13)	0.74 (0.20)	0.58 (0.07)	0.59 (0.09)	0.67 (0.08)	0.475	<0.001	0.015
BFR/BS ($\mu\text{m}^3/\mu\text{m}^2/\text{day}$)	243.9 (143.3)	347.4 (123.7)	128.2 (100.9)	53.4 (34.8)	41.4 (16.8)	74.4 (41.4)	0.491	<0.001	0.061
ES/BS (%)	2.8 (2.3)	4.8 (2.3)	2.1 (0.8)	4.0 (1.5)	4.4 (2.9)	3.7 (1.8)	0.133	0.511	0.198

* indicates significant difference compared to SHAM at the same time-point.

MS/BS – Mineralizing surface per bone surface

MAR – Mineral apposition rate

BFR/BS – Bone formation rate per bone surface

ES/BS – Eroded surface per bone surface