Is there a time delay to achieve stable compressive osseointegration fixation?

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Compressive osseointegration fixation using the Compress® is an alternative to traditional intramedullary fixation for endoprosthetic reconstruction. The aims of this retrospective review are to evaluate if there is a time delay to achieve stable compressive osseointegration fixation using the Compress device, and to determine if anatomic location affected any time delay. Between 2006 and 2014, surgeons at one center treated 116 patients with 137 Compress® implants for lower extremity oncologic reconstruction, revision arthroplasty, and fracture nonunion or malunion. Patients were prescribed limited weight bearing for 6 weeks and we report on minimum of 2-year follow up (mean 4 years; range 2-9 years). Kaplan-Meier survival plots with 95% Hall-Wellner bands were produced; survivorship free from overall and aseptic failure at 2 months, 6 months, 1 year and 2 year time points was calculated along with 95% confidence intervals. Cox and extended cox models were used to examine the relationship between location and time with hazard of failure. Twenty-seven failures (including 6 aseptic failures) occurred among the 116 implants. No aseptic failures were observed prior to 2 months in any group, with the first aseptic failure occurring at 81 days. Cox proportional hazards modeling demonstrated differences in hazard ratio (HR) by location (p=0.049). The extended cox model demonstrated an increased hazard for the proximal tibia group relative to the proximal femur group (HR=4.42, p=0.052) for overall failure, along with a time dependent interaction (p=0.008), reflecting that the increased hazard for the proximal tibia group occurred at 4-6 months, with no failures after this point. We were unable to identify a clear temporality for aseptic failure and compressive osseointegration fixation in our patient series, and the 6-week post-operative time point showed no relationship with increased risk of failure. More research is necessary to understand the early stability of compressive osseointegration fixation and its ability to withstand physiologic loads, i.e. immediate weight-bearing, prior to biologic osseointegration.

Keywords: Compressive osseointegration; Compress®; endoprosthetic reconstruction; limb salvage surgery; revision surgery; stress shielding


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**Introduction**

Cemented and uncemented stemmed implants are the most commonly employed fixation methods for endoprosthetic reconstruction (EPR) for oncologic reconstructions, revision arthroplasty, and fracture malunion/nonunion purposes [1-4]. These implants rely on osseointegration at the bone-implant interface [5]; failures are due to aseptic loosening, particle-induced osteolysis, infection, periprosthetic fracture, and stress-shielding [6-9]. The majority of patients undergoing oncological limb salvage are children and young adults in whom revision surgery is likely as medical management of their disease improves and the patient survives longer than their implant [4, 6, 10-14]. A greater understanding of aseptic failure, the main cause of EPR failure at mid- to long-term [15, 16], is needed because revision surgery for traditional stemmed endoprostheses is complicated by bone resorption secondary to stress shielding, osteolysis, periprosthetic fracture, cement extrication, and short-segment fixation [2, 4, 6, 17, 18].

A more recent technology, compressive osseointegration fixation (Compress® Compliant Pre-Stress Device, Biomet, Warsaw, IN, USA), has been developed and is FDA-approved for femoral limb-salvage reconstruction since 2003 [4, 19-23]. Compressive osseointegration fixation offers an alternative to traditional cemented and non-cemented stemmed implants. This technology uses a spring-loaded device to generate an axially-directed compressive force across the bone-implant interface. This self-adjusting compressive force is continuously applied promoting biologic fixation by inducing bone hypertrophy and osseointegration at the implant interface [4, 5, 15, 21, 24-26] which has the potential to decrease the rate of aseptic mechanical failure [19, 27]. Other advantages of the Compress® device include the ability to use it for short-segment fixation and it prohibits loss of bone stock [4, 19, 20, 25, 28, 29] if later revision surgeries are required [4].

Aseptic mechanical failure of compressive osseointegration fixation occurs when stable bony integration at the bone-implant interface fails to develop in the absence of infection, potentially leading to implant loosening at the spindle or fracture around the anchor plug [15, 23, 24, 27, 28, 30, 31]. Current manufacturer recommendations include 6 weeks of restricted weight bearing to allow for osseointegration to occur; however, the time delay to achieve stable fixation has yet to be established. Limited published research has suggested increased early aseptic failure with compressive osseointegration, potentially because at later time points, bone-implant integration improves as bone hypertrophy and osseointegration develops [15, 19, 24, 25, 32]. Distal femoral radiographs have confirmed progressive bone hypertrophy from 0-6 months, as measured by femoral cortical width at the bone-implant interface, and plateauing of cortical hypertrophy at 6 months in patients not receiving chemotherapy [24]. However, these radiographic findings were not correlated clinically to patient outcomes, weight-bearing status, or aseptic failures.

Additionally, survivorship may differ with compressive osseointegration based on location due to differences in mechanical forces across the hip and the knee [33] and differences in bone quality at the different anatomic locations. A previous study found that risk of overall failure of proximal tibia and distal femur reconstructions was increased compared to the proximal femur with the Compress® device [27].

We therefore asked: (1) Is there an initial period of increased risk of aseptic failure suggesting a time delay to achieve stability using compressive osseointegration fixation? (2) Is there a difference in the time delay to achieve stable fixation based on anatomic location (proximal femur, distal femur, proximal tibia)?

**Patients and methods**

Between 2006 and 2014, surgeons at one center treated 116 patients with 137 Compress® implants for lower extremity reconstructions. Indications for the use of compressive osseointegration fixation were reconstruction of the proximal femur, distal femur, and proximal tibia where there was massive bone loss from previous failed arthroplasty, fracture malunions or nonunions, or after oncologic resection. Older age was not a contraindication for use. Study inclusion criteria was a minimum clinical and radiographic follow up within the past year were contacted by phone. Two-year follow up. Patients without radiographic and clinical follow up within the past year were contacted by phone. Two patients (2%) with 2 implants were unable to be reached by phone after having completed a minimum of 2-year follow up and censored to the date of the most recent follow up. Mean follow up in this series was 4 years (range, 2-9 years). Institutional review board approval was obtained for the study.

Of the 116 patients, 23 patients (20%) with 26 implants died and 20 patients (17%) failed before 2 years. Ultimately, 116 implants were available for analysis with a minimum of 2-year follow up. Patients without radiographic and clinical follow up within the past year were contacted by phone. Two patients (2%) with 2 implants were unable to be reached by phone after having completed a minimum of 2-year follow up and censored to the date of the most recent follow up. Mean follow up in this series was 4 years (range, 2-9 years). Institutional review board approval was obtained for the study.

The compression force applied was based on the cortical thickness of the bone at the point of application, measured intraoperatively, and preference for 800 lb/square inch was given if the cortical bone was sufficient. The spindle surface type (hydroxyapatite or porous titanium) was determined by
the availability of the implants. Antirotation pins were not routinely used. For all proximal femoral reconstructions, the decision to perform hemiarthroplasty versus total hip arthroplasty and the choice of specific acetabular and bearing surface components were determined individually by the operating surgeon based on the patient age and preexisting arthritis. For all distal femoral and proximal tibial reconstructions, the Biomet Orthopaedic Salvage System (OSS™, Warsaw, IN, USA) rotating hinge knee arthroplasty components were used. All patients were instructed to follow a strict touchdown weight-bearing protocol for 6 weeks followed by progression to weight-bearing as tolerated.

Post-operative follow up was performed at 2 weeks, 6 weeks, 3 months, and then every 3 to 12 months depending on individual patient factors. Operative reports, implant records, clinic notes, and radiographs for each patient were reviewed. Survivorship free from aseptic mechanical failure was defined as patients without failure of osseointegration at the bone-implant interface requiring revision surgery in the absence of infection. Patients who underwent reoperation for exchange of a femoral head, acetabular liner, or another modular component were not considered a failure of compressive osseointegration.

Demographic data were recorded for every patient. The indication for surgery was categorized as primary oncologic reconstruction, revision arthroplasty, or fracture nonunion or malunion. Patients treated for a failed primary oncologic reconstruction were classified into the revision arthroplasty group. Patients who received chemotherapy and radiation therapy were noted, although we were unable to subdivide this group to determine who received chemotherapy pre-operatively, post-operatively, or both. Operative details, including the use of antirotation pins, compression force, and spindle surface type were recorded. Spindle size and shape were determined based on the individual patient’s.

Kaplan-Meier survival plots with Hall-Wellner bands were produced to examine survival time of the Compress® free from overall and aseptic mechanical failure. Cox regression modeling with sandwich variance estimation (to account for within-subject correlation) was used to generate hazard ratios (HR) and 95% confidence intervals (CI) for potential risk factors for failure. Extended Cox regression was used to evaluate anatomic location of reconstruction because the proportional hazard assumption was not met for that variable. All statistical analysis was performed in SAS 9.41 software (Cary, NC, USA). Clinically meaningful categories were selected for age, and BMI was dichotomized around the mean of our population at 30 kg/m2.

Results

Aseptic failure

Among the 116 implants, there were six aseptic failures and 27 overall failures. Kaplan-Meier survivorship free from aseptic mechanical failure was 100% at 2 months, 99% at 3 months (95% CI, 97-100%), 97% at 6 months (95% CI, 94-100%), 96% at 9 months (95% CI, 93-99%), 95% at 18 months (95% CI, 91-99%), and 93% at 48 months (95% CI 86-99%) (Figure 1). The first aseptic failure occurred at 81 days. Median time to aseptic failure was 6.3 months (range 81-1534 days).

Among all patients, our cohort by location had 37 proximal femur, 64 distal femur and 13 proximal tibia
patients. Cox proportional hazards modeling demonstrated a significant overall effect of location \( (p=0.047) \) driven by 0 fails in the proximal femur group \( (HR \text{ proximal femur}=0, \ p<0.0001; \ HR \text{ proximal tibia}=2.68 \ (95\% \ CI, 0.57-12.09, \ p=0.2139; \HR \text{ distal femur HR}=1 \) (referent).

Overall failure

In addition to six revisions for aseptic mechanical failure, 17 revisions were performed for infection, two for periprosthetic fractures around the anchor plug, one for local progression of oncologic disease, and one amputation for a dysvascular leg. Survivorship free from overall failure at 2 months was 92\% \( (95\% \ CI, 84-100) \) for proximal femur reconstructions, 98\% \( (95\% \ CI, 95\%-100\%) \) for distal femur reconstructions, and 100\% for proximal tibia reconstructions (Figure 2). At 6 months, the survivorship free from overall failure was 89 \( (95\% \ CI, 80-99) \), 91 \( (95\% \ CI, 83-98) \) and 69 \( (95\% \ CI, 44-94) \) percent for proximal femur, distal femur, and proximal tibia reconstructions, respectively. No additional failures were observed among the proximal tibia group. At 1 year the survivorship was 87\% \( (95\% \ CI 77-98) \) for proximal femur reconstructions and 84\% \( (95\% \ CI 75-93) \) for distal femur reconstructions. Between 1 and 2 years, only the distal femur group experienced failure (4 failures), with 2 year survivorship of 84\% \( (95\% \ CI 75-93) \). After 2 years, a total of 4 more failures occurred (3 in proximal femur group, 1 in distal femur group). Cox proportional hazards modeling demonstrated overall difference in hazard by location \( (p=0.0494) \). Extended Cox modeling demonstrated an increased hazard for the proximal tibia group relative to the distal femur group \( (HR=4.42, \ p=0.052) \), that was time dependent \( (interaction \ p \ value=0.008) \), reflecting that the increased hazard for the proximal tibia group occurred at 4-6 months, with no failures after this point.

Discussion

There was no increased risk of aseptic failure during the initial 6-week period post-compressive osseointegration fixation. No aseptic failures occurred before 81 days, suggesting initial stability. There was also no clear temporality for aseptic failure and compressive

Figure 2. Kaplan Meier Plot for Overall Failure based on Location with 95% Hall-Wellner Bands.
osseointegration fixation at later time points.

The overall aseptic mechanical failure rate is similar to published rates of 4-12% \([4, 15, 23, 25, 31]\) and slightly less than a large multicenter review of 2174 traditional intramedullary stemmed endoprostheses, which had an aseptic failure rate of 12%.

Pedtke et al. studied a series of 26 patients with compressive osseointegration fixation for endoprosthetic reconstruction and found that only 1 of the 26 had aseptic failure, and none after 2 years \([15]\). Additionally, Tyler et al. reported peri-prosthetic fractures sustained between 2-20 months in 6 (2.7%) of 221 patients treated with the Compress® device \([30]\). The site of osseointegration was examined at the time of revision and found to be intact. This supports the notion that stable osseointegration can be achieved before 2 months, and in their series was achieved before 20 months in all patients.

Avedian et al. evaluated radiographic distal femoral bone hypertrophy from 0-24 months after compressive osseointegration fixation and found that in patients not receiving chemotherapy, the cortical width increased incrementally from 0 to 3 to 6 months, by which time the maximal cortical width was reached \([24]\). Patients receiving chemotherapy experienced a slower, incremental increase in cortical width until 12 months and then plateaued. After 12 months, cortical width was equivalent in chemotherapy and non-chemotherapy groups. Thus it appears that radiographic bony hypertrophy, one component of osseointegration, begins post-operatively and is complete by 6 months in patients not receiving chemotherapy.

There was a difference in the time delay to achieve stable fixation based on anatomic location. We found an increased risk of aseptic failure for the proximal tibial group at time less than 6 months; this was only in this subset of patients and may reflect differing mechanical forces across the implants. There was a similar time dependent increased risk of overall failure of the proximal tibial group occurring at 4-6 months, which is likely related to the subcutaneous nature of proximal tibial reconstructions and increased risk of infection.

This study had several limitations. It was a retrospective study with the potential for selection bias: 41 patients during the study period were treated with traditional intramedullary stemmed endoprostheses, and may have been candidates for Compress® fixation. However, the use of intramedullary stemmed fixation at this institution decreased rapidly and only eight were performed in the last 5 years of the study period. This was a single-center patient cohort and the results may not be generalizable to the broader population. Functional outcomes data were not available with this review, and although important, this study’s intent was to identify survivorship and not to assess functional outcomes. A multivariate analysis was unable to be performed based on the number of patients in the series; however, this still represents the largest series to our knowledge with minimum 2-year follow up. Due to the nature of this retrospective review, we were unable to accurately assess or measure patients’ adherence to weight-bearing recommendations, or to study differing weight-bearing restrictions in matched cohorts as would be ideal in a randomized controlled trial. Other modes of failure of compressive osseointegration fixation include periprosthetic fracture around a stable implant, infection, or progression of oncologic disease \([4, 23, 27, 28, 31]\), all of which are clinically relevant but outside the scope of this study.

To our knowledge, this is the first study to evaluate temporality of failure of compressive osseointegration fixation. We did not identify an increased risk of early aseptic mechanical failure or a time frame when stable compressive osseointegration occurs, but did find an increased risk of failure in the proximal tibia group. More research is necessary to understand the biomechanical stability of compressive osseointegration fixation and its ability to withstand physiologic loads, i.e. immediate weight-bearing, prior to biologic osseointegration.

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Conflicting interests

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Author contributions

RK contributed in conception, design, and acquisition of data, analysis and interpretation of data, was involved in drafting the manuscript and has given final approval of the version to be published. DO contributed in the analysis and interpretation of data, was involved in drafting the manuscript and has given final approval of the version to be published. SH contributed to the analysis and interpretation of the data, specifically developing the statistical
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