

Original research

Depression Is Transiently Increased in Patients Undergoing Two-Stage Revision Arthroplasty

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ABSTRACT

Background: The implications of two-stage revision on mental health are poorly understood. The purpose of this study is to determine (1) whether patients undergoing two-stage revision total hip and knee arthroplasty for prosthetic joint infection were more likely to get Patient-Reported Outcomes Measurement Information System (PROMIS) Depression scores consistent with major depressive disorder (MDD) than those undergoing aseptic revision and (2) whether these symptoms resolved after the procedure.

Methods: Records of all 366 patients that underwent revision total hip or knee arthroplasty from January 1, 2015, – June 20, 2019, were reviewed. Forty-two patients were excluded for missing PROMIS Depression scores or incomplete treatment. Preoperative (<3 months), early postoperative (2–8 weeks), and final postoperative (6–18 months) Depression scores were collected. Patients crossing the PROMIS Depression threshold equivalent to a Patient Health Questionnaire-9 score ≥ 10 , indicative of MDD, were evaluated.

Results: More two-stage revision patients developed Depression scores indicative of MDD perioperatively than the aseptic cohort (20.0% vs 6.5%, $P = .01$). Two-stage revision patients had higher (worse) median Depression scores preoperatively (54.8 vs 51.3, $P = .04$) and at early follow-up (54.3 vs 49.9, $P = .01$), but not at final follow-up (50.4 vs 49.1, $P = .39$). Across all patients, Depression scores improved by 2.4 points at early follow-up (95% confidence interval: 1.1–3.7; $P < .001$) and 3 points at final follow-up (95% confidence interval: 1.5–4.5; $P < .001$; minimal clinically important difference 3.0).

Conclusions: Twenty percent of two-stage revision arthroplasty patients, compared to <7% of aseptic revision patients, developed PROMIS Depression scores consistent with MDD during treatment. At final follow-up, a clinically significant improvement in Depression scores from baseline was evident in both cohorts.

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Introduction

Prosthetic joint infection (PJI) is a major complication after total joint arthroplasty (TJA), with a reported prevalence of up to 2.5% in total hip arthroplasty and 2% in total knee arthroplasty in standard US populations [1,2]. Two-stage revision, currently the most commonly performed treatment for PJI in the United States, carries substantial morbidity [2–5]. The process involves an initial revision surgery to remove infected hardware and place an antibiotic-laden cement spacer followed by a minimum of 6 weeks of IV antibiotics, often while remaining non-weight-bearing and immobilized. The

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two-stage revision is then completed with a second surgery to remove the antibiotic spacer and replace the prosthesis, often after an antibiotic holiday that adds additional time for the patient before reimplantation. Medical complications, hospitalization time, patient mobility, and cost have been compared between one- and two-stage revisions; however, the mental health implications of these treatments have not been studied [3,4].

Depressed patients undergoing primary or revision TJA have been shown to have worse outcomes, including more pain, poorer functional status, and increased rates of readmission and infection [6–10]. In addition, pharmacologic treatment of depression is associated with greater improvements in physical function post-operatively in primary TJA patients [11]. Therefore, understanding the mental health risks of patients undergoing revision TJA is a critical component of their management.

The Patient Health Questionnaire-9 (PHQ-9) is a well-validated tool that is widely used in a variety of medical settings to screen, diagnose, and monitor treatment of major depressive disorder (MDD) [12–14]. Using a score cutoff of ≥ 10 , indicating “moderate depression,” maximizes the PHQ-9’s sensitivity and specificity for diagnosis of MDD [14,15]. While the PHQ-9 is both effective and reliable, there has been considerable interest in reducing the number of questions presented to patients for ease and speed of screening [16,17].

Utilization of computer adaptive testing, including the NIH-developed Patient-Reported Outcomes Measurement Information System (PROMIS), has allowed for simpler patient screening while maintaining high precision and reliability [18–20]. Depressive symptoms can be assessed by PROMIS. Because PROMIS Depression scores have been defined in relation to PHQ-9, they can be easily converted to PHQ-9 scores [21]. This is most clinically relevant for PROMIS Depression scores of ≥ 59.9 , which is equivalent to a PHQ-9 score of ≥ 10 , and can be used to support a diagnosis of MDD [21,22]. Our goal in this study was to determine (1) whether patients undergoing two-stage revision for PJI are more likely to develop PROMIS Depression scores consistent with MDD in the perioperative period than those undergoing aseptic revision and (2) whether these symptoms resolved after surgery.

Material and methods

After IRB approval, an a priori power analysis was performed and identified that 300 patients would be required to detect clinically relevant differences in PROMIS Depression scores between aseptic and two-stage revision cohorts at our enrollment ratio of 1.88 to 1. Differences in PROMIS Depression scores of 3 points have been established as the minimal clinically important difference (MCID) in multiple noncancer patient populations [18,23].

A retrospective review was performed by querying a database of 24 attending orthopedic surgeons and fellows practicing at two hospitals within a single academic institution. All patients older than 18 years who underwent revision of THA or TKA from January 1, 2015, through June 20, 2019, were initially included. This produced a list of 366 patients, of which 15 were excluded from the study for missing PROMIS scores. Among those who began two-stage revision treatment for PJI, 12 were excluded for undergoing amputation, 8 were excluded for undergoing knee fusion, and 9 were excluded for otherwise not completing the second (replant) stage of the revision. During the study period, no patients at our institution were treated for PJI with one-stage revision arthroplasty or debridement, antibiotics, and implant retention. The final study population included 210 patients that underwent one-stage revision for aseptic failure as determined by Musculoskeletal Infection Society criteria and 112 patients that underwent a completed two-stage revision for PJI. Two of the 112 two-stage revision patients

had undergone prior failed liner exchange, and three had undergone prior failed two-stage revision.

Medical records were reviewed to identify patient age, sex, height, weight, body mass index (BMI), American Society of Anesthesiologists (ASA) score, prior diagnosis of depression documented in past medical history, prior diagnosis of anxiety, or active prescription of antidepressants. PROMIS depression scores were collected at four perioperative time points for those who underwent two-stage revision for PJI: less than 3 months before explant, less than 1 month before replant, 2–8 weeks after replant (early follow-up), and 6–18 months after replant (final follow-up). For those who underwent one-stage revision, PROMIS depression scores were collected at three time points: less than 3 months before revision, 2–8 weeks after revision (early follow-up), and 6–18 months after revision (final follow-up). Scores that were obtained outside of these perioperative periods were discarded. The proportion of patients with PROMIS Depression scores ≥ 59.9 at each time point was noted, as this corresponds to a score ≥ 10 on the PHQ-9 and thus has high sensitivity and specificity for diagnosis of MDD [15,21]. Weight-bearing status in the time between explant and replant surgeries was also recorded in the two-stage revision cohort.

Comparisons of demographic information and PROMIS scores between the two-stage and aseptic revision cohorts were conducted via Kruskal-Wallis and Pearson’s chi-square testing (Figs. 1 and 2). No categorical comparisons had small enough cohorts to require the use of Fisher’s exact testing. A repeated measures mixed model was used to determine the overall effect of demographic variables and time since the final surgery on PROMIS Depression scores.

Results

A total of 322 patients, including 189 females and 133 males, were included in the study (Table 1). The median age at time of revision was 66 years (range 19 – 93 years), and the median BMI was 30.5 (range 15.7 – 61.55). Seventy-seven percent (112 of 145) of patients who began two-stage revision treatment for PJI underwent replant and were thus eligible to be included in the analysis. The median time between explant and replant in the two-stage revision cohort was 15.9 weeks (range 0.6 – 82.3 weeks; interquartile range 12.3 – 20.4 weeks). Of the 112 patients who completed two-stage revision treatment, there was no known recurrence of infection at final follow-up clinic visit in 102 cases (91%). Eighty-two percent (92 of 112) of the two-stage revision cohort had a static antibiotic spacer placed and were non-weight-bearing in the time between explant and replant surgeries. The remaining 18% (20 of 112) of the two-stage revision cohort had an articulating spacer placed and could bear weight between explant and replant surgeries.

Compared to the one-stage revision cohort, patients undergoing two-stage revision for PJI had higher BMI (29.8 vs 31.6, $P = .006$), had higher ASA (2.8 vs 2.6; $P = .013$), and had been diagnosed with anxiety (48% vs 15%; $P < .001$) and depression at a higher rate (64% vs 18%; $P < .001$). All other demographic information was similar between the two cohorts (Table 1).

Ten of 50 patients (20%) with preoperative Depression scores < 59.9 undergoing two-stage revision developed Depression scores indicative of new-onset or re-emergent MDD perioperatively (Fig. 2). Eight of 124 patients (6.4%) with preoperative Depression scores < 59.9 undergoing aseptic revision developed new-onset or re-emergent scores indicative of MDD (Fig. 2, $P = .013$). Patients undergoing two-stage revision for PJI had significantly higher (worse) median PROMIS Depression scores than those undergoing aseptic revision preoperatively (54.8 vs 51.4, $P = .04$) and at early follow-up (54.3 vs 49.9, $P = .01$; Fig. 1). No significant difference in

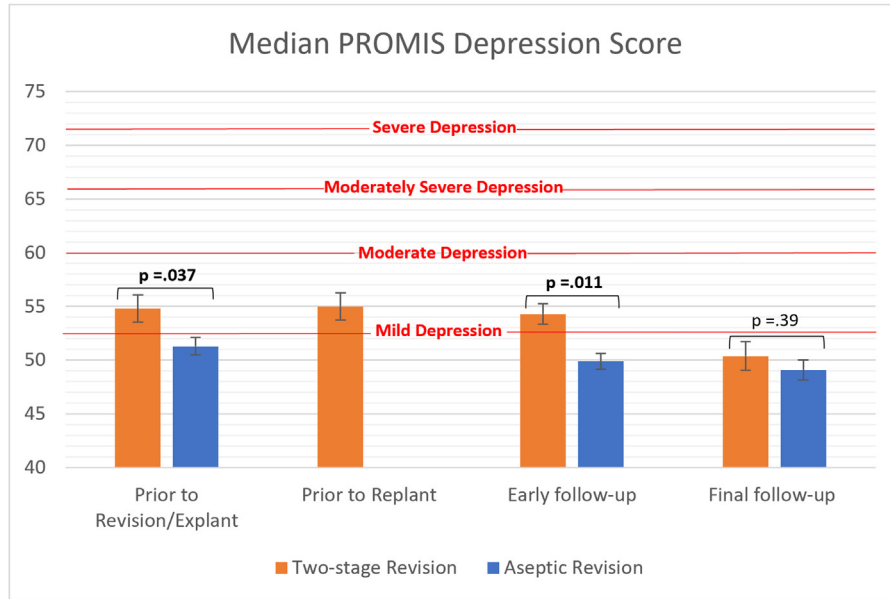


Figure 1. Median perioperative PROMIS Depression scores in context of the PHQ-9. Red lines represent Depression scores equivalent to cutoff values for the PHQ-9 categories. Median PROMIS Depression scores were significantly higher in the two-stage revision cohort before revision/explant and at early follow-up. No differences between cohorts remained at the final follow-up. Median Depression scores for both cohorts failed to reach the PHQ-9 threshold for moderate depression. PHQ-9 scores indicative of moderate depression have the highest sensitivity and specificity in diagnosis of major depressive disorder [15].

Depression was observed between the two cohorts at the final follow-up (50.4 vs 49.1, $P = .39$; Fig. 1). Within the 2-stage revision cohort, no difference in median Depression scores was noted between patients with articulating vs nonarticulating antibiotic spacers at any time point ($P > .05$ for all). The overall rates of MDD-range scores in each cohort, regardless of preoperative Depression scores, are listed in Table 2.

On multivariate analysis, previously diagnosed depression was found to be an independent predictor of higher (worse) PROMIS Depression scores ($\Delta 3.4$; 95% CI 0.5–6.3; $P = .02$). Active antidepressant prescription before surgery was another independent predictor of higher Depression scores ($\Delta 5.4$, $P < .001$). Despite significant findings on a univariate analysis, revision for PJI was not an independent predictor of worse PROMIS scores on multivariate

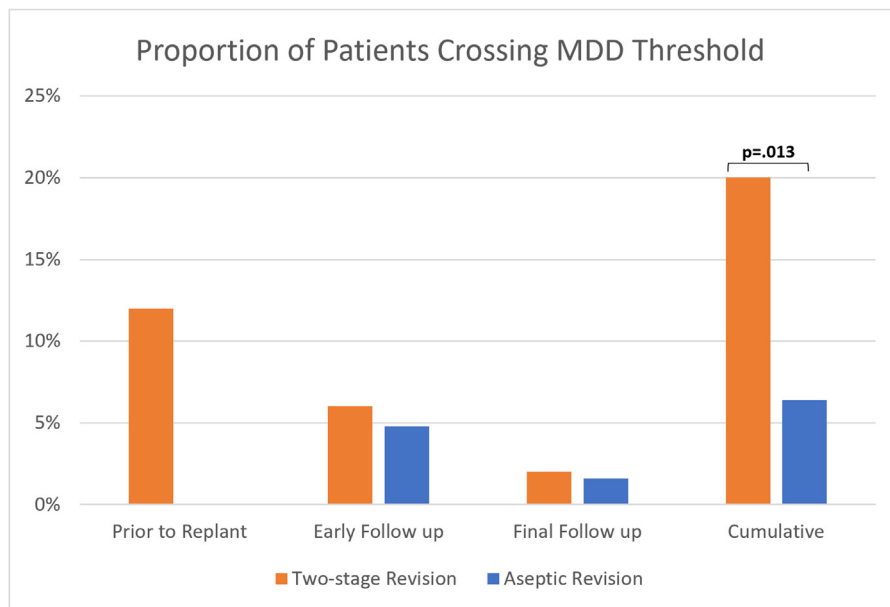


Figure 2. Development of PROMIS Scores indicative of new-onset or re-emergent major depressive disorder (MDD). Patients with preoperative Depression scores below the PHQ-9 cutoff for moderate depression were included in this analysis. Twelve percent of the two-stage revision cohort developed Depression scores indicative of MDD before replant. An additional 6% crossed the MDD threshold by early follow-up and 2% more did by the final follow-up, for a total of 20% of the cohort (10/50). By early follow-up, 4.8% of the aseptic revision cohort had developed Depression scores indicating MDD, and an additional 1.6% had done so by the final follow-up, for a total of 6.4% of the cohort (8/116). PHQ-9 scores indicative of moderate depression have the highest sensitivity and specificity in diagnosis of major depressive disorder [15].

Table 1
Demographic comparisons of two-stage vs aseptic revision cohorts.

Factor	Total (N = 322)	Aseptic revision (N = 210)	Two-stage revision (N = 112)	P value
Age (y)	66.0 [60-73]	67.0 [60-75]	65.0 [60-72]	0.085 ^a
BMI	30.5 [26-36]	29.8 [26-34]	31.6 [27-39]	0.006^a
ASA	2.61 [2-3]	2.56 [2-3]	2.76 [2-3]	0.013^a
Sex				0.76 ^b
Male	189 (59%)	122 (58%)	67 (60%)	
Female	133 (41%)	88 (42%)	45 (40%)	
PMH depression				<0.001^b
No	212 (66%)	172 (82%)	40 (36%)	
Yes	110 (34%)	38 (18%)	72 (64%)	
PMH anxiety				<0.001^b
No	235 (73%)	178 (85%)	57 (52%)	
Yes	85 (27%)	32 (15%)	53 (48%)	
Antidepressant				0.59 ^b
No	158 (49%)	106 (51%)	52 (47%)	
Yes	162 (51%)	104 (49%)	58 (53%)	

PMH depression, anxiety, diagnosis available in patient's medical record at the time of preoperative clinic visit.

Data not available for all subjects. Missing values: BMI = 1, ASA = 40, PMH anxiety = 2, antidepressant = 2.

Bolded values indicate statistical significance.

^a ANOVA.

^b Kruskal-Wallis test.

analysis ($P > .05$). Time since final surgery was identified as an independent predictor of lowered (better) Depression scores compared with preoperative baseline: this effect did not meet MCID by early follow-up ($\Delta 2.5$; 95% CI: 1.1–3.7; $P < .001$) but did meet MCID by the final follow-up ($\Delta 3.0$; 95% CI: 1.5–4.5; $P < .001$).

Discussion

Compared with the aseptic revision cohort, a greater proportion of patients undergoing two-stage revision developed PROMIS scores indicative of new-onset or re-emerged MDD. PROMIS Depression scores were increased preoperatively in patients undergoing two-stage compared with aseptic revision, but this difference resolved by the final postoperative follow-up. Pre-existing depression and active antidepressant use were found to independently predict worsened PROMIS scores throughout the perioperative period for all patients. Finally, Depression scores improved from preoperative baseline by early follow-up, although not reaching the MCID. This improvement reached the MCID by the final follow-up.

There are multiple possible reasons for the observed differences in PROMIS Depression scores between cohorts in this study. The high morbidity of two-stage revision as a potential etiology of depression has been documented. Carroll et al. (2020) found that patients who underwent either one- or two-stage revision arthroplasty for PJI strongly preferred having only one operation and minimizing the time from start of treatment to resumption of normal activities [24]. Notably, preoperative PROMIS scores in this study were generally obtained before any discussion of surgical treatment, so the elevated preoperative Depression scores in our PJI patients are likely not related to anticipation of the length and morbidity of a two-stage revision. Preoperatively, the presence of PJI itself, with its associated pain and dysfunction, may contribute more to preoperative depression than the morbidity of the two-stage revision [25]. Later in the perioperative period (before explant, early follow-up), elevated Depression scores may be due to a combination of two-stage revision morbidity and residual symptoms from PJI [24,25].

Our study also found that active antidepressant use before surgery was associated with worsened perioperative Depression scores in our patient population. This cohort likely had severe pre-existing MDD exacerbated by the course of surgical treatment. Conversely, greater time since final operation was found to be an

independent predictor of lower (better) PROMIS Depression scores. This suggests that even those patients who require antidepressant therapy in the two-stage revision perioperative period experience improvement as they recover. Thus, patients with MDD undergoing TJA revision may benefit from frequent re-evaluation of depressive symptoms and discontinuation of pharmacologic antidepressants when indicated.

Prior studies have shown that depressed TJA patients have worse functional outcomes, as well as increased pain, rates of readmission, and PJI [6–10]. Causality has not been established, so it is possible that depression contributes to worse pain/function, that worse pain/function contribute to depression, or a combination of both [6–10]. Mental health issues can become obstacles to participation in rehabilitation, appropriate nutrition and self-care, and ability to comply with follow-up and treatment for orthopedic as well as other medical conditions; any of these could potentially contribute to the aforementioned issues [26–29]. As such, recognizing and treating clinical depression could represent an opportunity to optimize patient outcomes.

The PHQ-9 has been identified as a valuable tool in all aspects of MDD treatment, including screening, treatment recommendations, and measurement of treatment response [30,31]. Because PROMIS Depression scoring in relation to the PHQ-9 has been defined, the potential benefits of PHQ-9 scoring in the TJA population can be

Table 2
Overall rates of PROMIS scores indicative of moderate depression.

Perioperative time point	Total	Aseptic revision	Two-stage revision	P value
Before explant/revision				.13
No/mild depression	174 (77%)	124 (81%)	50 (69%)	
Moderate depression	51 (23%)	29 (19%)	22 (31%)	
Before replant				NA
No/mild depression	50 (66%)	NA	50 (66%)	
Moderate depression	26 (34%)	NA	26 (34%)	
Early follow-up				.14
No/mild depression	246 (73%)	162 (85%)	84 (77%)	
Moderate depression	53 (27%)	28 (15%)	25 (23%)	
Final follow-up				.16
No/mild depression	164 (83%)	110 (87%)	54 (77%)	
Moderate depression	33 (17%)	17 (13%)	16 (23%)	

Values presented as N (column %). P values calculated via Pearson's chi-square test. Data not available for all subjects. Missing values: before explant/revision = 97, before replant = 36, early follow-up = 23, final follow-up = 125. All patients were included in this analysis regardless of preoperative Depression score.

obtained more quickly via computer adaptive PROMIS testing [32]. The proportions of patients of both study cohorts with PROMIS Depression scores ≥ 59.9 are substantial (Fig. 2, Table 2). While causality cannot be proven, certain patients may have improved psychological and perioperative outcomes with initiation or increase of treatments, such as pharmacologic antidepressants and/or cognitive behavioral therapy [6,9,11]. We, therefore, recommend frequent screening for MDD and referral for antidepressant therapy when indicated for patients undergoing revision arthroplasty.

Study limitations

This study is substantially limited by its retrospective design. Depression scores were not available for all desired time points for every patient. Although our data would suggest that two-stage revision patients who do not undergo reimplantation would have the worst PROMIS Depression scores of all groups, the low rate of Depression score availability in this subcohort precluded this analysis. In addition, patients in the aseptic and two-stage revision cohorts differed in several respects. On average, patients undergoing two-stage revision had ASA scores 0.2 points higher, a difference that was statistically but likely not clinically significant (2.76 vs 2.56, $P = .013$). More relevant, patients undergoing two-stage revision for PJI had higher BMI (31.6 vs 29.8, $P = .006$) and were more likely to have a past medical history including depression than those undergoing aseptic revision (64% vs 18%, $P < .001$). The association of elevated BMI and depression has been well-documented in the literature as well [33–35]. Our finding of elevated BMI in the two-stage revision cohort is consistent with literature indicating that periprosthetic infection risk increases with obesity [36–38]. The higher rates of pre-existing depression observed in the two-stage revision cohort are also consistent with studies indicating that depressed patients are at increased risk of PJI [9,38]. Notably, we did not find elevated BMI to be an independent risk factor for worse Depression scores in our regression analysis, potentially because other factors were correlated with BMI and so absorbed some of its effect.

Because single-stage revision was not used as a treatment for PJI at our institution during the study period, we did not have such a cohort available for comparison. As such, we were unable to determine the extent to which differences in perioperative PROMIS scores between the cohorts were related to the underlying condition (ie, infection) or its treatment. We were likewise unable to distinguish between the effects of specific treatment factors, including the period of immobility, need for a second revision surgery, antibiotics, or prolonged duration of treatment. A follow-up study comparing patient-reported depression scores in those who underwent one-stage vs two-stage revision for PJI would be needed to better characterize the etiology of the depressive symptoms we observed.

Antidepressant therapy regimens were not initiated or managed as part of the present study. As such, further research is needed to determine whether initiating or increasing treatment is effective in patients who develop clinically significant depression based on perioperative PROMIS scores. Finally, our study was not designed to capture the population of patients who did not complete a two-stage revision procedure and may be at high risk for depression.

Conclusion

Approximately three times more patients undergoing two-stage revision for PJI develop PROMIS Depression scores indicative of new-onset or re-emergent MDD than those undergoing aseptic revision. A pre-existing diagnosis of depression is an independent predictor for clinically significant worsening of PROMIS Depression scores during revision arthroplasty and should be aggressively

managed. In all patients, time since final operation is an independent predictor of improved PROMIS Depression scores, highlighting the substantial long-term benefits of revision arthroplasty in appropriately selected populations.

Conflicts of interest

The senior author has the following conflicts of interest to report: Paid consultant for LINK Biocorp and DePuy Synthes. Board member/Committee appointments for a Society, Women In Arthroplasty Committee member, AAHKS; Education Committee member, Musculoskeletal Tumor Society. No other authors have any conflicts of interest to report.

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